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DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 02-091153- -00025-0000

Fecha: 2010-10-21 16:54:59 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 74

Re: P1.-JAGOTEC AG.-Solicitud de Patente de Invención en Fase Nacional PCT para "FORMULACIÓN DE DOSIFICACIÓN EN MATRIZ POLIMÉRICA HIDROFÍLICA/LIPOFÍLICA".-Clase A61K 9/24.-Expediente número 02-091.153.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista el 11 de Junio de 2010, así como a mi solicitud de plazo de fecha 24 de Agosto de 2010 para dar respuesta al auto antes mencionado.

2. Con el fin de responder a las objeciones expuestas por el señor Examinador en su Concepto Técnico No. **1128** bajo el acápite de Nivel Inventivo, atentamente me permito presentar los siguientes argumentos técnicos por medio de los cuales no sólo se superan dichas objeciones, sino que además se demuestra en forma contundente la patentabilidad de dicha invención.

3. **NIVEL INVENTIVO DE LA SOLICITUD**

El señor Examinador ha objetado el nivel inventivo de la solicitud en cuestión basándose en las enseñanzas de los siguientes documentos:

(D1) → WO 97/03670

(D2) → WO 98/00115

En este sentido, el señor Examinador argumenta básicamente que la única diferencia con el documento D1 es que la solicitud en cuestión menciona explícitamente que el compuesto activo presente en la tableta multicapas de liberación controlada es ropinirol. Sin embargo, de acuerdo con el señor Examinador la solicitud es obvia porque el experto medio en la materia enfrentado al problema de lograr integrar el ropinirol en una formulación de liberación controlada y conociendo el estado de la técnica haría una formulación multicapas tal como se enseña tanto en D1 como en D2, realizando los ajustes necesarios a lo ya conocido mediante ensayos rutinarios de preformulación, con el fin de lograr que un principio activo soluble en agua tenga un buen perfil de liberación fisiológica.

Visto lo anterior y con el ánimo de demostrar que la solicitud en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas de los documentos D1 y D2, atentamente me permito presentar ante ese Despacho las siguientes consideraciones técnicas:

3.1 Características técnicas generales de la invención bajo estudio

La solicitud de patente en cuestión revela una novedosa tableta multicapa de liberación controlada que comprende: **(a)** una capa activa que contiene, i) 0.05% a 20% en peso de ropinirol o sales farmacéuticamente aceptables del mismo; ii) sustancias poliméricas hidrofílicas que se hinchan y/o gelifican y/o erosionan al contacto con líquidos acuosos; iii) sustancias lipofílicas (en donde la relación en peso de las sustancias poliméricas hidrofílicas y las sustancias lipofílicas contenidas en dicha capa activa se encuentran en el rango entre 7:1 y 1:1); y, iv) 5%-50% en peso de sustancias excipientes; y, **(b)** una o más capas de barrera que limitan la superficie de liberación de la capa activa y que contienen una o más de: sustancias poliméricas hidrofílicas las cuales se hinchan y/o gelifican y/o erosionan al contacto con líquidos acuosos, sustancias lipofílicas y sustancias excipientes.

Tal y como se menciona en la descripción de la solicitud en cuestión, la tableta multicapa revelada tiene aplicación en el tratamiento de la enfermedad de Parkinson (ver las páginas 25 y 26 de la descripción). Allí se menciona, por ejemplo, que la tableta de liberación controlada de ropinirol es ventajosa frente a las tabletas de liberación inmediata conocidas en el estado de la técnica anterior porque permite lograr una concentración sistémica de compuesto activo sobre un período de 24 horas, evitando la necesidad de administrar dicho compuesto activo en numerosas ocasiones durante el día y evitando algunos de los efectos secundarios propios de los medicamentos administrados a través de mecanismos de liberación inmediata. Ahora, tal como se analizará más adelante en el presente escrito, la formulación de dosificación revelada por el solicitante permite lograr estas y otras ventajas que de ninguna manera habrían podido predecirse con anticipación. Sin embargo, con el ánimo de enfocar de manera adecuada el entorno de la presente invención, a continuación me permito presentar un resumen de la materia técnica conocida en el arte previo.

3.2 Antecedentes técnicos que conforman el estado de la técnica anterior

La enfermedad de Parkinson implica un desorden a nivel del movimiento. Durante muchas décadas atrás se había asumido que tal enfermedad era causada primordialmente por la pérdida de las neuronas dopaminérgicas, lo cual daba lugar a una disminución en los niveles de dopamina en el cuerpo estriado del cerebro.

Diversas posibles terapias han sido probadas con el objetivo de tratar la enfermedad de Parkinson, pero muchas de ellas han sido asociadas con diversos inconvenientes. Así, por ejemplo, el compuesto L-dopa ha sido probablemente el medicamento más utilizado en

el tratamiento de la enfermedad de Parkinson, a pesar de que su uso está asociado con el desarrollo de movimientos involuntarios anormales denominados disquinesias. De otro lado, diversos compuestos agonistas de dopamina también han sido utilizados para tratar el Parkinson, toda vez que se ha demostrado que su empleo reduce el riesgo de desarrollar disquinesias. En este sentido, los agonistas de dopamina aprobados para su uso terapéutico se dividen en dos clases: i) agonistas de dopamina derivados de ergot (ergolina), y ii) agonistas de dopamina no derivados de ergot (no-ergolina), donde la primera clase de dichos compuestos ha sido frecuentemente asociada con efectos adversos, incluyendo pleurosis pleuropulmonar y retroperitoneal, mientras que la segunda clase (agonistas de dopamina no ergolina), entre los que se cuenta el ropinirol, se caracterizan por presentar un perfil de eventos adversos aceptable.

Sin embargo, una desventaja asociada con todos los compuestos agonistas de dopamina, incluyendo aquellos no-ergolina, es la demora en el mejoramiento sintomático, hecho que es ocasionado porque dichos compuestos también actúan por fuera del sistema nervioso central, ocasionando efectos adversos adicionales tales como náusea e hipotensión postural. Ahora, debido a que los pacientes desarrollan algún grado de tolerancia a tales efectos adversos tan sólo de manera gradual, era altamente recomendada la administración de dosis pequeñas de agonistas de dopamina, incrementándola gradualmente hasta llegar a los niveles terapéuticos requeridos. En este punto resulta de gran importancia mencionar que, por ejemplo, cerca de la mitad de los pacientes que reciben una terapia que incluye la administración de ropinirol mediante formulaciones de liberación inmediata, responden a dosis entre 4,5 y 7,5 mg por día (ver el documento Kaye and Nicholls, 2000, Clin. Pharmacokinetic, 39(4):243-254, particularmente la página 252, columna 1). Sin embargo, si los pacientes siguieran el modo de administración indicado, la mitad de dichos pacientes únicamente percibirá los beneficios terapéuticos luego de 5 a 6 semanas después de haber iniciado el tratamiento (ver los resúmenes de los documentos titulados "*Summary of product characteristics for Requip®*", de fechas Diciembre 21 de 1998 y Agosto 21 de 2000).

De conformidad con lo anterior, es claro que el tiempo requerido para observar una respuesta terapéutica al emplear compuestos agonistas de dopamina siempre ha sido considerado como un inconveniente, razón por la cual algunos médicos incluso prefieren prescribir tratamientos con L-dopa debido a que si bien dicho tratamiento provoca disquinesias, los beneficios sintomáticos se observan con mayor rapidez (ver el documento Rascol et al., 2000, N. Eng. J. Med., 342: 1484-1491, particularmente la página 1484, columna 2, líneas 1 a 17).

Ahora bien, en el estado de la técnica anterior había sido sugerido que la terapia ideal para tratar la enfermedad de Parkinson implica la restauración de las funciones normales de la dopamina, lo cual, de acuerdo con lo mencionado en el documento Obeso et al., 1994, Eur. J. Neurosci., 6:889-897, particularmente la página 895, columnas 1 y 2, implica la necesidad de llevar a cabo una administración continua de compuestos dopaminérgicos, lo cual implica un serio inconveniente debido a la necesidad de poner en

práctica un tratamiento invasivo que permita dicha administración continua. En consecuencia, es claro que en el estado de la técnica se requería de un método no invasivo que permitiera lograr una estimulación dopaminérgica continua. Sin embargo, los intentos que han sido realizados en este sentido no han resultado satisfactorios, toda vez que los medicamentos MADOPAR CR® y SINEMET CR® no permitieron proporcionar un nivel de L-dopa constante en el plasma sanguíneo y por lo tanto no permitieron proporcionar una estimulación dopaminérgica permanente. Por su parte, si bien el compuesto denominado cabergolina presenta una vida media cercana a las 60 horas, dicho compuesto es un agonista de dopamina ergolina, por lo que, tal como se discutió previamente, su administración implica serios eventos secundarios adversos.

Como consecuencia de lo anterior, **es claro que en el estado de la técnica existía la necesidad de una formulación que permitiera superar los inconvenientes ocasionados por las formulaciones conocidas en el estado del arte. Específicamente, en el estado de la técnica permanecía la necesidad de una formulación que permitiera poner en práctica una terapia no invasiva capaz de proporcionar una rápida mejoría sintomática y una continua estimulación dopaminérgica, pero evitando los efectos adversos asociados típicamente a la administración de compuestos de dopamina ergolina.** Ahora, tal como se analizará a continuación, la formulación de dosificación revelada en la solicitud de patente en cuestión reúne la totalidad de dichos requerimientos terapéuticos, representando un importante avance en el estado de la técnica en cuestión.

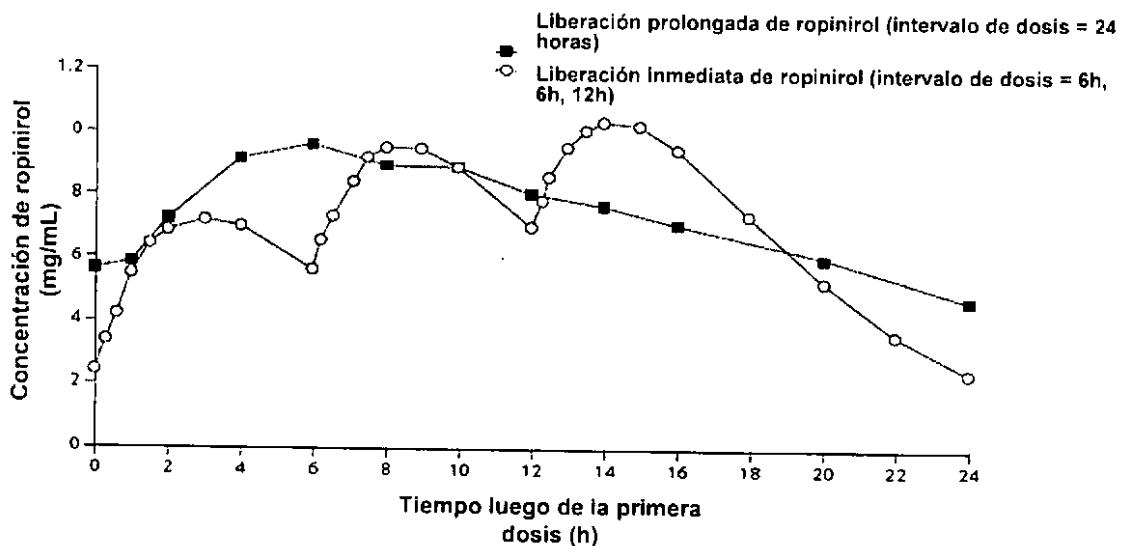
3.3 Ventajas técnicas de la tableta reivindicada

La formulación de dosificación revelada en la presente invención se caracteriza porque es capaz de controlar la liberación del compuesto activo ropinirol durante periodos de tiempo prolongados. En este sentido, las figuras 10 a 13 de la descripción muestran, por ejemplo, que diferentes dosis de la formulación revelada en el ejemplo 24 son capaces de liberar ropinirol durante un período de 24 horas, siendo éste el período más largo de liberación de un compuesto activo administrado por vía oral. Por su parte, los ejemplos 13 a 18 también describen la liberación de ropinirol durante un período de 24 horas in vitro, hecho que resulta ser óptimo para lograr un tratamiento eficaz de la enfermedad de Parkinson.

Así mismo, los perfiles de disolución in vitro de los diferentes ejemplos divulgados en la descripción muestran que el ropinirol es liberado a una velocidad sustancialmente constante. En otras palabras, el solicitante de la invención en cuestión ha encontrado de manera sorprendente que con la utilización de la forma farmacéutica revelada en la presente solicitud de patente, es posible obtener una velocidad de liberación de ropinirol similar o idéntica, aún si dicha tableta contiene cantidades muy diferentes de la misma sustancia activa.

Lo anterior resulta ser de gran utilidad en diferentes modelos patológicos en donde cobra importancia la necesidad de contar con formas farmacéuticas que presenten un contenido de principio activo variable (para favorecer, por ejemplo, la personalización de la posología), pero que sin embargo tengan la capacidad de liberar dicho principio activo con un perfil cinético idéntico (o al menos similar) independientemente de la cantidad de sustancia activa transportada.

A éste respecto, se ha llevado a cabo el modelamiento de la farmacocinética en estado estacionario de ropinirol que es administrado a pacientes mediante una formulación de liberación inmediata (administración de 2,5 mg de ropinirol durante el desayuno, almuerzo y cena, esto es, cada 6, 6 y 12 horas). Los resultados de dicho modelamiento aparecen divulgados en la figura 5 del documento Thompson and Vearer, 2007, Clin. Ther., 29:2654-2666, donde se muestra que el perfil farmacocinético del régimen de 6, 6 y 12 horas muestra mayores fluctuaciones en el nivel de compuesto activo en plasma en comparación con el perfil farmacocinético en estado estacionario determinado experimentalmente para una formulación de liberación prolongada (administración del compuesto activo una vez diaria). Como puede observarse, existe una fluctuación en el nivel de ropinirol en plasma de aproximadamente cinco (5) veces entre la concentración máxima y mínima de ropinirol en pacientes tratados con formulaciones de liberación inmediata, mientras que dicha fluctuación en pacientes tratados con formulaciones de liberación controlada es de tan sólo dos (2) veces.



Uno de los beneficios de las fluctuaciones reducidas es que los pacientes a quienes se les administra ropinirol mediante una formulación de liberación inmediata, es decir, con las comidas diarias, muestran una concentración de ropinirol en plasma dos veces menor con respecto a aquellos pacientes a los que se les administra ropinirol a través de una formulación de liberación prolongada (ver los documentos Thompson and Vearer, 2007, Clin. Ther., 29: 2654-2666, particularmente la página 2664, columna 2, líneas 4-8; y Ropinirol prolonged release: a guide to its use in Parkinson's disease, 2009, Drugs and Therapy perspectives, 25(6), 1-5, particularmente la página 2, columna 1, líneas 14-18).

Por otro lado, los altos niveles en plasma de ropinirol cuando dicho compuesto activo es administrado a través de una formulación de liberación prolongada permite lograr un mejor control de los síntomas propios de la enfermedad de Parkinson en las primeras horas de la mañana, momento del día particularmente complicado para aquellos pacientes tratados con formulaciones de liberación inmediata debido a la aquinética que deben padecer como consecuencia de los bajos niveles de principio activo en el cuerpo (ver el documento Ropinirol prolonged release: a guide to its use in Parkinson's disease, 2009, Drugs and Therapy perspectives, 25(6), 1-5).

Adicionalmente, la eficacia y tolerabilidad de las formulaciones de liberación prolongada de ropinirol han sido ampliamente estudiadas mediante pruebas clínicas. Así, por ejemplo, la eficacia de las formulaciones de liberación controlada de ropinirol ha sido comparada con la eficacia de las formulaciones de liberación inmediata en pacientes que padecen de Parkinson avanzado. Los resultados de dicho estudio muestran la obtención de significativas ventajas en términos de control de síntomas y de mejoramiento en las habilidades motoras (ver el documento Ropinirol prolonged release: a guide to its use in Parkinson's disease, 2009, Drugs and Therapy Perspectives, 25(6), 1-5.) Adicionalmente, ese tipo de estudios comparativos también han revelado que el porcentaje de pruebas clínicas satisfactorias es mucho mayor al emplear formulaciones de liberación controlada (52%) que al emplear formulaciones de liberación inmediata (35%) (ver el documento Pahwa et al., 2007, Neurology, 68: 1108-1115).

De otro lado, las formulaciones de liberación prolongada reveladas en la solicitud de patente en cuestión también permiten una reducción en la frecuencia de dosificación, lo cual representa un significativo beneficio clínico, toda vez que esto permite evitar los riesgos inherentes a métodos de tratamiento que implican la frecuente administración a un paciente de un determinado compuesto activo (ver el documento Edin et al., Adherence among patients with Parkinson disease taking ropinirol immediate release at least three times daily, 12th International Congress on Parkinson's disease and movement disorders, Chicago, Illinois, USA, 22nd-26th June 2008). Prueba de lo anterior es un estudio clínico en el cual un grupo de pacientes a los que previamente se les estaba administrando tres veces al día ropinirol de liberación inmediata, se les comenzó a administrar ropinirol de liberación prolongada una vez al día, y encontrándose que el 86% de los pacientes expresó su preferencia por el tratamiento de dosis única diaria (ver el documento Szczudlik et al., Long term safety and patient preference for dose frequency in patients receiving ropinirole prolonged release in early or advanced Parkinson's disease, 19th annual meeting of the European neurological society, Milan, Italy, 20-24th, June 2009, particularmente la columna 4). Adicionalmente, estudios clínicos adicionales también han demostrado que el incumplimiento de las dosis diarias dentro del tratamiento del Parkinson da lugar a un serio empeoramiento de la sintomatología padecida por los pacientes, hecho que se evita ampliamente al ofrecer la posibilidad de una formulación de dosis única diaria (ver el documento Kulkarni et al., 2008, Mov. Dis., 23: 359-365, particularmente la columna 1, página 364).

Así mismo, es claro que la administración de ropinirol mediante formulaciones de liberación prolongada permite lograr un mejoramiento sintomático más eficiente, hecho que ha sido comprobado en pacientes en los que dicho modo de administración del principio activo les permitió observar un control apropiado de la sintomatología tan sólo una semana después de iniciado el tratamiento (ver el documento Ruzicka et al., Maintained increase in "on" time with ropinirole prolonged release in advanced Parkinson's disease, 3rd World Congress of controversies in Neurology, Prague, Czech Republic, 8th-11th October 2009, particularmente columna 3).

Dicho rápido mejoramiento sintomático es el resultado de que cada dosis exhibe de manera inesperada una velocidad de liberación de orden cero, hecho que implica que tales formulaciones de liberación prolongada de ninguna manera implican un aumento repentino de los niveles de ropinirol en plasma. Así mismo, de manera sorprendente ha sido encontrado que las formulaciones de ropinirol de liberación prolongada reveladas en la solicitud de patente en cuestión presentan una cinética de liberación que no se ve afectada por la cantidad de compuesto activo (ver páginas 5 y 6 de la descripción, así como la figura 13, en donde se muestra que los perfiles de disolución in vitro de tabletas que presentan dosis de ropinirol que difieren cerca de 10 veces son idénticos). Lo anterior resulta ser altamente sorprendente debido a que diferentes modelos matemáticos conocidos en el estado de la técnica para el análisis de la liberación de medicamentos a partir de formulaciones de matriz (tal como aquella reivindicada en la solicitud de patente en cuestión) predicen que una formulación con una alta carga de medicamento debe exhibir una velocidad de liberación fraccional rápida (ver el documento Venkatramen et al., An overview of controlled release systems, chapter 22 in Handbook of pharmaceutical controlled release technology, 2000, particularmente la página 436, ecuación 3). Adicionalmente, dicho fenómeno también ha sido demostrado experimentalmente por Lee y compañeros (Lee and Kim, 1991, J. Controlled release, 16: 229-236) mediante pruebas utilizando oxoprenalol.

En resumen, la novedosa formulación de dosificación revelada en la presente invención permite lograr de manera sorprendente una liberación dopaminérgica continua y un rápido mejoramiento de la sintomatología propia de la enfermedad de Parkinson. Adicionalmente, dicha formulación permite disminuir la frecuencia de administración del principio activo al paciente bajo tratamiento.

Finalmente y tal como se discutió con anterioridad en el presente memorial, es claro que en el estado de la técnica existía la necesidad de una formulación que permitiese poner en práctica una terapia que combinara las ventajas de una dosificación dopaminérgica continua, un beneficio sintomático rápido y una disminución en los efectos adversos durante el tratamiento de la enfermedad de Parkinson. En este sentido, se habían llevado numerosos intentos para resolver dicho problema, pero el solicitante de la presente invención es quien por primera vez logró desarrollar una formulación de dosificación que

combina las ventajas previamente mencionadas, hecho que indiscutiblemente evidencia el nivel inventivo de la solicitud.

3.4 Análisis del nivel inventivo de la invención frente a D1 y D2

Ahora bien, el señor examinador citó los documentos D1 y D2 aseverando que dichas anterioridades revelan formulaciones multicapas que permiten lograr la liberación controlada de medicamentos. En este sentido, el señor Examinador considera que la persona medianamente versada en la materia debió haber considerado tales documentos al momento de plantearse el objetivo de obtener formulaciones de liberación controlada alternativas a aquellas conocidas en el arte previo.

Con respecto a lo anterior, me permito señalar que si dicha persona medianamente versada en la materia estuviera simplemente intentando desarrollar formulaciones alternativas a las ya conocidas en el estado de la técnica, habría podido considerar la modificación de todos los aspectos relacionados con dichas formulaciones divulgadas en los documentos D1 y D2. En este sentido, tal como el señor Examinador afirma en su Concepto Técnico, la persona medianamente experta habría considerado modificar, por ejemplo, el agente activo. Sin embargo, es así mismo posible que dicha persona experta también hubiera considerado modificar la clase y/o la cantidad de cualquiera o todos los excipientes que hacen parte de las formulaciones enseñadas en el arte previo. **Por lo tanto, teniendo en cuenta lo anterior es absolutamente claro que, al momento de analizar el nivel inventivo de una solicitud de patente la pregunta a realizar no es si la persona medianamente versada en la materia habría podido realizar los cambios requeridos para llegar a la invención reivindicada, si no si dicha persona habría hecho tales modificaciones a la luz de las enseñanzas del estado de la técnica anterior.**

Teniendo en cuenta lo anterior, me permito mencionar que para obtener la formulación de dosificación reivindicada partiendo de las tabletas ejemplificadas en el documento D1 (ejemplos 8 y 10), al menos dos cambios son requeridos:

1. Reemplazar el agente activo clorhidrato de paroxetina por ropinirol o una sal farmacéuticamente aceptable del mismo; y,
2. Modificar la proporción entre las sustancias poliméricas hidrofílicas y las sustancias lipofílicas en la capa activa, toda vez que la proporción entre sustancias poliméricas hidrofílicas y sustancias lipofílicas en los ejemplos de D1 es 18:1 (ejemplo 8), 25:1 (ejemplo 10) y 17:1 (ejemplos 11 y 12), mientras que el rango de proporciones permitidas en la tableta reivindicada es de 7:1 a 1:1.

Sin embargo, **de la atenta lectura de D1 es absolutamente claro que en dicha anterioridad no existe motivación alguna para realizar dichos cambios. En consecuencia, la persona medianamente versada en la materia no habría sugerido realizar tales modificaciones, a menos que se le concediera el beneficio de manejar en retrospectiva la información técnica divulgada en la solicitud de patente en cuestión.**

Sumado a lo anterior, considero de gran importancia resaltar una vez más que el documento D1 únicamente sugiere la utilización de formulaciones de matriz hidrofílica, las cuales, de acuerdo con modelos matemáticos como el divulgado en el documento *Venkatramen et al., An overview of controlled release systems, chapter 22 in Handbook of pharmaceutical controlled release technology, 2000*, no son adecuadas de manera alguna para medicamentos fuertemente solubles en agua, tal como el ropinirol, toda vez que se esperaría una alta velocidad de liberación de ese tipo de compuestos activos (el clorhidrato de ropinirol es cerca de 25 veces más soluble en agua que el clorhidrato de paroxetina, el cual es el agente activo empleado en las formulaciones enseñadas en D1)

De otro lado, me permito manifestar que la persona medianamente versada en la materia no habría podido predecir a partir de las enseñanzas del documento D1 que la novedosa formulación de dosificación revelada en la solicitud de patente en cuestión se caracteriza por exhibir una cinética de liberación que es independiente de la cantidad de ropinirol. Lo anterior es evidente al tener en cuenta que D1 no hace mención alguna a éste respecto y los modelos matemáticos conocidos en el estado de la técnica anterior predicen una velocidad de liberación mayor con dosis altas de compuesto activo. Por lo tanto, es claro que la persona medianamente versada en la materia no habría esperado que una formulación de matriz tal como aquella divulgada en D1 fuera capaz de proporcionar una cinética de liberación que es independiente de la cantidad de compuesto activo.

Ahora bien, el señor Examinador afirma en su Concepto Técnico que la persona medianamente versada en la materia habría podido hacer cambios a la formulación enseñada en D1 con el fin de optimizarla a un medicamento más soluble (como el ropinirol) y de esta manera obtener una formulación de dosificación con el perfil de liberación deseado. En este sentido, atentamente me permito aclarar al señor Examinador que a lo largo del documento D1 no existe indicación técnica alguna que sugiera la necesidad de modificar la formulación allí divulgada para lograr dicho perfil cinético.

De otro lado, con respecto al documento D2 me permito señalar que dicha anterioridad divulga una formulación que permite lograr el control de la liberación de un compuesto activo a través del recubrimiento total del medicamento, de forma tal que dicho compuesto activo no puede ser liberado sino hasta que se logre la erosión de la capa empleada como recubrimiento. Sin embargo, el señor Examinador sugiere en su Concepto Técnico que la persona medianamente versada en la materia contemplaría de manera evidente la realización de las modificaciones necesarias para obtener la formulación de dosificación revelada en la solicitud en cuestión a partir de las formulaciones enseñadas en

D2, al parecer sin tener en cuenta que tales modificaciones no sólo representan importantes cambios en la formulación, sino que además de ninguna manera son sugeridos por los autores de dicha anterioridad.

Visto lo anterior, me permito manifestar que la formulación de dosificación revelada por el solicitante es inventiva frente a las enseñanzas de D1 y D2 debido a que tales documentos no proporcionan algún tipo de motivación técnica para que la persona medianamente versada en la materia hubiera sugerido la realización de las modificaciones necesarias para obtener la formulación reivindicada a partir de aquellas formulaciones conocidas en el arte previo. De manera específica me permito señalar que el arte previo indica que las formulaciones de matriz no son adecuadas para agentes activos como el ropinirol, hecho que desviaría la atención de la persona experta hacia una formulación completamente diferente a la reivindicada. Así mismo, dicha persona experta no consideraría eliminar el recubrimiento total que es característico de las formulaciones enseñadas en D2 porque eso es lo que precisamente permite controlar la liberación del agente activo.

Ahora bien, aparte de lo anterior, considero de gran importancia resaltar que si se tiene en cuenta que el objetivo técnico planteado por el solicitante era el de desarrollar una formulación de ropinirol que permitiera poner en práctica una terapia que combinara las ventajas de una dosificación dopaminérgica continua, un beneficio sintomático rápido y una disminución de los efectos adversos durante el tratamiento de la enfermedad de Parkinson, **¿por qué la persona medianamente experta emplearía los documentos D1 y D2 como punto de partida, sabiendo que en el estado de la técnica se conoce una amplia variedad de tecnologías para lograr una estimulación dopaminérgica continua y un beneficio sintomático eficaz, y sabiendo adicionalmente que las matrices hidrofílicas de ninguna manera estaban consideradas como una opción atractiva para controlar la liberación del ropinirol durante un período de tiempo prolongado?**

Como ha sido explicado previamente, la persona experta no habría considerado dentro de sus opciones la utilización de una matriz hidrofílica (como aquella enseñada en D1) para lograr el objetivo técnico planteado debido principalmente a las características fisicoquímicas del ropinirol. Sin embargo, surge entonces la siguiente pregunta: **¿Qué habría hecho la persona experta, es decir, cuáles serían sus opciones para resolver el problema técnico a partir de las enseñanzas del estado del arte?** La respuesta es que dicha persona experta habría seleccionado, por ejemplo, una tecnología de liberación controlada mediante la cual la alta solubilidad y difusibilidad del agente activo de interés no fuera crítico o determinante. En este sentido, habría podido seleccionar una formulación osmótica, toda vez que en ese caso la velocidad de liberación es independiente de las propiedades farmacocinéticas del agente activo (por ejemplo su solubilidad). Otra posibilidad es que dicha persona experta hubiera considerado emplear formulaciones como aquellas divulgadas en D2, hecho que claramente lo llevaría a lograr una formulación de

características técnicas completamente diferentes en comparación a aquella revelada en la presente invención.

Visto lo anterior, me permito manifestar ante ese Despacho que la solicitud de patente en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas de los documentos D1, D2 o la combinación de los mismos, cumpliendo por lo tanto a cabalidad con las disposiciones de patentabilidad establecidas en el Artículo 18 de la Decisión Andina 486 de 2000.

4. **CONCLUSIÓN**

De conformidad con lo mencionado en el presente memorial, me permito manifestar que las formulaciones de dosificación reveladas en la solicitud de patente en cuestión son inventivas frente a las enseñanzas de los documentos D1, D2 ó la combinación de los mismos, toda vez que de ninguna manera podrían combinarse las enseñanzas de tales anterioridades para predecir que las novedosas formulaciones reveladas en la presente invención permiten lograr un excelente perfil de liberación prolongada del principio activo ropinirol.

En efecto, dichas tabletas multicapa preparadas en concordancia con la presente invención exhiben la capacidad de proporcionar una cinética de liberación muy similar cuando se formula una misma sustancia activa pero en cantidades diferentes dentro de la capa activa en la tableta multicapa. En otras palabras, el solicitante de la invención en cuestión ha encontrado de manera sorprendente que con la utilización de la forma farmacéutica revelada en la presente solicitud de patente, es posible obtener una velocidad de liberación de ropinirol similar o idéntica, aún si dicha tableta contiene cantidades muy diferentes de la misma sustancia activa.

De otro lado, las tabletas de dosificación de la presente solicitud de patente se caracterizan porque en términos estructurales, la(s) capa(s) de barrera previamente mencionadas están diseñadas para limitar parcialmente la superficie de liberación de la capa activa, y por ende, para permitir que dicha sustancia activa sea liberada únicamente a través de la superficie no cubierta que es capaz de entrar en contacto con el medio de disolución.

Por lo tanto, teniendo en cuenta los argumentos técnicos presentados para demostrar el inequívoco carácter inventivo de la invención en cuestión, resulta completamente claro que se han superado las objeciones expuestas por el señor Examinador en su Concepto Técnico, y por lo tanto, dicha invención es merecedora del privilegio de patente solicitado.

5. Anexo al presente memorial me permito presentar:

- i. Copia del documento *Kaye and Nicholls, 2000, Clin. Pharmacokinet., 39(4): 243-254.*
- ii. Copia del documento *Summary of product characteristics for Requip® dated 21 December 1998.*
- iii. Copia del documento *Summary of product characteristics for Requip® dated 10 August 2000.*
- iv. Copia del documento *Rascol et al., 2000, N. Eng. J. Med., 342: 1484-1491.*
- v. Copia del documento *Obeso et al., 1994, Eur. J. Neurosci., 6: 889-897.*
- vi. Copia del documento *Venkatramen et al., An overview of controlled release systems, chapter 22 in Handbook of pharmaceutical controlled release technology, 2000.*
- vii. Copia del documento *Lee and Kim, 1991, J. Controlled release, 16: 229-236.*
- viii. Copia del documento *Tompson and Vearer, 2007, Clin. Ther., 29:2654-2666.*
- ix. Copia del documento *Ropinirole prolonged release: A guide to its use in Parkinson's disease, 2009, Drugs and Therapy Perspectives, 25(6), 1-5.*
- x. Copia del documento *Pahwa et al., 2007, Neurillogy, 68: 1108-1115.*
- xi. Copia del documento *Edin et al., Adherence among patients with Parkinson's disease taking ropinirol immediate release at least three times daily, 12th international congress on Parkinson's disease and movement disorders, Chicago, Illinois, USA, 22th-26th June 2008.*
- xii. Copia del documento *Szczudlik et al., Long term safety and patient preference for dose frequency in patients receiving ropinirole prolonged release in early or advance Parkinson's disease, 19th Annual Meeting of the European Neurological Society, Milan, Italy, 20-24th June 2009.*
- xiii. Copia del documento *Kulkarni et al., 2008, Mov. Dis., 23: 359-365.*
- xiv. Copia del documento *Ruzicka et al., Maintained increase in "on" time with ropinirole prolonged release in advanced Parkinson's disease, 3rd World congress on controversies in neurology, Prague, Czech Republic, 8th-11th October 2009.*

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6. En vista de lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las argumentaciones presentadas y conceder el privilegio de patente solicitado.

Señor Superintendente,



ALICIA LLORED A RICAURTE

T.P. 53.215

Tagotec AG

Exp. 02-091.153

(I)

DRUG DISPOSITION

Clin Pharmacokinet 2000 Oct; 39 (4): 243-254
0312-5963/00/0010-0243/\$20.00/0

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Clinical Pharmacokinetics of Ropinirole

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Abstract

Ropinirole is a selective non-ergoline dopamine D₂ receptor agonist indicated for use in treating Parkinson's disease. When taken as oral tablets, ropinirole is rapidly and almost completely absorbed, and it is extensively distributed from the vascular compartment. The bioavailability is approximately 50%. Ropinirole shows low plasma protein binding. The drug is inactivated by metabolism in the liver, and none of the major circulating metabolites have pharmacological activity. The principal metabolic enzyme is the cytochrome P450 (CYP) isoenzyme CYP1A2.

Ropinirole shows approximately linear pharmacokinetics when given as single or repeated doses, and is eliminated with a half-life of approximately 6 hours. Population pharmacokinetics have demonstrated that gender, mild or moderate renal impairment, Parkinson's disease stage and concomitant illnesses or the use of several common concomitant medications have no effect on the pharmacokinetics of ropinirole. Clearance is slower for patients older than 65 years compared with those who are younger, and in women taking hormone replacement therapy compared with those who are not. The CYP1A2 inhibitor ciprofloxacin produced increases in the plasma concentrations of ropinirole when these 2 drugs were coadministered, but no interaction was seen with theophylline which, like ropinirole, is also a substrate for CYP1A2. There is no obvious plasma concentration-effect relationship for ropinirole.

Ropinirole (Requip®) is a novel non-ergoline dopamine D₂ receptor agonist indicated for the treatment of Parkinson's disease. Several clinical trials have demonstrated its effectiveness both as a monotherapy for early Parkinson's disease and as an adjunct to levodopa in treating later stages of the disease. When used in early disease, ropinirole has been shown to have similar or superior effectiveness, over at least 3 years, to the dopamine agonist bromocriptine^[1,2] and to the gold standard therapy levodopa.^[3,4] Moreover, in the long term, ropinirole has been shown to produce significantly fewer motor complications than levodopa,^[4-9] and it permits a reduction in levodopa dose when it is used as an adjunct.^[10] Overnight switching from other dopamine agonists to ropinirole has been shown to be a well tolerated therapeutic approach.^[11] Recent *in vitro* and *ex vivo* data from animals also indicate that ropinirole may have neuroprotective effects in the parkinsonian brain, which could involve activation of glutathione catalase or superoxide dismutase, and therefore this drug may have the potential to slow the progression of the disease.^[12,13] Encouraging preliminary results have been obtained with ropinirole in patients with restless leg syndrome.^[14,15] Several reviews of ropinirole, focusing on its pharmacology and therapeutics, have recently been published.^[16-22]

1. Pharmacology

Ropinirole is a selective agonist of dopamine D₂-like receptors, the D₂, D₃ and D₄ receptor sub-

types.^[23-25] It has negligible affinity for the dopamine D₁ receptor, or for other common neurotransmitter receptors,^[23] and is about 20 times more active at the central D₃ than at the D₂ receptor.^[19] Ropinirole binds to both central and peripheral dopamine receptors. In the central nervous system, ropinirole binds to postsynaptic dopamine D₂ receptors, acting as a replacement stimulus for the dopaminergic neurotransmission that is lost through the pathogenesis of Parkinson's disease. The action of ropinirole at presynaptic central dopamine receptors can also reduce the turnover and release of dopamine from presynaptic terminals.^[26] It is postulated that this may produce neuroprotective effects by reducing the production of toxic metabolites, and therefore oxidative stress.^[27] In a parkinsonian monkey model, ropinirole treatment restores motor activity and has an extremely low potential to induce dyskinesias compared with levodopa.^[28] In the periphery, the action of ropinirole at dopamine D₂ receptors increases sympathetic tone. Activity at peripheral presynaptic dopamine receptors results primarily in hypotension and nausea,^[29] but these can be reduced by slow titration of the ropinirole dosage.^[19] In addition, coadministration with domperidone enables rapid dosage escalation of ropinirole to be considered.^[30]

2. Human Pharmacokinetics

The adverse effects of ropinirole make even small doses of this drug, as low as 1 mg, difficult to tolerate in healthy volunteers who have normal lev-

els of dopamine,^[31,32] whereas in patients with Parkinson's disease who have subnormal dopamine levels, the drug is better tolerated.^[31] Therefore, most pharmacokinetic studies have been conducted in patients rather than in volunteers. Nevertheless, some pharmacokinetic studies have been carried out with low doses of ropinirole in healthy volunteers under domperidone cover, as well as studies using ¹⁴C-labelled ropinirole. The use of low doses prevented full characterisation of the terminal elimination phase of ropinirole in healthy volunteers, but this was better defined in patients receiving higher doses. Assay methods for ropinirole included high performance liquid chromatography with ultraviolet light detection (HPLC-UV)^[33] or radioimmunoassay.^[34] The main pharmacokinetic parameters of ropinirole in patients are shown in tables I and II.

2.1 Absorption

In healthy volunteers, ropinirole is rapidly and almost completely absorbed, as has been demonstrated by the similar urinary excretion of radioactivity after oral and intravenous administration of approximately 10% or less.^[35] The systemic pharmacokinetics of ropinirole are highly variable. Maximal plasma concentrations (C_{max}) are generally reached after about 1.5 hours [time to reach maximal concentration (t_{max}), range 0.5 to 4 hours], and the elimination half-life appears to be approximately 3 hours, although this was not well defined in healthy volunteers. The average bioavailability of the oral tablet formulation is approximately 50%.^[19] Ropinirole is also rapidly absorbed in patients with Parkinson's disease, t_{max} being around 1.5 hours, but again within a wide range of 0.5 to 6 hours.^[21,36] It is necessary to titrate the dosage upwards to provide the desired clinical effect on an individual basis, partly because the drug exhibits large interindividual variability in its pharmacokinetics.

2.2 Distribution

As expected for a lipophilic amine, ropinirole is rapidly and extensively distributed from the vascu-

lar compartment. The volume of distribution at steady state is approximately 7.2 L/kg after oral administration (population pharmacokinetic data).^[37] Ropinirole shows low plasma protein binding (10 to 39%) that is independent of its plasma concentration.^[38,39] Therefore, ropinirole is unlikely to take part in interactions involving displacement from plasma protein binding sites. The blood : plasma ratio of 1.2 suggests that ropinirole is taken up, to some extent, by blood cells.^[40,41]

2.3 Metabolism

Most of the absorbed dose of ropinirole is cleared by metabolism in the liver, with only 10% of the administered dose being excreted as unchanged ropinirole.^[35,42] The main metabolite of ropinirole (32 to 45% of the dose) is the *N*-despropyl metabolite SK&F 104557 (fig. 1).^[35,43] The glucuronide of the metabolite SK&F 89124 and the carboxylic acid metabolite SK&F 97930 both represent about 10% of the administered dose. Neither of these metabolites is pharmacologically active; SK&F 89124

Table I. Summary of pharmacokinetic parameters of ropinirole following single oral doses by tablet (0.6 to 12mg) in patients with Parkinson's disease. Values are from the manufacturer's database on the pharmacokinetics of ropinirole

Parameter	n	Mean value	Range
C_{max}/D [(μ g/L)/mg]	37	1.92	0.61-5.90
AUC_t/D [(μ g/L $\cdot$ h)/mg]	16 ^a	6.44	2.32-14.6
	37 ^b	8.97	2.32-30.8
AUC_{∞}/D [(μ g/L $\cdot$ h)/mg]	13	16.0	2.60-35.0
t_{max} (h) ^c	37	1.5	0.50-6.0
$t_{1/2}$ (h)	13	5.8	2.0-10.0
CL/F (L/h) ^d	13	66.7	46.9-91.9
V_{ss}/F (L/kg)	13	6.7	3.4-16.5

a Last sampling time 6 to 7.5 hours post-dose.

b Last sampling time 6 to 24 hours post-dose.

c Median value.

d Patients with Parkinson's disease usually have bodyweights in the range 65 to 75kg.

AUC_t/D = dose-normalised area under the concentration-time curve to time *t*; AUC_{∞}/D = dose-normalised area under the concentration-time curve to infinity; CL/F = apparent oral clearance; C_{max}/D = dose-normalised peak plasma drug concentration; t_{max} = time to reach peak concentration; *n* = number of participants; $t_{1/2}$ = elimination half-life; V_{ss}/F = apparent volume of distribution at steady state.

Table II. Summary of the pharmacokinetic parameters of ropinirole when given as repeated oral doses (0.32 to 2.5mg) in patients with Parkinson's disease. Values are from the manufacturer's database on the pharmacokinetics of ropinirole

Parameter	Dosage interval (h)	n	Mean value	Range
C_{max}/D [(µg/L)/mg]	12	8	2.01	0.97-5.57
	16 ^a	11	2.74	1.60-6.11
	8	46	4.59	1.90-10.2
AUC_0/D [(µg/L · h)/mg]	12	8	10.7	4.90-38.5
	16 ^a	11	19.4	11.8-55.7
	8	46	23.2	7.60-60.3
t_{max} (h) ^b	12	8	2.50	1.00-5.00
	16 ^a	11	2.00	0.50-6.00
	8	46	1.00	0.50-7.00
C_{min}/D [(µg/L)/mg]	12	8	0.48	0.10-3.87
	16 ^a	11	0.61	0.30-2.56
	8	52	1.83	0.36-5.97
$(C_{max}/D)/(C_{min}/D)$	12	8	4.38	1.44-13.4
	16 ^a	11	4.79	2.39-6.41
	8	46	2.24	1.71-3.56
CL/F (L/h) ^c	16 ^a	11	59.2	18.0-87.5
	8	46	55.5	18.5-132

a Dosage interval (τ) was alternately 8 and 16 hours, pharmacokinetic parameters were measured during the 16-hour dosage interval.
b Median values.
c Patients with Parkinson's disease usually have bodyweights in the range 65 to 75kg.
AUC₀/D = dose-normalised area under the concentration-time curve over the dosage interval; **CL/F** = apparent oral clearance; **C_{max}/D** = dose-normalised peak plasma drug concentration; **C_{min}/D** = dose-normalised trough plasma drug concentration; n = number of participants; **t_{max}** = time to reach peak concentration.

has some activity but is rapidly glucuronidated, and so it circulates at only low concentrations.^[44] Therefore, all of the pharmacological activity achieved by orally administered ropinirole can be attributed to the parent molecule.

In vitro studies in human microsomes have demonstrated that the main enzyme responsible for the metabolism of ropinirole is the cytochrome P450 (CYP) enzyme CYP1A2, which is accompanied by a low affinity component, CYP3A, making only a minor contribution.^[43] It is known that human CYP1A2 exhibits considerable individual variation in its activity and is inducible by smoking, but it is not thought to exhibit genetic polymorphisms.^[45]

2.4 Excretion

The excretion of ropinirole-derived products is predominantly via the urine.^[35,42] After a single oral dose, ropinirole is eliminated in a monoexponential manner, with a mean terminal elimination half-life of about 6 hours (range 2 to 10 hours) that is independent of dose.^[46]

2.5 Steady-State Pharmacokinetics

Pharmacokinetic parameters were studied in patients with Parkinson's disease receiving repeated oral doses of 0.6 to 8mg of ropinirole, either twice or 3 times daily.^[46] The currently recommended regimen for ropinirole is 3 times daily. As would be expected for a drug with an elimination half-life of 6 hours,^[46] there is minimal accumulation during twice daily administration, and a 2-fold higher steady-state plasma concentration of ropinirole when the drug is given 3 times daily. Likewise, the average dose-normalised C_{max} and area under the concentration-time curve (AUC) are about twice as high at steady state after 3 times daily administration than following single dose administration. The average peak : trough ratio for plasma drug concentration is around 2, and it is relatively constant across the dose range tested.^[19] There is no marked difference in the clearance of ropinirole between single and repeat dose administration. Studies in Japanese patients have indicated that the pharmacokinetics of ropinirole in this population are similar to those in Caucasians.^[47,48]

2.6 Dose Proportionality

When single doses of ropinirole in the range 2 to 12mg are administered, C_{max} and AUC increase approximately in proportion to the administered dose.^[46] These parameters also show approximate dose-linearity at steady state, when the drug is administered either 2 or 3 times daily (tables III and IV). This linear pharmacokinetic behaviour of ropinirole is also indicated by its constant oral clearance over a wide dose range.^[37]

2.7 Effects of Food

The effect of food on the pharmacokinetics of ropinirole was studied in 12 patients with Parkinson's disease receiving ropinirole.^[50] Pharmacokinetic parameters were measured in the fasted state and after a high-fat breakfast. The mean C_{max}

was reduced by 25% following a high-fat breakfast and the median t_{max} was delayed by 2.6 hours, compared with results obtained in the fasted state. There was also a small but significant reduction (13%) in the AUC for ropinirole (95% confidence interval 77 to 98%). It was concluded that food reduces the rate of absorption but affects only min-

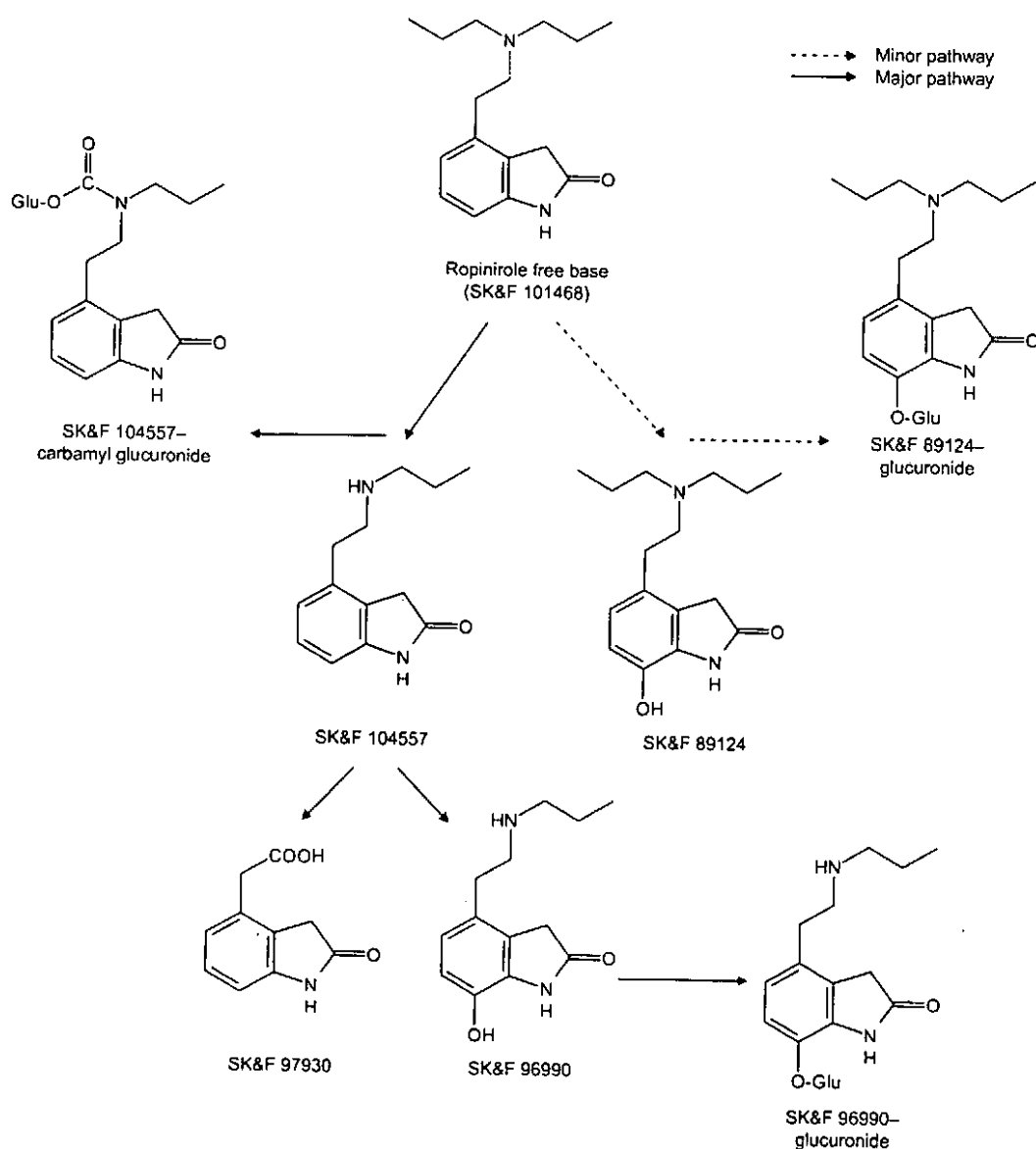


Fig. 1. The metabolic pathways of ropinirole. Glu = glucuronide.

Table III. Pharmacokinetic parameters of single doses of ropinirole in patients with Parkinson's disease. Values given are mean (standard deviation) [reproduced from Taylor et al.,^[49] with permission]

Dose (mg)	n	C _{max} (µg/L)	AUC _∞ (µg/L · h)	t _{1/2β} (h)
2	6	5.94 (3.10)	32.6 (3.4)	6.59 (2.02)
4	6	11.6 (6.21)	70.0 (38.4)	6.11 (1.88)
6	6	10.3 (4.70)	65.3 (23.8)	4.94 (0.93)
8	5	18.3 (6.01)	152 (96.9)	6.17 (0.91)
10	6	19.7 (8.91)	112 (44.2)	5.95 (2.92)
12	4	33.1 (11.1)	253 (149)	5.19 (1.56)

AUC_∞ = area under the concentration-time curve to infinity; C_{max} = maximum drug plasma concentration; n = number of participants; t_{1/2β} = elimination half-life.

imally the extent of absorption of ropinirole. These effects are not expected to be of any clinical consequence.

3. Population Pharmacokinetics

The absence of effects on the pharmacokinetics of ropinirole of age, gender, rate of creatinine clearance, Parkinson's disease stage, concurrent illness and use of concomitant medications was demonstrated in a population pharmacokinetic study.^[37,44] Sparse plasma samples (1 to 3 per patient) were collected prospectively over a period of 6 months from 213 patients participating in 2 clinical trials of ropinirole. All patients were receiving ropinirole at dosages of 1 to 8mg 3 times daily. Retrospective data from 3 single dose studies and 1 study of twice daily administration were added to the database to support the definition of the basic pharmacokinetic model.^[37]

The final database consisted of 178 patients with sparse sampling from the prospective studies, and 35 patients with full pharmacokinetic profiles from the retrospective studies (8 of whom had received twice daily administration). A one-compartment model with first-order absorption (no lag) and first-order elimination adequately described the data. The population mean values for clearance and volume of distribution were 47.3 L/h and 7.2 L/kg, respectively,^[37] and did not show any obvious trend with dose. The interindividual variability was 46% for clearance and 33% for volume of distribution, and intraindividual variability was approximately 34% for both. These estimates of clearance and volume of distribution were consistent with those obtained from studies of single dose and steady-state pharmacokinetics of ropinirole. The population pharmacokinetic model was validated against data obtained from an additional 40 patients, and the model was found to predict reliably the population mean and the variability of the plasma concentrations of ropinirole.^[44]

3.1 Effects of Age

Patients aged 65 years and older showed a 15% slower clearance of ropinirole than patients under 65 years (p < 0.001) [table V].^[37] Clearance in patients older than 75 years was, again, somewhat slower than that observed in patients aged 65 to 75 years. There was no marked change in the volume of distribution but the terminal-phase half-life increased with patient age. These findings are to be expected as the drug is mainly metabolised by the liver and rates of hepatic drug metabolism are

Table IV. Pharmacokinetic parameters of repeated doses of ropinirole in patients with Parkinson's disease. Values given are mean (standard deviation) [reproduced from Taylor et al.,^[49] with permission]

Dose (mg)	tid regimens			bid regimens		
	n	C _{max} (µg/L)	AUC ₀₋₈ (µg/L · h)	n	C _{max} (µg/L)	AUC ₀₋₁₆ (µg/L · h)
1	12	5.27 (1.67)	27.5 (9.98)	11	3.48 (1.32)	25.6 (12.9)
2	9	9.75 (4.75)	53.8 (27.9)	5	4.52 (1.11)	35.5 (11.7)
4	4	23.7 (12.6)	136 (85.1)	4	12.0 (4.15)	76.6 (35.6)
6	2	26.9 (6.08)	110 (10.3)	2	13.2 (2.62)	89.5 (22.3)

AUC_x = area under the concentration-time curve to x hours; bid = twice daily; C_{max} = maximum drug plasma concentration; n = number of participants; tid = 3 times daily.

Table V. Population pharmacokinetic parameters of ropinirole in patients with Parkinson's disease.^[44] Values given are means (range)

Parameter	n	CL/F (L/h) ^a	V _{ss} /F (L) ^a	t _{1/2β} (h)
Age (y)				
<65	97	62.1 (18.2-166)	497 (216-811)	5.6 (2.7-17)
65-75	63	45.5 (17.1-137)	456 (255-707)	7.0 (1.8-20)
>75	11	41.7 (23.3-70.2)	535 (317-891)	8.9 (3.3-26.5)
Gender				
Male	99	58.7 (23.3-146)	524 (216-891)	6.2 (3.2-26.5)
Female taking estrogen	16	33.2 (17.6-78.2)	429 (244-716)	9.0 (6.3-13.9)
Female not taking estrogen	56	51.8 (18.2-132)	485 (221-1159)	6.5 (6.8-8.4)
Creatinine clearance (ml/min)				
<50 (29.8-49.8)	18	37.3 (18.4-77.9)	407 (279-891)	7.6 (3.4-12.2)
≥50 (51.3-175)	44	45.9 (17.1-104)	502 (255-822)	5.6 (2.9-19.6)

a Patients with Parkinson's disease usually have bodyweights in the range 65 to 75kg.

CL/F = apparent oral clearance; n = number of participants; t_{1/2β} = elimination half-life; V_{ss}/F = apparent volume of distribution at steady state.

known to decrease with age.^[51] Nevertheless, as ropinirole is titrated upwards to effect the desired clinical response, these age-related differences are unlikely to be of clinical consequence.

3.2 Effects of Gender

There were no apparent differences in the clearance or volume of distribution between men and women who were not taking hormone replacement therapy (HRT).^[37,44] In those women who were taking HRT, there was a significant reduction (33%) in the clearance of ropinirole compared with those not taking estrogen ($p < 0.005$) [table V].^[37,52] which produced a concomitant increase to 9 hours in the elimination half-life of ropinirole.^[44] This finding is not unexpected, given that HRT is known to inhibit CYP1A2.^[53]

3.3 Effects of Renal and Hepatic Impairment

In a population pharmacokinetic analysis,^[44] patients with creatinine clearance in the range 30 to 177 ml/min did not appear to have different oral clearance values of ropinirole. Those patients with moderate renal impairment, defined as creatinine clearance rates of less than 50 ml/min, showed little difference in ropinirole pharmacokinetic parameters from those patients with mild or no renal impairment.^[44] Again, these results are to be expected as the clearance of ropinirole is mainly nonrenal,

and they indicate that dosage adjustments of ropinirole should not be necessary in patients with mild or moderate renal impairment. No pharmacokinetic data have been obtained with ropinirole for patients with severe renal impairment. It is anticipated that hepatic impairment would affect the pharmacokinetics of ropinirole,^[54] but this also has not been studied, and so the use of ropinirole in these patient groups is not recommended.

3.4 Effects of Concomitant Diseases

Using a population pharmacokinetic^[37,44] approach, it was found that common concomitant diseases of Parkinson's disease – hypertension, depression, osteoporosis/arthritis and insomnia – were not influential covariates of the pharmacokinetics of ropinirole.^[44] In addition, these parameters were not affected by the severity of Parkinson's disease as defined by the Hoehn and Yahr classification stage.^[44]

4. Drug Interactions

Ropinirole is predominantly cleared by the CYP1A2 enzyme system.^[43] It is, therefore, possible that ropinirole might interact with other drugs that are cleared by, or are inhibitors or inducers of, this enzyme.^[55] It is also possible that inhibitors or inducers of CYP1A2 might affect the clearance of ropinirole. However, ropinirole and its circulating

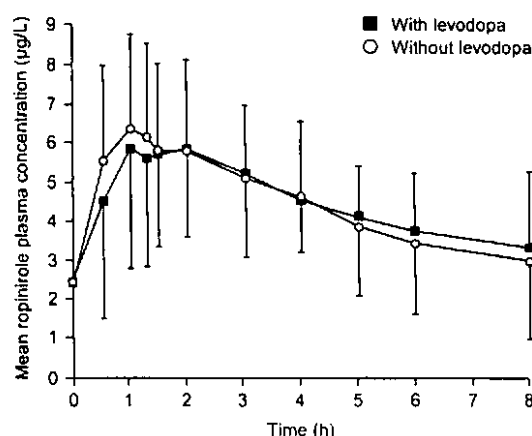


Fig. 2. Mean plasma concentrations of ropinirole following repeated 3 times daily oral administration of a 2mg dose with and without levodopa 100mg plus carbidopa 10mg twice daily at steady state (reproduced from Taylor et al.,^[58] with permission).

metabolites do not inhibit most CYPs *in vitro* and have only a weak potential for inhibiting CYP-2D6.^[56,57] Interaction with theophylline, a substrate of CYP1A2, was investigated, as was the effect of an inhibitor of this enzyme, ciprofloxacin, in patients with Parkinson's disease. In addition, interactions with drugs commonly prescribed to patients with Parkinson's disease were also investigated, but no other significant effect on the clearance of ropinirole was found.

As smoking is known to induce CYP1A2, it is possible that the pharmacokinetics of ropinirole will be altered in smokers compared with non-smokers, although no data are available to specifically examine this question. However, this would only be of possible importance if smoking habits were to change during therapy with ropinirole. As mentioned in section 3.2, it has been shown that HRT reduces the clearance of ropinirole. Thus, if HRT is introduced or withdrawn during therapy with ropinirole, the dosage of ropinirole may need to be adjusted.

4.1 Levodopa

Possible interactions between ropinirole and Sinemet® 100/10 (levodopa 100mg plus carbidopa 10mg) twice daily were investigated in 28 pa-

tients.^[58] There were no differences in the rates of absorption or the availability of ropinirole, with and without levodopa (fig. 2). In the 23 evaluable patients, there were also no marked changes in the absorption, availability or elimination half-life of levodopa when coadministered with ropinirole. The C_{max} of levodopa increased by 16% when administered with ropinirole, but this change was not considered to be clinically relevant as peak concentrations of levodopa are typically highly variable.

4.2 Domperidone

The dopamine antagonist domperidone may be used by some patients taking dopamine agonists to alleviate the peripheral dopaminergic adverse effects of the agonist.^[30] Pharmacokinetic interactions between domperidone and ropinirole were investigated using single doses of these drugs in 9 healthy volunteers. Domperidone 20mg administered 1 hour before ropinirole 0.8mg had no effect on the plasma pharmacokinetics of ropinirole.^[34]

4.3 Digoxin

Interactions between digoxin and ropinirole were studied at steady state, as digoxin is a treatment commonly used by elderly patients with Parkinson's disease. Pharmacokinetic parameters were assessed in 10 patients with Parkinson's disease who were taking stable doses of digoxin and levodopa.^[59] Cotreatment with ropinirole was associated with reductions in the C_{max} (25%) and AUC (10%) for digoxin. However, when data from 1 outlier patient were excluded from the analysis of AUC, this estimate was within the acceptable range for bioequivalence [90% confidence intervals for the ratio of means (digoxin + ropinirole)/(digoxin alone) were contained within the range 0.80 to 1.25]. C_{max} values showed an unexpectedly high intraindividual variability, which may have accounted for some of the difference seen with ropinirole treatment. Moreover, there was no change in the minimum plasma concentrations (C_{min}) for digoxin during ropinirole cotreatment. This parameter is thought to be the most reliable for assessment of the steady-state concentrations of digoxin,^[60] and

therefore changes in C_{min} are a guide for clinically significant drug interactions with digoxin. Overall, it was therefore concluded that the changes in digoxin pharmacokinetic parameters seen were of no clinical consequence, and no dosage adjustment is indicated when digoxin is coadministered with ropinirole.

4.4 Theophylline

The xanthine derivative theophylline is used to treat asthma and, like ropinirole, it is primarily metabolised by the CYP isoenzyme CYP1A2.^[61] It is therefore possible that this commonly used drug would interact competitively with the metabolism of ropinirole, or *vice versa*. However, no interaction of these 2 drugs was demonstrated in a study of 12 patients with Parkinson's disease who started treatment with ropinirole that was titrated to a dosage of 6mg daily.^[62] The pharmacokinetics of single intravenous doses of theophylline, and of ropinirole with and without concomitant steady-state oral theophylline, were studied.

The steady-state pharmacokinetics of ropinirole were similar in the presence and absence of oral theophylline. The geometric mean ratios for C_{max} and AUC of ropinirole with and without theophylline were close to unity, indicating that the extent and time-course of absorption of ropinirole did not change significantly when theophylline was coadministered. The geometric mean ratios for C_{max} and AUC values for theophylline before and during administration of ropinirole were also close to unity, indicating that ropinirole had no effect on the single dose pharmacokinetics of theophylline.

4.5 Ciprofloxacin

The quinolone antibacterial agent ciprofloxacin is known to be a powerful inhibitor of CYP1A2 and, thus, it has the potential to affect ropinirole pharmacokinetics.^[20] Interactions between this drug and ropinirole were studied in 12 patients with Parkinson's disease who were given ropinirole, titrated to 6mg daily, which was then combined with ciprofloxacin 500mg twice daily.^[63] Coadministration of ciprofloxacin produced in-

creases in the C_{max} and AUC of ropinirole of 60 and 84%, respectively. However, ropinirole was well tolerated when administered with and without ciprofloxacin, and there were no clinically important changes in patients' vital signs or electrocardiograms. Nevertheless, it would seem prudent to consider adjusting the dosage of ropinirole if drugs known to be inhibitors of CYP1A2 are either introduced to or withdrawn from patients on a stabilised regimen of ropinirole.

4.6 Other Drugs

As part of a population pharmacokinetic analysis of phase III data,^[37,44] it was found that selegiline (deprenyl), amantadine, tricyclic antidepressants, benzodiazepines, ibuprofen, thiazides, anticholinergics and antihistamines had no effects on the oral clearance of ropinirole.^[44] Coadministration of ropinirole and centrally active dopamine antagonists may diminish the activity of one or both of these drugs.^[19]

5. Pharmacokinetic/ Pharmacodynamic Relationship

The relationship between the plasma concentration of ropinirole and therapeutic response was studied in 2 clinical trials. In one, 80 patients with early Parkinson's disease were given ropinirole as a monotherapy.^[64] Responders to treatment were defined as those patients showing at least a 30% improvement in their motor function; 42 patients were classified as responders. In the other trial, 61 patients with later stages of Parkinson's disease were given ropinirole as an adjunct to existing levodopa therapy.^[10] Responders were defined as those patients who showed a 20% reduction in the levodopa dose required and at least a 20% reduction in their awake time spent 'off'; 18 patients were classified as responders.

As part of a population pharmacokinetic analysis,^[44] scatter plots of the predicted average plasma concentrations of ropinirole at steady state plotted by response or nonresponse suggested that ropinirole plasma concentration was on average slightly higher in patients classified as responders than in

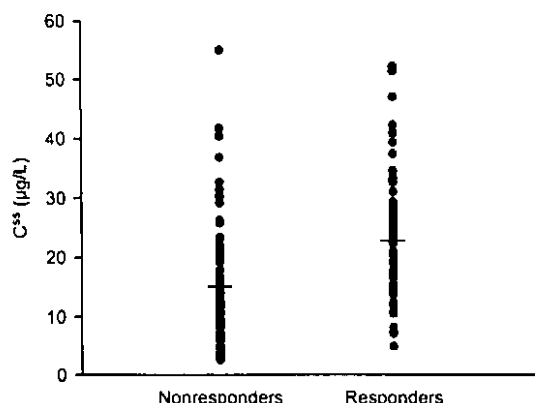


Fig. 3. Predicted steady-state plasma ropinirole concentrations (C_{ss}) for responders and nonresponders to the drug from 2 clinical trials. The horizontal line indicates the average C_{ss} , and data are means and standard deviations.

those classified as nonresponders (fig. 3). However, there was considerable overlap in the concentration ranges between the 2 groups, demonstrating that no obvious concentration-effect relationship exists when using this relatively crude measure of treatment effect.

6. Dosage and Administration

Ropinirole is given 3 times daily in oral tablet form. The dosage must be titrated upwards slowly in order to avoid peripheral dopaminergic adverse effects, such as nausea and postural hypotension. Therefore, treatment is started at a dosage of 0.25mg 3 times daily and increased slowly over a period of weeks until the desired clinical effect is reached. About half of the patients receiving treatment will respond at dosages of ropinirole between 4.5 and 7.5mg per day.^[65] When ropinirole was used initially as a monotherapy for early Parkinson's disease, the mean dosage in clinical trials was 10mg per day after 6 months' treatment. In one long term trial, the mean daily dosage of ropinirole at 6 months was 8.3mg; this increased to 10.3mg after 48 weeks and 12mg at 3 years.^[2] In a second long term trial, the mean daily dosage of ropinirole monotherapy was 16.5mg after 5 years;^[4] the maximum daily dosage is 24mg.

7. Conclusion

Ropinirole is rapidly and almost completely absorbed and shows approximately linear pharmacokinetics after single dose and steady-state administration. The drug is extensively metabolised in the liver, primarily by the CYP1A2 isoenzyme. All of the major circulating metabolites are pharmacologically inactive. Population pharmacokinetic studies have shown that the pharmacokinetics of ropinirole are unaffected by gender, mild-to-moderate renal impairment and the presence of several common concomitant diseases or several common concomitant drug treatments. Clearance is slower in patients older than 65 years, but as the drug is titrated for effectiveness, this is of no clinical concern. Dosage adjustment of ropinirole should be considered if HRT or ciprofloxacin treatment is started or discontinued during ropinirole therapy. There is no clear plasma concentration-effect relationship for ropinirole. Following upwards titration, most patients initially require a dosage of ropinirole 4.5 to 7.5mg per day for a clinical effect to be achieved; this dosage can be increased over time. In a 5-year clinical study, patients maintained on ropinirole monotherapy were receiving mean daily dosages of 16.5mg at the 5-year time-point. The therapeutic utility of ropinirole, however, may be explored up to a maximum daily dosage of 24mg (8mg 3 times daily).

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Appendix V Amended SPC

There is a minor amendment to the pharmaceutical particulars in the table describing the components of the film coats.

Current Section of SPC (Pharmaceutical Particulars)

The five tablet strengths of ropinirole are distinguished by colour. The composition of the film coat therefore varies. All film coats contain the following and the variations are shown in the table below; hydroxypropyl methylcellulose and polyethylene glycol.

Tablet colour	Tablet Strength				
	0.25	0.5	1.0	2.0	5.0
	White	Yellow	Green	Pink	Blue
Titanium Dioxide	✓	✓	✓	✓	✓
Iron Oxide Yellow		✓	✓	✓	
Iron Oxide Red		✓		✓	
Indigo Carmine		✓	✓		✓
Aluminium					
Polysorbate 80	✓				✓
Talc					✓

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The five tablet strengths of ropinirole are distinguished by colour. The composition of the film coat therefore varies. All film coats contain the following and the variations are shown in the table below; hydroxypropyl methylcellulose and polyethylene glycol.

Tablet colour	Tablet Strength				
	0.25	0.5	1.0	2.0	5.0
	White	Yellow	Green	Pink	Blue
Titanium Dioxide	✓	✓	✓	✓	✓
Iron Oxide Yellow		✓	✓	✓	
Iron Oxide Red		✓		✓	
Indigo Carmine		✓	✓		✓
Aluminium					
Polysorbate 80	✓				✓

'Requip' Tablets

PART IB - SUMMARY OF PRODUCT CHARACTERISTICS (Guideline III/9163/89)

1. TRADE NAME OF THE MEDICINAL PRODUCT

'Requip'

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ropinirole hydrochloride equivalent to 0.25, 1.0, 2.0 or 5.0 mg ropinirole free base.

3. PHARMACEUTICAL FORM

Film-coated, pentagonal-shaped tablets for oral administration. The tablet strengths are distinguished by colour; 0.25 mg (white), 1.0 mg (green), 2.0 mg (pink) and 5.0 mg (blue).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of idiopathic Parkinson's Disease:

- Ropinirole may be used alone (without levodopa) in the treatment of idiopathic Parkinson's disease.
- Addition of ropinirole to levodopa may be used to control "on-off" fluctuations and permit a reduction in the total daily dose of levodopa.

4.2 Posology and method of administration

Individual dose titration against efficacy and tolerability is recommended.

Ropinirole should be taken three times a day, preferably with meals to improve gastrointestinal tolerance.

Treatment initiation: The initial dose should be 0.25 mg t.i.d. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

	Week			
	1	2	3	4
Unit dose (mg)	0.25	0.5	0.75	1.0
Total daily dose (mg)	0.75	1.5	2.25	3.0

Therapeutic regimen: After the initial titration, weekly increments of up to 3 mg/day may be given. Ropinirole is usually given in divided doses three times per day.

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. If sufficient symptomatic control is not achieved, or maintained, the dose of ropinirole may be increased until an acceptable therapeutic response is established. Doses above 24 mg/day have not been investigated in clinical trials and this dose should not be exceeded.

When ropinirole is administered as adjunct therapy to L-dopa, the concurrent dose of L-dopa may be reduced gradually by around 20% in total.

When switching treatment from another dopamine agonist to ropinirole, the manufacturer's guidance on discontinuation should be followed before initiating ropinirole.

As with other dopamine agonists, ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

In parkinsonian patients with mild to moderate renal impairment (creatinine clearance 30-50 ml/min) no change in the clearance of ropinirole was observed, indicating that no dosage adjustment is necessary in this population

The use of ropinirole in patients with severe renal (creatinine clearance <30 ml/min) or hepatic impairment has not been studied. Administration of ropinirole to such patients is not recommended.

Elderly: The clearance of ropinirole is decreased in patients over 65 years of age, but the dose of ropinirole for elderly patients can be titrated in the normal manner.

Children: Parkinson's disease does not occur in children. The use of ropinirole in this population has therefore not been studied and it should not be given to children.

4.3 Contra-indications

Hypersensitivity to ropinirole

In light of the results of animal studies and the lack of studies in human pregnancy, ropinirole is contra-indicated in pregnancy, lactation and in women of child-bearing potential unless adequate contraception is used.

4.4 Special warnings and special precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease should be treated with caution.

Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. As with other dopaminergic drugs, caution should be exercised when these

compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Patients with major psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks (see also Section 4.5).

4.5 Interaction with other medicaments and other forms of interaction

Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these drugs with ropinirole should be avoided.

No pharmacokinetic interaction has been seen between ropinirole and L-dopa or domperidone which would necessitate dosage adjustment of either drug. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson's disease but, as is common practice, care should be taken when adding a new drug to a treatment regimen. Other dopamine agonists may be used with caution.

In a study in parkinsonian patients receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.

It has been established from *in vitro* experiments that ropinirole is metabolised by the cytochrome P450 enzyme CYP1A2. There is, therefore, the potential for an interaction between ropinirole and substrates (such as theophylline) or inhibitors (such as ciprofloxacin, fluvoxamine and cimetidine) of this enzyme. In patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when these drugs are introduced or withdrawn.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, if HRT is stopped or introduced during treatment with ropinirole, dosage adjustment may be required.

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.

4.6 Pregnancy and lactation

Ropinirole should not be used during pregnancy. In animal studies, administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg (approximately three times the AUC of the maximum dose in man), increased foetal death at 90 mg/kg (~x5) and digit malformations at 150 mg/kg (~x9). There was no teratogenic effect in the rat at 120 mg/kg (~x7) and no indication of an effect on development in the rabbit. There have been no studies of ropinirole in human pregnancy.

Ropinirole should not be used in nursing mothers as it may inhibit lactation.

4.7 Effects on ability to drive and use machines

No data are available on the effect of ropinirole on the ability to drive or use machinery. Patients should be cautioned about their ability to drive or operate machinery whilst taking ropinirole because of the possibility of somnolence or dizziness.

4.8 Undesirable effects

The most common adverse experiences reported by early therapy patients receiving ropinirole in clinical trials, and not seen at an equivalent or greater incidence on placebo, were; nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope.

Similarly, the most common adverse experiences reported in adjunct therapy clinical trials were; dyskinesia, nausea, hallucinations and confusion.

The incidence of postural hypotension, an event commonly associated with dopamine agonists, was not markedly different from placebo in clinical trials with ropinirole. However, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur.

4.9 Overdose

There have been no incidences of intentional overdose with ropinirole in clinical trials. It is anticipated that the symptoms of ropinirole overdose will be related to its dopaminergic activity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ropinirole is a non-ergoline dopamine agonist.

Parkinson's disease is characterised by a marked dopamine deficiency in the nigral striatal system. Ropinirole alleviates this deficiency by stimulating striatal dopamine receptors.

Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

5.2 Pharmacokinetic properties

Oral absorption of ropinirole is rapid and essentially complete. Bioavailability of ropinirole is approximately 50% and average peak concentrations of the drug are achieved at a median time of 1.5 hours post-dose. Wide inter-individual variability in the pharmacokinetic parameters has been seen but, overall, there is a proportional increase in the systemic exposure (C_{max} and AUC) to the drug with an increase in dose, over the therapeutic dose range. Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 8 l/kg) and is cleared from the systemic circulation with an average elimination half-life of about six hours. Plasma protein binding of the drug is low (10-40%). Ropinirole is metabolised primarily by oxidative metabolism and

ropinirole and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

No change in the oral clearance of ropinirole is observed following single and repeated oral administration. As expected for a drug being administered approximately every half life, there is, on average, two-fold higher steady-state plasma concentrations of ropinirole following the recommended t.i.d. regimen compared to those observed following a single oral dose.

5.3 Preclinical safety data

General toxicology: Ropinirole is well tolerated in laboratory animals in the dose range of 15 to 50 mg/kg. The toxicology profile is principally determined by the pharmacological activity of the drug (behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and salivation).

Genotoxicity: Genotoxicity was not observed in a battery of *in vitro* and *in vivo* tests.

Carcinogenicity: Two-year studies have been conducted in the mouse and rat at dosages up to 50 mg/kg. The mouse study did not reveal any carcinogenic effect. In the rat, the only drug-related lesions were Leydig cell hyperplasia/adenoma in the testis resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores: hydrous lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

The four tablet strengths of ropinirole are distinguished by colour. The composition of the *film coat* therefore varies. All film coats contain hydroxypropyl methylcellulose and polyethylene glycol. The variations are shown in the table below:

Tablet Colour	Tablet strength (mg) and colour			
	0.25 White	1.0 Green	2.0 Pink	5.0 Blue
Titanium Dioxide	✓	✓	✓	✓
Iron Oxide Yellow		✓	✓	
Iron Oxide Red			✓	
Indigo Carmine Aluminium		✓		✓
Polysorbate 80	✓			✓

6.2 Incompatibilities

None known

6.3 Shelf-life

Two years

6.4 Special precautions for storage

This product should be stored in a dry place at or below 25°C and protected from light.

6.5 Nature and contents of container

Tablets 0.25 mg, in opaque PVC/PVdC blister starting pack of 210.

Tablets 1 mg, in 60 ml HPDE bottle of 84.

Tablets 2 mg, in 60 ml HPDE bottle of 84.

Tablets 5 mg, in 60 ml HPDE bottle of 84.

6.6 Instructions for use/handling

None

7 MARKETING AUTHORISATION HOLDER

SmithKline Beecham plc
SB House
Great West Road
Brentford
Middlesex TW8 9BD

Trading as: SmithKline Beecham Pharmaceuticals and/or Bridge Pharmaceuticals
and/or Bencard and/or Beecham Research and/or Smith Kline & French Laboratories
and/or SmithKline Beecham Hospitals, all at Welwyn Garden City, Hertfordshire
AL7 1EY.

8. MARKETING AUTHORISATION NUMBER

'Requip' Tablets 0.25 mg	10592/0085
'Requip' Tablets 1 mg	10592/0087
'Requip' Tablets 2 mg	10592/0088
'Requip' Tablets 5 mg	10592/0089

9. DATE OF FIRST AUTHORISATION

2nd July 1996

10. DATE OF TEXT

21 December 1998

Legal category POM

Any queries should be addressed to the Medical Information Department at the address below.

SB Logo SmithKline Beecham
Pharmaceuticals

Welwyn Garden City, Hertfordshire AL7 1EY
Telephone: Welwyn Garden (01707) 325111

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SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

'Requip'

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ropinirole hydrochloride equivalent to 0.25, 0.5, 1.0, 2.0 or 5.0 mg ropinirole free base.

3. PHARMACEUTICAL FORM

Film-coated, pentagonal-shaped tablets for oral administration. The tablet strengths are distinguished by colour; 0.25 mg (white), 0.5 mg (yellow), 1.0 mg (green), 2.0 mg (pink) and 5.0 mg (blue).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of idiopathic Parkinson's Disease:

- Ropinirole may be used alone (without levodopa) in the treatment of idiopathic Parkinson's disease.
- Addition of ropinirole to levodopa may be used to control "on-off" fluctuations and permit a reduction in the total daily dose of levodopa.

4.2 Posology and method of administration

Individual dose titration against efficacy and tolerability is recommended.

Ropinirole should be taken three times a day, preferably with meals to improve gastrointestinal tolerance.

Treatment initiation: The initial dose should be 0.25 mg t.i.d. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

	Week			
	1	2	3	4
Unit dose (mg)	0.25	0.5	0.75	1.0
Total daily dose (mg)	0.75	1.5	2.25	3.0

Therapeutic regimen: After the initial titration, weekly increments of up to 3 mg/day may be given. Ropinirole is usually given in divided doses three times per day.

A therapeutic response may be seen between 3 and 9 mg/day, although adjunct therapy patients may require higher doses. If sufficient symptomatic control is not achieved, or maintained, the dose of ropinirole may be increased until an acceptable therapeutic response is established. Doses above 24 mg/day have not been investigated in clinical trials and this dose should not be exceeded.

When ropinirole is administered as adjunct therapy to L-dopa, the concurrent dose of L-dopa may be reduced gradually by around 20% in total.

When switching treatment from another dopamine agonist to ropinirole, the manufacturer's guidance on discontinuation should be followed before initiating ropinirole.

As with other dopamine agonists, ropinirole should be discontinued gradually by reducing the number of daily doses over the period of one week.

In parkinsonian patients with mild to moderate renal impairment (creatinine clearance 30-50 ml/min) no change in the clearance of ropinirole was observed, indicating that no dosage adjustment is necessary in this population

The use of ropinirole in patients with severe renal (creatinine clearance <30 ml/min) or hepatic impairment has not been studied. Administration of ropinirole to such patients is not recommended.

Elderly: The clearance of ropinirole is decreased in patients over 65 years of age, but the dose of ropinirole for elderly patients can be titrated in the normal manner.

Children: Parkinson's disease does not occur in children. The use of ropinirole in this population has therefore not been studied and it should not be given to children.

4.3 Contra-indications

Hypersensitivity to ropinirole

In light of the results of animal studies and the lack of studies in human pregnancy, ropinirole is contra-indicated in pregnancy, lactation and in women of child-bearing potential unless adequate contraception is used.

4.4 Special warnings and special precautions for use

Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease should be treated with caution.

Co-administration of ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. As with other dopaminergic drugs, caution should be exercised when these compounds are given concomitantly with ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

Patients with major psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks (see also Section 4.5).

Rarely, sudden onset of sleep has been reported during daily activities (see sections 4.7 and 4.8). These episodes have been reported in some cases without prior warning signs or apparent daytime sleepiness. Patients must be informed not to drive and to avoid other potentially dangerous activities. Where data are available, most cases have recovered after dose reduction or on withdrawal of the drug; if this event occurs, dose reduction or withdrawal of the drug should be considered. In most cases the patients were also receiving medication with potential sedating properties. Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with ropinirole.

4.5 Interaction with other medicaments and other forms of interaction

Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these drugs with ropinirole should be avoided.

No pharmacokinetic interaction has been seen between ropinirole and L-dopa or domperidone which would necessitate dosage adjustment of either drug. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson's disease but, as is common practice, care should be taken when adding a new drug to a treatment regimen. Other dopamine agonists may be used with caution.

In a study in parkinsonian patients receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.

It has been established from *in vitro* experiments that ropinirole is metabolised by the cytochrome P450 enzyme CYP1A2. There is, therefore, the potential for an interaction between ropinirole and substrates (such as theophylline) or inhibitors (such as ciprofloxacin, fluvoxamine and cimetidine) of this enzyme. In patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when these drugs are introduced or withdrawn.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, if HRT is stopped or introduced during treatment with ropinirole, dosage adjustment may be required.

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.

4.6 Pregnancy and lactation

Ropinirole should not be used during pregnancy. In animal studies, administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg (approximately three times the AUC of the maximum dose in man), increased foetal death at 90 mg/kg (~x5) and digit malformations at 150 mg/kg (~x9).

There was no teratogenic effect in the rat at 120 mg/kg (~x7) and no indication of an effect on development in the rabbit. There have been no studies of ropinirole in human pregnancy.

Ropinirole should not be used in nursing mothers as it may inhibit lactation.

4.7 Effects on ability to drive and use machines

Rarely, cases of sudden onset of sleep have been reported (see sections 4.4. and 4.8). These episodes can be life-threatening depending on the circumstances and have been reported in some cases without awareness of warning signs. Patients must be informed not to drive and to avoid other potentially dangerous activities.

If this event occurs, dose reduction or withdrawal of the drug should be considered. In most cases the patients were receiving medication with potential sedating properties.

4.8 Undesirable effects

The most common adverse experiences reported by early therapy patients receiving ropinirole in clinical trials, and not seen at an equivalent or greater incidence on placebo, were; nausea, somnolence, leg oedema, abdominal pain, vomiting and syncope.

Similarly, the most common adverse experiences reported in adjunct therapy clinical trials were; dyskinesia, nausea, hallucinations and confusion.

The incidence of postural hypotension, an event commonly associated with dopamine agonists, was not markedly different from placebo in clinical trials with ropinirole. However, decreases in systolic blood pressure have been noted; symptomatic hypotension and bradycardia, occasionally severe, may occur.

As with another dopamine agonist, extreme somnolence and/or sudden onset of sleep have been reported rarely during post-marketing experience, occasionally when the patient was driving (see sections 4.4 and 4.7). Patients experiencing this phenomenon can not resist the urge to sleep, and on waking may be unaware of any tiredness prior to the sleep. Most patients were taking other medication with potentially sedating properties. There is no clear relationship between treatment dose or duration and onset of symptoms.

4.9 Overdose

There have been no incidences of intentional overdose with ropinirole in clinical trials. It is anticipated that the symptoms of ropinirole overdose will be related to its dopaminergic activity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Ropinirole is a non-ergoline dopamine agonist.

Parkinson's disease is characterised by a marked dopamine deficiency in the nigral striatal system. Ropinirole alleviates this deficiency by stimulating striatal dopamine receptors.

Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

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Oral absorption of ropinirole is rapid and essentially complete. Bioavailability of ropinirole is approximately 50% and average peak concentrations of the drug are achieved at a median time of 1.5 hours post-dose. Wide inter-individual variability in the pharmacokinetic parameters has been seen but, overall, there is a proportional increase in the systemic exposure (C_{max} and AUC) to the drug with an increase in dose, over the therapeutic dose range. Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 8 l/kg) and is cleared from the systemic circulation with an average elimination half-life of about six hours. Plasma protein binding of the drug is low (10-40%). Ropinirole is metabolised primarily by oxidative metabolism and ropinirole and its metabolites are mainly excreted in the urine. The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

No change in the oral clearance of ropinirole is observed following single and repeated oral administration. As expected for a drug being administered approximately every half life, there is, on average, two-fold higher steady-state plasma concentrations of ropinirole following the recommended t.i.d. regimen compared to those observed following a single oral dose.

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Genotoxicity: Genotoxicity was not observed in a battery of *in vitro* and *in vivo* tests.

Carcinogenicity: Two-year studies have been conducted in the mouse and rat at dosages up to 50 mg/kg. The mouse study did not reveal any carcinogenic effect. In the rat, the only drug-related lesions were Leydig cell hyperplasia/adenoma in the testis resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores: hydrous lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate.

The four tablet strengths of ropinirole are distinguished by colour. The composition of the *film coat* therefore varies. All film coats contain hydroxypropyl methylcellulose and polyethylene glycol. The variations are shown in the table below:

Tablet Colour	Tablet strength (mg) and colour				
	0.25 White	0.5 Yellow	1.0 Green	2.0 Pink	5.0 Blue
Titanium Dioxide	✓	✓	✓	✓	✓
Iron Oxide Yellow		✓	✓	✓	
Iron Oxide Red		✓		✓	
Indigo Carmine Aluminium		✓	✓		✓
Polysorbate 80	✓				✓

6.2 Incompatibilities

None known

6.3 Shelf-life

Two years

6.4 Special precautions for storage

This product should be stored in a dry place at or below 25°C and protected from light.

6.5 Nature and contents of container

Tablets 0.25 mg, in opaque PVC/PVdC or PVC/Aclar blister starting pack of 210
 Tablets 0.25 mg, in opaque PVC/PVdC or PVC/Aclar blister starting pack of 126 *
 Tablets 0.25 mg, in opaque PVC/PVdC or PVC/Aclar blister pack of 21 *
 Tablets 0.5 mg, in opaque PVC/PVdC or PVC/Aclar blister pack of 21 *
 Tablets 0.5 mg, in 60 ml HPDE bottle of 84 *
 Tablets 1 mg, in opaque PVC/PVdC or PVC/Aclar blister pack of 21 *
 Tablets 2 mg, in opaque PVC/PVdC or PVC/Aclar blister pack of 21 *
 Tablets 5 mg, in opaque PVC/PVdC or PVC/Aclar blister pack of 21 *
 Tablets 1 mg, in 60 ml HPDE bottle of 84.
 Tablets 2 mg, in 60 ml HPDE bottle of 84.
 Tablets 5 mg, in 60 ml HPDE bottle of 84.

* These are not currently marketed and will be removed at time of printing.

6.6 Instructions for use/handling

None

7 MARKETING AUTHORISATION HOLDER

SmithKline Beecham plc
Great West Road
Brentford
Middlesex TW8 9BD

Trading as: SmithKline Beecham Pharmaceuticals at Welwyn Garden City,
Hertfordshire AL7 1EY.

8. MARKETING AUTHORISATION NUMBER

'Requip' Tablets 0.25 mg 10592/0085

9. DATE OF FIRST AUTHORISATION

2nd July 1996

10. DATE OF TEXT

10th August 2000

Legal category POM

A FIVE-YEAR STUDY OF THE INCIDENCE OF DYSKINESIA IN PATIENTS WITH EARLY PARKINSON'S DISEASE WHO WERE TREATED WITH ROPINIROLE OR LEVODOPA

OLIVIER RASCOL, M.D., PH.D., DAVID J. BROOKS, M.D., D.Sc., AMOS D. KORCZYN, M.D., PETER P. DE DEYN, M.D., PH.D., CARL E. CLARKE, M.D., AND ANTHONY E. LANG, M.D., FOR THE 056 STUDY GROUP*

ABSTRACT

Background There is debate about whether the initial treatment for patients with Parkinson's disease should be levodopa or a dopamine agonist.

Methods In this prospective, randomized, double-blind study, we compared the safety and efficacy of the dopamine D2-receptor agonist ropinirole with that of levodopa over a period of five years in 268 patients with early Parkinson's disease. If symptoms were not adequately controlled by the assigned study medication, patients could receive supplementary levodopa, administered in an open-label fashion. The primary outcome measure was the occurrence of dyskinesia.

Results Eighty-five of the 179 patients in the ropinirole group (47 percent) and 45 of the 89 patients in the levodopa group (51 percent) completed all five years of the study. In the ropinirole group, 29 of the 85 patients (34 percent) received no levodopa supplementation. The analysis of the time to dyskinesia showed a significant difference in favor of ropinirole (hazard ratio for remaining free of dyskinesia, 2.82; 95 percent confidence interval, 1.78 to 4.44; $P < 0.001$). At five years, the cumulative incidence of dyskinesia (excluding the three patients who had dyskinesia at base line), regardless of levodopa supplementation, was 20 percent (36 of 177 patients) in the ropinirole group and 45 percent (40 of 88 patients) in the levodopa group. There was no significant difference between the two groups in the mean change in scores for activities of daily living among those who completed the study. Adverse events led to the early withdrawal from the study of 48 of 179 patients in the ropinirole group (27 percent) and 29 of 89 patients in the levodopa group (33 percent). The mean ($\pm$ SD) daily doses given by the end of the study were 16.5 ± 6.6 mg of ropinirole (plus 427 ± 221 mg of levodopa in patients who received supplementation) and 753 ± 398 mg of levodopa (including supplements).

Conclusions Early Parkinson's disease can be managed successfully for up to five years with a reduced risk of dyskinesia by initiating treatment with ropinirole alone and supplementing it with levodopa if necessary. (N Engl J Med 2000;342:1484-91.)

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ALTHOUGH the antiparkinsonian effect of the dopamine precursor levodopa was first demonstrated 30 years ago,¹ and that of dopamine D2-receptor agonists more than 25 years ago,² the most appropriate time to begin these two treatments in patients with Parkinson's disease remains controversial.³ Some neurologists promote the early use of levodopa, emphasizing the rapid symptomatic benefit⁴ and the possible reduction in mortality that the drug provides.⁵ Others, more concerned about the potential neurotoxicity⁶ and the long-term complications, such as dyskinesia, associated with the use of levodopa,⁷⁻¹¹ encourage the early use of dopamine agonists. This long-standing controversy remains largely unresolved,¹² although recent data suggest that initiating treatment with a dopamine agonist confers some advantage.^{13,14} Data from studies of monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine have demonstrated that dopamine agonists are less likely than levodopa to induce dyskinesia in animals that have not been exposed to levodopa.¹⁵ Because dyskinesia is one of the most debilitating effects of levodopa therapy, we studied the incidence of dyskinesia associated with the two treatments in a large, prospective, randomized, five-year study.

Ropinirole is a non-ergot-derived D2-like dopamine-receptor agonist that is effective in the treatment of early^{14,16,17} and late^{18,19} Parkinson's disease. The effectiveness of ropinirole in the treatment of early Parkinson's disease has already been demonstrated through a planned interim analysis of the data from the study described here, conducted six months after the study was begun, in which the primary end point was the score for motor function on the Unified Parkinson's Disease Rating Scale (UPDRS).¹⁷ We present here the results of the final five-year analysis, in which

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*The investigators who participated in the study are listed in the Appendix.

the primary outcome measure was the incidence of dyskinesia.

METHODS

Study Population

A total of 268 patients were enrolled at 30 centers (in Europe, Israel, and Canada). All patients were 30 years of age or older, had a clinical diagnosis of Parkinson's disease²⁰ with a Hoehn-Yahr rating of stage 1 through 3 (with stage 1 indicating unilateral, early disease and stage 3 more advanced, bilateral disease),²¹ and required dopaminergic therapy. Prior short-term treatment with levodopa or dopamine agonists was limited to a maximum of six weeks and had to be discontinued at least two weeks before entry into the study.

Patients were excluded if they had severe dizziness or fainting, severe systemic disease, major psychosis, severe dementia, alcoholism or drug dependence, or a contraindication to levodopa. In addition, treatment with a monoamine oxidase inhibitor within two weeks before entry (with the exception of selegiline) or previous treatment with ropinirole were reasons for exclusion.

Study Design

This prospective, randomized, double-blind study was designed to compare the risk of dyskinesia in early Parkinson's disease among patients treated with ropinirole (Requip, SmithKline Beecham, Philadelphia) with that among patients treated with a combination of levodopa and benserazide (Madopa, Hoffmann-La Roche, Nutley, N.J.; referred to hereafter as levodopa) over a period of five years. Random treatment assignment was performed with a ropinirole-to-levodopa ratio of 2:1. Benserazide has been shown previously to have properties that are similar to those of carbidopa (used with levodopa in Sinemet [Dupont Merck, Wilmington, Del.]) in blocking dopa decarboxylase in the periphery.^{22,23} Blinding of the study was maintained with the use of a double-dummy technique. Sealed copies of the randomization code were held by the principal investigator at each site and by the study sponsor.

Patients underwent a single-blind placebo run-in period lasting seven days to demonstrate at least 80 percent compliance with taking study medication. Patients were then randomized (with stratification according to whether they were receiving concomitant selegiline therapy), and assessments were performed at weekly intervals for the first month, every two weeks for the next two months, every month up to six months, and every two months thereafter.

The study was conducted in accordance with Good Clinical Practices guidelines and the Declaration of Helsinki. The protocol was approved by an ethics committee at each center, and written informed consent was obtained from each patient.

Treatment

Both ropinirole and levodopa were taken orally in tablet form. The dose of study medication was adjusted weekly as required, with 13 possible increasing dose levels. Ropinirole therapy was initiated (dose level 1) at 0.75 mg per day (0.25 mg three times daily) and levodopa therapy at 50 mg once daily plus placebo twice daily. The maximal daily doses of study medication allowed (dose level 13) were 24 mg of ropinirole per day (8 mg three times daily) and 1200 mg of levodopa per day (400 mg three times daily). Investigators were encouraged to treat patients only with the assigned study medication. Patients whose symptoms were not adequately controlled by the adjustment of study medication alone (i.e., those with recurrent, persistent, or functional disability), despite use of the highest tolerated dose, could be given supplementary levodopa in open-label fashion. No other antiparkinsonian therapies were permitted after the start of the study. Domperidone was permitted according to the normal practice at each individual study center, to control severe dizziness, nausea, or vomiting.

Clinical Assessments

Dyskinesia

Dyskinesia (the incidence of which was assessed in patients before withdrawal from the study or until completion of the study) was considered to be present if a patient had a score of 1 or more (on a scale from 0 to 4, where a score of 0 indicates no dyskinesia and a score of 4 indicates dyskinesia during most waking hours) on item 32 of the UPDRS²⁴ ("Duration: what proportion of the waking day are dyskinesias present?") or if dyskinesia was reported as an adverse event. In addition, all reports of adverse events consisting of abnormal movements considered to be dyskinesia were reviewed before the randomization code was broken.

Additional Variables

"Disabling" dyskinesia was defined as a score of 1 or more on items 32 and 33 of the UPDRS ("How disabling are the dyskinesias?").

The scores for activities of daily living and motor function were measured with the use of parts II and III of the UPDRS (items 5 through 17 [range of possible scores, 0 to 52, where 0 indicates no disability and 52 indicates maximal impairment] and items 18 through 31 [range of possible scores, 0 to 108, where 0 indicates no disability and 108 indicates maximal impairment]), respectively, for the patients who completed the study.

"Wearing off" (defined as periods of increased severity of parkinsonian symptoms as medication wears off) was assessed by reviewing the data from patients who reported increases in the duration of time awake and in an "off" period on item 39 of the UPDRS. "Freezing when walking" was assessed by reviewing responses to item 14 of the UPDRS.

Safety and Tolerability of the Drugs

Adverse events were assessed in a standard manner by the investigator. Neuropsychiatric adverse events (i.e., hallucinations, confusion, delirium, psychosis, illusion, delusion, depersonalization, personality disorder, abnormal thinking, amnesia, dementia, impaired concentration, and other related events, as defined by the World Health Organization) were the only predetermined measures of safety in the statistical analyses.

Statistical Analysis

We planned to enroll 240 patients into the study (160 randomly assigned to ropinirole and 80 to levodopa); this number was calculated on the assumption of an underlying rate of response to treatment of 85 percent. Samples of 110 patients in the ropinirole group and 55 in the levodopa group who could be evaluated at the six-month interim analysis¹⁷ provided the study with an 80 percent chance of demonstrating equivalent efficacy in the two groups (with a 90 percent confidence interval), on the assumption that the response rate in the levodopa group would not be more than 15 percent higher than that in the ropinirole group. It was anticipated that 30 patients in the ropinirole group and 50 in the levodopa group would complete all five years (predicted withdrawal rates, 30 percent and 10 percent per year, respectively). These numbers of patients provided the study with 88 percent power to detect a difference ($P < 0.05$) in the incidence of dyskinesia between the two groups, assuming an incidence of 5 percent in the ropinirole group and an incidence of 30 percent in the levodopa group.

All analyses (except those based on the scores for activities of daily living and motor function) were performed on an intention-to-treat basis and include all randomized patients who had at least one assessment after receiving study medication. Patients were not followed up for assessment of dyskinesia after withdrawal from the study.

The rates of dyskinesia and disabling dyskinesia in the two groups were compared with the use of the Cox proportional-hazards model²⁵ in an analysis of failure time (time to an episode of dyskinesia or disabling dyskinesia). Kaplan-Meier curves,²⁶ haz-

ard ratios with 95 percent confidence intervals, and P values were calculated. Data on patients were censored at the time they withdrew from the study without having dyskinesia.

Statistical analyses of variance of the mean changes in the scores for activities of daily living and motor function between base line and the end of the study were based on data from the patients who completed the study. The results of these analyses are presented as adjusted treatment differences, with 95 percent confidence intervals and P values. It was not possible to analyze these scores over the duration of the study without bias because the number of patients at each time point varied and because of the problems with performing multiple tests.

The proportions of patients with neuropsychiatric adverse events in the two groups were compared with the exact chi-square test.

Statistical tests were performed using two-tailed tests at the 5 percent level of significance.

RESULTS

Patients and Treatment

Of the 268 patients who entered the trial, 179 were randomly assigned to ropinirole and 89 to levodopa (Fig. 1). The demographic characteristics of

the two groups were similar (Table 1). Two patients in the ropinirole group and one in the levodopa group had dyskinesia at base line and were excluded from the analyses of the incidence of dyskinesia. Eighty-five of the patients in the ropinirole group (47 percent) and 45 of those in the levodopa group (51 percent) completed the study. Of these patients, 29 in the ropinirole group (34 percent) and 29 in the levodopa group (64 percent) did so without open-label levodopa supplementation. The reasons for withdrawal from the study are presented in Figure 1.

Mean ($\pm$ SD) daily doses at the completion of the study were 16.5 ± 6.6 mg of ropinirole (plus 427 ± 221 mg of open-label levodopa in patients requiring supplementation) and 753 ± 398 mg of levodopa (including open-label supplements). Fifty-two patients in the ropinirole group (29 percent) and 24 in the levodopa group (27 percent) received domperidone at some time during the five-year study.

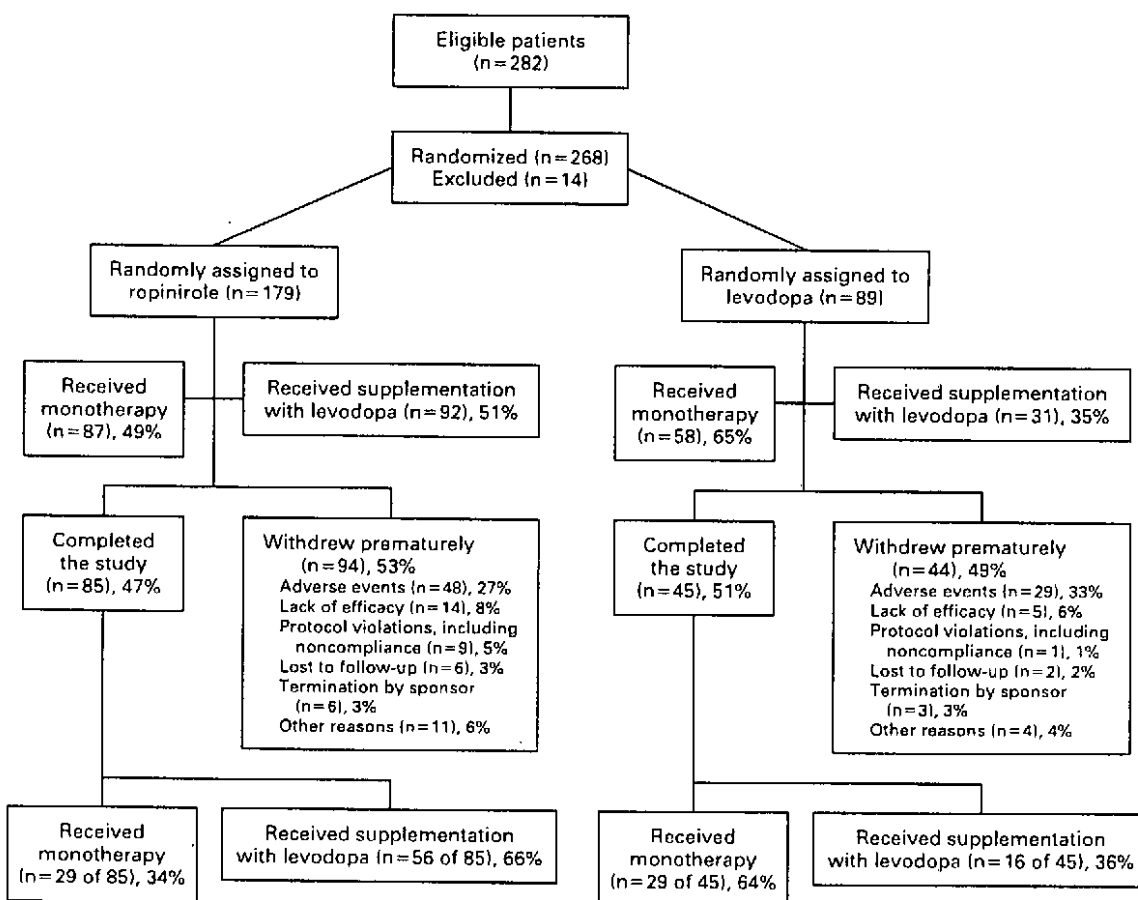


Figure 1. Enrollment and Treatment of the Study Patients.

"Termination by sponsor" refers to one center that was closed early by agreement with the investigator because of noncompliance with the protocol.

TABLE 1. CHARACTERISTICS OF THE INTENTION-TO-TREAT POPULATION.*

CHARACTERISTIC	ROPINIROLE (N=179)	LEVODOPA (N=89)
Age — yr	63±9	63±9
Sex — no. (%)		
Male	113 (63.1)	52 (58.4)
Female	66 (36.9)	37 (41.6)
Selegiline treatment at start of study — no. (%)	81 (45.3)	39 (43.8)
Prior levodopa treatment for ≤6 wk — no. (%)	26 (14.5)	7 (7.9)
Duration of disease — mo	30±34	29±27
Hoehn-Yahr stage — no. (%)†		
1	23 (12.8)	20 (22.5)
1.5	27 (15.1)	8 (9.0)
2	66 (36.9)	33 (37.1)
2.5	46 (25.7)	19 (21.3)
3	17 (9.5)	9 (10.1)
UPDRS Score‡		
Base-line score for ADL	8.0±5.0	8.0±4.6
Base-line for motor function score	21.5±10.5	21.7±11.3

*Plus-minus values are means ±SD.

†The stages range from 1, indicating unilateral, early disease, to 3, indicating more advanced, bilateral disease.

‡UPDRS denotes Unified Parkinson's Disease Rating Scale, and ADL activities of daily living. The range of possible scores for activities of daily living is 0 to 52, with a higher score indicating more severe dysfunction. The range of possible scores for motor function is 0 to 108, with a higher score indicating more severe dysfunction.

Incidence of Dyskinesia

The reduced risk of dyskinesia among the patients in the ropinirole group, regardless of levodopa supplementation, is evident in Figure 2 (hazard ratio for remaining free of dyskinesia in the ropinirole group, as compared with the levodopa group, 2.82; 95 percent confidence interval, 1.78 to 4.44; $P<0.001$). There were too few patients with dyskinesia in the ropinirole group to calculate the length of time until dyskinesia developed in 50 percent of the patients remaining in the study. However, the length of time until dyskinesia developed in 25 percent of the patients remaining in the study was 214 weeks among the patients in the ropinirole group and 104 weeks among the patients in the levodopa group. Overall, dyskinesia developed in 36 of the 177 patients in the ropinirole group (20 percent) and in 40 of the 88 in the levodopa group (45 percent), as assessed by item 32 of the UPDRS and by reports of adverse events. Before the addition of supplementary levodopa, 9 of 177 patients in the ropinirole group (5 percent) and 32 of 88 in the levodopa group (36 percent) had dyskinesia.

Other Variables

The risk of disabling dyskinesia was significantly lower in the ropinirole group, regardless of whether

the patient received supplementary levodopa (hazard ratio for remaining free of disabling dyskinesia in the ropinirole group as compared with the levodopa group, 3.02; 95 percent confidence interval, 1.52 to 6.02; $P=0.002$). Fourteen of the 179 patients in the ropinirole group (8 percent) had disabling dyskinesia, as compared with 20 of the 89 in the levodopa group (23 percent).

Figure 3 shows the mean scores for activities of daily living throughout the study. Among the patients who completed the study, the mean ($\pm$ SD) change from base line in the score for activities of daily living was an increase of 1.6 ± 5.4 points (a slight worsening) among the patients in the ropinirole group and 0.0 ± 4.7 points among those in the levodopa group. This difference was not significant (adjusted difference, 1.53 points; 95 percent confidence interval, -0.14 to 3.22; $P=0.08$).

Figure 3 also shows the mean scores for motor function during the study. For the patients who completed the study, there were mean decreases from base line in motor-function scores of 0.8 ± 10.1 point (a slight improvement) among the patients in the ropinirole group and 4.8 ± 8.3 points among those in the levodopa group. The difference in mean scores was significant in favor of levodopa (adjusted treatment difference, 4.48 points; 95 percent confidence interval, 1.25 to 7.72; $P=0.008$).

The length of time until 25 percent of the patients remaining in the study first had an increase in the wearing-off effect was 199 weeks in the ropinirole group and 145 weeks in the levodopa group. Of the patients for whom data were available, 39 of 172 patients in the ropinirole group (23 percent) and 29 of 85 in the levodopa group (34 percent) had an increase in symptoms due to the wearing off of the drugs during the study.

The length of time until 25 percent of the patients remaining in the study first had an increase in freezing while walking was 166 weeks in the ropinirole group and 207 weeks in the levodopa group. Of the patients for whom data were available, 57 of 178 patients in the ropinirole group (32 percent) and 22 of 88 in the levodopa group (25 percent) had an increase in freezing while walking.

Fourteen of the 179 patients in the ropinirole group (8 percent) withdrew from the study early because of a lack of efficacy, as compared with 5 of 89 in the levodopa group (6 percent). Aggravated parkinsonism was responsible for the withdrawal of 6 of the 179 patients in the ropinirole group (3 percent) and 3 of the 89 in the levodopa group (3 percent).

Adverse Events

Relevant adverse events that occurred in more than 10 percent of the study population over the course of the study are listed in Table 2. There was no significant difference in the incidence of neuropsychiat-

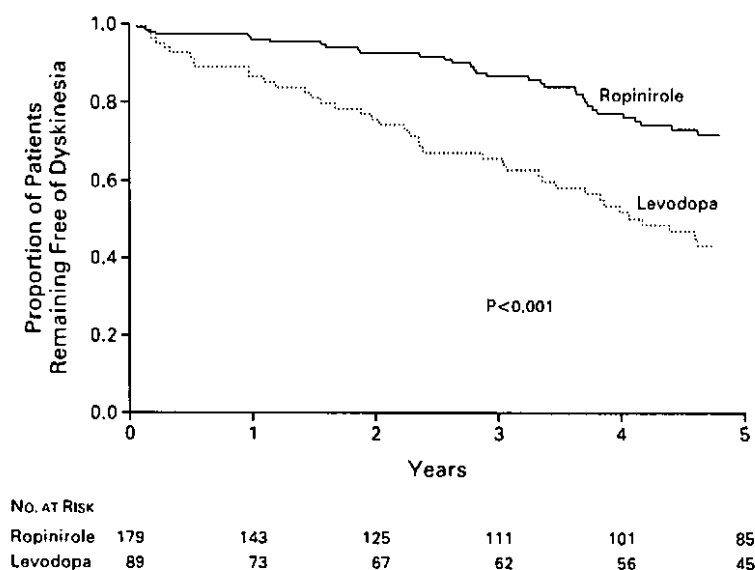


Figure 2. Proportions of Patients Remaining Free of Dyskinesia in the Ropinirole and Levodopa Groups. The hazard ratio for remaining free of dyskinesia in the ropinirole group as compared with the levodopa group was 2.82 (95 percent confidence interval, 1.78 to 4.44).

ric adverse events between the two groups (43 of 179 patients in the ropinirole group [24 percent] and 15 of 89 patients in the levodopa group [17 percent]; $P=0.18$ by the chi-square test), although the incidence of hallucinations was higher in the ropinirole group (31 of 179 patients [17 percent]) than in the levodopa group (5 of 89 patients [6 percent]).

Adverse events caused the early withdrawal from the study of 48 of the 179 patients in the ropinirole group (27 percent) and 29 of the 89 patients in the levodopa group (33 percent). The two most common reasons for early withdrawal due to adverse events were nausea (ropinirole group, 5 of 179 patients [3 percent]; levodopa group, 5 of 89 patients [6 percent]) and hallucinations (ropinirole group, 8 of 179 patients [4 percent]; levodopa group, 2 of 89 patients [2 percent]). No other individual adverse event caused the early withdrawal of 4 percent or more of the patients in either group. No more than 3 percent of the patients in either treatment group died during the study (ropinirole group, 5 of 179 patients [3 percent]; levodopa group, 2 of 89 patients [2 percent]). No deaths were directly attributed to the study medications.

DISCUSSION

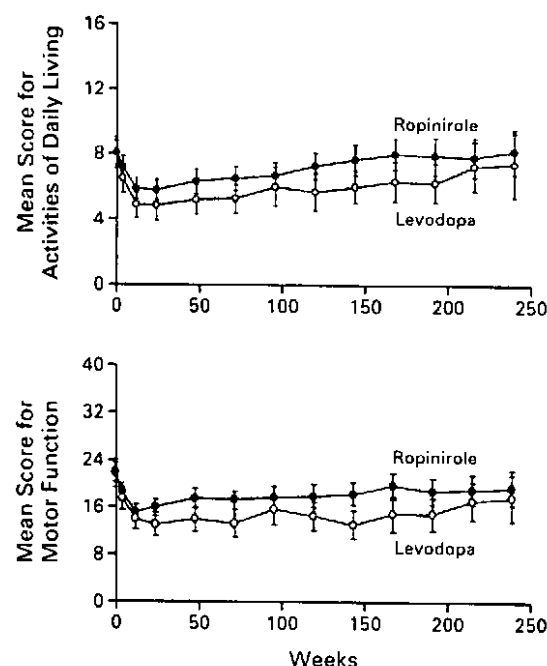
This study shows that the early use of the dopamine agonist ropinirole significantly reduces the risk of dyskinesia in patients with Parkinson's disease. When all the patients randomly assigned to ropinirole were compared with those randomly assigned to

levodopa, the risk of dyskinesia was lower by a factor of almost three in the ropinirole group (Fig. 2). The overall incidence of dyskinesia at five years was 20 percent in the ropinirole group, as compared with 45 percent in the levodopa group. This difference was even more striking among the patients who did not require supplementary levodopa (rates of dyskinesia: ropinirole group, 5 percent; levodopa group, 36 percent). The clinical relevance of these differences between treatment groups is emphasized by the significant difference in favor of ropinirole in the incidence of dyskinesia considered to be disabling.

These results confirm the findings of several previous open-label studies^{29,10} and shorter blinded studies,^{13,27} in which fewer motor complications were reported among patients who initially received dopamine agonists. The incidence of dyskinesia in the patients assigned to levodopa in our study differed from that reported in a five-year trial comparing immediate-release and sustained-release levodopa, in which less than 25 percent of patients had dyskinesia.²⁸ This difference may be related to the different doses of levodopa used and different methods of assessment of the occurrence of dyskinesia. Generally, most authors report an incidence of dyskinesia similar to that found in our study.²⁹

The reason why the early use of ropinirole reduced the risk of dyskinesia remains unclear. Factors implicated as contributing to the development of dyskinesia include a higher dose of levodopa, greater severity of underlying disease,²⁹ and abnormal pulsatile

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No. at Risk

Ropinirole	179	143	125	111	101	85
Levodopa	89	73	67	62	56	45

Figure 3. Mean Scores for Activities of Daily Living and Motor Function.

The scores are for part II (activities of daily living) and part III (motor function) of the Unified Parkinson's Disease Rating Scale. The range of possible scores for part II is 0 to 52; the range for part III is 0 to 108. Higher scores indicate more severe disability and more severe dysfunction. Error bars indicate ± 2 SE.

stimulation of dopamine receptors as a result of the short elimination half-life of levodopa.³⁰ Ropinirole has a longer elimination half-life than levodopa (6 to 8 hours vs. 1.5 to 2 hours), thus providing more continuous stimulation of dopamine receptors. Patients treated with ropinirole also had reduced cumulative exposure to levodopa, since levodopa was used only later and at a lower dose, if necessary. The design of this study did not permit us to determine whether there was an additional neuroprotective effect of ropinirole.

The early use of ropinirole did not reduce the occurrence of wearing-off and freezing during walking to the same extent as it did the occurrence of dyskinesia. This finding suggests that these complications of motor function may not have the same pathophysiologic mechanisms as dyskinesia.

Delaying treatment with levodopa to prevent dyskinesia can be justified only if the underlying symptoms of Parkinson's disease are sufficiently controlled. The mean scores for activities of daily living remained

TABLE 2. REPORTS OF ADVERSE EVENTS OCCURRING IN 10 PERCENT OR MORE OF EITHER GROUP IN THE INTENTION-TO-TREAT ANALYSIS.

ADVERSE EVENT*	ROPINIROLE (N=179)	LEVODOPA (N=89)
	no. (%)	
Nausea	87 (48.6)	44 (49.4)
Somnolence	49 (27.4)	17 (19.1)
Insomnia	45 (25.1)	21 (23.6)
Aggravated Parkinson's disease	40 (22.3)	18 (20.2)
Dyspepsia	37 (20.7)	15 (16.9)
Dizziness	36 (20.1)	17 (19.1)
Hallucinations	31 (17.3)	5 (5.6)
Vomiting	29 (16.2)	10 (11.2)
Tremor	29 (16.2)	11 (12.4)
Abdominal pain	27 (15.1)	13 (14.6)
Depression	26 (14.5)	20 (22.5)
Headache	25 (14.0)	16 (18.0)
Edema of the legs	25 (14.0)	5 (5.6)
Ataxia	25 (14.0)	8 (9.0)
Anxiety	21 (11.7)	8 (9.0)
Postural hypotension	21 (11.7)	11 (12.4)
Constipation	17 (9.5)	11 (12.4)
Dyskinesia†	16 (8.9)	23 (25.8)
Dystonia	12 (6.7)	11 (12.4)
Increased sweating	11 (6.1)	9 (10.1)

*Patients often had more than one adverse event.

†Dyskinesia, the primary outcome measure, was assessed on the basis of both the Unified Parkinson's Disease Rating Scale and reports of adverse events.

similar in the two groups at each time point during the study (a difference of less than 1.5 points), and the changes between base line and completion of the study in the two groups were not significantly different. For the UPDRS motor score, although there was no significant difference between the two groups in the absolute value at the completion of the study, there was a significant difference in the change from base line in favor of levodopa. This difference, however, may not be clinically relevant, since it was not reflected in the measurements of activities of daily living. Moreover, the rates of early withdrawal from the study as a result of insufficient efficacy and aggravated parkinsonism were similar in the two treatment groups.

The fact that 85 of the 179 patients in the ropinirole group (47 percent) and 45 of the 89 in the levodopa group (51 percent) completed the study serves to confirm that the safety and efficacy profiles of the two treatment strategies are similar. A further measure of efficacy with respect to antiparkinson effect, sometimes used as a surrogate end point in clinical trials, is whether patients require supplementary levodopa. Although a higher percentage of ropinirole-

treated patients received supplementary levodopa than of those treated initially with levodopa in our study, this difference cannot be regarded as a reliable indicator of efficacy. The reason is that the investigators, aware of the association between levodopa and dyskinesia, appeared to be less willing to give patients with dyskinesia supplementary levodopa: of the patients in whom dyskinesia developed, only 17 percent (13 of 76) received supplementary levodopa after the onset of dyskinesia, whereas 58 percent of the patients without dyskinesia (110 of 189) received supplementary levodopa. Since dyskinesia was much more common in the levodopa group (45 percent) than in the ropinirole group (20 percent), a lower rate of supplementation in the levodopa group may have resulted.

Some physicians are cautious about using dopamine agonists, because they believe that such agents induce more adverse events (including nausea, hypotension, and hallucinations) than levodopa. This belief is based on experience gained in treating advanced Parkinson's disease, in which patients are generally older, are often receiving multiple medications, and may have a number of coexisting conditions. The doses of ropinirole administered in this study (mean, 16.5 ± 6.6 mg per day at five years) were higher than those currently used in clinical practice in Europe and the United States. These higher doses, however, were well tolerated, with rates and profiles of adverse events that were similar for the two drugs and typical for any effective dopaminergic agent.

Neuropsychiatric adverse events are a major concern when dopamine agonists are used in the treatment of Parkinson's disease. In this study, there was no significant difference in the overall incidence of these complications, including the occurrence of somnolence, between the two treatment groups. There were no reports of falling asleep suddenly in either treatment group.³¹ Although hallucinations were more frequent in the ropinirole group than in the levodopa group, they were mild and easily managed in most patients. No risk factors were identified that would predispose patients to have such adverse events with either treatment.

Our study, therefore, demonstrates that Parkinson's disease can be successfully managed for up to five years with ropinirole, with supplemental levodopa given as a second step if necessary. Such treatment significantly lowers the risk of dyskinesia as compared with treatment with levodopa alone.

Supported by SmithKline Beecham Pharmaceuticals.

Presented at the XIII International Congress on Parkinson's Disease, Vancouver, Canada, July 24–28, 1999.

Drs. Rascol, Brooks, Korczyn, Clarke, and Lang have served as paid consultants to SmithKline Beecham.

We are indebted to Niall Quinn and Anette Schrag for reviewing the data on adverse events; to Jason Gardner, Julian Keens, and Sandy Macrae for their assistance in the development of the manu-

script; to Mary Oldham and Jacqui Warner for performing all statistical analyses; and to all the coinvestigators and nurses who participated in the study.

APPENDIX

The following investigators participated in the 056 Study: Belgium — P.P. De Deyn, I. Harman, J. Jacquy; Canada — D. King, A.E. Lang, W. Martin; France — A. Destee, F. Durif, O. Rascol; Israel — J. Aharon-Peretz, A. Korczyn, A. Reches; Italy — R. Bergamasco, F. Bracco, L. Fratola, P. Nordera, G. Pezzoli, G. Scarlati, F. Stocchi; the Netherlands — A. Hovestadt; and United Kingdom — R. Abbott, M. Bakheit, G. Roddick, D.I. Brooks, C.E. Clarke, R. Corston, C. Hawkes, C. Kennard, L. Loizou, L. McLellan, D. Park, H. Sagar, E. Spokes, C. Ward, S.V. Wroe.

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REVIEW

The Role of Pulsatile Versus Continuous Dopamine Receptor Stimulation for Functional Recovery in Parkinson's Disease

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¹Present address: Servicio de Neurología, Hospital Gregorio Marañón, Madrid, Spain²Present address: Facultad de Medicina, Universidad de Murcia, Spain³Special Research Projects, Schering AG, Berlin, Germany**Key words:** Parkinson's disease, receptor stimulation, continuous and intermittent dopaminergic stimulation

Abstract

More effective measures to control and replace the dopaminergic deficit of Parkinson's disease are being actively sought. One basic problem is how the striatal dopamine loss should be replaced in order to mimic most accurately the physiological state. Animal electrophysiology indicates that the dopaminergic nigrostriatal pathway has a dual tonic and phasic action. Intermittent dopaminergic stimulation is associated with behavioural hyposensitivity both in animal models and in patients with Parkinson's disease. Continuous dopaminergic stimulation provides a tonic background and improves some clinical problems but is also associated with tolerance. None of the available pharmacological approaches can restore the dopamine deficiency of Parkinson's disease to physiological levels. Continuous dopaminergic stimulation for <24 h, associated with small doses of levodopa or a short-acting dopamine agonist, appears to be the best, albeit imperfect, therapeutic approach until other, more efficacious remedies are developed.

Introduction

Levodopa is still the best and most widely employed drug for the treatment of Parkinson's disease. Treatment of this disease with levodopa has traditionally consisted of three or four doses of 100–250 mg plus a dopa decarboxylase inhibitor. After 7–10 years of levodopa therapy at least 80% of patients with Parkinson's disease have developed some important complications (Marsden and Parkes, 1976). Daily motor fluctuations ('wearing off' and 'on-off' phenomena), dyskinesias and psychiatric symptoms (vivid night dreams, hallucinations, psychosis) are the major problems associated with the chronic use of levodopa (Fahn, 1982; Marsden *et al.*, 1982; Obeso *et al.*, 1989). These complications have been alleviated somewhat by the use of dopamine agonists and other newer therapeutic strategies, but in spite of this a large proportion of patients remain very incapacitated. Past attempts to explain the origin of such complications have emphasized the peripheral pharmacokinetics of levodopa, central dopamine storage capability, the biochemical mechanism of action of dopaminergic drugs (D1 versus D2 receptor stimulation) and the possible role of other neurochemical abnormalities which accompany dopamine deficiency in Parkinson's disease, such as reduced serotonin and noradrenalin levels (Marsden *et al.*, 1982; Obeso *et al.*, 1989). However, we believe that the problem of how the dopamine deficit should be replaced requires greater attention.

The questions that need to be answered are: (i) are the problems of long-term levodopa therapy drug induced? and (ii) what is the role played by the intermittent delivery of levodopa? Motor fluctuations and dyskinesias are not seen in parkinsonian patients or monkeys whose nigrostriatal dopaminergic pathway is intact when they are treated with levodopa or a dopamine agonist (Obeso *et al.*, 1989; Boyce *et al.*, 1990). Even psychiatric complications are very rarely encountered in patients who receive a dopaminergic drug but have normal nigrostriatal function (i.e. patients with prolactinoma). The degree of dopamine denervation seems an essential factor in the origin of the problems associated with chronic levodopa therapy in Parkinson's disease. Indeed, daily motor fluctuations and dyskinesias may occur very soon after initiating levodopa treatment when lesion of the substantia nigra is very severe, as occurs in humans and monkeys intoxicated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Langston and Ballard, 1984; Boyce *et al.*, 1990). Moreover, Papa *et al.* (1993) have shown that the development of a wearing off response in hemiparkinsonian rats depended critically on the extent of the dopaminergic lesion.

The commonest experience is that patients respond perfectly well to levodopa therapy for 3–5 years before problems arise. While disease progression cannot be entirely ruled out, some studies have found a

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Received 29 September 1993, revised 20 December 1993, accepted 21 January 1994

correlation between the duration of treatment and the occurrence of motor complications (Lesser *et al.*, 1979; De Jong *et al.*, 1987). In the model of parkinsonism induced by MPTP in monkeys, where progression of the lesion is certainly not taking place, fluctuations and dyskinesias may only become noticeable after weeks of treatment (Crossman *et al.*, 1987; Luquin *et al.*, 1992a). The available data indicate that both dopaminergic denervation secondary to progressive substantia nigra degeneration and levodopa therapy play a role in the origin of the complications after chronic treatment of Parkinson's disease. Presumably, fluctuations start once the loss of nigrostriatal dopaminergic fibres is such that the swings in levodopa plasma levels cannot be buffered (Fabbrini *et al.*, 1988). This 'storing' hypothesis predicts that the greater the dopaminergic loss the shorter the response (Fabbrini *et al.*, 1988; Mouradian *et al.*, 1988). In this stage of preferential 'presynaptic' involvement, treatment with continuous dopaminergic stimulation should produce the best therapeutic response (Mouradian *et al.* 1987; Chase *et al.* 1989). Additional involvement of striatal mechanisms is supported by several observations. The response duration becomes briefer, but at the same time, and perhaps more importantly, the magnitude of the response ('off-on' difference) increases (Nutt *et al.*, 1993b) and the dyskinesia threshold is reduced (Mouradian *et al.*, 1989). All these changes occur in response not only to acute levodopa administration but also to apomorphine (Rodriguez *et al.*, 1994), which does not depend for its action on any storing mechanism. A substantial participation of pharmacodynamic, 'post-synaptic' striatal mechanisms is therefore, strongly suggested by the available data.

How might levodopa contribute to those problems? The possibility that some levodopa metabolites are neurotoxic has been raised but not yet proved (Arts *et al.*, 1991; Dogani *et al.*, 1991). We propose here that levodopa-mediated side effects may be related to repetitive and pulsatile delivery of the drug.

This review will examine the importance of intermittent versus continuous dopaminergic stimulation in Parkinson's disease and animal models of Parkinson's disease. This outlook is relevant not only for the drug management of Parkinson's disease, but also for the design of newer therapeutic strategies such as the use of subcutaneous polymers (Sabel *et al.*, 1990); the intrastriatal delivery of dopamine (Home *et al.*, 1989) and implants of genetically engineered cells (Horellou *et al.*, 1990).

Neurophysiology of the nigrostriatal dopaminergic pathway

A good understanding of how the dopaminergic nigrostriatal system normally works should guide a physiological therapeutic approach to Parkinson's disease. Unfortunately, electrophysiological recording of substantia nigra pars compacta (SNc) neurons projecting to the striatum has received relatively little attention. In monkeys, DeLong *et al.* (1983) found low (0.5–8 Hz) and relatively constant firing rates of SNc neurons with minimal changes during periods of active movement. Similarly, in awake cats SNc cell activity was not correlated with phasic muscle contraction (Strecker and Jacobs, 1985). These and other, similar findings have been widely used to support the concept that the dopaminergic nigrostriatal pathway exerts a tonic influence upon the striatum (Bunney *et al.*, 1973). However, in cats the firing rate of SNc neurons was significantly increased during active wakefulness compared to a quiet waking state or sleep (Steinfels *et al.*, 1988). Auditory and visual stimulation is also associated with changes of firing rate in SNc neurons in the awake cat (Chiodo *et al.*, 1980). In monkeys, Schultz (1986) and Schultz and Romo (1990) have shown changes in the discharge frequency of SNc cells in relation to movement. This modification mainly consisted in excitation (the firing rate increased by ~30%) some 0–400 ms after

a large arm displacement. Movements of small amplitude were not associated with any modulation of SNc neurons. An important factor influencing whether or not dopaminergic neurons in the SNc respond to sensory stimuli is their behavioural significance (Schultz and Romo, 1990). According to Schultz and Romo (1990) only stimuli which are novel, indicate reward or will trigger a movement are clearly associated with rapid and robust changes in SNc firing. This is also the case, particularly for dopaminergic neurons in area 10, during the learning of complex motor tasks (Schultz *et al.*, 1993). Using *in vitro* slice preparations from rats, Kitai's group has found that subthalamic neurons exert an excitatory action on both SNc and substantia nigra pars reticulata cells which may substantially modify their threshold for spike generation (Nakanishi *et al.*, 1987). Such an observation is particularly interesting in view of the very potent excitatory projections from the motor cortex to the subthalamic nucleus (Kitai and Deniau, 1981) and the good correlation between neuronal firing in the motor cortex and subthalamic nucleus during movement (Georgopoulos *et al.*, 1983). Overall, the present evidence strongly suggests that SNc neurons have movement-related increments in their firing rate, although this is not as overt as in the substantia nigra pars reticulata, subthalamic nucleus and red nucleus.

Relatively minor variations of dopamine release can produce substantial changes in the targeted striatal neurons (Williams and Millar, 1990). It is possible that small modifications in SNc activity and the accompanying release of dopamine may induce phasic changes in the striatum. For instance, by combining microelectrode recording with voltammetry it was recently shown that the same striatal neuron increased its firing rate in response to low dopamine levels, but was inhibited by higher levels of released dopamine (Williams and Millar, 1990). Transient modification of SNc neuronal firing is now known to exert mainly phasic changes in dopamine release (Pani *et al.*, 1990). This phasic effect may be highly circumscribed to a given striatal region (Grace and Bunney, 1983; Kawagoe *et al.*, 1992), is short-lasting (~30 ms) (Nicolayson *et al.*, 1988) and can be quantitatively modulated by changing the mode and firing frequency of dopaminergic cells (Gonon and Buda, 1985). Manley *et al.* (1992) recently showed by microdialysis that stimulus-induced increase in dopamine was augmented by bursting stimulation compared with an evenly spaced stimulation pattern. Such an increase in dialysate dopamine was augmented by higher stimulus frequencies.

Recordings of striatonigral dopaminergic neurons in freely moving rats have shown a switch from slow, tonic firing to highly synchronized bursting activity during certain movements (Freeman *et al.*, 1985).

Dopamine release is governed by another mechanism independent of SNc neuronal firing but mediated by the presynaptic activity of glutamatergic corticostriatal afferents (Cheramy *et al.*, 1986; Calabresi *et al.* 1993). The time course of this release is slow, and takes place over a period of from several minutes to a few hours, producing a tonic effect (Nieoullon *et al.*, 1978; Abercrombie *et al.*, 1989), which may stimulate wider striatal regions than phasic dopamine release (Grace, 1991). Dopaminergic D2 receptors located on corticostriatal terminals control glutamate release under normal conditions (Calabresi *et al.*, 1993).

It has been proposed that this dual organization of dopamine release ultimately serves a unitary function. Thus, tonic dopamine release would modulate the background level of responsiveness, on top of which phasic changes could exert a more localized and time-limited effect (Grace, 1991).

In addition, it has been widely demonstrated that the SNc is not a homogeneous structure. Neuroanatomical studies have shown that nigrostriatal projections to the caudate nucleus and putamen arise from separate clusters of cells distributed throughout the entire SNc. Only

a few nigral neurons send afferents to both structures. Jimenez-Castellanos and Graybiel (1987) have established the existence of separate cell groups within the SNc based on differences in tyrosine hydroxylase activity. Neurons of the SNc with low tyrosine hydroxylase activity project mainly to the striosomes while nigral cells projecting to the matrix show high tyrosine hydroxylase activity. This compartmental organization of the SNc reflects the mosaic-like arrangement of the striatum. The striosomes are rich in D1 receptor binding sites, while D2 receptors are abundant in the matrix. Electrophysiological data suggest that D1 receptors are inhibitory and D2 receptors are excitatory (Ohno *et al.*, 1987). Recent findings *in vitro* indicate that the high-affinity constant (K_h) for dopamine receptor binding is ~ 50 nM while the low-affinity state (K_l) has a value > 2 μ M (Ross, 1991). The extrasynaptic concentration of dopamine following neuronal firing may transiently approach K_h values (Kawagoe *et al.*, 1992) but tonically released dopamine is very unlikely to reach such levels due to the uptake mechanisms. Normally, non-synaptic chemical communication within the striatum may be possible by the high affinity of D2 receptors.

The overall conclusion is that the nigrostriatal pathway is finely organized to tune dopamine release and activity according to the subject's state and requirements. With this in mind, we shall now examine the pharmacological effect of dopaminergic stimulation and replacement therapy for Parkinson's disease.

Pharmacology

There is ample experimental evidence indicating that the behavioural effect of a given drug may change depending upon its temporal pattern of administration (Post, 1980). This applies both to endogenous as well as to exogenously administered substances.

One of the best biological examples (indicated to us by Dr S. Stahl, Stanford University, California) is the regulatory control by growth hormone of synthesis of the liver protein prolactin—growth hormone receptors and major urinary protein in mice. Growth hormone is continuously secreted in females, in which it mainly produces prolactin—growth hormone receptor protein, but only intermittently in males, which synthesize major urinary protein. Mice genetically deficient in growth hormone do not produce either protein. In such animals, continuous growth hormone delivery by means of a miniosmotic pump induces a female secretion pattern (prolactin—growth hormone protein), while repeated injections, which imitate pulsatile stimulation, produce a male response (secretion of major urinary protein). Another endocrinological example is the case of luteinizing hormone releasing hormone; the same amount of this molecule will induce pituitary luteinizing hormone release when given in a pulsatile way but will produce inhibition when administered as an infusion (Wildt *et al.*, 1981). Thus, in both cases the same endogenous substance evoked an entirely different response depending upon its delivery pattern. A situation more closely related to the motor system can be found in the modification by amphetamine of the acoustic startle-response in mice. Amphetamine potentiates the startle response when given intermittently but not when administered continuously (Kokkimidis, 1984). The potential consequences of these examples for levodopa therapy in Parkinson's disease are readily appreciated, but very little experimental data exists regarding dopamine-mediated motor behaviour and drug delivery pattern.

Intermittent dopaminergic stimulation

Experimental data

In rats with unilateral 6-hydroxydopamine (6-OHDA) lesion, dopamine striatal levels after levodopa are much lower and decline more quickly

on the denervated side (Spencer and Wooten, 1984; Brannan *et al.*, 1990). However, administration of a very large dose of levodopa is accompanied by very high extracellular levels of dopamine in the lesioned striatum (Abercrombie *et al.*, 1990). This contrasts with the effect of a much lower dose, which provokes a very brief increase in extracellular dopamine followed by reduced dopamine concentration. These findings indicate that dopamine synthesized from exogenous levodopa can be stored in the denervated striatum in small quantities, but large doses lead to uncontrolled release of dopamine (Abercrombie *et al.*, 1990).

Using the rotatory model in the rat, Castro *et al.* (1986) showed that repeated apomorphine injections (2 h intervals) were accompanied by a significant and progressive reduction in turning behaviour, while one daily dose resulted in increased rotational response. In another study, the potency of apomorphine to induce yawning in rats was decreased by a prior dose 30 or 60 min before the test, but there was no modification when the drug was given with an interval of 3 h between injections (Ljunberg *et al.*, 1989). In the cat, apomorphine-induced limb flicking, abortive grooming and hallucinatory-like behaviour was significantly reduced in response to a second injection given with a 2 or 6 h interval (Trulsson and Criepe, 1982). Such behavioural tolerance to apomorphine disappeared when the interval between injections was 24 h.

In monkeys in which parkinsonism was induced by intravenous administration of MPTP we found behavioural hyposensitivity to repeated apomorphine administration (Luquin *et al.*, 1993). This was very significant when low doses (minimal effective dose, MED) were administered at a short interval (30 min) (Fig. 1A) compared with a longer interval (3 h), but less pronounced when higher doses ($4 \times$ MED, $8 \times$ MED) were given (Fig. 1B and C). In the same animals, repeated intermittent administration of (+)-4-propyl-9-hydroxynaphthoxazine (+PHNO, a D2 agonist) or CY 208243 (a D1 partial agonist) was also accompanied by tolerance (Obeso *et al.*, 1992).

Clinical data

In parkinsonian patients with daily motor fluctuations we found that repeated administration of apomorphine (average dose 2.5 mg) was associated with a progressive reduction in the duration of motor improvement (Grandas and Obeso, 1989), reproducing the findings in rats and monkeys (Castro *et al.*, 1986; Luquin *et al.*, 1993). In this study each injection was given 15 min after the beginning of an 'off' period, and the dose was just above the motor threshold. In another study apomorphine injections were given at 2 and 4 h intervals (Grandas *et al.*, 1992). A significant reduction in the duration of the 'on' period induced by the second injection was observed with the 2 h but not with the 4 h interval (Fig. 2). Gancher *et al.* (1989, 1992) also observed a reduction in the motor response induced by paired apomorphine injections, the second one given 5 min after the effect of the previous injection had disappeared. In contrast, two other recent studies (Hughes *et al.*, 1991a, b; Gervason *et al.*, 1993) did not find tolerance to repeated apomorphine administration in parkinsonian patients given consecutive apomorphine injections with different intervals ranging from 5–10 to 80–120 min after the effect of the preceding dose had vanished. In these two studies the apomorphine dose was well above threshold, which may explain by itself (Fig. 1) the lack of tolerance (Obeso *et al.*, 1992). In addition, variation in the individual response to apomorphine tends to reduce the likelihood of statistical significance for the overall observation (Obeso *et al.*, 1992).

A recent study showed that repeated administration of levodopa (four boluses of 50–100 mg) was not accompanied by tolerance (Davis *et al.*, 1991). This observation may be related to differences in the central kinetics and mechanism of action of levodopa compared to dopamine agonists. On the other hand, it has been known for many years that

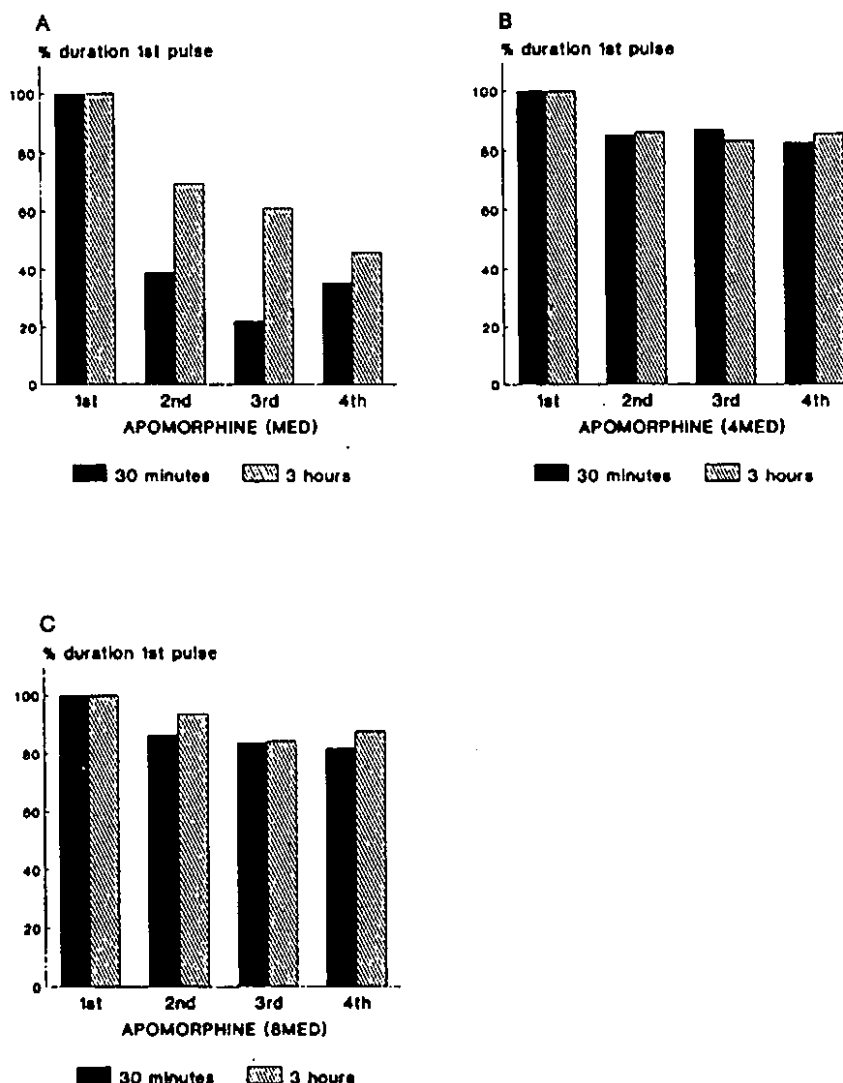


FIG. 1. Duration of the motor response (given as percentage of the first response) elicited in five parkinsonian monkeys by repeated administration of apomorphine given 30 min after the end of the previous response (darker rectangles) or with an interval of 3 h (lighter rectangles). Three doses were used in different experiments: (A) the minimal effective dose (MED) (2.4 µg/kg), (B) four times the MED and (C) eight times the MED. Behavioural tolerance was particularly striking and significant with the MED for injections given with a short interval (30 min). Reproduced from Luquin *et al.* (1993).

substantial increments (100% or more) in the daily levodopa dose can lead to worsening of parkinsonism (Yahr *et al.*, 1970), and we observed reduced sensitivity to apomorphine after doubling levodopa consumption for 1 day (Vaamonde *et al.*, 1989). Furthermore, in the study of Davis *et al.* (1991) peak levodopa plasma levels rose by 50% from the first to the fourth boluses, yet the response duration and magnitude were not augmented, indicating some sort of hyposensitivity.

In summary, the findings both in animal models and in Parkinson's disease are in keeping with the existence of a time-dependent period of reduced striatal dopamine responsiveness following acute and intermittent delivery of dopaminergic drugs. This phenomenon of tolerance probably has no practical implication for the use of dopamine agonists (i.e. apomorphine) as 'rescue' drugs to overcome 'off' periods in Parkinson's disease (Frankel *et al.*, 1990), but may be relevant to the origin of motor fluctuations. Thus, a common clinical approach to the treatment of the wearing off effect is to reduce the interval between levodopa doses. This strategy may not allow the striatum to recover its

normal responsiveness by the time the next dose is given. The increased dopaminergic threshold may be overcome by providing a higher dose, but in practice pharmacokinetic factors interact to actually reduce central dopamine availability. Both problems together reduce the probability of achieving an adequate response. This is in fact what happens—for the majority of patients, the first morning dose is the most effective, and afternoon and evening dose are far less effective (Marsden *et al.*, 1982).

Continuous dopamine stimulation

Continuous delivery of an antiparkinsonian drug poses two immediate questions: (i) will tolerance develop as predicted from classical pharmacology? and (ii) is the 24 h delivery regime the best approach?

Experimental data

Intraventricular infusion of dopamine, lisuride and pergolide to three groups of rats with unilateral 6-OHDA lesion was accompanied by a

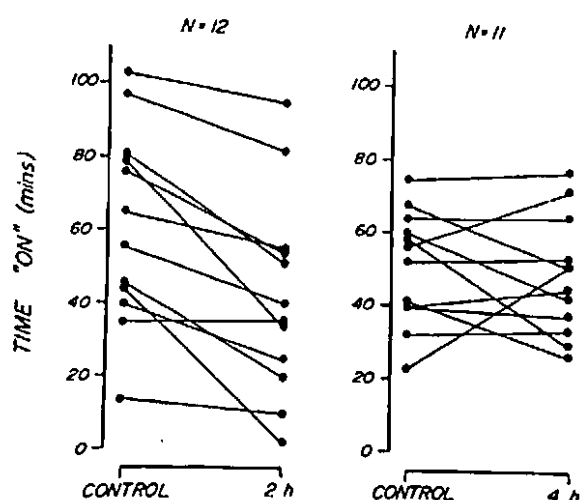


Fig. 2. Duration of 'on' time elicited by paired apomorphine injections separated by intervals of 2 h (left) and 4 h (right) in 12 patients with Parkinson's disease. A 40% reduction in the duration of the response produced by the second injection given at 2 h intervals is shown. Reproduced from Grandas *et al.* (1992).

reduction in the rotatory response after 5 days of treatment (De Yebenes *et al.*, 1987). Similarly, continuous infusion of apomorphine produced tolerance to apomorphine-induced rotation in mice with a 6-OHDA lesion (Winkler and Weiss, 1986). Infusion of the D2 agonist quinpirole for 6 days in the intact mice provoked down-regulation of striatal D2 receptors and a significant reduction in proenkephalin messenger RNA, but no change in D1 receptors (Chen *et al.*, 1993). In parkinsonian monkeys De Yebenes *et al.* (1990) reported that the motor response was maintained during continuous intraventricular infusion of +PHNO (up to 5 consecutive days). In another study (Alexander *et al.*, 1991) +PHNO was continuously given to three parkinsonian monkeys for up to 40 days, and after an initial brief period of hyperactivity the movement scores returned to the untreated level. Postmortem studies revealed a significant (40–70%) decrease in D2 sites in the caudate and putamen compared to untreated parkinsonian monkeys.

Clinical data

In patients with Parkinson's disease, Mouradian *et al.* (1987) showed that continuous (24 h) intravenous levodopa administration for up to 11 days practically eliminated 'off' periods in mildly to moderately affected patients with the wearing off phenomenon, although it had a less dramatic impact on the motor stability of severe patients with on–off fluctuations. Sage *et al.* (1989) used continuous enteral levodopa infusions in nine patients for over 2 years with excellent results. In this study the infusion was stopped during the night and an acute levodopa dose ('pulse') was given in the morning. No evidence of tolerance was observed in these patients, and the daily levodopa infusion rate was actually reduced over the months of treatment. Kurth *et al.* (1993) have given duodenal levodopa infusion to ten parkinsonian patients under double-blind conditions. In seven patients the number of 'on' hours was mildly increased, two showed no improvement and one showed slight deterioration. In all cases the infusion was given over 8 h per day and was complemented with oral levodopa–carbidopa for the rest of the day. Cedarbaum *et al.* (1990) reported in detail a well-studied patient who received levodopa via a nasoduodenal catheter to treat severe on–off fluctuations. The infusion was maintained for 24 h daily but after initial improvement the infusion rate (daily levodopa dose) had to be increased several times, despite which the motor status continued to deteriorate.

Subsequently, the infusion was shortened to 6 h daily, resulting in marked clinical improvement. Recently, a patient treated with continuous levodopa infusion during the night has been described (Sage and Mark, 1991). In this case the interest lies in that, despite remaining on conventional levodopa–carbidopa therapy during the waking day, the 'off' time and severity of dyskinesias improved both at night and during the waking hours. Nutt *et al.* (1993a) found that the 'on' duration was shorter after discontinuing a long (21 h) intravenous levodopa infusion than after a short (2 h) levodopa infusion. This observation is in keeping with the development of tolerance during continuous levodopa infusion.

A difficulty in keeping severe Parkinson's disease patients constantly 'on' has also been observed with dopamine agonists (Obeso *et al.*, 1986, 1987a). Thus, intravenous or subcutaneous infusion of apomorphine or lisuride infusions have also been associated with some 'off' episodes, despite using very high infusion rates (Obeso *et al.*, 1987b), unless supplemented with intermittent oral levodopa (Fig. 3). In fact, increasing the dose of the agonist could even produce a worsening of the response in some patients (Obeso *et al.*, 1988; Vaamonde *et al.*, 1989).

The duration of improvement following discontinuation of a long (22–31 h) apomorphine infusion was shorter than when a briefer (6 h) infusion was given (Gancher *et al.*, 1992). We also found that continuous enteral administration of +PHNO for 3–5 days in five parkinsonian patients never achieved adequate control of mobility unless combined with oral administration of levodopa–carbidopa (Grandas *et al.*, 1990). Chronic treatment (> 1 year) by subcutaneous infusion of either lisuride or apomorphine provided a significant increase in daily 'on' hours (Frankel *et al.*, 1990; Vaamonde *et al.*, 1991). Lisuride has usually been given for 24 h daily, while most patients treated with apomorphine stopped the infusion pump for a few hours overnight. No clear indication of tolerance has emerged from patients treated chronically with either drug (Vaamonde *et al.*, 1990, 1991; Frankel *et al.*, 1990). On the contrary, Baronti *et al.* (1992) have recently reported in seven parkinsonian patients a substantial increment in the duration of action of levodopa and in the therapeutic window following 3 months of treatment with continuous lisuride subcutaneous infusion (plus a small levodopa dose of ~300 mg/day). Such effects were three times greater than those induced by 9 days of levodopa infusion (Baronti *et al.*, 1992).

The present experience suggests that the best and most stable motor response is obtained with a constant infusion, but given for <24 h, or with the combination of continuous delivery and small pulsatile stimulation (Fig. 3).

Side-effects are an important problem for the application of continuous dopaminergic stimulation. The most important of these is psychiatric disturbance. Thus, continuous (24 h) lisuride infusion has been associated with a high incidence of psychiatric manifestations (Vaamonde *et al.*, 1991). Psychiatric complications have been much less frequent in patients treated with lisuride infusion for 12–14 h/daily (Stocchi *et al.*, 1988) and in patients treated with apomorphine infusion (14–16 h daily) (Frankel *et al.*, 1990). Similarly, patients receiving levodopa infusions (<24 h) have not been besieged by psychiatric side-effects. It seems necessary, therefore, to obtain a compromise between the motor benefit and the duration of infusion in order to minimize this risk. Other practical difficulties with the present pumping systems are the development of nodules caused by subcutaneous infusion (Frankel *et al.*, 1990; Vaamonde *et al.*, 1991) and the cumbersome paraphernalia associated with enteral levodopa delivery (Sage *et al.*, 1989; Cedarbaum *et al.*, 1990; Sage and Mark, 1991).

Pulsatile versus continuous dopamine stimulation

Biochemical data from animal work have not provided clear evidence of the changes induced by chronic dopaminergic stimulation (Jenner

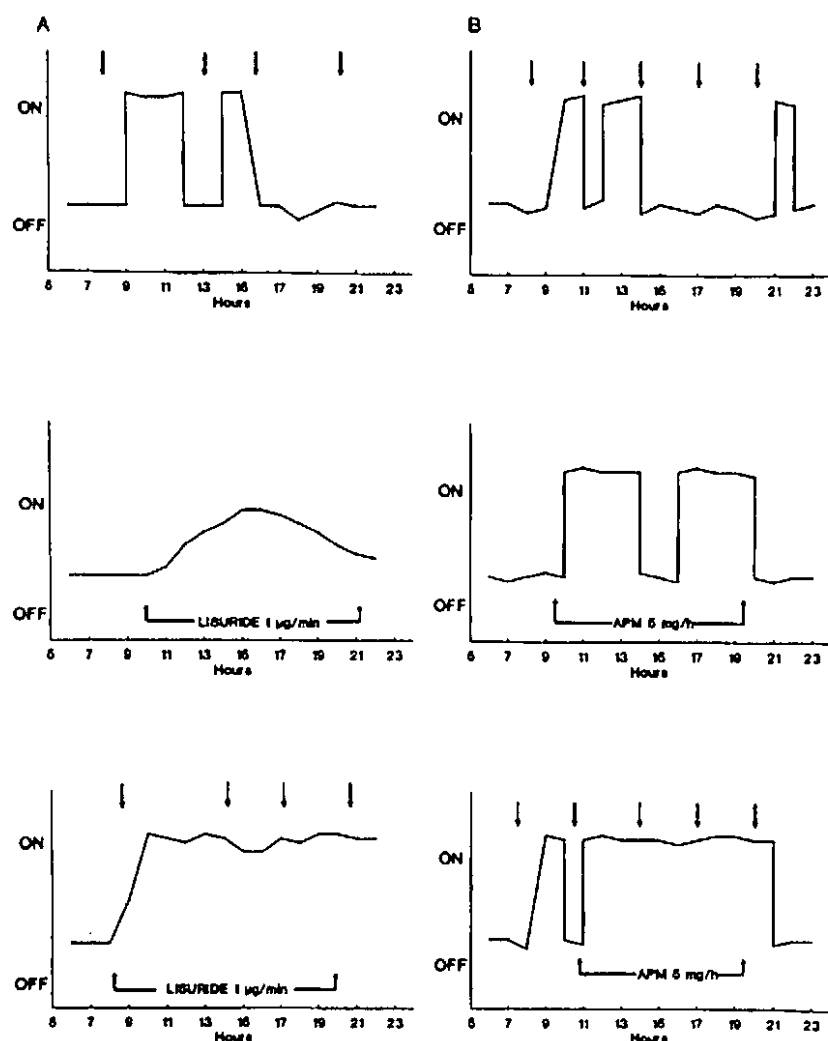


FIG. 3. Motor response to continuous infusion of lisuride (left panels) and apomorphine (right panels) in a patient with Parkinson's disease. Top: on-off oscillations on a normal day in response to several oral doses (arrows) of levodopa + carbidopa (250 and 25 mg respectively). Centre: response to lisuride and apomorphine infusions given intravenously for several hours. Bottom: response to a combination of intravenous lisuride or apomorphine with oral levodopa. The best control was achieved with the combination of continuous and intermittent dopaminergic stimulation.

et al., 1988). Recently, Engber *et al.* (1989) described a differential effect of D1 versus D2 receptor stimulation in rats with 6-OHDA lesion depending upon the levodopa administration regime. Levodopa infusions (90–100 mg/kg i.p., 90 days) increased the rotational response to quinpirole (D2 agonist) but had no effect on the response elicited by SKF 38393 (D1 agonist) or apomorphine (D1 and D2 agonist). On the other hand, treatment with discontinuous levodopa (50 mg i.p., twice daily for 19 days) markedly enhanced the effect of quinpirole, reduced the response to SKF 38393 and mildly increased the number of rotations induced by apomorphine. Using a similar experimental protocol, the same group (Engber *et al.*, 1991) showed that intermittent levodopa administration provoked a dramatic increase in dynorphin striatal level, a moderate increase in Substance P (SP) and no change in enkephalin. Continuous infusion of levodopa did not modify dynorphins and SP with respect to control rats, but increased enkephalin concentration. The significance of these changes in relation to the therapeutic problems of Parkinson's disease (Marsden *et al.*, 1982; Obeso *et al.*, 1989) is not entirely clear, but deserves some attention in view of the present

understanding of striatopallidal connections (Gerfen *et al.*, 1990). Thus, there is a direct putameno-medial pallidal (GPM) GABA projection, colocalized with SP and dynorphin, the net effect of which is to facilitate movement via the GPM–thalamus–precentral motor cortex (DeLong, 1990). A second, indirect pathway, involves the putamen–lateral pallidum (GPI), subthalamic nucleus, subthalamo-GPM–thalamic circuit. The net effect of corticostriatal stimulation via this circuit is movement inhibition (Albin *et al.*, 1989). The putamen–GPI projection is GABAergic and colocalized with enkephalin. A reduction in the inhibitory activity of this relay is experimentally associated with hemichorea–hemiballism (Crossman *et al.*, 1984) and could be the basis of levodopa-induced dyskinesias in Parkinson's disease (Crossman, 1990; Luquin *et al.*, 1992b). The dopaminergic nigrostriatal pathway is thought to inhibit GABA–enkephalin neurons through activation of D2 receptors and to excite the direct GABA–SP–dynorphin circuit by D1 receptor activation (Gerfen *et al.*, 1990). According to this simplified view of basal ganglion functional organization (Marsden and Obeso, 1994), the increase in dynorphin and SP levels, obtained without reducing

enkephalin by intermittent administration of a D2 agonist (quinpirole) (Engber *et al.*, 1989, 1991), could come close to the functional restoration of the striatal mechanism. Of course, much more detailed behavioural analysis in a suitable model of Parkinson's disease, like the parkinsonian monkey, is needed before reaching any definitive conclusion.

Pulsatile levodopa administration induces widespread metabolic changes in many brain regions which are not seen, at least with similar intensity, after continuous infusion (Engber *et al.*, 1990). Thus, levodopa administration (100 mg i.p., 19 days) in rats with a 6-OHDA lesion reduced glucose utilization (measured by 2-deoxyglucose autoradiography) in various basal ganglia nuclei (accumbens, subthalamic nucleus) and related projection targets. The same levodopa doses given for an equal period by continuous intraperitoneal infusion only increased 2-deoxyglucose consumption in the nucleus accumbens (Engber *et al.*, 1990).

Behavioural studies have also shown some differences in the motor response depending upon the delivery pattern. Thus, the pergolide dose required to restore normal motor behaviour in reserpinized rats was lower when given by continuous intraperitoneal infusion than in a single daily injection (Costall *et al.*, 1983). Juncos *et al.* (1989) found increased rotational behaviour in response to apomorphine after intermittent (twice daily), but not continuous, levodopa administration over a 30 day period in rats with a unilateral 6-OHDA nigrostriatal lesion. In these animals turning behaviour was markedly increased in response to the selective D2 agonist quinpirole after intermittent levodopa, but this effect was much weaker in rats treated with a levodopa infusion. Lastly, it should also be taken into account that the kinetics of the effect of dopaminergic drugs at the receptor level may influence the dopaminergic effect on the motor system. In intact rats, subcutaneous lisuride administration over 30 days as a single daily bolus caused strong behavioural sensitization, including motor hyperactivity, whilst continuous subcutaneous infusion was associated with motor tolerance (Horowski and Wachtel, 1979). In the case of β receptors, and probably also of other G protein-coupled receptors, it was proposed recently that long-duration receptor exposure produces receptor down-regulation and desensitization, whereas short-duration exposure results in sensitization (Collins *et al.*, 1989).

The results summarized above indicate substantial differences in the biochemical changes induced by pulsatile versus continuous levodopa administration, and suggest that neither pulsatile nor continuous dopaminergic stimulation returns striatal chemistry to normal levels. The behavioural data also indicate a difference in responsiveness to continuous and intermittent dopaminergic stimulation.

Conclusions

Under normal conditions the dopaminergic nigrostriatal pathway exerts both tonic and phasic activation. The latter depends upon the physiological integrity of dopaminergic mechanisms, lasts milliseconds and is somatotopically organized. This contrasts with the generalized, unregulated and long-lasting (minutes or hours) effect produced by dopaminergic drugs. Thus, the physiological mechanisms of phasic dopaminergic stimulation cannot be mimicked pharmacologically in Parkinson's disease. Only anatomical reconstruction of the nigrostriatal pathway, as intended with neuronal grafting techniques (Björklund *et al.*, 1980; Dunnett and Annett, 1991), seems capable of restoring the phasic, presynaptic mediated dopamine release in the striatum.

It appears fairly clear from the available data that the administration of dopaminergic drugs, either by pulsatile or constant delivery, is far from being a perfect approach to the restoration of dopamine deficiency in Parkinson's disease, but the response to continuous dopaminergic

stimulation seems more adequate. Chronic therapy with intermittent levodopa almost certainly leads to severe complications (Marsden and Parkes, 1976; Fahn, 1982; Obeso *et al.*, 1989; Cedarbaum *et al.*, 1991; Grandas *et al.*, 1992b). It is expected that treating Parkinson's disease in a more physiological way could avoid or minimize such complications. In the near future it should be possible to provide relatively constant but low-tone dopamine stimulation by giving small doses of a long-acting dopamine agonist (pergolide, cabergoline) combined with small doses of levodopa (100–200 mg twice a day) or another short-acting dopamine agonist (apomorphine, lisuride). By so doing, one can hope to mimic more closely the tonic discharge rate of nigrostriatal dopaminergic projections and at the same time provide a pharmacological stimulus that will produce minor phasic changes. This combination will not really mimic the physiological characteristics of the nigrostriatal pathway as stated above, but might reduce the incidence of complications without losing therapeutic efficacy due to the development of tolerance.

For the future, the data reviewed here suggest that, among the possible technological advances (dopamine-secreting cells, microcapsules, polymers, etc.) for local dopaminergic reposition, those capable of storing and secreting dopamine tonically, but coupled with neuronal firing from afferent connections to modulate phasic dopamine release, will provide the best and most durable results.

Acknowledgements

Supported by a research grant from Schering Spain and the Spanish Government (grant 90/0550 CICYT). Ms M. Mar López, Isabel Sanchez and C. Elsdon prepared the article for publication.

Abbreviations

GPI	lateral pallidum
GPM	medial pallidum
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
6-OHDA	6-hydroxydopamine
+PHNO	(+)-4-propyl-9-hydroxynaphthoxazine
SNC	substantia nigra pars compacta
SP	Substance P

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An Overview of Controlled Release Systems

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I. INTRODUCTION

The term *drug delivery* covers a very broad range of techniques used to get therapeutic agents into the human body. The limitations of the most obvious and trusted drug delivery techniques, those of the ingested tablet and of the intravenous (IV)/subcutaneous/intramuscular (IM) injections, have been recognized for some time now. The former delivers drug into the blood only through the hepatic system, and hence the amount in the bloodstream may be much lower than the amount formulated into the tablet (i.e., it has low bioavailability); furthermore, liver damage is an unfortunate side effect of many soluble tableted drugs. The injection mode of delivery can be used to deliver any size of drug molecule and is versatile in this regard, but it suffers from the obvious disadvantage of being invasive and painful, and the less obvious disadvantage of shortness of duration (for drugs with short half-lives). To overcome some of these limitations, other modes of delivery of drugs into the body were investigated, beginning in the early 1970s. Transdermal (through the intact skin), transmucosal (through the intact mucosa of the mouth, intestine, rectum, vagina, or nose), transocular (through the eye), transalveolar (inhalation, through lung tissue), implantable (subcutaneous and deeper implants, delivery into surrounding tissue), and injectable (IM or subcutaneous) modes of delivery have all been explored extensively over the last 25 years, with varying degrees of commercial and therapeutic success. Of the above modes, the transdermal, transmucosal (specifically intestinal), transocular, injectables and the subcutaneous implant have found varying degrees of commercial acceptance. Of the rest, the inhalation route appears promising for a limited class of agents and at least three companies have products in advanced clinical trials. In the next 5 years, this route of administration is very likely to become acceptable to patients and hence commercially successful.

Currently, two other modes of injectable drug delivery are receiving increased attention. One focuses on the use of nanoparticles for delivering DNA or genes to cells for transfection. These particles have the unique ability to be taken up by targeted cells via various transcellular entry mechanisms. Another mode is needleless (and hence painless) injectables, which are being investigated by at least two companies. These approaches are in feasibility or early clinical trials.

The common theme underlying these delivery modes is increased therapeutic efficiency as well as increased patient compliance. The common key ingredient of all these technologies is polymeric material. In this chapter we focus on the demands made on the polymer material, which is often the component that controls drug delivery.

A. Drug Delivery Technologies

The main focus of this chapter will be four delivery modes: oral controlled release, transdermal, implantable, and particulate drug delivery. As mentioned above, all four modes have found commercial acceptance to varying degrees. The thrust of this chapter will be on the polymeric component and the requirements that each mode of delivery places on the polymer component. As can be imagined, the polymeric component must not only satisfy the design criteria for each mode of delivery, but also its toxicological and manufacturing requirements. Innovations in polymers drive improvements in these delivery technologies; therefore, each section will highlight the need for polymer improvements.

Regardless of the delivery mode, the polymer in each instance is required to perform a set of functions. To understand these functions, it is instructive to review the features and some of the shortcomings of the most popular forms of drug delivery, i.e., oral tablets and intravenous injections. In broad terms, these are summarized below as follows:

1. Tablets

1. All drugs enter the main circulation via the liver; a portion of the delivered drug is metabolized. In addition, for certain drugs, liver toxicity is an issue.
2. Drugs are typically absorbed in the stomach and in the small intestine (SI), where pH effects can influence extent of delivery.
3. For drugs with short half-lives, duration of action is limited to the maximum transit time through the stomach and SI, approximately 6 h.
4. The delivery profile typically has "peaks" and "valleys," i.e., fast onset followed by rapid decay. Constancy of drug levels in blood is rarely achieved.
5. There is a low level of patient compliance, i.e., patients forget to take the required dose at the correct time.

2. Intravenous Delivery

1. There is no metabolism by the liver.
2. Duration of action of a drug is determined solely by clearance rates for the drug; no control is possible (except for infusion control).
3. Macromolecules can be delivered.
4. The method is invasive and often painful, and therefore is not suitable for chronic indications.

Thus, alternative drug delivery modalities are needed to address the above shortcomings. The most important shortcomings are the duration of action and its control, by which is meant not only extended release of drug into the bloodstream, but also controlled release, i.e., achieving the desired plasma profile for the drug. In addition, the alternative modality must be acceptable to the patient (noninvasive) and must increase the level of patient compliance. There are also pharmacoeconomics and quality-of-life issues to be addressed.

Therefore, what the polymer is required to do, in these alternative drug delivery approaches, is to extend and control the release of the drug into the bloodstream via the various portals of entry (skin, oral mucosa, etc.). This is true of all modalities, except those where external fields are used to modulate drug delivery, such as iontophoresis (covered elsewhere in this book) and sonophoresis. The primary role of the polymer is diffusional control of active agents, and the secondary role is disintegration or dissolution control of the dosage form employed.

For reasons of editorial space, we will not be able to cover extensively the fields of buccal, rectal, or vaginal drug delivery, each of which is an active area of research. References to some of these concepts will be made in Section V.

B. Commercialized Technologies

As mentioned above, the transdermal delivery mode (commonly referred to as "patches") and controlled release orals are perhaps the most successful alternative delivery modes. Because of their similarity to bandages, transdermals found easy acceptance with patients. The duration of action of the first patch introduced (Transderm-Scop[®] developed by ALZA Corporation for Novartis Co. in 1981) was 72 h, easily surpassing the capability of existing tablets (Dramamine[®]) to provide continuous relief from sea or air sickness. The next type of transdermal introduced was for nitroglycerin delivery, and it also found immediate acceptance. Several companies introduced nitroglycerin transdermals, examples being Transderm-Nitro[®], Nitro-Dur[®]. The duration of action was 24 h. With the introduction of Estraderm[®] by the then Ciba-Geigy Corporation, 3.5 days of delivery was achieved. Since then, we have seen the introduction of 7-day systems (Catapres TTS[®] for clonidine delivery, Climara[®] and FemPatch[®] for estradiol delivery). The transdermal market witnessed a surge in the early 1990s when the first nicotine patches were introduced for smoking cessation. Since then, the overall market has climbed to over \$1 billion per annum for this mode of delivery.

Controlled release orals enjoy a large share of the drug delivery marketplace as well. Extended release dosage forms were introduced fairly early, but since these dosage forms do not strictly control drug delivery, they will not be discussed here (with the exception of dissolution-controlled delivery, Section II.A). The earliest form of controlled release oral dosage form was the osmotic tablet, developed by ALZA Corporation, for controlled delivery of phenylpropanolamine. This early product has been succeeded by several ethical pharmaceutical products, the most successful introduction being that of Procardia XL[®] by Pfizer: this product delivers a calcium channel blocker (CCB), nifedipine, in a controlled manner for 24 h using ALZA's proprietary osmotic tablet technology. To date, this technology is the most successful oral controlled release technology with about \$2 billion of the total \$6.2 billion in annual revenues for oral controlled release (CR) products. Other commercialized oral delivery technologies include R.P. Scherer's Zydis[®] (rapid-dissolve) and Elan Corporation's SODAS[®], PRODAS[®], and IPDAS[®] technologies. Of these, Zydis is not, strictly speaking, a controlled release technology, and it should be treated in the same manner as extended release branches of non-CR drug delivery technology. By our estimate, the CR share of the oral drug delivery market is about \$3.5 billion—still much larger than the closest competing technology, transdermal delivery.

The other commercialized technology is implants. This delivery mode had about \$1 billion in sales in 1996, largely from Norplant[®] (contraception), Atrisorb[®] and Atridox[®] from Aatrix (dental implants for caries). Polymers play a large role in this technology as well, and we will explore this in detail in Section IV.

C. Technologies in Development

There are some CR technologies in various stages of development that have yet to see the marketplace. Noteworthy among these are controlled release via the alveoli (inhalation CR), controlled release via buccal tissue (buccal CR), and controlled release using microparticles or nanoparticles (particulate CR). The last named could have any of several modes of entry into the body. The most common mode of delivery for microparticles is as injectables (where the

product Lupron Depot[®] is a commercial success), the nasal mucosa and the gastrointestinal (GI) tract being the other two routes. While discounting extended duration nasal sprays for congestion as being an extended rather than a controlled release system, it must be said that truly controlled release products in this category are still in the research or early clinical phase. Inhalation CR is now being pursued by three or four major companies, with Inhale Therapeutic Systems and Aradigm Corporation in the lead with products in phase II or phase III clinicals, and the Dura Corporation concentrating on delivery to the upper lung (local delivery). Whether the inhalation products being developed are strictly controlled release products is debatable; however, their potential for displacing injections as a route for administering important new therapeutic entities (proteins and peptides) is beyond any debate. In any event, the role of polymers in the delivery of inhalation products is clearly peripheral rather than central, and therefore these products will not be discussed. While polymers do play a central role in buccal controlled release products, products are still in pre-clinical or phase I, with the 3M Company finding it relatively difficult to market its proprietary buccal platforms (as of 1998, no partner deals have been announced for its CyDot[®] transmucosal delivery (TMD) technology). Theratech (now part of Watson Pharmaceuticals) is the other major player in this arena, and has announced a *peptide* development agreement with Eli Lilly for an undisclosed peptide. Therefore, in Section V, we will concentrate on particulate drug delivery, since polymers do play a central role in this technology, and products have either been commercialized or are likely to be commercialized soon.

D. Synthetic vs. Natural Polymers

Natural polymers can be defined for our purposes as polymers derived from natural sources, such as cellulose. In the broadest sense, sources of such polymers may include animals (bovine collagen, chitosan) and plants (cellulose); recently, polymers that are identical to or similar to those occurring in the human body have also received closer attention. Examples are poly(lactic acid), poly(glycolic acid), and hyaluronic acid. The naturally occurring type of polymer continues to be expensive and therefore is indicated for use only when stringent biocompatibility is required, such as in long-term implants. Animal-derived polymers have found limited use in drug delivery systems, although they have been used extensively in applications such as wound healing. Plant-derived polymers have been used extensively in drug delivery systems; hydroxy derivatives have in particular, being found to be benign for oral delivery. In general, synthetic polymers have found far wider application in drug delivery systems, for reasons that will be made clearer in the following sections.

E. Some General Toxicological Considerations

The potential adverse effects of polymers must be evaluated prior to testing a drug delivery system in humans. Potential adverse effects may result from contact with the polymer or from leachables such as residual monomers, reactive agents, or processing additives. The effects of polymers or extracts will be dependent on unique chemical characteristics and the amount (or dose) of polymer/extract administered. There should be an evaluation of whether the polymer is in direct or indirect contact with the drug-containing component of the system or with tissues of the patient. These evaluations will assist in the determination of the types of safety assessments that may be required during the various stages of the development process. To assist in the selection of materials, a review of the manufacturer's and published scientific literature should be conducted to gather clinical and nonclinical safety information. If necessary, in vivo and in vitro tests are used to evaluate the biocompatibility of the polymer and/or extract and of

the drug delivery system, ensuring the safety of the system. In vitro studies should be conducted prior to initiating in vivo studies. Cytotoxicity tests are simple, rapid in vitro procedures that can provide predictive information on in vivo biocompatibility of polymeric materials (1). In vivo tests can then be conducted on the polymer and the drug delivery system.

II. ORAL DRUG DELIVERY SYSTEMS

Among all routes of administration, the oral route has been most popular and successful. This is, in part, because of the inherent simplicity of both the oral route and oral delivery systems. On the other hand, the oral route is constrained by short and variable GI transit time, first-pass metabolism, limited absorption in the lower part of the GI tract, and the size of the system.

A. Designs

Oral controlled delivery systems can be broadly divided into following categories, based on their mechanism of drug release:

1. Dissolution-controlled release
 - a. Encapsulation dissolution control
 - b. Matrix dissolution control
2. Diffusion-controlled release
 - a. Reservoir devices
 - b. Matrix devices
3. Ion exchange resins
4. Osmotic controlled release
5. Gastroretentive systems

1. Dissolution-controlled release

Dissolution-controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer, and coating drug particles or granules with polymeric materials of varying thickness. The rate-limiting step for dissolution of a drug is the diffusion across an aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant-fluid diffusional boundary layer (2). The rate of dissolution (dm/dt) can be approximated by Eq. 1.

$$\frac{dm}{dt} = \frac{ADS}{h} \quad (1)$$

In Eq. 1, S is the aqueous solubility of the drug, A is the surface area of the dissolving particle or tablet, D is the diffusivity of the drug, and h is the thickness of the boundary layer.

Some examples of drugs with limited dissolution rate include digoxin, griseofulvin, salicylamide (3), and nifedipine (Adalat Retard tablet) (2). Unfortunately, this approach does not allow for a constant release rate because the surface area (A) changes with time. Also, the solubility (S) of the drugs, which are weak acids or bases, is affected by the variable pH of the GI tract.

Drug delivery using rate of dissolution as a controlled release mechanism can be achieved by *encapsulation* of a drug-polymer matrix with a relatively insoluble polymeric membrane. The coated beads can be compressed into tablets or capsulated, as was done with the Spansule® products (4). Since the time required for the membrane coat to dissolve is a function of membrane

thickness, granules with varying thicknesses can be employed to achieve sustained release of the drug. Examples of drugs delivered in this manner include antispasmodic-sedative combinations (5), phenothiazines (6,7), and anticholinesterase agents (8).

One of the most common approaches used to achieve sustained release is to incorporate a drug in a hydrophobic matrix such as wax, polyethylene, polypropylene, and ethylcellulose; or a hydrophilic matrix such as hydroxypropylcellulose, hydroxypropylmethylcellulose, methylcellulose, and sodium carboxymethylcellulose. The rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. It depends on the porosity of the compressed structure. In the case of a water-soluble drug in a hydrophobic matrix, the rate of drug availability.

2. Diffusion-Controlled Release

Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution-controlled systems, the diffusion-controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion-controlled device (9), the rate of drug released (dm/dt) can be calculated using Eq. 2.

$$\frac{dm}{dt} = ADK \frac{\Delta C}{\ell} \quad (2)$$

In Eq. 2, A is the area, D is the diffusion coefficient, K is the partition coefficient of the drug between the drug core and the membrane, ℓ is the diffusional pathlength, and ΔC is the concentration difference across the membrane. In order to achieve a constant release rate, all of the terms on the right side of Eq. 2 must be held constant. It is very common for diffusion-controlled devices to exhibit a non-zero-order release rate due to an increase in diffusional resistance and a decrease in effective diffusion area as the release proceeds.

Another configuration of diffusion-controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer (10-13). For instance, bupropion hydrochloride (Zyban[®], Glaxo Wellcome) is formulated using carnuba wax and hydroxypropylmethylcellulose (13). The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution. Equation 3 describes the amount of drug released from the systems as derived by Higuchi (14):

$$Q = \left[\frac{D\epsilon}{\tau} (2C - \epsilon S) S t \right]^{1/2} \quad (3)$$

In Eq. 3, Q is the amount of drug released per unit surface area, D is the diffusion coefficient of the drug in the release media, ϵ is the porosity, τ is the tortuosity of the matrix, S is the solubility of the drug in the release media, and C is the concentration of the drug in the tablet.

3. Osmotically Controlled Release

In the early 1970s, Theeuwes et al. (15) developed an elementary osmotic pump (EOP) to achieve controlled drug delivery. The delivery of the drug from the system is controlled by solvent influx across a semipermeable membrane, which in turn carries the drug outside through a laser-drilled orifice. The osmotic and hydrostatic pressure differences on either side of the semipermeable membrane govern fluid transport into the system. Therefore, the rate of drug

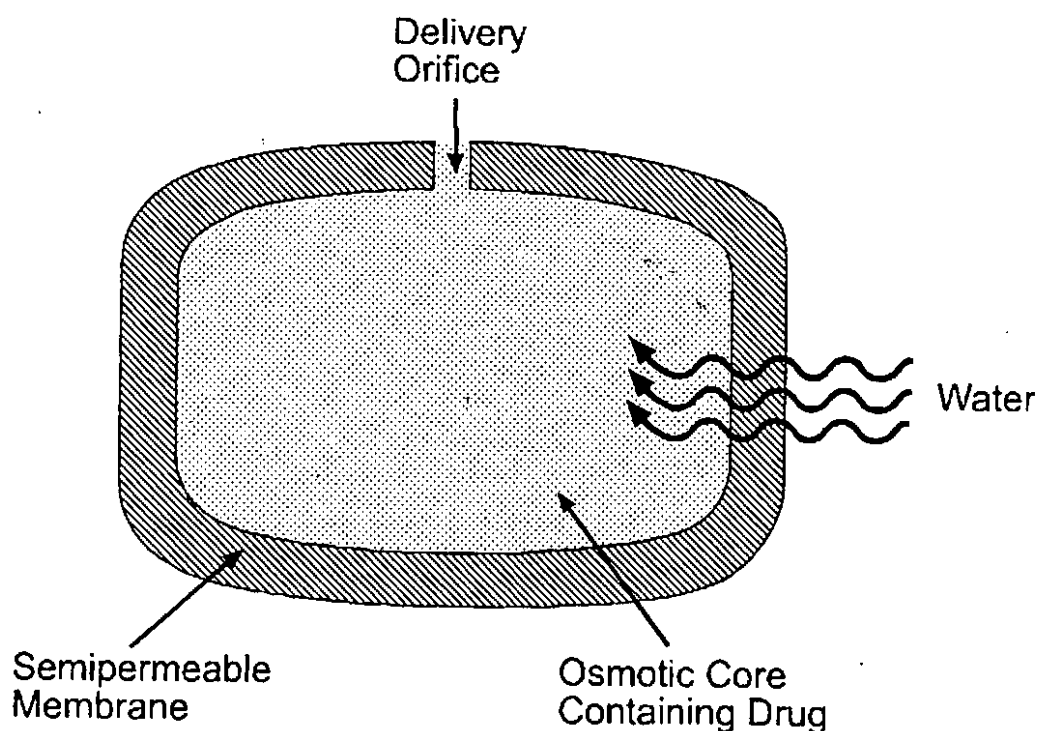


Figure 1 Schematic of elementary osmotic pump (EOP). (Courtesy ALZA Corporation.)

delivered from the system is dependent on the osmotic pressure of the formulation (π_s) as shown in Eq. (4). A schematic of an elementary pump is shown in Fig. 1 (16,17).

$$\frac{dm}{dt} = \frac{A}{h} k \pi_s S \quad (4)$$

where A is the membrane area, k is the membrane permeability, and h is the membrane thickness.

More recently, ALZA Corporation has developed several other controlled release technology platforms based on the original concept of osmosis across a semipermeable membrane. OROS Push-Pull technology has proven to be very useful for delivering compounds of very high or very low solubility such as oxybutynin chloride and nifedipine (18), respectively. OROS Push-Pull technology is capable of zero-order drug delivery for 24 h. As shown in Fig. 2, the system is made of two compartments that are compressed into a bilayer core. The top layer contains the drug and the lower layer contains an osmotic polymeric driving agent. The bilayer tablet is coated with a semipermeable membrane that is drilled on the drug side to allow delivery of the drug formulation through an orifice. During operation, OROS systems imbibe water across the membrane. The push layer expands and drives the drug out of the system in the form of a solution or suspension through the orifice. The release rate of the drug from a push-pull system can be estimated by Eq. 5:

$$\frac{dm}{dt} = \frac{k}{h} \left[A_p (\pi_p - \pi_d) + A \pi_d \right] F C_0 \quad (5)$$

Where F is the initial drug fraction in the drug compartment, C_0 is the solid concentration of the suspension dispensed from the system, A_p is the area of the push layer, A is the total area

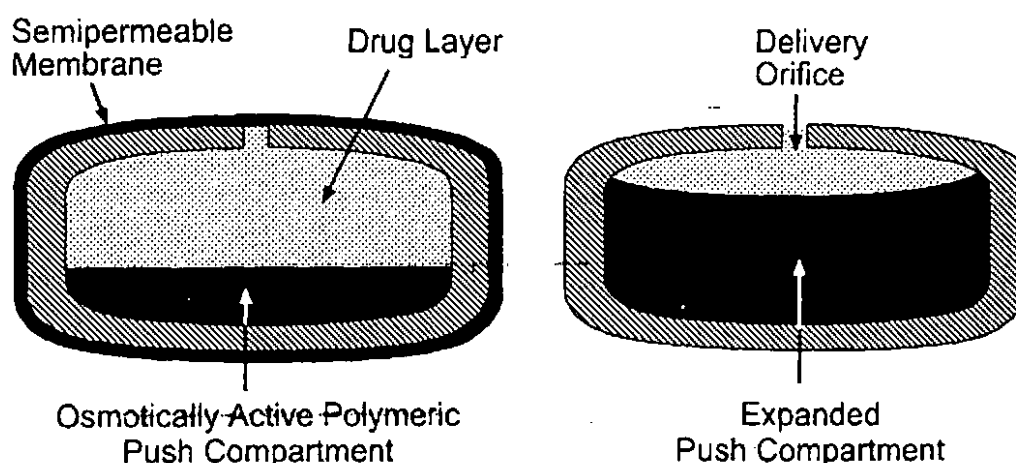


Figure 2 Schematic of OROS "Push-Pull" System (Courtesy ALZA Corporation.) (a) Represents the pump before operation. (b) Represents the pump during operation.

of the system, π_d is the osmotic pressure of the drug compartment, and π_p is the osmotic pressure of the push layer.

Typically, a push-pull system can deliver drug at a constant rate for 80% or more of its theoretical content. OROS systems can maintain zero-order delivery for 24 h. OROS Push-Pull technology has been applied to several commercial products, including oxybutynin chloride (Ditropan XL[®]), nifedipine (Procardia XL[®]), and isradipine (Dynacirc CR[®]). A typical release-rate profile for Ditropan XL[®] developed by Alza Corporation demonstrates a constant zero-order drug delivery (Fig. 3). The OROS technology has also been customized to suit the needs of a particular drug therapy. A classic example of such an application is OROS verapamil HCl (Covera HS[®]) for the treatment of hypertension and angina pectoris. The once-a-day system is programmed to provide a delayed onset of drug release after 4–5 h administration. The peak concentration (C_{max}) coincides with early morning hours (when the probability of a stroke is maximum), followed by a constant zero-order delivery.

4. Ion Exchange Resins

The idea of using ion exchange resins for controlled drug delivery was adapted from analytical and protein chemistry. Resins are water-insoluble materials containing anionic groups such as amino or quaternary ammonium groups, cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the resin chain. A drug-resin complex is formed by prolonged exposure of drug to the resin.

Theoretically, this controlled delivery approach is relatively immune to the conditions of the GI tract because an ionic environment is required to displace the drug from the resin. Biphedamine[®], a capsule containing equal quantities of amphetamine and dextroamphetamine complexed to a sulfonic acid cation exchange resin, has been used as an antiobesity drug and for behavior control in children (20). Nicorette[®] is a widely used product based on ion exchange technology as an adjunct to smoking cessation programs. It contains nicotine absorbed to a carboxylic acid ion exchange resin (nicotine polacrilex) in a flavored chewing gum (21). Delsym[®] (dextromethorphan, Pennwalt), a 12-h cough medication taken as a liquid suspension, is another example of this type of dosage form (22). Further improvement of the ion exchange type of delivery system is illustrated by the development of the Pennkinetic[®] system (Fig. 4).

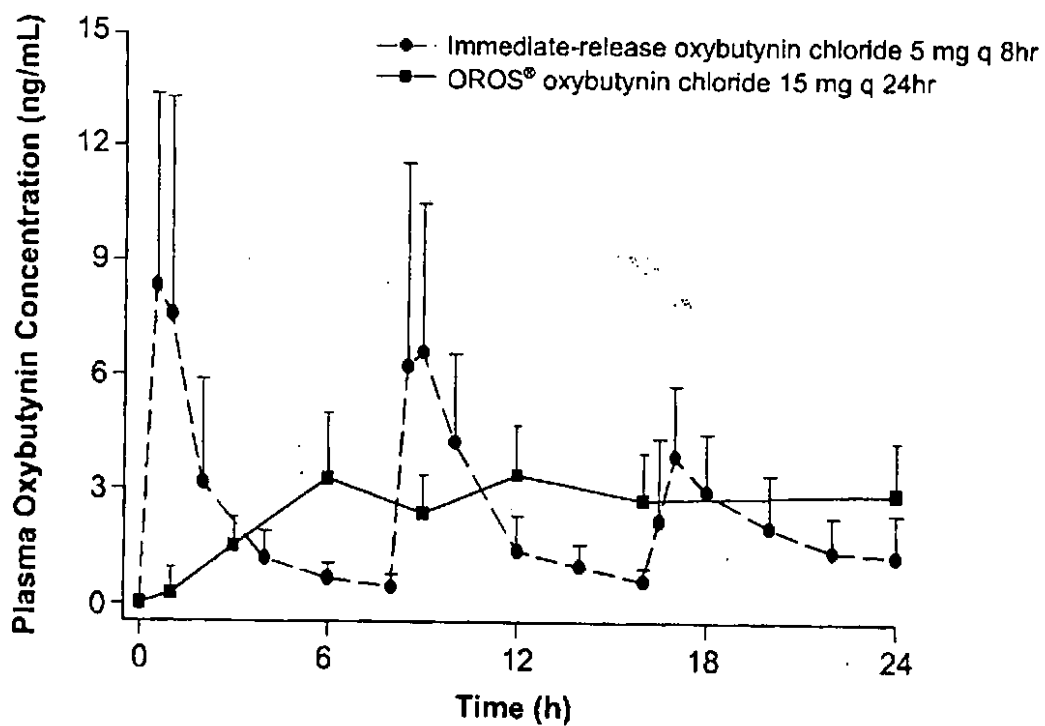


Figure 3 Comparison of mean plasma concentration of immediate release oxybutynin chloride (5 mg, administered every 8 h) with once-a-day OROS oxybutynin chloride (15 mg, administered once daily) after 1 day of administration.

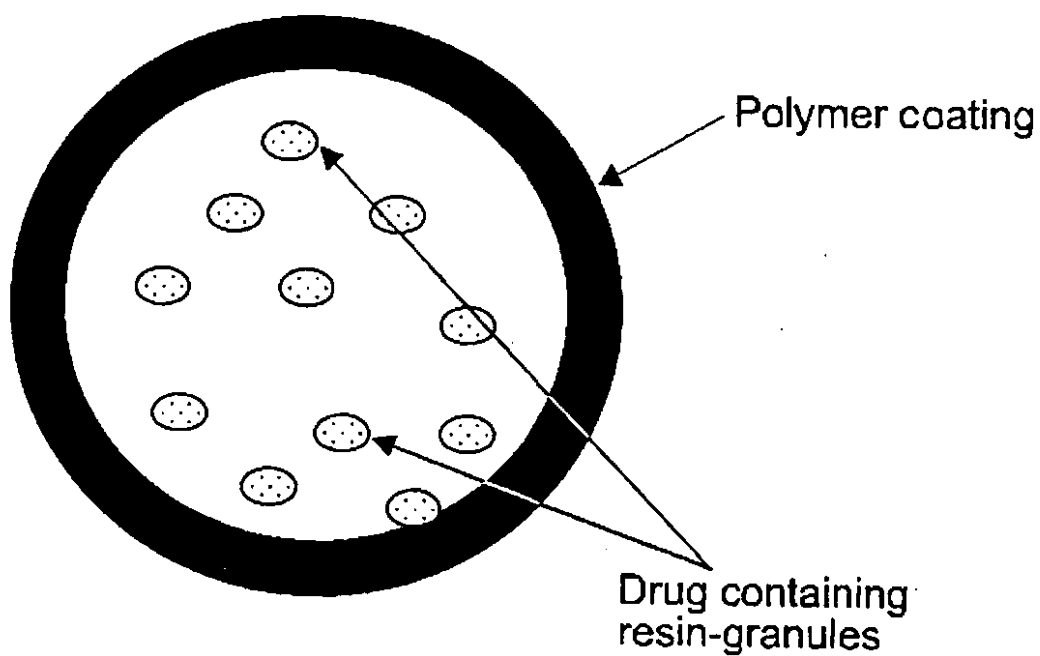


Figure 4 Polymer-coated drug-resin design.

In this system, drug containing resin granules is first treated with a polymer such as polyethylene glycol 4000 to retard the rate of swelling in water, and then further coated with a water-permeable polymer such as ethylcellulose to act as rate-limiting barrier to control drug release.

5. Gastroretentive Systems

Variability in GI transit time is a concern for oral-controlled drug delivery systems (23). Drugs with a narrow absorption window in the GI tract are particularly susceptible to variation in both bioavailability and times to achieve peak plasma levels. If successful, gastroretentive controlled release formulations could offer a potential solution to the problem by offering a prolonged gastric residence time (24). A drug that is released from the dosage form in a controlled manner in the stomach will exit the stomach together with gastric fluids and have the whole surface area of the small intestine available for absorption. This type of drug delivery also offers a potential for enhanced drug therapy for local conditions affecting the stomach, e.g., antibiotic administration for *Haemophilus pylori* eradication in the treatment of peptic ulcer.

Researchers in this area have attempted to achieve prolonged gastric retention by several means, including altering the density of the formulations and bioadhesion to the stomach lining. Several strategies have been employed to make the dosage forms float in the stomach. Hydrodynamically balanced system (HBS) was the first formulation that used the floating property of a device with density lower than water (25). HBS is a capsule containing drug, gel-forming hydrophilic polymers (e.g., hydroxypropylcellulose), and some hydrophobic fatty materials (e.g., stearates) (26). In a different approach for gastric retention, ion exchange resin beads are loaded with bicarbonate, which, on contact with media containing hydrochloric acid, release carbon dioxide, causing the resin to float (27). Extension of the floating time is achieved by coating the bicarbonate-coated beads with a semipermeable membrane. Recently, a multiple-unit floating dosage form has been prepared from freeze-dried calcium alginate. In fed subjects, these floating units were retained in the stomach for 5.5–9.0 h (28).

Some hydrogels and superporous hydrogels offer a promising approach to gastric retention. These materials have a swelling ratio of over 1000 (23). They can be made by crosslinking water-soluble polymer chains or by polymerizing hydrophilic monomers in the presence of cross-linking agents. Superporous hydrogels (29) have unique superswelling properties combined with pore sizes in the range of few hundred micrometers to a millimeter. These materials can swell to the equilibrium size in less than 1 min, which is an important requirement for gastric retention devices based on size.

B. Toxicological Considerations

The nonclinical toxicology program required for polymers in oral drug delivery systems depends on a subject's level of exposure to the polymer and to the final product. Exposure should be quantified and should include evaluation of absorption from the GI tract, local distribution, and local tolerance. If the polymer is not a new chemical entity (NCE), a review of the manufacturers' and published scientific literature should be conducted to gather clinical and nonclinical safety information. If the polymer is not absorbed or data indicate that blood levels are acceptable based on historical exposure or existing toxicology data, then it may be sufficient to conduct toxicology studies with the final drug delivery formulation with a written review and justification of the use of the polymer.

If the polymer is an NCE, a series of in vitro and in vivo (animal) genotoxicity studies should be conducted. These mutagenicity and clastogenicity studies determine if the polymer harms the cell's DNA. If the assays reveal a genotoxic result in multiple assays, development of

the polymer should be halted. If no genotoxic activity is present, the next step is to quantify exposure. Is the polymer absorbed from the GI tract? If the polymer is absorbed, a full toxicology program consisting of acute, chronic, reproduction, and carcinogenicity testing is likely to be required. If the polymer is not absorbed, studies up to 6 months long may be required with an evaluation of any proliferative changes. If proliferative changes occur, a carcinogenicity study might be indicated. Whether the polymer is absorbed or not, additional toxicology studies need to be conducted with the final formulation at multiple doses.

C. Functions of Polymers in Oral Controlled Release

For the most part, oral controlled release systems utilize principles such as diffusion, dissolution, and permeation for achieving a constant rate of drug delivery. Polymers are uniquely suited as materials of construction for oral delivery systems. They offer a wide range of properties such as diffusivity, permeability, and solubility that are important to achieving controlled delivery. They can be processed relatively easily into tablets and membranes by a variety of methods. Active ingredients and property modifiers can be incorporated either by physical or chemical means. In reservoir-type devices, polymers are ideal materials to form a membrane around the tablet or granule. These membranes are strong enough to maintain their integrity during normal handling and operation of these systems. Drugs can be dispersed or dissolved into polymers to manufacture matrix-type oral dosage forms. Ion exchange resins are types of polymers to which the drug substances are attached chemically. In general, polymers have little or no toxicity. Superporous hydrogel systems offer excellent ability to swell at a very fast rate, making them potential candidates for gastroretentive devices.

1. Polymer Properties That Affect the Release of Active Substances

A good understanding of polymer properties such as diffusion, solubility, and structural considerations is important in the selection of materials to be used as system components to regulate the fluxes of active ingredients. This section reviews some of these important properties affecting drug permeation.

The flux of a species migrating through a polymeric film is given by Eq. 6:

$$\text{Flux} = \frac{\text{area}}{\text{length}} \times (\text{permeability}) \times (\text{concentration difference}) \quad (6)$$

Area is the surface through which a species is diffusing, and length is the film thickness. Permeability is given by the product of partition coefficient and diffusivity (30).

a. **Diffusivity.** Diffusivity is the component of permeability that accounts for the geometrical constraints encountered by the diffusing species in weaving across the polymeric film. Consequently, diffusivity increases as the free volume of the polymer increases relative to the dimensions of the diffusing species. Jacobs and Mason (31) have listed various factors that affect the diffusivity of a molecule in a polymeric medium as shown below:

Increases in factor	Effect on diffusivity
Interchain forces	-
Segmental mobility	+
Permeant molecular weight	-
Polymer crystallinity	-
Plasticizer	+
Copolymerization	+

Increases in factor	Effect on diffusivity
Temperature	+
Glass transition	-

b. Solubility Parameter. The active ingredient is either suspended or dissolved in a polymeric matrix in monolithic controlled release systems. Polymers are dissolved in a solvent and coated onto tablets and granules. In reservoir-type systems, for both monolithic and reservoir-type systems, the addition of a second component, such as a drug or solvent, to a polymer can change the strength of polymer intermolecular forces and therefore the physical properties of the polymer. The strength of the intermolecular forces of a polymer is measured by its cohesive energy density (CED). The solubility parameter of a polymer also describes intermolecular forces. The relationship between the solubility parameter, δ , and CED is shown in Eq. 7:

$$\delta = (\text{CED})^{0.5} \quad (7)$$

The solubility parameters for many polymers are documented elsewhere (32). The choice of an ideal solvent to dissolve a polymer for any further processing can be made by comparing the solubility parameters of both polymer and solvent. For example, solvents and polymers with similar solubility parameters will most likely be compatible and soluble in each other. A polymer will precipitate from a solvent with a significantly different solubility parameter.

c. Structural Considerations. The structure of the polymer used in the drug delivery system is a very important parameter determining the mechanism of drug release. The diffusivity of a drug molecule dispersed in a hydrophobic polymer is dependent on the porous structure of the polymer (33,34). The solute diffuses through the solvent-filled pores. As the porosity increases, the release rate of the drug increases. For instance, in macroporous polymers, it is necessary to correct the diffusion coefficient for the porosity, tortuosity, and partition coefficient. For microporous polymers, additional steric hindrance and frictional resistance of the pores also need to be included. For nonporous polymeric networks, both solute molecule and structure of the polymeric network become important in determining the diffusion coefficient. The polymer structure-related factors affecting diffusivity include the degree of crystallinity, the size of the crystallites, the degree of swelling, the molecular weight between crosslinks, and the state of the polymer (whether glassy or rubbery) (35).

Many controlled release tablets and granules utilize hydrophilic polymers for retarding drug release. The mechanism of drug release is dependent on the swelling and dissolution process. An example of such a release mechanism could be demonstrated using tablets manufactured by dispersing drug in hydroxypropyl and hydroxymethylcellulose matrix. In this case, the early part of the release process is marked by swelling due to conversion of the polymer from a glassy to a rubbery state due to water penetration. Subsequently, when the water concentration at the polymer surface exceeds a critical concentration of macromolecular disentanglement, the true dissolution process occurs. Diffusivity through a swollen polymer is much higher than through nonswollen polymers and in fact approach diffusion coefficients in solution.

A detailed listing of polymers used in controlled release oral dosage forms is given in Table 1.

D. Fabrication Techniques

Oral controlled release forms most commonly involve either dispersing the drug into a polymeric matrix, or encapsulating the drug containing core or granules with a rate-controlling membrane. This section describes the most common unit operations involved in the manufacture of oral controlled release products.

Table 1 Polymers Used in Oral Controlled Release Technologies

Method of achieving controlled release	Polymer used	Examples of dosage forms
Matrix or Embedding		
(a) Hydrophillic Carriers	Methyl Cellulose Sodium Carboxymethylcellulose [38] Carboxymethylcellulose Hydroxypropylmethylcellulose [36,37] Hydroxyethylcellulose Methacrylate Hydrogels [39] Polyethylene Glycols Galactose Mannate Sodium Alginate Polyacrylic acid	Multilayer tablets with slow releasing cores Compression-coated tablets
(b) Hydrophobic Carriers		
(i) Soluble Carrier (digestible base)	Glycerides Waxes Fatty Alcohols Fatty Acids	
(ii) Insoluble Carrier (nondigestible base)	Polyethylene Polyvinyl chloride Polyvinyl acetate Waxes [40] Calcium Sulfate	Matrix tablets
Reservoir Type		
(a) Coating with insoluble membrane	Ethyl Cellulose [36, 37]	Granules, pellets, tablets
Osmotic Systems	Vapor permeable walls [41] - Tenite 808A polyethylene - Kynar 460 polyvinylidene fluoride Hydroxypropyl methyl cellulose Hydropropyl cellulose Sodium carboxymethyl cellulose Ethyl cellulose	Vapor permeable capsules Vapor permeable tablets Single and bilayer tablets
Ion-exchange Resins	Dowex® 50, 1, 2 [19] Amberlite® IR 120, 400, 4B [19] Amberlite® IRC 50 [19] With polystyrene-based polymeric backbone	Controlled release capsules Chewable tablets Chewable gums Liquid suspension
Gastric Retention Systems	Hydroxypropyl methylcellulose [24] Agar, Carrageenans, Alginic acid [24] Oils, porous calcium silicate [24] Superporous hydrogels [29] Ion-exchange resin beads coated with bicarbonate [27,29] Ethyl cellulose for coatings	Compressed tablets Gelatin Capsules

1. *Wet Granulation*

Drug is uniformly dispersed into a polymeric matrix using traditional high-shear granulation (HSG) or fluidized-bed granulation (FBG) techniques. In an HSG technique, an aqueous or a hydroalcoholic binder solution, such as 5% polyvinylpyrrolidone in water, is sprayed onto a polymeric powder bed, such as 85% hydroxypropylmethylcellulose containing the drug. The powder bed is subjected to a very high shear rate to obtain granules incorporating a uniform mixture of drug, binder, and the polymeric excipient. The wet granules could be dried either in a traditional tray dryer, fluidized-bed dryer, or microwave dryer. In an FBG technique, a powder bed consisting of drug, polymer, and other excipients is fluidized in an expansion chamber. The binder solution is sprayed through a nozzle from the top or bottom of the bed depending on the equipment design. The droplet size and bed humidity are the two most important process parameters, which control the granule size and other mechanical properties. The agglomerated mixture can be dried in the same equipment.

2. *Spray Drying*

Spray drying has been used to produce microencapsulated and matrix formulations of several drug substances including theophylline, acetaminophen, and sulfaethylthiazole. It involves three basic steps. First, a liquid feed is atomized into fine droplets. Second, these fine droplets are mixed with heated gas stream, allowing the liquid to evaporate and leave dried solids. Finally, the dried powder is separated from the gas stream and collected. The final product usually has the same size and shape as the atomized droplet.

3. *Spray Congealing*

This process consists of suspending the drug particles in a low-melting polymer or wax and pumping the resultant slurry through an atomizer into a spray dryer in which cold air is circulated. The slurry droplets congeal on coming in contact with the air and are collected in the same manner as the spray-dried product. The spray congealing process requires a much higher ratio of coating agent to active material than does spray drying because only the molten coating agent constitutes the liquid phase.

Encapsulation of drug-containing cores and granules in the manufacture of reservoir-type oral controlled released product can be accomplished by the following coating methods:

4. *Pan Coating*

Pan coaters are one of the earliest types of equipment to be used for encapsulating a drug-containing tablet core. Pan coating involves spraying an atomized coating solution through nozzles on a moving bed of tablets. The distribution of the coating is accomplished by movement of the tablets perpendicular to the application of the coating solution. Drying of the coating solution from the tablet bed is accomplished by directing heated airflow from the front to the back of the partially or fully perforated pan. The popular models include the Hi-Coater from Vector Corporation and the Glatt coater from Glatt Air Techniques Inc.

5. *Air Suspension Coating*

Granules and pellets are often coated in an air suspension process. Sometimes this technology is also used to apply release-controlling membranes around tablets. Fluidization of tablets or granules is achieved in a columnar chamber with upward flow of drying air. The airflow is controlled so that more air enters the center of the column, causing the tablets to rise in the center. The movement of the tablets is upward toward the center of the chamber. They then fall toward the

chamber wall and move downward to reenter the air stream at the bottom of the chamber. Because tablets and granules hit against the chamber wall during coating, friable tablets are prone to chipping. The drying efficiency of the air suspension coaters is very good. Constant motion of the tablets and granules in the fluidized bed, along with efficient drying, prevents any twinning of tablets or particle agglomeration. Coating solution is applied continuously from a spray nozzle located either at the bottom of the chamber, as in the Wurster process, or atop the cascading tablet bed by nozzles located in the upper region of the chamber. Several models available on the market offer fully automated process capability. Coating uniformity is excellent.

6. *Compression Coating*

Rate-controlling polymer in the dry powder state can be compressed around the drug-containing core using a special tablet press. This process eliminates the use of any solvents from the manufacturing process. Most often the core tablets containing the drug are prepared prior to the compression coating step. During the compression coating operation, a lower layer of rate-controlling membrane is dosed at the bottom. The drug-containing core is guided to the center of the die followed by another layer of the polymer. Finally, the die contents are compressed under rolls to achieve a hard tablet encapsulated in a rate-controlling polymer. Geomatrix technology uses compression coating to lay a barrier coating of ethylcellulose on a hydrophilic core made of hydroxypropylmethylcellulose to achieve a near-zero-order release rate (36).

E. *Future Research*

Advances in the design of oral drug delivery systems can be realized by a better understanding of the biology of the GI tract and drug absorption process. So far polymers have contributed immensely to the development of technologies for delivering drug over extended periods. The present state of the art restricts the duration of delivery of oral CR forms to about 24 h. More research effort is needed to retain the dosage forms in the stomach to achieve prolonged as well as higher absorption from the upper GI tract. For instance, new polymers could be designed not only with an extremely rapid onset of swelling, but also with a higher extent of swelling, resulting in prolonged gastric retention. In addition, peptides and proteins are evolving as an important class of therapeutic agents in drug therapy, and absorption of these unstable substances from oral medications is challenging. Polymers could be designed to safely carry these moieties through the GI tract without presystemic clearance, resulting in substantially higher bioavailability.

III. **TRANSDERMAL DRUG DELIVERY SYSTEMS**

Transdermal systems are currently enjoying widespread consumer acceptance of both prescription and over-the-counter (OTC) products. To many users, the technology is an extension of the "bandage" concept, and therefore relatively noninvasive and easy to use. To a large extent, materials found acceptable for bandages were the starting points for transdermal delivery systems.

A. *Designs*

There are two predominant designs in transdermal systems: membrane-controlled systems and matrix systems. A brief discussion of the features of each, based mostly on a review article (42), is given below

1. Membrane-Controlled Systems

This type of design essentially consists of three major components: the drug reservoir (often a liquid-containing "form-fill-seal," or FFS, type), the rate-controlling membrane (RCM), and the adhesive. The drug permeates the membrane and the adhesive to reach the skin. Typically, the drug reservoir contains a solution of the drug and liquid excipients. One common excipient used is an enhancer, which also permeates the layers to the skin, where it exerts its enhancing effects by modulating the skin permeability in some fashion. (A variation of this design is the "multi-laminate" RCM design, whereby the drug reservoir is made of solid polymer, with drug dispersed/ dissolved in it; an example is Transderm-Scop.[®]) In the matrix-type design, the adhesive performs the roles of drug reservoir and adhesive, and to some extent, the role of the rate-controlling membrane as well. (See Fig. 5 for schematics of the two systems.)

The major material components of membrane-controlled systems are as follows:

1. The membrane
2. The adhesive
3. The backing, which is also the FFS material

2. Matrix Systems

In this design, the role of the drug reservoir is performed by the adhesive. The drug and excipients are formulated into the adhesive, typically into adhesive solution, and the solvent evaporated to yield the matrix film. The matrix-adhesive film is then laminated to a backing film. Thus, the major components in a matrix design are as follows:

1. The adhesive
2. The backing

The chief advantage of a matrix system is that the entire system can be made thin and elegant, as well as very comfortable to wear. In principle, it is much easier to make an extended wear system (>3 days) using a matrix design than using a membrane-controlled design, as the bulkiness of the FFS type of RCM systems is usually detrimental to comfortable wear. On the other hand, stability issues are more likely to occur in the case of matrix systems, as the drug

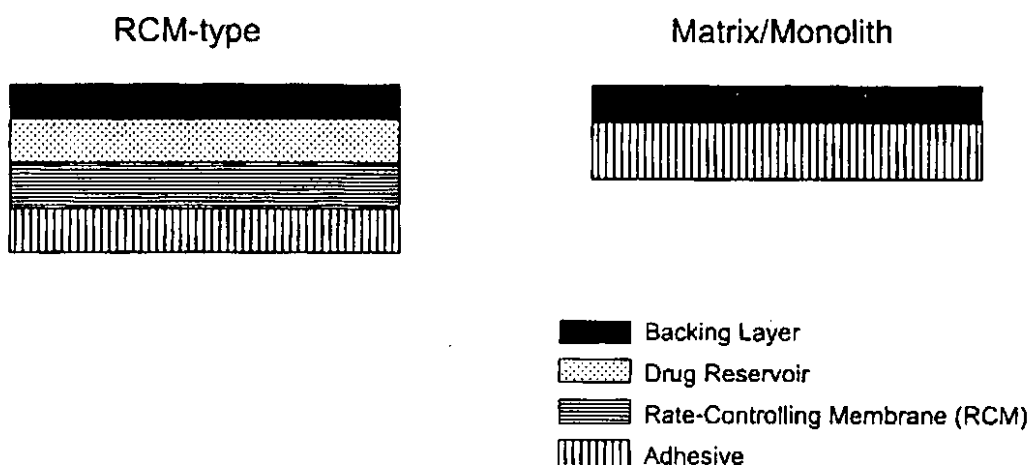


Figure 5 Schematic of membrane-controlled and matrix types of transdermal design.

and excipient may undergo phase changes (e.g., dissolved drug may crystallize or dispersed drug may agglomerate). Both of these causes of instability could adversely affect adhesive properties.

B. Toxicological Considerations

Polymers used in transdermal drug delivery systems may not penetrate the skin themselves, but there may be components of the polymer that migrate. The polymer and extracts should be biocompatible since they are in contact with components that do penetrate the skin. The tests listed in ISO/ANSI/AAMI Standard 10993, Biological Evaluation of Medical Devices are intended to provide testing strategies for medical devices. There are similar guidelines in the U.S. Pharmacopoeia 23 for plastics used as drug containers. These tests may also be used to test biocompatibility of polymers used in transdermal drug delivery systems. Extracts may also be tested for the potential to cause topical sensitization. Preparation of polymer extracts is defined by the guidelines, but the choice of conditions should come close to the conditions of manufacture of the drug delivery system. Extracts are evaluated in *in vitro* cytotoxicity tests and in *in vivo* irritation, intracutaneous injection, systemic injection, and implantation studies. A sample of the polymer may also be evaluated in these *in vivo* tests. The final transdermal drug delivery system must also be evaluated in standard nonclinical toxicology studies to evaluate the safety of the system. These studies should detect adverse effects of the system as well as any adverse effects of polymer extracts that are not detected in the previous tests. Study duration will depend on whether the active drug is an NCE and on its duration of use.

C. Delivery Profiles/Performance

The strength of the RCM-based design is constancy of drug delivery to the skin. In kinetic terms, the RCM design affords the possibility of zero-order release, i.e., the rate of drug delivery to the skin is constant with time. On the other hand, the matrix design can yield only a non-constant rate of drug delivery to the skin. Typically, this rate decreases with time such that the amount delivered is proportional to the square root of time rather than to time. In either case, the likelihood of constancy of delivery of drug to the bloodstream is determined by the flux through skin relative to flux through the system alone. In limiting cases, the following is true:

When drug flux through skin is very low ($<$ approximately 10% of flux through device), the skin is termed rate controlling: in this instance, both types of designs can yield zero-order delivery to the bloodstream.

When drug flux through skin is high ($>$ approximately three times the rate through device), then only the RCM design can yield zero-order kinetics for drug delivery to the bloodstream.

When dealing with potent drugs or with drugs that have a narrow therapeutic window, the RCM design yields a greater margin of safety, but the level of safety is contingent on the level of control attained by the device as opposed to the skin. In addition, RCM systems also tend to demonstrate a lesser degree of patient-to-patient variability, for the same reasons outlined above. Matrix systems, on the other hand, are preferred for drugs that have very low skin flux, as they can achieve higher release rates. In addition, as mentioned above, matrix systems tend to be more appealing to the patient and may lead to greater acceptance.

Table 2 shows the commercial transdermal systems by type of design, and lists the materials used in each system.

Table 2 Family of Commercial Transdermal Systems

Product name	Innovator	Marketer	Active ingredient	Systems area(s)	Delivery rate(s)	Rated duration	Enhancer	Type
Alora [®]	TheraTech	P&G Pharm.*	17 β -estradiol	18, 27, 36 cm ²	0.05, 0.075, 0.1 mg/d	4 days	sorbitan monoleate	Adhesive matrix
Climara [®]	3M Pharm.	BerlexLabs	17 β -estradiol	12.5 & 25 cm ²	0.05 & 0.1 mg/d	7 days	fatty acid esters	Adhesive matrix
Deponit [®]	Lohman	Pharma	Nitroglycerin	16 & 32 cm ²	0.2 & 0.4 mg/h	12-14 hr	"a plasticizer"	Adhesive matrix
	Neuwied FRG	Schwarz					propylene glycol monolaurate	
FemPatch [®]	Cygnus	ParkeDavis	17 β -estradiol	30 cm ²	0.025 mg/d	7 days	none	Adhesive matrix
Habitrol [®]	Novartis	Novartis	Nicotine	10, 20, 30 cm ²	7, 14, 21 mg/d	24 hrs	none	Pad in adh. matrix
Minitran [®]	3M Pharm.	3M Pharm.	Nitroglycerin	20 cm ²	0.6 mg/h	12-14 hr	fatty acid esters	Adhesive matrix
Nitroderm [®]	Key Pharm.	Key Pharm.	Nitroglycerin	10, 20, 30, 40 cm ²	0.2, 0.3, 0.4, 0.6, 0.8 mg/h	12-14 hr	none	Adhesive matrix
Testoderm [®] with adhesive	Alza	Alza	Testosterone, USP	60 cm ²	6 mg/d	24 hrs	none	Matrix, striped adh
		Ciba, RPR-Novo					oleic acid, propylene glycol	Adhesive matrix
Menorect [®] , Vivelle [®]	Noven	Nordisk**	17 β -estradiol	11 & 29 cm ²	4 Rates, 25-100 ug/d	3-4 days	none	Adhesive matrix
Nicotrol [®]	Cygnus	McNeil	Nicotine	30 cm ²	15 mg/16 h (1 day)	16 hrs	ethanol, glyceryl monooleate, methyl laureate, glycerin	Adhesive matrix
		SmithKline						FFS***, peripheral adhesive
Androderm [®]	TheraTech	Beecham	Testosterone, USP	37 & 44 cm ²	2.5 & 5 mg/d	24 hrs	polyethylene glycol, isopropyl palmitate	Matrix, peripheral adhesive
Prostep [®]	Elan	Elan	Nicotine	3.5 & 7 cm ²	11 or 22 mg/d	24 hrs	none	Matrix, peripheral adhesive
Nitrodisc [®]	Searle	Searle	Nitroglycerin	8, 12, 16 cm ²	0.2, 0.3, 0.4 mg/h	24 hrs	polyethylene glycol, isopropyl palmitate	Matrix, peripheral adhesive
Catapres TTS [®]	Alza	Boehringer	Clonidine	3.5, 7 & 10.5 cm ²	0.1, 0.2, 0.3 mg/d	7 days	none	rate-control memb.
Duragesic [®]	Alza	Janssen	Fentanyl	10, 20, 30, 40 cm ²	25, 50, 75, 100 ug/d	3 days	ethanol	rate-control memb.
Estraderm [®]	Alza	CibaGeneva	17 β -estradiol	10 & 20 cm ²	0.05 & 0.1 mg/d	3 days	ethanol	rate-control memb.
		SmithKline						
Nicoderm [®] CQ	Alza	Beecham	Nicotine	7, 15 & 22 cm ²	7, 14 & 21 mg/d	24 hrs	none	rate-control memb.
Transderm-Nitro [®]	Alza	CibaGeneva	Nitroglycerin	5, 10, 20, & 30 cm ²	0., 0.2, 0.4 & 0.6 mg/h	12-14 hrs	none	rate-control memb.
Transderm Scop [®]	Alza	Novartis	Scopolamine	2.5 cm ²	0.5 mg/3 d	3 days	none	rate-control memb.

*Procter and Gamble Pharmaceutical; **RPR = Rhone-Poulenc Rohrer; ***FFS = Form-fill-seal.

D. Polymer Requirements

For the sake of convenience, this discussion of materials used is divided in terms of the design type.

1. RCM-Based Systems

As mentioned above, the chief components of RCM designs are the FFS material, the rate-controlling membrane itself, and the adhesive.

a. **FFS materials.** The requirements for the FFS material is that it should be as follows:

1. Thermoformable
2. Sealable to the membrane material
3. Occlusive (low moisture-vapor transmission rate; MVTR)
4. Impermeable to volatile excipients of the formulation
5. Nonabsorptive for the drug

Materials that meet these requirements include polyester (PET)/heat-seal layer laminates, or PET/metal/heat-seal layer laminates. Available trade names include Scotchpak® from 3M Company and Mediflex® from Bertek, Inc., in a range of thicknesses. These two vendors are also willing to custom-fabricate laminates. The PET layer confers the impermeability and low-MVTR attributes to the device backing, while the occlusivity is attained by the combination of material and thickness. Thermoformability is not a requirement when the drug formulation has high viscosity and can be contained relatively easily. However, when the drug formulation is predominantly liquid-like, the material must be capable of being formed (preferably by thermal means) into a cavity. An example of such material includes polypropylene.

Examples of products that use the RCM design include Estraderm®, Transderm-Nitro®, and Testoderm TTS®; the first two are marketed by Novartis, while ALZA Corporation markets Testoderm TTS.

b. **Membranes.** The RCM is the critical component of the membrane design. It must satisfy the following criteria:

1. A diffusion coefficient for the drug under consideration that ranges from about 10^{-7} to 10^{-9}
2. Capable of being fabricated into a film of thickness from 1 to 5 mils
3. Low solubility for the drug and its excipients
4. Should be capable of being laminated to the FFS material on one side and the adhesive on the other
5. Should soften well above shipping temperatures
6. Modulus should be about 1000 to 1 MM Pa

Both homopolymer and copolymer films can be found that satisfy the above criteria. The 3M Company has developed the CoTran® series of membranes based on polyethylene and ethylene vinyl acetate (EVA, 9% vinyl acetate). The polyethylene films can be nonporous or microporous, whereas EVA is an extruded film. Also noteworthy are the Celgard® membranes from Hoechst-Celanese; these are also microporous films based on polyethylene and polypropylene. These are produced by a patented stretching process that introduces pores into the film. Celgard films are available with both hydrophobic and hydrophilic surfaces.

The copolymer EVA has long been the polymer of choice in this category. This is primarily because the vinyl acetate content can be varied to tune its permeability to meet the requirements of the drug under consideration. In general, the variables available for manipulation of the permeability of the material are the vinyl acetate content, thickness, crystallinity of the

ethylene components, and domain structure of the fabricated film. The following table lists the various grades of EVA available and measured diffusion coefficients for selected drugs (43):

Percent EVA	9% EVA		18% EVA		40% EVA	
	K.I	$D \times 10^9$	K.I	$D \times 10^9$	K.I	$D \times 10^9$
19-nor-Progesterone	4.9	4	18	3	105	5
Testosterone	4.0	4			88	5
Estriol	0.0048	4	0.025	3		

K.I = normalized permeability coefficient, $\mu\text{g}/\text{cm.s}$.

D = coefficient of diffusion, cm^2/s .

Note that in the above examples, the diffusion coefficient remains unchanged for the different EVAs, whereas the permeability changes by factors of 10–25. This is explained by postulating that the diffusion coefficient is dependent on factors such as pore size, which in turn is determined by the amount of crystallinity in the material and how the crystallites are distributed (morphology). In this instance, as long as the average pore size is above a threshold value, the diffusion coefficient is unchanged in going from 9% to 40% EVA. The permeability, which is also dependent on the partition coefficient, is expected to change as the EVA content changes. This is borne out experimentally.

c. **Adhesives.** In membrane-controlled systems, the adhesive must exhibit permeability for the drug and the enhancer that is defined by the delivery profile of the drug under consideration. At any time it is likely that the adhesive has measurable amounts of drug and enhancer dissolved in it to their solubility limits, as the typical process is one of partitioning followed by diffusion. If the solubility of either component is low, then the permeation process does not appreciably affect the adhesive. If it is substantial ($>3\%$ by weight), then the following effects may be anticipated: liquid excipients (including drug) will "plasticize" the adhesive to some degree; if the period of wear is long (>24 h), this could lead to unsightly residue and oozing on skin. The "oozing", in addition to being unsightly, also collects dirt and lint, and occasionally sticks to clothing. If the drug and excipients are solids, the adhesive may increase in cohesive strength and lose some of its adhesive characteristics, particularly tack. Thus, the optimum choice of adhesive for the RCM design depends on drug and excipient solubility.

All of the commonly used adhesives are derived from the pressure-sensitive adhesive (PSA) industry. Used in such products as Post-It® notes, and also in automotive decals, office labels, and other applications, the same basic adhesives have been requalified for use in the transdermal field. Requalification typically involves animal and human toxicology testing, as well as incorporation of the material into a Drug Master File (DMF).

Classes of PSAs available include:

1. Polyacrylate are copolymers of acrylates with vinyl acetate, alkyl acrylate, acrylic acid, or other functional monomers and are by far the most commonly used. Major suppliers include National Starch & Chemical Co., Morton-Thiokol, the Solutia division of Monsanto Chemical Co., and Adhesives Research. The 3M Company formulates its own acrylic adhesives for incorporation into 3M transdermal products (predominantly matrix-type constructions).
2. Silicones are also used in many transdermal systems, due primarily to their excellent adhesion characteristics and a perceived hypoallergenic nature. However, these are

made by two suppliers, Dow-Corning and NuSil Technology, and continue to be expensive.

3. Polyisobutylenes (PIBs), in mixtures with polybutene and tackifiers, are also heavily used. Suppliers, including Adhesives Research, Inc. ALZA Corporation, and Cygnus, Inc., have their own versions of PIB adhesives in some of their transdermal systems.
4. Natural rubber—and synthetic rubber-based adhesives are also available from National Starch Co. However, some of these suffer from complexity in their composition, while the natural rubber-based adhesives tend to be also somewhat more irritating than their counterparts.

2. Matrix Designs

The major components of this type of design are the backing material and the adhesive.

a. **Backing Materials.** The backing material must satisfy the following criteria:

1. Occlusive (low MVTR)
2. Impermeable to volatile excipients of the formulation
3. Nonabsorptive for the drug

Since the requirements are less stringent than those for FFS materials, a wider choice is available. Typically, polyesters, e.g., poly(ethylene terephthalate) (PET), polyolefins (HDPE or LDPE), multilayered films (Saranex from Dow Chemical), or elastomers can be used. In fact, it is claimed (44) that the elastomeric backings have more acceptable long-term wear. A sandwich of polyurethane/polyisobutylene/polyurethane has also been claimed (45). The commercial system, Fempatch[®], utilizes an elastomeric backing layer. Patents for other elastomeric backings also exist (46).

b. **Adhesives.** Although the same classes of adhesives mentioned above are also used for the matrix systems, other additives have to be formulated into these adhesives. Therefore, the demands made of the adhesive in this design are far more exacting. The adhesive contains all of the drug and any excipients. The drug and excipient could be dissolved or dispersed, depending on the amount needed for the appropriate delivery profile. If the additives need to be dissolved and stay dissolved, then the choice of adhesive is determined solely by solubility characteristics. In the case of dispersed systems, the range of useful adhesives increases, but the effect on properties is different. Dissolved additives tend to decrease moduli and render the adhesive more susceptible to creep/cohesive failure. Dispersed additives tend to reinforce the adhesive, especially if the additive is a solid. Thus, adhesive selection for matrices is more complicated and entails compatibility studies, long-term stability studies of the adhesive, and optimization of the formulation, based on the nature of the additives.

E. Fabrication

For RCM designs, fabrication involves the incorporation of the drug formulation into an FFS construction. This process may involve forming, filling, and sealing, or just filling and sealing, depending on the state of the formulation (paste, viscous liquid, or liquid). Once the formulation is contained, the subsequent steps involve sealing the FFS material to the membrane and the lamination of membrane to adhesive. Sometimes the membrane is made part of the FFS material by a suitable lamination process prior to incorporation of drug formulation.

The major steps in the fabrication process for RCM systems are as follows:

1. Mixing of drug formulation
2. Form, fill, and seal

3. Lamination to adhesive
4. Die-cut, pouch, label, and package

The throughput is mostly dependent on the first of these processes. The FFS operation itself is dependent on formulation viscosity or dispensing speed. Metering pumps are often used for the dispensing process. Typical line speeds are about 30 ft/min.

For matrix designs, fabrication includes the following steps:

1. Mixing of drug formulation with adhesive solution
2. Casting mixture onto backing material or release liner
3. Evaporation of solvent
4. Laminating to backing material
5. Die-cut, pouch, label, and package

The throughput is determined mostly by the casting operation, which involves spreading the adhesive/drug formulation onto a moving web, and then evaporation of the volatile components. The line speed is determined by the nature of the solvent. Typical speeds are about 5–20 ft/min.

F. Issues and Opportunities

The factors limiting the advancement of transdermal technology are not related to polymers. The key factors are the ability to push small molecules through the skin faster and the problems associated with sensitization from certain drug classes. For example, the so-called lag time in transdermal administration (the time required for the drug to reach efficacious blood levels) is still of the order of 2–4 h for most drugs, and this may be unacceptable if immediate relief is desired. In another example, the flux requirements for a given drug are so high that very large patches are needed. In these cases, advancement will occur through the invention/discovery of new enhancers rather than new polymers, although new polymers may be needed to accommodate and deliver the new enhancers at an acceptable rate. Similarly, the issue of sensitization by certain drugs cannot be overcome by the use of new polymers. Coadministration of immune suppressants or modification of drug structure to an immunologically inert form may be required. Such advances will enable the transdermal administration of antihistamines, for example.

IV. IMPLANTABLE DRUG DELIVERY SYSTEMS

For the purposes of this chapter, implantable drug delivery systems are defined as long-term (greater than 30 days) implantable products that are resorbable or removable. The resorbable "implants" are really injectables incorporating lyophilized microspheres and will be discussed further in Section V. The removable version is typically a subcutaneous implant, requiring a minor outpatient procedure for both insertion and removal. The main commercialized product in this category is Norplant[®], a contraceptive implant. A limited number of other companies have announced products in various stages of development, the leading candidate being the Duros technology from ALZA Corporation (currently in phase III trials). Medtronic Corporation has two products in the implantable area that allow drug delivery into the intrathecal space (where the spinal fluid circulates). One of these products delivers baclofen for spasticity and the other delivers anesthetics for pain control. Both products utilize Medtronic's SynchroMed[®] infusion pump, which can be electronically programmed to deliver any type of preset dose. However, this type of product falls outside the scope of this chapter, which will focus on removable implanted passive devices.

A. Designs

The Norplant[®] product was developed by the International Committee for Contraception Research (ICCR) of Population Council, Inc. It is marketed in the United States as a 5-year implant by Wyeth-Ayerst. The first-generation product consists of a set of five cylindrical pieces that are inserted subdermally using a simple procedure. This particular version of Norplant is a capsule system (labeled case I in Fig. 6) in that crystals of levonorgestrel (LN) are encapsulated by Silastic[®] polymer. Later designs being tested internationally by the ICCR include a Silastic matrix (case II in Fig. 6), in which micronized LN is dispersed and a covered rod (case III in Fig. 6), which is a membrane-coated matrix. The three designs are depicted schematically in Fig. 6. The three designs yield very different release profiles, partly due to the nature and amount of drug loading, and partly due to design features. The three release profiles (47) are shown schematically in Fig. 7.

As can be seen from the figures, the drug release rate in case I is constant after 450 days (~15 months), whereas case II (matrix) yields a rate that varies as the square root of time, and case III yields a nearly constant rate over time. Although in principle cases I and III (membrane-controlled systems) are expected to yield constant-rate (zero-order) profiles, case I yields an initial nonconstant rate because of the nature of the drug present in the capsules. Levonorgestrel is present as crystals in the capsule, and it has been noted that water permeates slowly into the capsule. At about ~450 days, the drug is virtually suspended in water, and the rate-determining step becomes the dissolution rate of levonorgestrel in water (48). Case II exhibits the classical matrix rate profile, whereas case III yields the classical membrane-controlled rate profile.

Research on optimizing the design in order to achieve constant rates over long periods, as well as to maximize drug loading (so that the size or number of rods can be reduced), continues, with contraception as the main focus.

Using a totally different approach, ALZA Corporation has developed the Duros[®] implant (see discussion elsewhere in this book) to deliver constant amounts of drug over periods

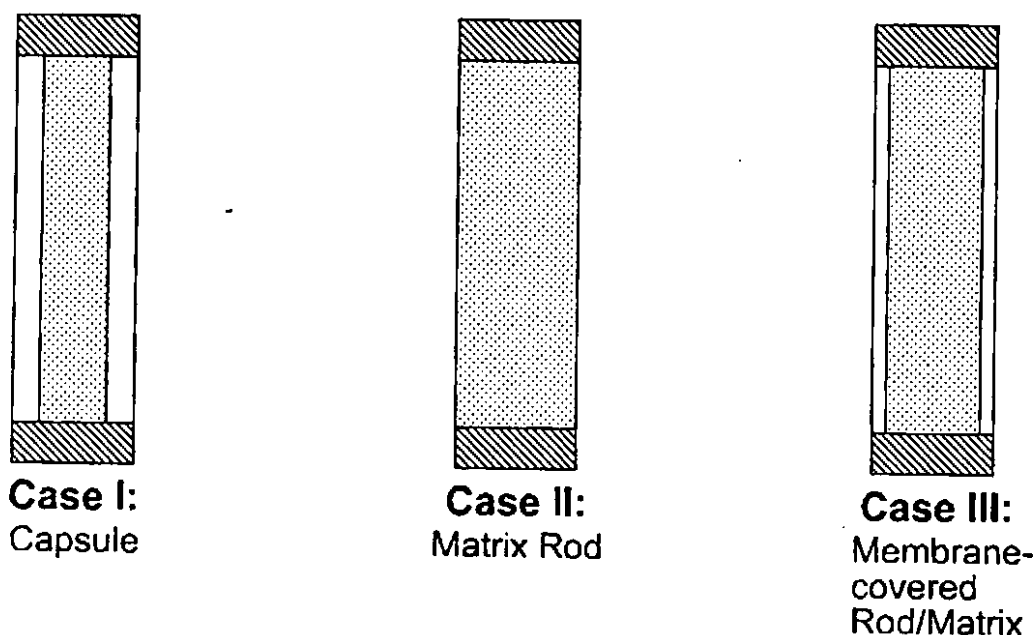


Figure 6 Three types of long-term implant designs.

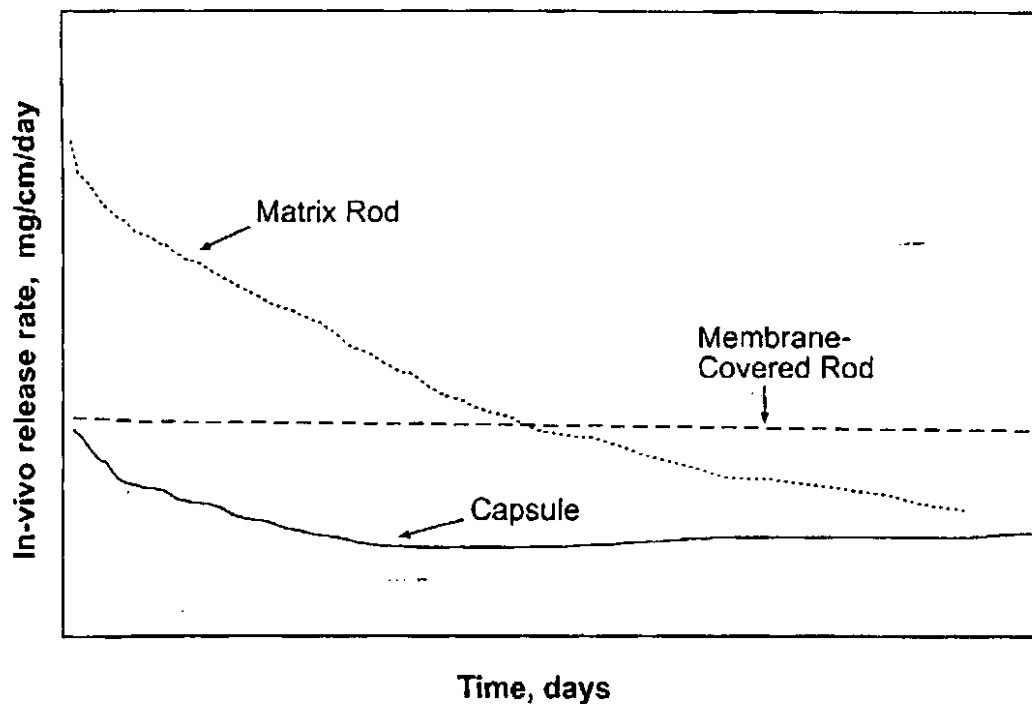


Figure 7 Drug release characteristics of three types of implants.

ranging from 3 to 12 months. The principle used in this design is essentially the same as the one used in the OROS system for oral controlled release. Basically, the osmotic engine draws in water at a constant rate through a semipermeable membrane, and this water causes an increase in hydrostatic pressure inside the device. That pressure pushes the drug out at a constant rate through a small orifice at the end opposite of the membrane. The rate of drug efflux is proportional to the rate of water ingress into the device. The water ingress rate is manipulated by the nature of the membrane material, as well as by its geometry.

Rates of drug release for the Duros are constant over 3–12 months, as shown in the chapter devoted specifically to this delivery system. The constancy of rate is achieved by regulating the rate of water ingress into the osmotic engine, rather than by manipulation of diffusion of drug, as is the case with the Norplant design. In that regard, the choice of the membrane material is the key to performance of the Duros device.

B. Toxicological Considerations

Polymers in implantable drug delivery systems must be toxicologically evaluated as with other drugs or excipients. The nonclinical toxicology program required for polymers in implantable drug delivery systems depends on exposure to the polymer, extracts (including residual monomers, process additives, and degradation products), and the final product. Exposure should be quantified and include evaluation of local distribution and local tolerance.

If the polymer is a structural component of the implant, a determination of leachables of the polymer in the drug vehicle is appropriate. The polymer and extracts should be biocompatible since they are in contact with components that are systemically released. The tests listed in ISO/ANSI/AAMI Standard 10993, Biological Evaluation of Medical Devices are intended to

provide testing strategies for medical devices. There are similar guidelines in the U.S. Pharmacopoeia 23 for plastics used as drug containers. These tests may also be used to test biocompatibility. Extracts may also be tested for the potential to cause topical sensitization. Preparation of polymer extracts is defined by guidelines, but the choice of conditions should come close to the conditions of manufacture of the drug delivery system. Extracts are evaluated by in vitro cytotoxicity tests and in vivo irritation, intracutaneous injection, systemic injection, and implantation studies. A sample of the polymer may also be evaluated in these in vivo tests.

If the polymer is released systemically and not a new chemical entity (NCE), a review of the manufacturers' and published scientific literature should be conducted to gather clinical and nonclinical safety information. If data indicate that blood levels are acceptable based on historical exposure or existing toxicology data, then conduct of toxicology studies that include the final drug delivery formulation with a written review and justification of the use of the polymer may be all that is necessary.

If the polymer is released systemically and is an NCE, a series of in vitro and in vivo genotoxicity studies should be conducted. These mutagenicity and clastogenicity studies will evaluate if the polymer and/or extract harms the cell's DNA. If the assays reveal a genotoxic result in multiple assays, development of the polymer should be halted. If no genotoxic activity is present, a full toxicology program consisting of acute, chronic, reproduction, and carcinogenicity testing will in all likelihood be required. Additional toxicology studies would necessarily be conducted with the final formulation.

C. Polymer Requirements

In the Norplant-type system, the membrane material has to satisfy the following criteria:

1. Should satisfy the long-term toxicological requirements, as outlined in Section IV.B.
2. Should not promote fibrotic tissue growth upon itself.
3. Should have the appropriate diffusion coefficient for small molecule drugs.
4. Should be capable of being fabricated into cylinders of varying sizes.
5. Should have low solubility for the drug in question.
6. Must be flexible enough so as not to be "felt" by the user. Typically, the modulus should be in the elastomer range of about 10^6 dynes/cm² or 100,000 Pa.

In actual use, the last of these requirements turns out to be inappropriate. While it is true that flexibility led to user acceptance, removal of the rods after use for prolonged periods in the body (~2 years or more) presented problems, as it became difficult to locate the rods. The ALZA design circumvents this problem by substituting a harder material for the body of the implant, at some cost to user acceptance. For the ALZA design, the two most important materials (outer container material and the rate-controlling membrane plug) must satisfy not only the toxicological and fibrotic growth requirement, but the container material must be rigid, and locatable either by feel or by other techniques, after prolonged use. This material must also have negligible solubility for the drug or the excipients, and negligible diffusion coefficient for the components of the drug formulation. The membrane plug material, on the other hand, must (in addition to the first two requirements above) have the following characteristics:

1. Possess a reproducible and well-defined permeability coefficient for water
2. Be moldable by standard polymer fabrication procedures
3. Retain its shape (under the constraints of the container material) without appreciable swelling in the presence of bodily fluids

In the next section, some of the materials and their characteristics will be explored.

D. Materials of Use

The earliest version of Norplant used six identical cylindrical rods (2.4 mm o.d., 1.57 mm i.d., 30 mm filled length) made of Silastic, a polydimethylsiloxane polymer made by Dow-Corning. The particular one used was Silastic medical-grade elastomer 382. This is a catalyst-cured siloxane elastomer, which for the implant application is also filled with silica. Essentially, thin-walled tubes were fabricated from this material, and sealed at the ends after having been filled with levonorgestrel crystals.

Later versions of Norplant include the rod and the covered rod. The rod is essentially a matrix of drug homogeneously dispersed inside the Silastic elastomer, whereas the covered rod comprises a core rod of PDMS and levonorgestrel, sealed inside thin-walled medical-grade Silastic tubing, using medical-grade Silastic adhesive. Practically all of this work derives from the early work of Folkman and Long (49), which evaluated the diffusion of small molecules through Silastic material. Repeated use of this material has ensured its continuance as an implant material, whereas others have not been subject to enough long-term studies to warrant use as a long-term implant material. In developmental work, however, poly(ϵ -caprolactone) has been studied extensively in a development product called Copranor[®] (50). In the reported study, effective diffusion rates were obtained for levonorgestrel, testosterone, and progesterone. Biodegradable polymers such as esters of poly(lactic acid) and poly(glycolic acid), while acceptable as implant materials, generally exhibit too low a diffusion rate for most drugs of interest. The reason for this is that the PLA-PGA copolymers generally have too high a T_g , whereas both poly(ϵ -caprolactone) and silicone elastomers have low, subambient T_g values.

In the Duros system, the outer container is constructed from a titanium alloy. The critical rate-controlling membrane is fabricated from a proprietary polyurethane developed specifically for ALZA Corporation. Early clinical data show little to no fibrotic growth around the implant body or its ends; more details are available elsewhere in this book.

E. Fabrication

The Norplant capsules are fabricated by first extruding tubes of Silastic, then filling with crystals of levonorgestrel, and then subsequently sealing the ends of the tube with silicone medical adhesive. Presumably, diffusion through the thin walls of the tube (approximately 15 mils) is the rate-controlling step, whereas diffusion through the ends (~150 mils) is much slower because of the higher pathlength.

The rods are fabricated by mixing about 25% by weight of steroid with a stannous octoate catalyst and Silastic 382; then pouring into a mold. Typical dimensions of rods are 2.4 mm diameter and 2 or 3 cm length.

Sterilization is carried out using ethylene oxide rather than radiation, since radiation further crosslinks the silicone and leads to a reduction in diffusion rates. Earlier studies had indicated that radiation affects the drug more than the polymer, but later studies have not borne this out. In any case, the preferred method of sterilization is by use of ethylene oxide.

Details of fabrication of the Duros device are given elsewhere in this book.

F. Issues and Opportunities

The use of biomaterials in human implants underwent a significant change in the early 1980s when the first of the silicone breast implant suits hit the courtrooms. Favorable and substantial awards to the plaintiffs resulted in bankruptcy for Dow-Corning. Subsequent lawsuits were directed at the parent companies of Dow-Corning, resulting in Dow Chemical making payments as well. All of this had very adverse consequences for the use of silicone materials

in humans. Several companies, particularly the larger ones such as DuPont, Shell Chemical, and Exxon, made it corporate policy to not allow the use of any of their materials in inside-the-body applications.

In this context, the passage of the recent Biomaterials Access Assurance Act (H.R.872, Public Law 105-230, passed 8/98) is of great significance to biomaterial suppliers. The Act specifically exempts a supplier from liability for harm to a client caused by an implant, provided the supplier is not the implant manufacturer, and provided the supplier has supplied raw materials that meet contractual requirements and specifications. This should open the door for small and big firms to enter or reenter the biomaterials supplier market, but economics may drive the decision more than the perceived exemption from liability. Certainly, if the market is sizable for the polymer in question and/or if manufacturers of the implant are willing to pay a premium for implantable biomaterials, bigger firms will reenter the field. Otherwise the status quo will prevail, with smaller firms supplying materials to the industry. However, in all likelihood, the number of suppliers for any given biomaterial will increase, eventually driving prices down to manageable levels. The onus of testing and proving the safety of the implanted biomaterial will rest squarely on the implant manufacturer in each instance.

V. MICRO- AND NANOPARTICLE DELIVERY

Microparticles and nanoparticles incorporate drug in matrix or encapsulated form, delivered to the body via injection (IM, IV, or subcutaneous), via the oral cavity or via the nose. Control of delivery is typically achieved by one of the following mechanisms:

1. Diffusion through the coating of the capsules (for encapsulated particles)
2. Diffusion through the matrix of the particles
3. Erosion of the coating material
4. Erosion of the matrix material

For nasal and oral delivery, the particles are typically in the 20- μ to 100- μ m range, since smaller particles can be inhaled and may make their way to the lung for alveolar delivery. For injectable delivery, to achieve prolonged duration of effect, the particles tend to be in the 50- to 100- μ m range. Nanoparticles are classified as having diameters below 1 μ m and tend to be used specifically for targeted drug delivery, usually via the injectable route.

The field of micro- and nanoparticles used in drug delivery is so broad an area of research that to list all of the applications and associated polymers is not practicable. It is convenient to subdivide this category as follows:

1. Bioadhesive microparticles
2. Injectable biodegradable depot formulations
3. Nanoparticles

The bioadhesive particles are typically formulated for mucosal delivery; this includes GI, buccal, nasal, and vaginal delivery. Injectable depot formulations invariably use biodegradable polymers, whereas nanoparticles may employ biodegradable and nonbiodegradable polymers. The rationale behind this subclassification is that for prolonged duration of delivery some bioadhesiveness is required of mucosal delivery vehicles, while depot formulations do not have this requirement. Nanoparticles are conceived to be used exclusively in injectable delivery and so are not required to bioadhere.

It is pertinent to make some general observations before proceeding to the specifics of each of these types of microparticulate delivery.

1. No product using bioadhesive particles has found commercial success to date. The products that offer prolonged action in mucosal delivery are nasal sprays, which do not employ bioadhesive microparticles. Therefore, we will survey the research on these particles to date and the materials employed in such formulations.
2. Depot formulations using biodegradable particles have been commercially successful, e.g., Lupron Depot®.
3. Nanoparticulate delivery is in early stages of research.
4. It is fair to say that, except for the case of biodegradable polymer matrices, formulations with microspheres tend not to have sustained or controlled release characteristics. Even in the case of microcapsules, the coating uniformity determines the degree of control over the release characteristics, even though in principle, membrane-coated particles can possess a controlled release profile. Furthermore, there is always a distribution of sizes in any of these preparations, and since surface-to-volume ratio also influences release kinetics, there is bound to be a distribution of rates achievable with any given preparation.

A. Mucosal Delivery: Bioadhesive Materials

In the field of mucosal delivery, the focus has been on two aspects of delivery:

1. Improving duration of action using mucoadhesive particles
2. Improving bioavailability of peptide drugs by enhanced delivery across the mucosa

For improving mucoadhesion, a variety of polymers have been tried with varying degrees of success. Perhaps the most mentioned polymer is a poly(acrylic acid) that is sold under the trade name Carbopol® by B.F. Goodrich. A variety of in vitro studies have claimed superior mucoadhesion for this polymer (51). In particular, the crosslinked poly(acrylic acid) known as polycarbophil has been claimed to have superior mucoadhesive properties. The crosslinking is usually carried out using divinyl glycol; crosslinked resins are available from B.F. Goodrich under the trade name Noveon®. This polymer has found successful use in three commercial products from Columbia Laboratories. These are not strictly microparticulate formulations but involve gels made of mucoadhesive polymer. They are discussed here as examples of commercialized mucoadhesive formulations:

- Replens®—a vaginal moisturizer product utilizing polycarbophil in an aqueous gel formulation; duration of action is claimed to be several days
- Advantage 24®—a vaginal contraceptive product, also utilizing a polycarbophil aqueous gel but containing a spermicide, nonoxynol 9 (3.5%); and
- Crinone®—a vaginal delivery system for progesterone, utilizing a suspension of progesterone in an oil-in-water emulsion, with the polycarbophil swollen to a gel by the water phase. The advantage of this delivery system is that the drug is localized in the vagina, supplying progesterone to the uterus where it is needed. The indications for Crinone are for use in assisted reproductive technology (ART) as well as for menopausal women. Duration of action is claimed to be 24 to 72 h, with the polycarbophil assisting in adhesion to the vaginal wall, and delivering the progesterone locally, from where it travels to the uterus to exert its effect. It is not clear exactly how control of release is achieved in the case of Crinone; the formulation composition suggests that it could be a combination of dissolution control and diffusion control. The contraceptive gel does not require controlled release of nonoxynol 9, as it is a one-use application.

In oral gastrointestinal applications, the efficacy of adhesion in humans of microparticles made of poly(acrylic acid) and polycarbophil continues to be controversial. One study using γ -scintigraphic techniques (52) demonstrated that while gastric retention in rats may be enhanced by the use of these polymeric microparticles, no such effect was observed in humans. Previous studies in rats had observed bioadhesion for these polymer particles (53,54). Currently, it is acknowledged that the unique environment of the human GI tract and the composition of its mucin layer may preclude the extrapolation of rat studies to humans, and that no effective bioadhesive works in the human GI tract. Research into this problem continues, and there may be a need for newer types of polymers that exhibit enhanced adhesion.

Several studies in humans have claimed bioadhesive characteristics for hydroxypropylcellulose (55,56) in both nasal and buccal delivery. In the nasal application, duration of action (or of adhesion) is approximately 2–4 h after application of a powder spray, whereas in the buccal application, the best patches adhere only for 30 min to 1 h.

The 3M Company has used a different approach to buccal adhesion. They investigated blends of polyolefins—polyisobutylene (PIB), polyisoprene (PIP), and poly(acrylic acid) (PAA)—and optimized the adhesion based on both invitro (peel strength) and in vivo studies (duration of adhesion). The optimization was directed to development of a removable buccal patch or tablet, which 3M markets under the name of the CyDot[®] delivery system. From reports of in vivo studies (57), it appears that the adhesive mixture consists of Vistanex[®] L-100 PIB (8%), Vistanex LMMH PIB (32%), and Polycarbophil poly(acrylic acid) (60%). In dogs, the duration of adhesion appears to be about 12–24 h, while another study using melatonin (58) shows data for 10-h adhesion in human volunteers.

In summary, the following points can be made regarding bioadhesive materials for drug delivery:

1. To date, no effective mucoadhesive has been identified for prolonging GI retention time in humans.
2. Some human data exist for bioadhesion of particles delivered intranasally.
3. A much bigger database attests to the viability of buccal adhesion using a variety of polymeric materials.

B. Injectable Depot Formulations/Materials and Performance

As mentioned above, all commercially successful depot formulations rely on the use of controlled biodegradation to prolong delivery of active agents. Duration of action ranges from a few weeks to several months. Two companies that are involved in the development of such formulations are TAP Pharmaceuticals and Alkermes. TAP has one line of depot products on the market, for delivery of leuprolide acetate, indicated for prostate cancer. Alkermes has announced preclinical and clinical studies for their products based on ProLease[®] technology. Both of these technologies utilize polylactide (PLA) or polyglycolide (PGA) in either homopolymer or copolymer form. (PLA is defined as the polylactic acid derived from polymerization of the lactide, and PGA is the polyglycolic acid derived from the glycolide.) Other biodegradable polymers that have been developed include the polyanhydrides (59), poly(ortho esters) (60), and the poly(ϵ -caprolactones) mentioned in Section IV.D, all of which have found limited commercial success when compared to the PLA-PGA polymers. Consequently, the discussion in this chapter will focus on the PLA-PGA-based systems.

Poly(lactide) is a stereoregular polymer that occurs in crystalline D or L forms, and is also available as the racemic DL-lactide. The DL form is mostly amorphous with a T_g of about 58°C. The glycolide is available mostly as a semicrystalline material with a T_g of 36°C and T_m of

230°C. The copolymers are amorphous with intermediate T_g values. Biodegradation of all of these polymers is thought to occur via simple hydrolytic cleavage of the ester bond, leading ultimately to the monomeric lactic or glycolic acids, which are metabolized via the Krebs cycle and excreted. Enzymes are speculated to be involved in the cleavage mechanism at later stages of degradation. The rate of degradation is dependent mostly on polymer composition, pH, surface area, and temperature. Therefore, these polymers do not show much variability in degradation rates from one body site to the next, a fact that accounts for their popularity in drug delivery applications.

The range of in vivo biodegradation times is from 2 months for a 50:50 copolymer to about 2 years for a poly(L-lactide). Both fabrication (manipulation of surface area) and polymer composition can be used to obtain a wide range of in vivo duration of action. The commercial product Lupron Depot[®], sold by TAP pharmaceuticals, will serve to illustrate this versatility.

Lupron Depot is an injectable formulation of leuprolide acetate that is available in lyophilized microsphere form. It is available in 1-month, 3-month, and 4-month dosages, and is administered via intramuscular injection. Dosages cover the indications of endometriosis and the palliative treatment of prostate cancer. The duration of action (1 month vs. 3 months) is manipulated strictly via the polymer composition. The 1-month injectable formulation contains approximately 75% of poly(DL-lactide-co-glycolide) and 15% D-mannitol as plasticizer, whereas the 3-month formulation contains 75% of poly(DL-lactide) and 15% D-mannitol. Clearly, the copolymer degrades faster in vivo than the poly(DL-lactide), and this accounts for the 1-month and 3-month periods of action. Although not specifically mentioned, the drug is dispersed in the polymer matrix and fabricated into microspheres via any one of the following techniques:

1. Solvent evaporation of an organic phase in water emulsion (useful for water-insoluble drugs)
2. Coacervation processes whereby the polymer is precipitated from an organic phase by addition of an aqueous drug solution (useful for water-soluble drugs)
3. Wurster air suspension coating process involving solution of drug and polymer in an organic solvent (useful for water-insoluble drugs, with the possibility of microcapsule formation)

The other product category where these polymers have been successfully used is the long-acting contraceptive category. Here microcapsules of norethisterone have been fabricated using poly(DL-lactide-co-glycolide) as the membrane material (61). The resulting microcapsules are formulated as a suspension in a sterile saline solution and injected intramuscularly. Up to 3 months of duration of action has been reported in clinical studies (62). These two categories (delivery of low molecular weight peptides and of steroids) continue to attract a lot of attention in the depot formulation attempts. More recent research is focusing on bigger entities such as human growth hormone and interferon.

C. Issues and Opportunities

In the injectable depot field, the major issues areas follow:

1. The lack of suitable polymers besides the PLA-PGA type with clearly defined in vivo degradation rates
2. The capability of delivering a range of proteins and peptides of differing solubility characteristics

The two issues are related in that the second capability is influenced to a large extent by the lack of suitable polymers. The lack of suitable polymers is really a lack of commercialized polymers, since a variety of polymers have been synthesized and studied in laboratories. With the hysteria surrounding breast implants and the liability issues arising from it, most companies have been reluctant to undertake large-scale manufacturing of suitable polymers. Remarks attributed to the implant field are equally applicable here in terms of opportunities for biomaterial suppliers.

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Exp. 02-091.153 (VII)

COREL 00586

Probing the mechanisms of drug release from hydrogels

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(Received May 13, 1990; accepted in revised form November 14, 1990)

The swelling and drug release kinetics in suspension polymerized glassy poly(hydroxyethyl methacrylate)/(PHEMA) beads have been studied in detail using model drugs of both high and low water solubilities: oxprenolol HCl (sol. in $H_2O \approx 77\%$) and diclofenac sodium (sol. in $H_2O \approx 2.65\%$). The current results verify our previous findings that the drug loading has a definite effect on the drug release mechanism from hydrogels. The initial swelling front penetration has been observed to behave more Fickian as drug loading increases. Such a transition can be considered as a change of relative importance of the diffusion process versus the polymer relaxation as a function of drug loading. The swelling fronts have also been observed to accelerate near the core. This is shown to be the natural outcome of the associated moving boundary problem in spherical geometry and not, as proposed by some authors, a super-Case II transport behaviour. In all cases, the swelling bead dimension goes through a maximum followed by a gradual approach to an equilibrium value during the drug release. In addition, a double-front formation (a swelling front and a drug dissolution front) has been observed for diclofenac sodium during the drug release due to the low drug solubility. We have also shown that by considering the increase in hydrogel bead dimension due to swelling and the decrease in dimension due to drug release, the swelling maximum in the transient dimensional changes can be qualitatively predicted. The osmotic contributions due to the presence of the drug can then be estimated from the differences between the experimental and calculated transient dimensional changes.

Introduction

Hydrogels are increasingly being utilized as delivery systems for a variety of therapeutic agents ranging from small molecular weight compounds to macromolecular peptide/protein drugs [1-3]. In addition to the equilibrium degree of swelling and biocompatibility, the permeability and swelling kinetics are the other two key properties of hydrogels which dictate the performance of hydrogel drug delivery systems [4]. For many applications, especially oral de-

livery, drug-loaded hydrogels in the dehydrated state are often employed. Since most hydrogels are glassy in the dehydrated state, the release of a water-soluble drug from such a system generally involves the simultaneous absorption of water and desorption of drug via a swelling-controlled mechanism. Such swelling and diffusion generally do not follow a Fickian diffusion mechanism. The existence of a slow macromolecular relaxation process in the swollen region is believed to be responsible for the observed non-Fickian behaviour. Depending on the relative magnitude of the rate of polymer swelling to the rate of drug diffusion, various release profiles may be possible [5]. Frequently, the rate of drug

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release from hydrogels can further be regulated by controlling the cross-linking density and the extent of water swelling [6]. To overcome the inherent first-order release behaviour due to geometry limitations, non-uniform initial drug distributions have also been employed to achieve zero-order drug release from spherical hydrogel beads [7, 8].

Various approaches have been proposed in the literature for predicting and interpreting drug release from swelling-controlled hydrogel matrices, however, only with limited success. These range from the phenomenological fitting of release data with a power function of time [9] and the determination of swelling interface number [10], to the moving boundary analyses of drug release from swellable polymers with constant or concentration dependent diffusion coefficients [11–14]. Most of these approaches have not considered the effect of local drug concentration on the swelling kinetics. However, we have shown [15] that the swelling behaviour and drug release kinetics in glassy hydrogels can be significantly affected by the local drug concentration. This is reflected in the observed transient dimensional changes and the penetrating solvent front movement during drug release from glassy hydrogel beads with different drug loadings. More recently, we demonstrated [16] that by the use of a time-dependent diffusion coefficient to account for the time-dependent polymer relaxation, various drug release behaviour in swelling-controlled hydrogels can be described by analytical solutions to the corresponding moving-boundary problem. The predicted release behaviour, ranging from Fickian to zero-order (or Case II), is consistent with both experimental observations and the Deborah number concept.

In this study, we attempt to verify some of our previous findings and to provide new results on the effect of drug solubility and drug loading on the transient swelling and dimensional changes in glassy hydrogel beads. The results obtained should be useful for the further elucidation of swelling and drug release mechanisms in glassy hydrogels.

Experimental

Poly(2-hydroxyethyl methacrylate) (PHEMA) beads used in this study were prepared, according to a previously published method [15, 17], by free radical suspension polymerization of purified 2-hydroxyethyl methacrylate monomer with 0.66 mol % of ethylene glycol dimethacrylate as crosslinker in a saturated salt solution at 80°C using *t*-butyl peroxy-2-ethylhexanoate as the initiator and freshly precipitated $\text{Mg}(\text{OH})_2$ as the suspending agent. After the completion of polymerization, these beads were filtered and extracted in a Soxhlet with methanol for over 24 h before being dried and fractionated. For the present study, the fraction of PHEMA beads with an average dry diameter of 0.08 cm and an equilibrium water content of 36% was used.

Oxprenolol HCl, a β -blocker with very high water solubility ($\approx 77\%$) and diclofenac sodium, an anti-inflammatory agent with low water solubility ($\approx 2\%$) were used as model drugs. Various drug loadings were achieved by equilibrating the PHEMA beads in an excess amount (> 10 to 1 ratio) of drug solutions prepared in ethanol/water mixtures. The loading solvent compositions were selected to maximize both the polymer swelling and the drug solubility. For example, a solution of 70% ethanol in water was selected for the loading of oxprenolol HCl, which gives an equilibrium solvent swelling of 60% in PHEMA beads and a maximum solubility of $> 70\%$ for oxprenolol HCl. Similarly, a solution of 84% ethanol in water was employed for the loading of diclofenac sodium which yields an equilibrium solvent swelling of 54% in PHEMA beads and a maximum solubility of $> 45\%$ for diclofenac sodium. After filtering, rinsing and drying, the loaded beads were then used for swelling and drug release studies in distilled water. The swelling experiments were performed in a water-jacketed cuvette maintained at 37°C with a circulating water bath. The swelling front movement was observed with a WILD M420 microscope equipped with camera attachments. The in vitro drug release at 37°C under perfect-

sink diffusion condition was monitored continuously in a stirred cuvette on a Hewlett-Packard 8452A diod-array UV-Vis spectrophotometer equipped with a water-jacketted cuvette holder and a built-in magnetic stirrer, at 274 nm for oxprenolol HCl and 252 nm for diclofenac sodium.

Results and discussion

The swelling kinetics and the transient dimensional changes during the release of a dissolved or dispersed drug from a glassy, initially dehydrated hydrogel are generally more complex than the case of a single penetrant transport in glassy polymers. The presence of a water soluble drug alters both the swelling osmotic pressure and the associated time-dependent relaxation of the hydrogel network during the simultaneous absorption of water and desorption of drug.

Many hydrogel systems reported in the literature may not be amenable to direct determination of swelling and solvent penetration mechanisms because of their ill-defined sample geometry and associated anisotropic swelling behaviour. Similar to the dimensional changes observed during sorption of organic penetrants in glassy polymers, the swelling of a hydrogel sheet in water may also exhibit a more rapid thickness increase than area followed by an abrupt decrease in thickness accompanied by an increase in area after the swelling fronts have met [18]. In contrast, the spherical hydrogel utilized here has the advantage of avoiding the anisotropy and the edge effects normally associated with swelling measurements in sheet samples. In addition, the swelling front position and dimensional changes are more amenable to direct observation in spherical hydrogel beads.

Swelling front penetration

Both the swelling and drug release studies were carried out in distilled water (pH 6.2). The reason to use distilled water rather than buffer solution was to avoid variable osmotic contributions from the countercurrent diffusion of buffering ions which could affect the observed

swelling front movement. The effects of drug loading on the fractional release of oxprenolol HCl and diclofenac sodium from glassy PHEMA beads at 37°C under perfect-sink condition are shown in Figs. 1 and 2. The associated penetrating front movements are presented in Figs. 3 and 4. In all cases, the solution pH changed from 6.2 to about 6.8 for diclofenac sodium, before and after the swelling and release experiments. Within such a narrow pH range, the solubilities for both drugs are essentially unchanged. For oxprenolol HCl, a drug with high water solubility, only one swelling front is observed at all drug loading levels and the penetration rate for the swelling front increases with increasing drug loading levels. On

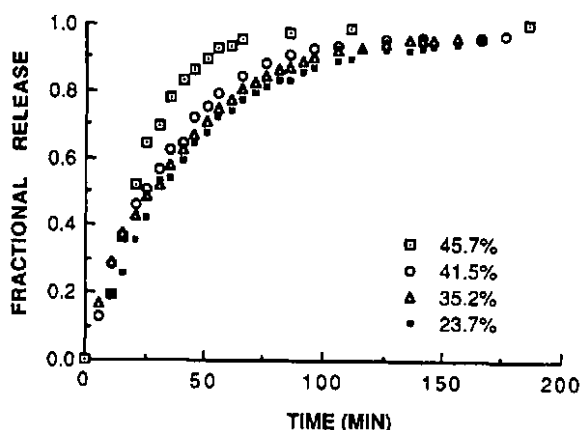


Fig. 1. Effect of loading level on the fractional release of oxprenolol HCl from glassy PHEMA beads at 37°C.

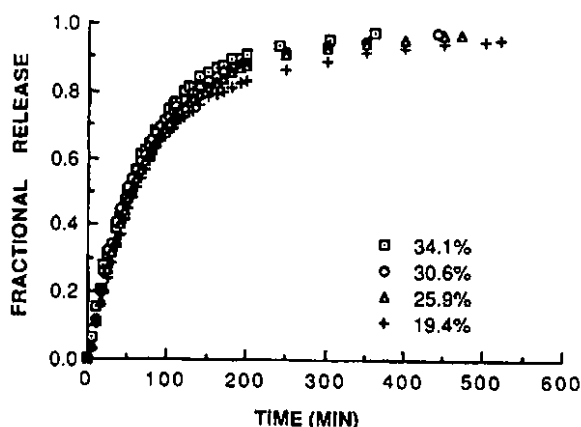


Fig. 2. Effect of loading level on the fractional release of diclofenac sodium from glassy PHEMA beads at 37°C.

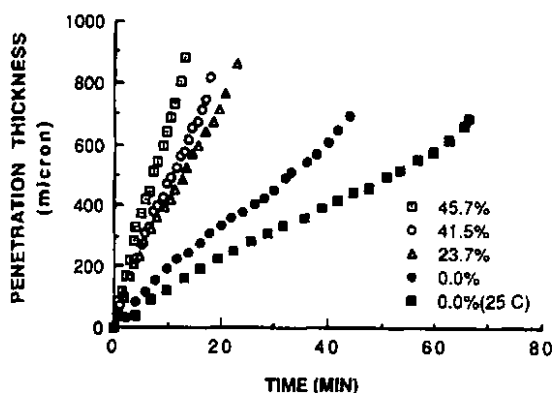


Fig. 3. Effect of loading level on the swelling front penetration during the release of oxprenolol HCl from PHEMA beads at 37°C.

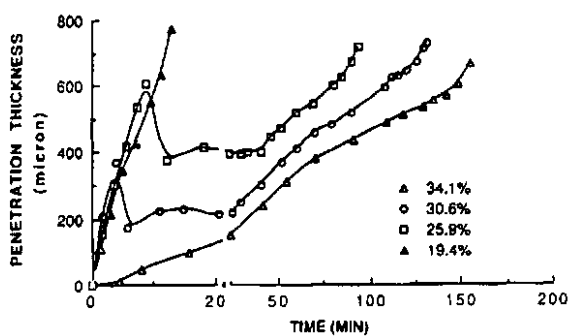


Fig. 4. Effect of loading level on the swelling and drug dissolution front penetration during the release of diclofenac sodium from PHEMA beads at 37°C.

the other hand, two moving boundaries are generally observed for diclofenac sodium, a drug with low water solubility, in a drug loading range of about 25–30% (Fig. 4). Below this range, a single fast-moving swelling front is observed, whereas above this range, a single slow-moving drug dissolution front separating an opaque drug core from a clear swollen region appears. Within the 25–30% diclofenac sodium loading range, a fast-moving swelling front is initially visible; however, a precipitation of diclofenac sodium starts to appear after a short penetration period and eventually develops into a slow-moving drug dissolution front. This transition of fronts is evident from Fig. 4, where the apparent sharp drop in penetration thickness reflects the transition from a fast-moving swelling front into a slow moving drug dissolution front. This transition

appears to happen sooner with higher diclofenac sodium loadings and becomes absent at loading levels above this range. The possibility that local pH effect contributed to the observed drug precipitation and front movement is ruled out since the pH of a saturated solution of diclofenac sodium is about 7.8, which is way above its reported pKa value of 3.8–4.7. The drug precipitation and associated front movement for diclofenac sodium most likely are a result of the high drug loading and limited drug solubility in the swollen PHEMA network, as well as the thermodynamic phase behaviour of the specific drug-solvent-polymer system.

When the initial penetration data for oxprenolol HCl loaded PHEMA beads in Fig. 3 are presented as square root of time plots in Fig. 5, it is evident that the initial swelling front penetration becomes more Fickian as drug loading increases. Similar observations for thiamine HCl in PHEMA beads were reported by us [15]. On the other hand, the swelling front penetration in unloaded control is clearly non-Fickian at both 25°C and 37°C as suggested by the non-linear square root of time plots. Such a transition can be considered as a change of relative importance of the diffusion process versus the polymer relaxation as a function of drug loading. Similar square root of time plots for diclofenac sodium loaded beads do not reveal useful information because of the development of an opaque, slow-

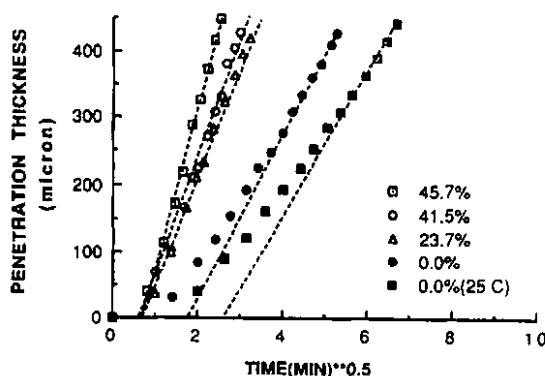


Fig. 5. Square root of time plots showing effect of loading level on the kinetics of swelling front penetration during the release of oxprenolol HCl from PHEMA beads at 37°C.

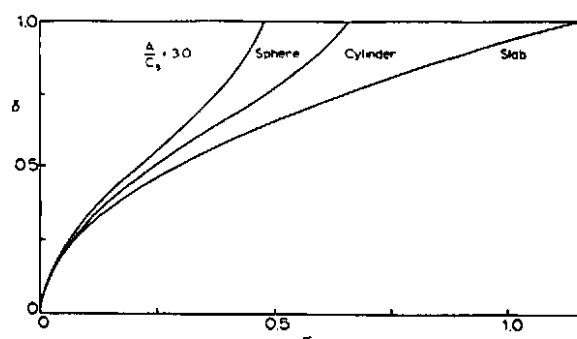


Fig. 6. Predicted effect of geometry on the moving boundary position as a function of time at a drug loading to solubility ratio (A/C_s) of 3.

moving drug dissolution front which masks the swelling front penetration.

The transient swelling front penetration behaviour as shown in Figs. 3 and 4 exhibits an initially non-linear region (ranging from Fickian to non-Fickian behaviour) followed by a short linear transition region before accelerating toward the core. Recently, by solving an associated moving boundary problem based on the Fickian diffusion equation, we have shown that the apparent acceleration of penetrating front near the core is a natural outcome of the spherical geometry [19] and not, as reported by some authors, a super-Case II transport behaviour. A typical theoretical plot for the penetrating behaviour in three different geometries is shown in Fig. 6 for a drug loading to solubility (A/C_s) ratio of 3. It is evident that the initial part of the moving boundary penetration is characteristically Fickian and an acceleration of penetrating front near the core is predicted in radially symmetric geometries (cylinders and spheres). However, such an acceleration is not predicted for the planar geometry.

Transient dimensional changes

The transient dimensional changes during the simultaneous solvent penetration and drug release from PHEMA beads are shown in Fig. 7 for oxprenolol HCl and in Fig. 8 for diclofenac sodium at various drug loading levels. In all cases, the swelling bead diameter goes through a maxi-

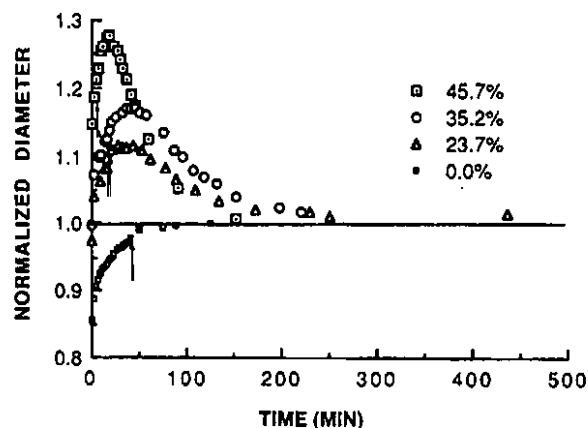


Fig. 7. Effect of loading level on the normalized dimensional changes (Relative to the equilibrium swollen dimension) during the release of oxprenolol HCl from glassy PHEMA beads at 37°C. †: Moving fronts meet.

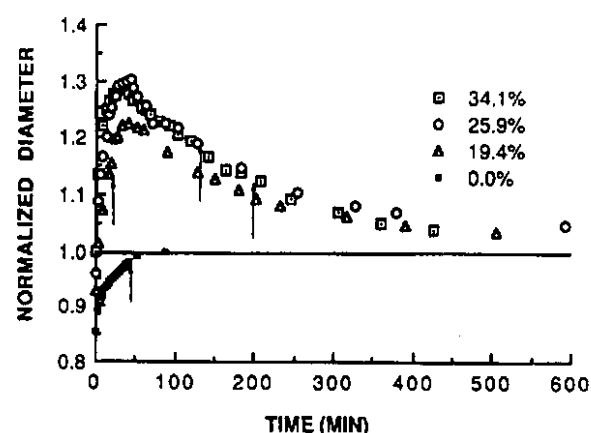


Fig. 8. Effect of loading level on the normalized dimensional changes (relative to the equilibrium swollen dimension) during the release of diclofenac sodium from glassy PHEMA beads at 37°C. †: Moving fronts meet.

mum followed by a gradual approach to an equilibrium value during drug release whereas the diameter of an unloaded PHEMA bead increases monotonically toward the equilibrium value, similar to our previous findings for thiamine HCl in PHEMA beads [15]. In both figures, the bead diameter was normalized to the equilibrium swollen diameter of the unloaded bead; therefore, the plots converge to the same equilibrium value, 1. Also, while the maximum peak height decreases with decreasing drug loading for both model drugs, the peak widens with a shift toward

longer time to achieve swelling maximum as one decreases the loading for oxprenolol HCl. On the other hand, relatively small changes in the peak width and time to reach maximum have been observed with changing diclofenac sodium loadings. These observations suggest that the osmotic contribution to the transient dimensional changes may be similar in diclofenac sodium loaded PHEMA beads due to the limited drug solubility in water. On the other hand, more variations in the osmotic contributions to swelling in the oxprenolol HCl loaded beads are expected due to the high drug solubility in water.

It is interesting to observe that the transient dimensional changes peak at 20–40 min for oxprenolol HCl loaded PHEMA beads depending on the drug loading; the higher the loading, the shorter the peak time. However, the peak time for diclofenac sodium loaded PHEMA beads appears to be around 35 min irrespective of loading levels. Also shown in Figs. 7 and 8 are time points when the penetrating swelling or dissolution fronts have met. As discussed in the previous section, the swelling fronts proceed much faster than that of the slow-moving drug dissolution fronts. As a result, the swelling fronts meet during the ascending portions of the swelling curves before reaching swelling maxima irrespective of the drug solubility, whereas the drug dissolution fronts, which only develop in diclofenac sodium loaded PHEMA beads, meet during the descending portions of the swelling curves after reaching swelling maxima.

The general schemes of observed swelling boundaries and dimensional changes during drug release in relation to drug solubilities are summarized in Fig. 9. It is clear that the presence of homogeneously dissolved or dispersed drug in PHEMA beads generates an additional osmotic driving force which alters both the total swelling osmotic pressure and the associated time-dependent relaxation of the hydrogel network during the simultaneous sorption of water and desorption of drug. As shown in the schematic drawings of Fig. 10, the swelling by water tends to increase, whereas the release of drug tends to decrease the dimension of the hydrogel bead. The

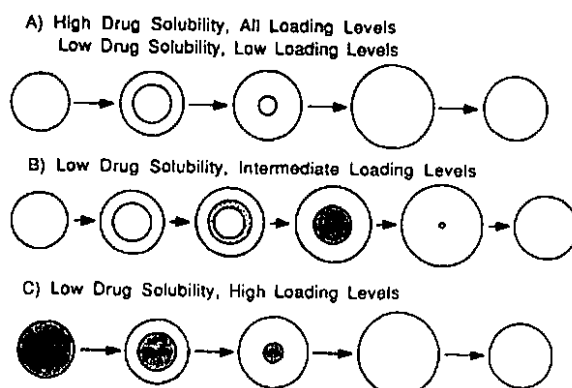


Fig. 9. Schematic drawing of observed swelling boundaries and dimensional changes during drug release in relation to drug solubilities.

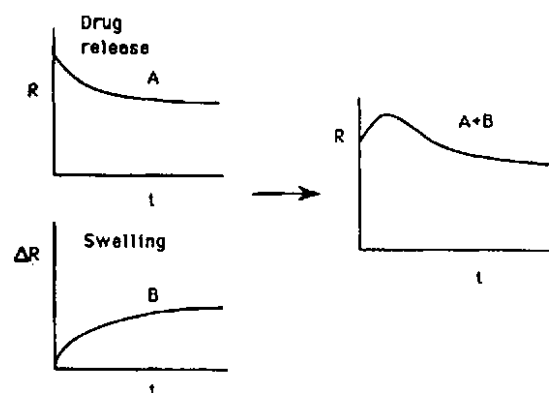


Fig. 10. Schematic drawing of a proposed mechanism for the observed dimensional changes in glassy hydrogel beads during drug release.

combination of these two competing processes should result in an observed maximum in the transient dimensional changes for the drug-loaded hydrogel beads. From the swelling data obtained in unloaded hydrogel beads and dimensional reductions calculated from release data assuming volume additivity, one can indeed obtain transient dimensional changes, to a first-order approximation, qualitatively agreeing with experimental observations. This is illustrated in Fig. 11a and b for two oxprenolol HCl loadings. Since the osmotic contribution from the drug has not been considered in the approximation scheme of Fig. 10, the difference between the experimentally obtained and the calculated transient dimensional changes in Fig. 11 will

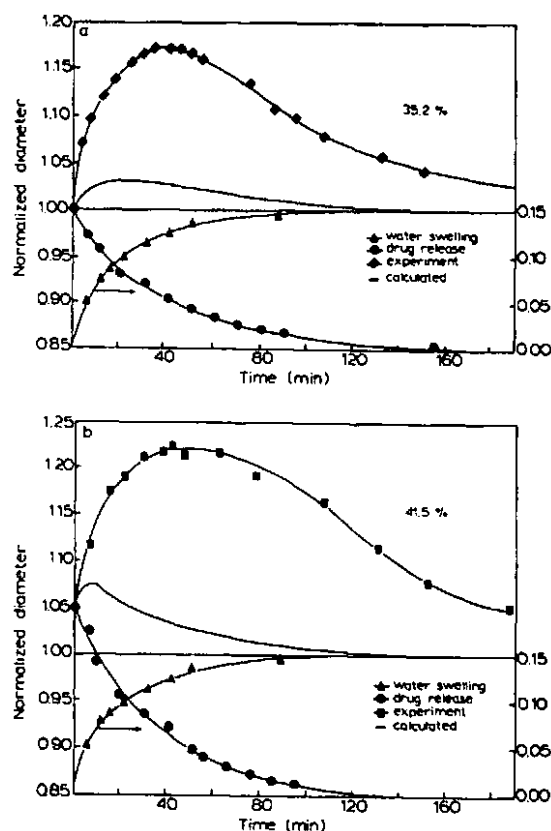


Fig. 11. Comparison of experimental and calculated dimensional changes during oxprenolol HCl release from glassy PHEMA beads. (a) 35.2% loading; (b) 41.5% loading.

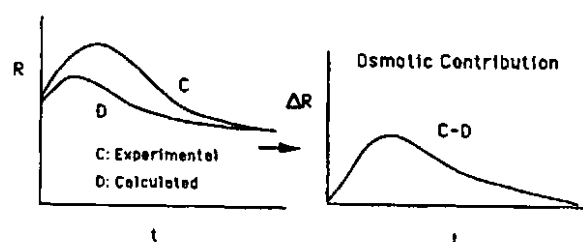


Fig. 12. Schematic drawing for the determination of the osmotic contribution to dimensional changes during drug release from glassy hydrogel beads. The calculated curve is determined according to the scheme in Fig. 10.

yield the osmotic contribution to the overall dimensional increases (Fig. 12). The osmotic contributions so obtained from Fig. 11a and b for oxprenolol HCl loaded PHEMA beads are presented in Fig. 13, where the osmotic contribution to the change in normalized bead diameter

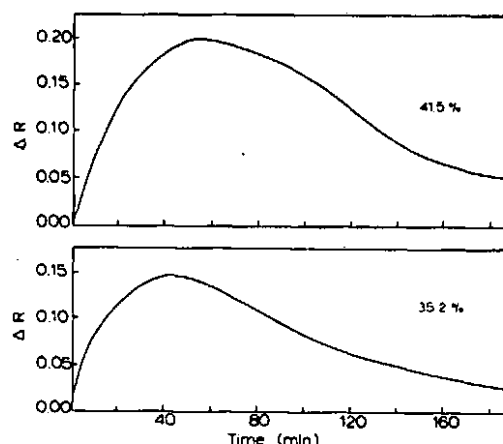


Fig. 13. Effect of oxprenolol HCl loading level on the osmotic contribution to the dimensional changes during drug release from glassy PHEMA beads.

is obviously larger with higher drug loading. It is evident that at the initial stage of the swelling process, the osmotic contribution from the drug loading continues to build up. However, after the completion of the solvent penetration, the internal drug concentration and hence, its role in the osmotic contribution decreases continuously as the drug release proceeds. In response to such a change in the total swelling osmotic pressure, the swollen elastic PHEMA network would have to reduce its dimension in accordance with thermodynamic requirements.

Acknowledgements

The authors would like to thank Ms. Shirlee Curtis for technical assistance. This work was supported by grants from the Medical Research Council of Canada (Grant Nos. DG-377, 378 and 379) and the Ontario Center for Materials Research (Grant No. TCJ-372) to PIL.

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Exp 02-091.153
(VIII)

Steady-State Pharmacokinetic Properties of a 24-Hour Prolonged-Release Formulation of Ropinirole: Results of Two Randomized Studies in Patients with Parkinson's Disease

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ABSTRACT

Background: Ropinirole 24-hour prolonged release is a new once-daily formulation of ropinirole that provides continuous delivery of ropinirole over 24 hours.

Objective: The studies described here were conducted to characterize the steady-state pharmacokinetics of ropinirole 24-hour prolonged release in patients with Parkinson's disease.

Methods: Study 164 was a 2-part study; Part A employed a crossover design to assess the relative bioavailability of steady-state ropinirole 24-hour prolonged release 8 mg QD and ropinirole immediate release 2.5 mg TID, and Part B evaluated the effect of food intake on the rate and extent of ropinirole absorption from ropinirole 24-hour prolonged release 8 mg QD. Study 165 assessed the dose proportionality of ropinirole 24-hour prolonged release 2-, 4-, and 8-mg tablets and the dose-strength equivalence of four 2-mg tablets compared with one 8-mg tablet. Intensive pharmacokinetic blood sampling was performed over 24 hours. Steady-state C_{max} , C_{min} , AUC from time zero to 24 hours after dosing (AUC_{0-24}), and T_{max} were determined by noncompartmental methods.

Results: Twenty-three patients (91% white; mean age, 67 years [range, 34–80 years]; mean weight, 84.5 kg [range, 57–103 kg]) were randomized to treatment in Study 164. Twenty-eight patients (86% white; mean age, 67 years [range, 47–87 years]; mean weight, 84.6 kg [range, 49–128 kg]) were randomized to treatment in Study 165. Compared with ropinirole immediate release, ropinirole 24-hour prolonged release had a smooth plasma concentration–time profile over 24 hours. AUC_{0-24} and C_{min} values, normalized to a 1-mg dose, were similar for ropinirole 24-hour prolonged release and ropinirole immediate release. Dose-normalized C_{max} was slightly lower (~12%) for ropinirole 24-hour prolonged release than for ropinirole immediate release. The AUC_{0-24} and C_{min} were similar in the fed and fasted states. The pharmacoki-

netics of ropinirole 24-hour prolonged release were dose proportional, as indicated by the estimated slopes for AUC_{0-24} and C_{max} being close to unity, along with the 90% CIs being contained within the predefined dose-range-adjusted limits. For C_{min} , the slope was close to unity (1.04), but the upper end of the 90% CI fell marginally outside the predefined range. Statistical analysis indicated that the dose strengths were equivalent when a single pharmacokinetic outlier was excluded from the analysis.

Conclusions: Ropinirole 24-hour prolonged release provided continuous delivery of ropinirole over 24 hours, resulting in a smooth plasma concentration–time profile, and food had no significant effect on absorption. Dose-normalized AUC_{0-24} and C_{min} were similar for both formulations, and dose-normalized C_{max} was slightly lower for ropinirole 24-hour prolonged release. These relative bioavailability data indicated that patients may switch overnight from ropinirole immediate release to ropinirole 24-hour prolonged release while maintaining similar daily exposure. The pharmacokinetics of ropinirole were dose proportional over the range from 2 to 8 mg. The dose strengths of four 2-mg tablets and one 8-mg tablet of ropinirole 24-hour prolonged release were found to be equivalent. (*Clin Ther.* 2007;29:2654–2666) Copyright © 2007 Excerpta Medica, Inc.

Key words: Parkinson's disease, ropinirole 24-hour prolonged release, pharmacokinetics, bioavailability, food effect, dose proportionality, dose-strength equivalence.

Accepted for publication November 1, 2007.

Express Track online publication December 13, 2007.

doi:10.1016/j.clinthera.2007.12.010

0149-2918/\$32.00

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INTRODUCTION

Ropinirole is a nonergoline dopamine agonist at dopamine D₂/D₃ receptors and acts both peripherally and centrally. The immediate-release formulation of ropinirole is approved for use as monotherapy in the treatment of early-stage Parkinson's disease (PD) (Hoehn-Yahr stage I-III)^{1,2} and as an adjunct to levodopa (L-dopa) therapy in more advanced disease.^{3,4} As with other dopamine agonists, ropinirole immediate release requires titration to an efficacious dose to minimize dopaminergic adverse effects. The initial dose of ropinirole immediate release is 0.75 mg/d; the dose is increased in 0.75-mg increments weekly over the first 4 weeks.⁴ Thirteen dose levels are available for titration up to the maximum approved dose of 24 mg/d (given as 8 mg TID). After 2 years of treatment, the median dose of ropinirole immediate release in patients with PD has been reported to be 12 mg/d,⁵ and an initial therapeutic response is expected at doses of 3 to 9 mg/d.⁴

Ropinirole immediate release has an established clinical pharmacology and safety profile.^{6,7} When taken as oral immediate-release tablets, ropinirole is rapidly and almost completely absorbed, with T_{max} generally reached 1 to 2 hours after dosing. The bioavailability of ropinirole is ~50%. Ropinirole is cleared primarily by metabolism in the liver, with only 10% of an administered dose excreted as unchanged ropinirole. In vitro data indicate that cytochrome P450 (CYP) 1A2 is the principal hepatic enzyme responsible for the metabolism of ropinirole, with a minor contribution from CYP3A4 at higher drug concentrations. At clinically relevant doses of ropinirole, CYP1A2 is the major hepatic enzyme responsible for clearance of ropinirole. Ropinirole and its circulating metabolites do not inhibit most CYP enzymes in vitro and have only a weak potential to inhibit CYP2D6.⁷ Reported 50% inhibition concentration values for CYP2D6 are at least 3-fold higher than the upper range of ropinirole concentrations associated with clinical doses up to and including 24 mg.⁸⁻¹⁰ Therefore, it appears unlikely that ropinirole will affect the pharmacokinetics of any concomitant medications that are CYP2D6 substrates via an inhibitory mechanism. Although no specific in vivo studies have been conducted to investigate the potential for interaction between ropinirole and drugs that are CYP2D6 substrates, no reports indicating such an interaction have been identified in the literature.

Circulating metabolites do not contribute significantly to the pharmacologic activity of administered ropinirole. Concomitant administration of inhibitors or inducers of CYP1A2 metabolism may affect the clearance of ropinirole. When given as a single or repeated dose, ropinirole has linear pharmacokinetics over the therapeutic dose range and is eliminated with a t_{1/2} of ~5 to 6 hours. A population pharmacokinetic analysis reported population mean estimates for ropinirole immediate-release clearance and Vd of 47.3 L/h and 7.3 L/kg, respectively.⁷ The interindividual variability was 46% for clearance and 33% for Vd. Ropinirole clearance was 33% slower in women receiving hormone replacement therapy (HRT) compared with those who were not, and was 15% slower in patients aged >65 years than in those aged ≤65 years; however, clearance was not affected by sex, mild or moderate renal impairment, or stage of PD. Because ropinirole is titrated to efficacy, use of HRT does not affect the dosing or titration schedule.

Because ropinirole has a t_{1/2} of ~5 to 6 hours, ropinirole immediate release must be taken 3 times daily, which results in fluctuations in drug concentrations throughout the day. A once-daily formulation—ropinirole 24-hour prolonged release—has been developed that provides controlled delivery of ropinirole over 24 hours (data on file, HC2005/00025/00, GlaxoSmithKline, Harlow, United Kingdom, 2006). The in vitro release rate of ropinirole from ropinirole 24-hour prolonged release is reported to be independent of pH and to be maintained in the presence of alcohol, suggesting that the formulation is resistant to dose dumping under these conditions (data on file).

The once-daily dosing of ropinirole 24-hour prolonged release provides a simplified regimen that involves fewer dose increments to attain an efficacious dose compared with ropinirole immediate release. The starting dose of ropinirole 24-hour prolonged release is 2 mg/d. The daily dose can be increased by 2 mg/d at weekly intervals up to 8 mg QD. Thereafter, the dose can be increased by up to 4 mg/d at weekly intervals up to a maximum of 24 mg/d.¹¹ The starting dose of ropinirole immediate release is 0.25 mg TID (0.75 mg/d). The daily dose can be increased by 0.75 mg/d at weekly intervals up to a dose of 3 mg/d, followed by an increase of 1.5 mg/d at weekly intervals up to a dose of 9 mg/d. Thereafter, the dose can be increased by 3 mg/d up to a maximum of 24 mg/d.

The once-daily dosing of ropinirole 24-hour prolonged release may also contribute to an improved tolerability profile and improvements in motor function and ability to perform activities of daily living. A once-daily formulation has the potential to increase patient compliance compared with therapies that are administered 2 or 3 times daily.^{12,13} Therapies that provide more continuous stimulation of dopamine receptors have been found to reduce motor complications in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys and in patients with PD.¹⁴ Thus, the continuous delivery of ropinirole from ropinirole 24-hour prolonged release may also delay or prevent the onset of L-dopa-related motor complications due to continuous dopaminergic stimulation.¹⁵

The efficacy and safety profiles of ropinirole 24-hour prolonged release have been established in 2 Phase III clinical trials. The EASE-PD (Efficacy And Safety Evaluation) Monotherapy trial¹⁶ was a 3-period, 2-treatment crossover study that compared ropinirole 24-hour prolonged release QD with ropinirole immediate release TID in 161 patients with early-stage PD. The study was designed in such a way that each patient received a treatment preceded or succeeded both by itself and by the alternative formulation. The results indicated that the upwardly titrated regimens of ropinirole 24-hour prolonged release and ropinirole immediate release had similar tolerability profiles. The findings also suggested the ease of switching overnight from ropinirole immediate release to ropinirole 24-hour prolonged release (based on similar total daily doses of ropinirole) while maintaining efficacy. The EASE-PD Adjunct study¹⁷ in 393 patients with advanced PD that was not optimally controlled with L-dopa also reported the efficacy and tolerability of ropinirole 24-hour prolonged release.

This paper reports the results of 2 Phase II clinical pharmacology studies that investigated the steady-state pharmacokinetics of ropinirole 24-hour prolonged release in patients with early PD. The relative bioavailability of the 2 formulations was investigated to support the dosing strategy of switching patients from ropinirole immediate release to ropinirole 24-hour prolonged release (or the reverse) in the EASE-PD Monotherapy study.¹⁶ Also investigated were the effect of a high-fat meal on the absorption of ropinirole 24-hour prolonged release and the dose proportionality of ropinirole 24-hour prolonged release over the dose range from 2 to 8 mg. The dose-strength equiva-

lence of four 2-mg tablets and one 8-mg tablet of ropinirole 24-hour prolonged release was assessed to investigate the pharmacokinetics of switching patients from multiple low-dose tablets to a single higher-dose tablet.

PATIENTS AND METHODS

Patient Populations

The 2 Phase II clinical pharmacology studies, Study 164 (protocol 101468/164) and Study 165 (protocol 101468/165), included patients aged ≥ 30 years with early-stage PD (Hoehn and Yahr stage I-III). All patients gave written informed consent before study participation. Patients were excluded from the studies if they had clinically significant laboratory or electrocardiographic abnormalities at screening; diastolic blood pressure ≥ 110 or ≤ 50 mm Hg or systolic blood pressure ≥ 180 or ≤ 90 mm Hg before dosing; or a history of any dopaminergic treatment (excluding ropinirole 24-hour prolonged release) within the 2 weeks before enrollment. In addition, patients participating in Study 164 were excluded if they had received any dose or preparation of L-dopa. Patients taking an L-dopa preparation could be included in Study 165 provided L-dopa treatment remained unchanged throughout the study. In both studies, patients were excluded if they had a recent history of severe dizziness or fainting due to postural hypotension; were taking medications known to affect restless legs syndrome or sleep; or underwent withdrawal, initiation, or a dose change of medications known to inhibit or induce CYP1A2.

Study Designs

The study protocols, informed consent form, and other relevant information were reviewed and approved by the appropriate institutional review boards. In both studies, patients were allocated to treatments through the use of a randomization schedule produced by a GlaxoSmithKline computer-generated randomization system before the start of the study.

The ropinirole 24-hour prolonged-release tablets used in the 2 trials were supplied as white, film-coated, capsule-shaped tablets containing ropinirole hydrochloride equivalent to 2, 4, or 8 mg of active drug substance. Ropinirole immediate-release tablets were supplied as white, film-coated, pentagonal tablets* con-

*Trademark: Tiltab® (GlaxoSmithKline, Brentford, United Kingdom).

taining ropinirole hydrochloride equivalent to 0.5 or 2 mg of active drug substance.

Study 164

Study 164 was a Phase II, randomized, open-label trial that consisted of 2 parts. Part A evaluated the relative bioavailability of ropinirole 24-hour prolonged release 8 mg QD and ropinirole immediate release 2.5 mg TID (given at 8-hour intervals) after an overnight switch in formulations. Part B assessed the effect of food intake on the extent and rate of absorption of ropinirole 24-hour prolonged release 8 mg (the highest available tablet strength) at steady state.

Before study entry, all patients had to have received ropinirole 24-hour prolonged release 8 mg for at least 3 days. Therefore, patients who had not previously received ropinirole 24-hour prolonged release underwent upward titration, starting with ropinirole 24-hour prolonged release 2 mg/d, with weekly dose escalation to 4, 6, and 8 mg/d. Patients who were already receiving ropinirole 24-hour prolonged release at study entry (as part of a long-term safety study [protocol 101468/196]) either underwent upward titration from their existing dose to 8 mg QD or downward titration from a maximum dose of 10 mg QD to 8 mg QD.

Once stabilized on ropinirole 24-hour prolonged release 8 mg for 3 days, patients underwent randomization (1:1) to 1 of 2 treatment sequences in which they either started with ropinirole 24-hour prolonged release and switched overnight to ropinirole immediate release at the end of period 1, or they started with ropinirole immediate release for period 1 and switched overnight to ropinirole 24-hour prolonged release for period 2. Each treatment period lasted 4 to 7 days, and patients switched formulations at the end of period 1. Blood samples for pharmacokinetic evaluation were obtained on the last days of period 1 and 2 for both treatment sequences. On completion of Part A, patients either entered Part B or left the study.

In Part B, the pharmacokinetics of ropinirole were compared when ropinirole 24-hour prolonged release 8 mg was administered in the fed and fasted states. In the fasted state, patients received ropinirole 24-hour prolonged release after an overnight fast of at least 10 hours and continued fasting for a further 4 hours. In the fed state, patients received ropinirole 24-hour prolonged release after a high-fat breakfast (as defined by the US Food and Drug Administration¹⁸), which they consumed 30 minutes before dosing. After dosing,

no further food was allowed for 4 hours. Two treatment assessment periods were separated by at least 3 days. Patients received ropinirole 24-hour prolonged release in either the fed or fasted state for the first treatment assessment and were then switched to the alternative state for the second treatment assessment.

In both parts of the study, blood samples were taken before dosing and up to 24 hours after dosing on the 2 pharmacokinetic assessment days. In patients receiving ropinirole immediate release, blood samples were taken at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours after each of the 3 doses of ropinirole immediate release. In patients receiving ropinirole 24-hour prolonged release, blood samples were taken at 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours after dosing.

Study 165

Study 165 was a 5-week, Phase II, randomized, open-label trial that evaluated the dose proportionality of ropinirole 24-hour prolonged release over the dose range from 2 to 8 mg and the dose-strength equivalence of ropinirole 24-hour prolonged release (four 2-mg tablets vs one 8-mg tablet).

Patients received ropinirole 24-hour prolonged release QD at a starting dose of 2 mg/d, with weekly escalation in 2-mg increments to a maximum of 8 mg/d. For the assessment of dose proportionality, steady-state pharmacokinetic evaluations were conducted at the 2-, 4-, and 8-mg dose levels. For assessment of the dose-strength equivalence of four 2-mg tablets compared with one 8-mg tablet at the 8-mg dose level, patients were randomized to 1 of 2 treatment sequences: one 8-mg tablet of ropinirole 24-hour prolonged release QD, followed by four 2-mg tablets of ropinirole 24-hour prolonged release QD; or four 2-mg tablets of ropinirole 24-hour prolonged release QD, followed by one 8-mg tablet of ropinirole 24-hour prolonged release QD. On the days with no pharmacokinetic assessments, patients took their medication at home, and, after ≥3 days of sequential dosing, returned to the clinic for pharmacokinetic evaluation. On pharmacokinetic assessment days, ropinirole 24-hour prolonged release was taken after breakfast, and all food and drink was standardized. Blood samples were taken 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, and 24 hours after dosing.

Plasma Sample Preparation

Blood samples for determination of concentrations of ropinirole in plasma were collected into 4-mL tubes

containing lithium heparin and were immediately chilled. Samples were separated by centrifugation at -4°C within 30 minutes of collection. Plasma was transferred into polypropylene tubes and frozen at 20°C until transported for analysis.

Assay Methods

Plasma samples were analyzed for ropinirole based on a solid-phase extraction procedure in acidified plasma, followed by liquid chromatography with tandem mass-spectrometric detection. For a 0.5-mL aliquot of human plasma, the lower limit of quantification for ropinirole was 0.02 ng/mL and the higher limit of quantification was 5 ng/mL. Quality control samples were assayed with each batch of samples against separately prepared calibration standards. The results for the quality control samples were used to assess the day-to-day performance of the assay.

Pharmacokinetic Analyses

Noncompartmental methods were used to determine the steady-state observed pharmacokinetic parameters of ropinirole ($C_{\max}$, $T_{\max}$, AUC from time zero to 24 hours after dosing [AUC_{0-24}], and $C_{\min}$).

The degree of fluctuation (DF) in ropinirole plasma concentrations over 24 hours was calculated as $\text{DF} = (C_{\max} - C_{\min})/C_{\text{avg}}$, where $C_{\text{avg}} = \text{AUC}_{0-\tau}/\tau$ and τ is the dosing interval.

Tolerability

In studies 164 and 165, the investigators were responsible for the detection and documentation of events meeting the definition of an adverse event (AE). An AE was defined as any untoward medical occurrence (ie, unfavorable and unintended sign, including an abnormal laboratory finding, symptom, or disease, new or exacerbated) in a patient that was temporally associated with the use of a medicinal product, whether or not considered related to that product.

Statistical Analyses

Relative Bioavailability

For analysis of the relative bioavailability of ropinirole 24-hour prolonged release QD and ropinirole immediate release TID, which was the primary focus of Study 164 Part A, the pharmacokinetic parameters AUC_{0-24} , $C_{\max}$, and $C_{\min}$ were normalized to a dose of 1 mg. Dose-normalized ropinirole AUC_{0-24} , $C_{\max}$, and

$C_{\min}$ values were analyzed separately by analysis of variance, fitting terms for sequence, patient within sequence, period, and regimen. Point estimates and 90% CIs were derived for the ratio of ropinirole 24-hour prolonged release QD to ropinirole immediate release TID for these parameters. Also assessed were the DF and $T_{\max}$.

Food Effects

For analysis of the effect of food intake on the pharmacokinetics of ropinirole 24-hour prolonged release, which was the primary focus of Study 164 Part B, point estimates and 90% CIs were derived for the fed:fasted ratio for AUC_{0-24} , $C_{\max}$, and $C_{\min}$. Also assessed were the DF and $T_{\max}$.

Dose Proportionality

For analysis of the dose proportionality of ropinirole 24-hour prolonged release over a dose range from 2 to 8 mg in Study 165, the estimated mean slopes and 90% CIs, based on the power model, were constructed for AUC_{0-24} , $C_{\max}$, and $C_{\min}$. Dose proportionality was demonstrated if the 90% CIs of the estimated mean slopes were within the range from 0.839 to 1.161. These ranges were based on the standard limits of 0.80 to 1.25,¹⁹ but were adjusted as follows to take into account the dose range under study:

$$\text{Lower limit} = 1 + \log_e(0.8)/\log_e(r)$$

$$\text{Upper limit} = 1 + \log_e(1.25)/\log_e(r)$$

where $\log_e$ is the natural logarithm and r is calculated as (highest dose)/(lower dose).

Dose-Strength Equivalence

To assess the dose-strength equivalence of ropinirole 24-hour prolonged release given as one 8-mg tablet daily and four 2-mg tablets daily in Study 165, point estimates and 90% CIs were computed for the ratio of one 8-mg tablet to four 2-mg tablets for AUC_{0-24} , $C_{\max}$, and $C_{\min}$. Dose-strength equivalence was demonstrated if the 90% CIs for the ratios were within the range from 0.80 to 1.25.¹⁹ Within-patient coefficients of variation (CVw) were calculated for AUC_{0-24} , $C_{\max}$, and $C_{\min}$, based on the following log-normal distribution:

$$\text{CVw}(\%) = 100 \times [\exp(\text{mean square error}) - 1]^{1/2}$$

RESULTS

Patients

Twenty-three patients were randomized to treatment in Study 164. Their mean age was 67 years (range, 34–80 years) and their mean weight was 84.5 kg (range, 57–103 kg). Twenty-one were white, 1 was Hispanic, and 1 was black. Twenty-eight patients were randomized to treatment in Study 165. Their mean age was 67 years (range, 47–87 years) and their mean weight was 84.6 kg (range, 49–128 kg). Twenty-four were white, 3 were Hispanic, and 1 was black.

Relative Bioavailability

Of the 20 patients who participated in Part A of Study 164, 19 provided pharmacokinetic data for the evaluation of relative bioavailability. After oral administration of ropinirole immediate release 2.5 mg TID, plasma concentrations of ropinirole increased rapidly, with median T_{max} occurring 2 hours after each dose. After oral administration of ropinirole 24-hour prolonged release, the rate of absorption was slower, with a median T_{max} occurring 6 hours after dosing. After attainment of C_{max} , the concentration of ropinirole 24-hour prolonged release slowly declined

until 24 hours after dosing (Figure 1). Table I provides a summary of the results of the statistical analysis of relative bioavailability at steady state.

The dose-normalized AUC_{0-24} and C_{min} values for ropinirole 24-hour prolonged release 8 mg QID relative to ropinirole immediate release 2.5 mg TID were similar, with the point estimates of the ratios being close to unity and the 90% CIs within the limits for bioequivalence (0.80–1.25). The dose-normalized C_{max} for ropinirole 24-hour prolonged release, however, was –12% lower than that for ropinirole immediate release.

The slightly lower C_{max} values for ropinirole 24-hour prolonged release and the similar C_{min} values for ropinirole 24-hour prolonged release and ropinirole immediate release resulted in a slightly smaller DF in ropinirole concentrations for ropinirole 24-hour prolonged release compared with ropinirole immediate release (0.66 vs 0.85, respectively) (Table II). The once-daily dosing regimen of ropinirole 24-hour prolonged release was also associated with a reduced frequency of fluctuations in ropinirole plasma concentrations compared with the thrice-daily dosing regimen of ropinirole immediate release (Figure 1).

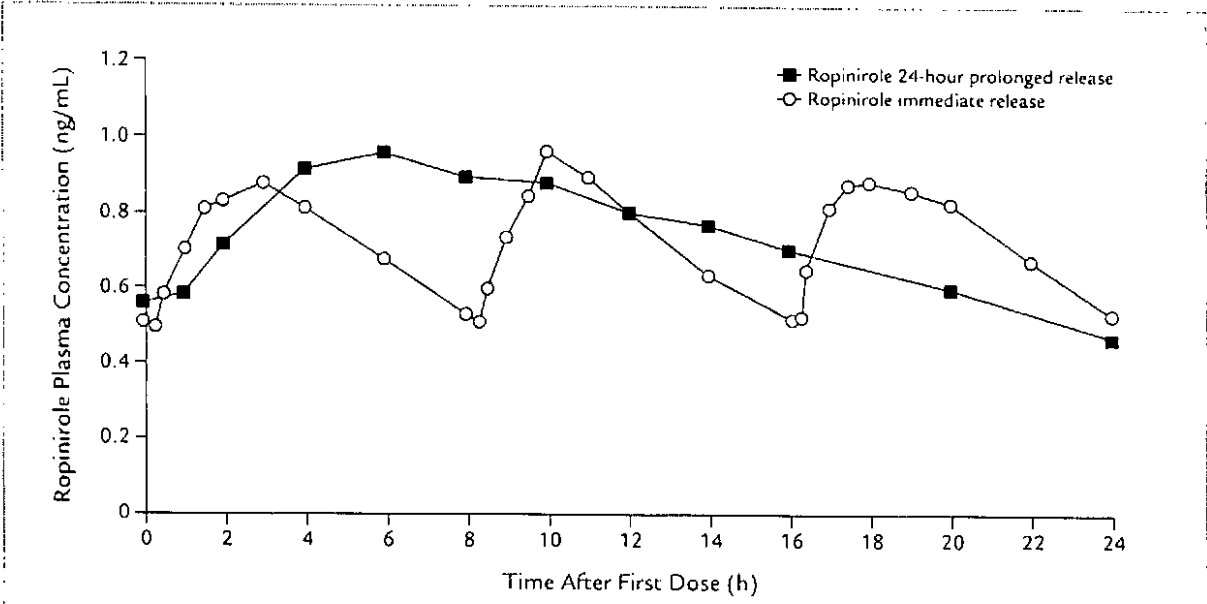


Figure 1. Dose-normalized plasma concentration–time profiles of ropinirole 24-hour prolonged release and ropinirole immediate release in patients with early Parkinson's disease.

Table I. Results of the statistical analysis of the steady-state relative bioavailability of ropinirole 24-hour prolonged release and ropinirole immediate release.

Parameter	Ratio, 24-Hour Prolonged Release: Immediate Release	90% CI	CVw, %
Dose-normalized AUC_{0-24} , ng · h/mL	1.02	0.96-1.09	11.4
Dose-normalized C_{max} , ng/mL	0.88	0.78-0.99	21.5
Dose-normalized C_{min} , ng/mL	0.98	0.90-1.06	14.8

CVw = within-patient coefficient of variation; AUC_{0-24} = AUC from time zero to 24 hours after dosing.

Table II. Summary of dose-normalized (to 1 mg) steady-state pharmacokinetic parameters for ropinirole 24-hour prolonged release and ropinirole immediate release in patients with Parkinson's disease. Values are geometric mean (between-patient coefficient of variation), unless otherwise indicated.

Parameter	Ropinirole 24-Hour Prolonged Release 8 mg QD (n = 19)	Ropinirole Immediate Release 2.5 mg TID (n = 19)
AUC_{0-24} , ng · h/mL/mg	16.3 (50.3)	16.0 (48.6)
C_{max} , ng/mL/mg	0.92 (50.1)	1.05 (42.3)
C_{min} , ng/mL/mg	0.44 (75.1)	0.45 (67.6)
T_{max} , median (range), h	6.00 (4.00-20.00)	2.00 (0.25-4.00)
Degree of fluctuation	0.66 (31.8)	0.85 (53.1)

AUC_{0-24} = AUC from time zero to 24 hours after dosing.

Effect of Food

Of the 21 patients who participated in Part B of Study 164, 20 had evaluable pharmacokinetic data in the fed and fasted states. Table III provides a summary of the pharmacokinetic parameters for ropinirole 24-hour prolonged release in patients in the fed and fasted states.

AUC_{0-24} and C_{min} values were similar in the fed and fasted states, based on the ratios of the geometric mean fed:fasted ratios being close to unity and the 90% CIs being within the limits for bioequivalence (0.80-1.25). C_{max} was 15% higher and T_{max} was delayed by ~2 hours when ropinirole 24-hour prolonged release was administered with a high-fat meal compared with the fasted state. There was no evidence that the controlled-release mechanism of ropinirole 24-hour prolonged release was affected by coadministration with food (ie, no evidence of dose dumping) (Figure 2).

Dose Proportionality

Of the 28 patients enrolled in Study 165, 22 completed the study and provided evaluable pharmacokinetic data for dose proportionality. Median plasma concentration-time profiles for ropinirole 24-hour prolonged release are illustrated in Figure 3.

When dose proportionality was evaluated in patients receiving one 2-mg tablet, one 4-mg tablet, and one 8-mg tablet of ropinirole 24-hour prolonged release, the slopes for AUC_{0-24} , C_{max} , and C_{min} were close to unity, indicating linearity (Table IV). The 90% CIs for the mean slopes of AUC_{0-24} , C_{max} , and C_{min} were all contained within the standard range (0.80-1.25). The 90% CIs for AUC_{0-24} and C_{max} were also within the dose-range-adjusted limits of 0.839 and 1.161, but the upper end of the 90% CI for C_{min} (1.17) fell marginally outside these dose-range-adjusted limits (Table IV).

Table III. Comparison of pharmacokinetic parameters for ropinirole 24-hour prolonged release in the fed and fasted states.

Parameter	Comparison	Ratio	90% CI	CVw, %
AUC_{0-24} , ng · h/mL*	Fed:fasted	1.06	0.95 to 1.19	21.1
C_{max} , ng/mL*	Fed:fasted	1.15	1.01 to 1.31	25.3
C_{min} , ng/mL*	Fed:fasted	0.96	0.85 to 1.08	23.3
T_{max} , h†	Fed – fasted	2.00	-0.02 to 4.00	

CVw = within-patient coefficient of variation; AUC_{0-24} = AUC from time zero to 24 hours after dosing.

*Represents the ratio of least squares geometric means between groups.

†Represents the estimated median difference between groups.

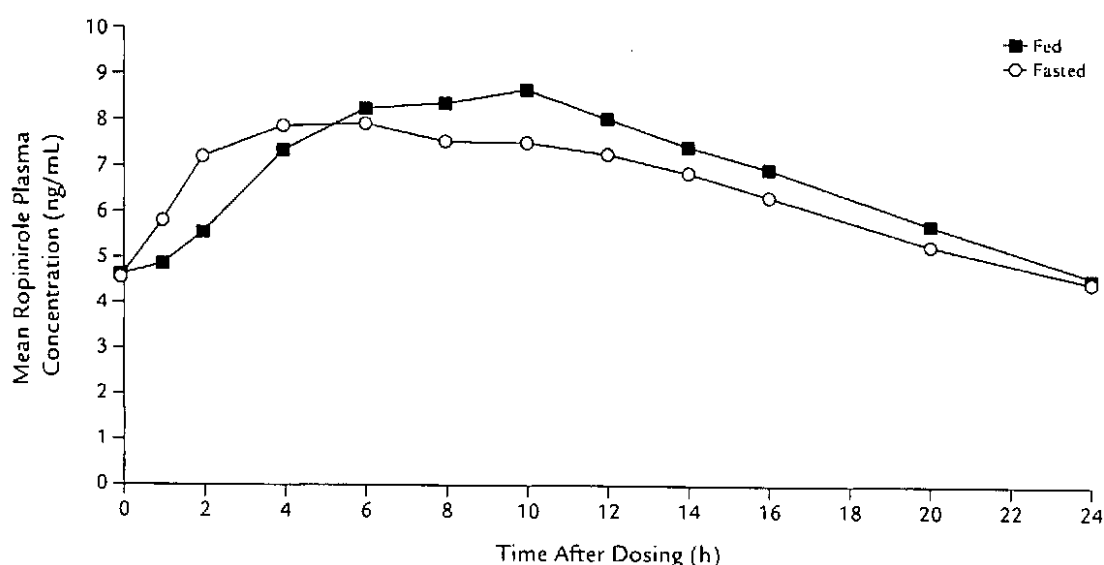


Figure 2. Mean ropinirole plasma concentration-time profiles after steady-state administration of ropinirole 24-hour prolonged release 8 mg in the fed (high-fat meal) and fasted states.

One patient who received one 8-mg tablet of ropinirole 24-hour prolonged release was identified as a potential pharmacokinetic and statistical outlier. The ropinirole concentrations for this patient were ~2-fold higher than those observed in the other patients following this regimen, and the concentration-time profile was also inconsistent with other pharmacokinetic profiles obtained for this patient. To fully evaluate the effect of this patient on the assessment of dose proportionality, the statistical analysis was also conducted without this patient. Analysis excluding this patient

indicated dose proportionality, with 90% CIs within the dose-range-adjusted limits for all 3 pharmacokinetic parameters (data not shown).

Dose-Strength Equivalence

All 22 patients who completed Study 165 had evaluable pharmacokinetic data for dose-strength equivalence. AUC_{0-24} and C_{max} values were ~10% higher after administration of one 8-mg tablet of ropinirole 24-hour prolonged release compared with four 2-mg tablets, and the 90% CIs were marginally

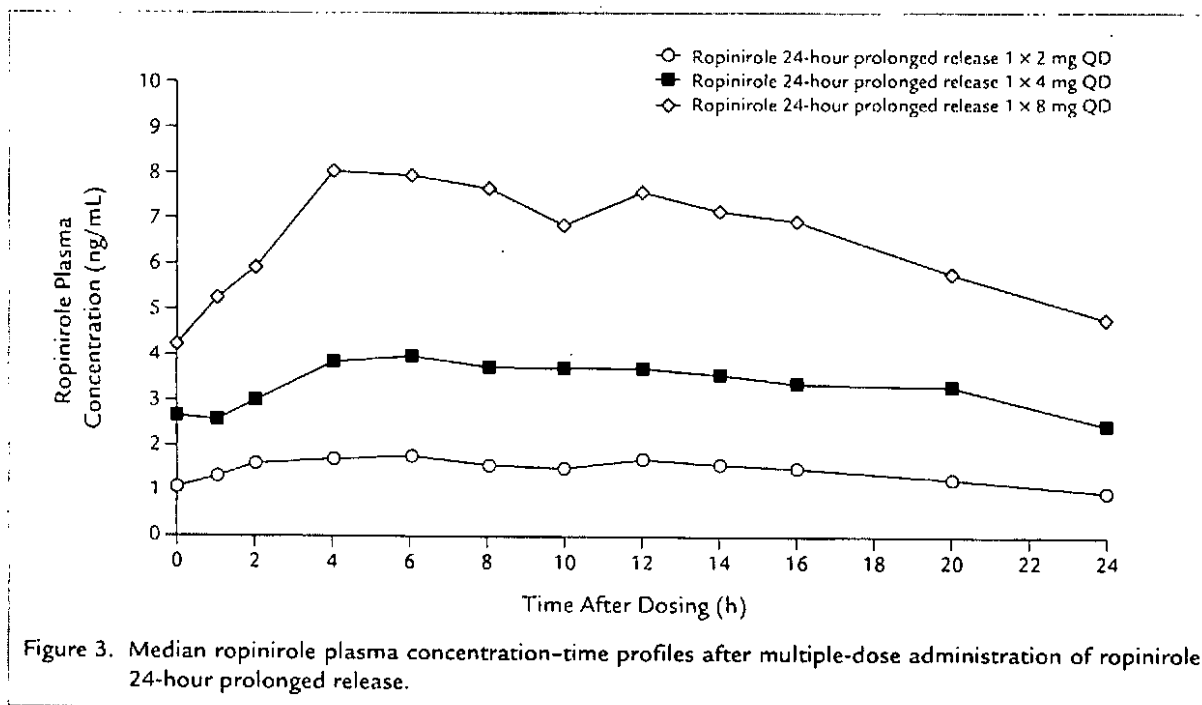


Figure 3. Median ropinirole plasma concentration-time profiles after multiple-dose administration of ropinirole 24-hour prolonged release.

Table IV. Results of the statistical analyses of the steady-state dose proportionality of ropinirole 24-hour prolonged release.

Parameter	Slope	90% CI
AUC_{0-24} , ng · h/mL	1.07	0.99-1.16
C_{max} , ng/mL	1.05	0.96-1.15
C_{min} , ng/mL	1.04	0.90-1.17

AUC_{0-24} = AUC from time zero to 24 hours after dosing.

Table V. Results of the statistical analyses of the steady-state dose-strength equivalence of ropinirole 24-hour prolonged release. All data are for the ratio of one 8-mg tablet to four 2-mg tablets.

Parameter	Ratio	90% CI	CVw, %
AUC_{0-24} , ng · h/mL	1.10	0.95-1.26	27.5
C_{max} , ng/mL	1.09	0.93-1.27	31.1
C_{min} , ng/mL	1.04	0.90-1.21	29.3

CVw = within-patient coefficient of variation; AUC_{0-24} = AUC from time zero to 24 hours after dosing.

outside the predefined limits (0.80-1.25), whereas C_{min} was contained within the predefined limits (Table V). To fully evaluate the effect of the previously mentioned pharmacokinetic outlier on the assessment of dose-strength equivalence, the statistical analysis was conducted without this patient. This analysis found dose-strength equivalence between one 8-mg tablet and four 2-mg tablets of ropinirole 24-hour prolonged release for AUC_{0-24} , C_{max} , and C_{min} , with all the corresponding 90% CIs within the limits for equivalence.

Median ropinirole 24-hour prolonged release plasma concentration-time profiles after multiple-dose administration of one 8-mg tablet and four 2-mg tablets are illustrated in Figure 4.

Tolerability

Ropinirole 24-hour prolonged release 2 to 8 mg QD was generally well tolerated in patients with PD in studies 164 and 165. In both studies, the 2-mg dose of ropinirole was associated with the highest incidence of AEs; tolerability improved as the ropinirole dose was titrated upward. As would be expected with a dopamine agonist, the majority of AEs involved dopaminergic effects.

In Study 164, 54 treatment-emergent AEs occurred in 15 of 23 patients (65%). The most frequently re-

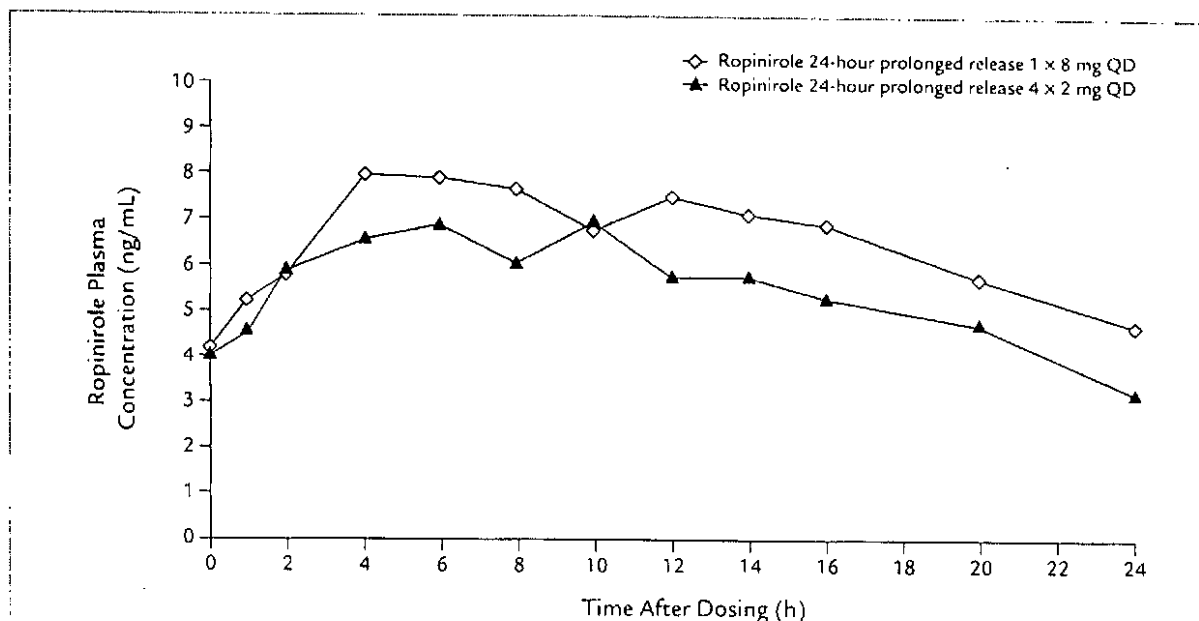


Figure 4. Median ropinirole plasma concentration-time profiles after multiple-dose administration of one 8-mg tablet and four 2-mg tablets of ropinirole 24-hour prolonged release.

ported AEs were dizziness, nausea, back pain, and hallucination. Of the 54 AEs, 98% were of mild or moderate severity. Ten AEs (19%) in 6 patients were considered by the investigator to be possibly related to ropinirole. In Part A, the tolerability profile for the 8-mg QD regimen of ropinirole 24-hour prolonged release was similar to that of the 2.5-mg TID regimen of ropinirole immediate release, with only 2 of 20 patients (10%) reporting AEs in each treatment period. In Part B, the tolerability profile was similar for the ropinirole 24-hour prolonged-release fed and fasted regimens, with 4 of 21 patients (19%) reporting AEs in the fed period and 3 of 21 patients (14%) reporting AEs in the fasted period.

In Study 165, 74 treatment-emergent AEs occurred in 21 of 28 patients (75%). The most commonly reported AEs were headache, somnolence, constipation, and dizziness. All 74 AEs were of mild or moderate severity. Twenty-six AEs reported by 10 patients (35%) were considered by the investigator to be possibly related or related to ropinirole 24-hour prolonged release. The incidence of AEs was similar for one 8-mg tablet of ropinirole 24-hour prolonged release (32%) and four 2-mg tablets of ropinirole 24-hour prolonged release (35%). The incidence of AEs that were considered possibly related or related to study medication

was also similar for one 8-mg tablet (1 patient) and four 2-mg tablets (2 patients).

DISCUSSION

This review summarizes pharmacokinetic data from 2 Phase II clinical pharmacology studies that investigated the steady-state pharmacokinetics of ropinirole 24-hour prolonged release in patients with early PD. The studies included an evaluation of the relative bioavailability of ropinirole 24-hour prolonged release and ropinirole immediate release to help determine the strategy for switching patients from the immediate-release formulation to the 24-hour prolonged-release formulation, and evaluations of food effects, dose proportionality, and dose-strength equivalence of ropinirole 24-hour prolonged release.

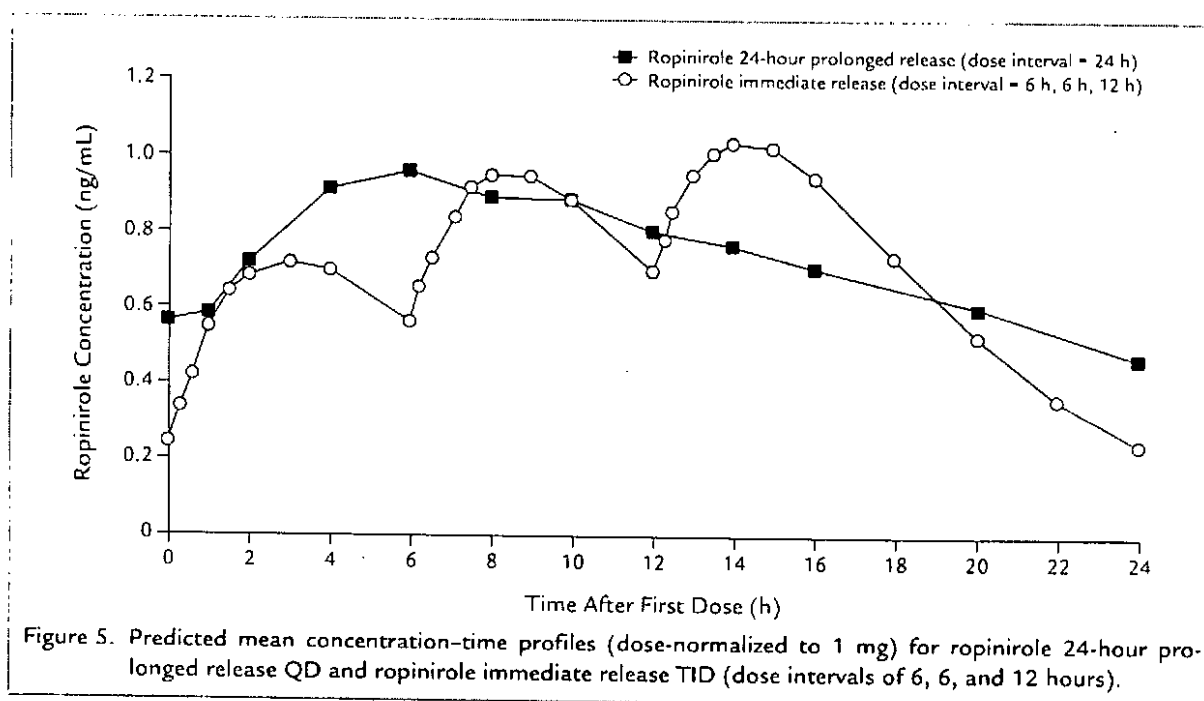
On a dose-for-dose basis, AUC_{0-24} and C_{min} values were similar for ropinirole 24-hour prolonged release QD and ropinirole immediate release TID. However, C_{max} values were ~12% lower for ropinirole 24-hour prolonged release than for ropinirole immediate release; this small difference is not considered to be clinically significant. Patients who received ropinirole immediate release (2.5 mg TID) were able to switch overnight to the closest dose of ropinirole 24-hour prolonged release (8 mg QD), with no effect on the

tolerability profile. This finding was supported by data from the EASE-PD Monotherapy study,²⁰ in which a population pharmacokinetic analysis indicated that on average, systemic exposure to ropinirole was similar when patients switched from ropinirole immediate release to ropinirole 24-hour prolonged release (based on the nearest total daily dose), with no clinically significant differences in efficacy or tolerability between the 2 formulations.

The mean DF for ropinirole 24-hour prolonged release was 0.66 and for ropinirole immediate release was 0.85, indicating that there was slightly lower variation in the range of ropinirole concentrations over a 24-hour period with ropinirole 24-hour prolonged release QD compared with ropinirole immediate release TID (Figure 1). As it is recommended that ropinirole immediate release be taken with meals,⁴ it appears likely that in clinical practice, ropinirole immediate release would be taken at breakfast, lunch, and dinner (eg, at 7:00 AM, 1:00 PM, and 7:00 PM), approximating a 6-, 6-, and 12-hour dosing regimen. This dosing regimen would be predicted to result in much larger fluctuations in plasma concentrations over a 24-hour period compared with ropinirole 24-hour prolonged release (Figure 5). With a 6-, 6-, and 12-hour regimen of ropinirole immediate release; there is ~5-fold fluctuation

between the maximum and minimum ropinirole concentrations, compared with a 2-fold fluctuation with ropinirole 24-hour prolonged release. Patients taking this regimen of ropinirole immediate release would, therefore, be predicted to have a 2-fold lower concentration of ropinirole first thing in the morning compared with patients taking ropinirole 24-hour prolonged release. Even without reference to the dosing frequency of ropinirole immediate release, the once-daily dosing regimen of ropinirole 24-hour prolonged release was associated with a reduced frequency of fluctuations compared with ropinirole immediate release (Figures 1 and 5).

There was no clinically relevant effect of food on the pharmacokinetics of ropinirole after administration of ropinirole 24-hour prolonged release in patients with PD. AUC_{0-24} and C_{min} values for ropinirole 24-hour prolonged release were similar in both the fed and fasted states. The C_{max} for ropinirole 24-hour prolonged release was higher (15%) and T_{max} delayed (~2 hours) in the fed state compared with the fasted state. This small increase in C_{max} and delay to T_{max} are unlikely to be of clinical relevance due to the relatively flat concentration-time profile of ropinirole after administration of ropinirole 24-hour prolonged release. In addition, there was no evidence to suggest



that the controlled release of ropinirole from the 24-hour prolonged-release formulation was affected by coadministration with food, and, therefore, dose dumping would not be expected to occur. These results suggest that ropinirole 24-hour prolonged release can be taken without regard to food intake.

The assessments of dose proportionality and dose-strength equivalence were complicated by the data from 1 patient receiving one 8-mg tablet of ropinirole 24-hour prolonged-release, who appeared to represent a pharmacokinetic and statistical outlier. Ropinirole concentrations for this patient were ~2-fold higher than those observed in other patients following this regimen, and this concentration-time profile was also inconsistent with other pharmacokinetic data obtained from this patient. No protocol deviations were noted and no other reason was found to explain the higher exposure to ropinirole with this regimen in this patient. There was no evidence to suggest that >1 tablet had been administered or that a concomitant medication had been taken that could have increased systemic exposure to ropinirole via inhibition of the CYP1A2 enzyme. No AEs were reported for this patient.

To fully evaluate the effect of this patient's data on the assessment of dose proportionality, statistical analysis was conducted with and without this patient, with the primary inference based on the analysis including this patient. Dose proportionality was found in terms of the AUC_{0-24} and C_{max} based on both the standard and dose-range-adjusted CI limits. There was a minor departure from dose proportionality for C_{min} , but dose proportionality was found over the dose range from 2 to 8 mg when the pharmacokinetic outlier was excluded, suggesting consistent pharmacokinetic performance across the range of available tablet strengths. Similarly, when the pharmacokinetic outlier was included in the analysis of dose-strength equivalence, AUC_{0-24} and C_{max} values were ~10% higher after administration of one 8-mg tablet compared with four 2-mg tablets, and the 90% CIs were marginally outside the predefined limits. Dose-strength equivalence was found between one 8-mg tablet and four 2-mg tablets of ropinirole 24-hour prolonged release for AUC_{0-24} , C_{max} , and C_{min} when the pharmacokinetic outlier was excluded.

The similarity in pharmacokinetics of the multiple- and single-tablet regimens was also reflected in the similar incidence of AEs between the 2 regimens. Therefore, these data suggest that patients beginning

treatment with ropinirole 24-hour prolonged release on a regimen of multiple low-dose tablets (four 2-mg tablets daily) can switch to an equivalent single dose of ropinirole 24-hour prolonged release (one 8-mg tablet daily) and maintain systemic exposure without any clinically relevant effects on tolerability.

CONCLUSIONS

In these 2 randomized, open-label studies in patients with PD, ropinirole 24-hour prolonged release provided continuous delivery of ropinirole over 24 hours, resulting in a smooth pharmacokinetic profile with reduced fluctuations in plasma levels over 24 hours compared with ropinirole immediate release. Systemic exposure was similar between ropinirole immediate release and ropinirole 24-hour prolonged release based on the same total daily dose, indicating that patients may switch overnight from the immediate-release formulation to a similar total daily dose of the prolonged-release formulation while maintaining similar daily exposure. Food was found to have no clinically relevant effect on absorption, and the pharmacokinetics of ropinirole were dose proportional over the dose range from 2 to 8 mg. Furthermore, patients taking multiple low-dose tablets (four 2-mg tablets) were able to switch to a single higher-dose tablet (8 mg) without a reduction in systemic exposure.

ACKNOWLEDGMENTS

The studies described in this paper were supported by GlaxoSmithKline Research and Development, Brentford, United Kingdom, and SkyePharma, London, United Kingdom. The authors thank Sarah Brown and Jackie van Bueren, Caudex Medical, Oxford, United Kingdom, for assistance in preparing the initial draft of the manuscript and collating author comments.

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DRUG AND PROFILE REPORTS

Ropinirole prolonged release: a guide to its use in Parkinson's disease

Adapted from *CNS Drugs* 2009; 23 (1): 81-90^[1]

What was the rationale for developing this formulation?

Parkinson's disease (PD) is a progressive age-related neurodegenerative disorder associated with the loss of dopaminergic cells in the substantia nigra.^[1] The condition, which has an average age of onset of 60 years, is estimated to affect ≈0.3% of the general population and ≈1% of adults aged >60 years. The cardinal symptoms of PD include bradykinesia, rest tremor and rigidity.^[1]

The introduction of levodopa revolutionized the treatment of PD, but the effectiveness of dopaminergic therapy is eventually limited by motor fluctuations and dyskinesia.^[1] Non-ergoline dopamine receptor agonists recommended to reduce motor fluctuations in patients with advanced PD include ropinirole, pramipexole and rotigotine.^[1]

Although ropinirole immediate release is effective in the treatment of PD, the need for multiple drug doses per day and an extended titration phase may affect patient compliance and hinder the achievement of optimal patient function.^[2] Thus, to further improve the management of PD, a prolonged-release formulation of ropinirole has been developed.

Ropinirole prolonged release¹ provides controlled delivery of ropinirole over 24 hours, which allows continuous dopaminergic input to the striatum and reduces the fluctuations (peaks and troughs) of ropinirole concentrations. Relative to dopaminergic agents that activate the striatum in a more pulsatile fashion, long-acting agents that provide continuous dopaminergic stimulation, such as ropinirole prolonged release, result in better control of the symptoms of PD and less dyskinesia.^[2-8] Moreover, long-acting agents are less likely to prime patients with early PD for the emergence of subsequent motor complications, particularly dyskinesia.^[2-9] Therefore, treating early PD with such agents may reduce the risk of developing motor complications and/or delay their emergence.

In addition, prolonged-release ropinirole is administered once daily and has a simpler and faster titration schedule than three-times-daily ropinirole immediate release, which may potentially improve patient compliance.^[1]

How does the drug work?

Ropinirole is a non-ergoline dopamine D₂/D₃ receptor agonist that stimulates striatal dopamine receptors, thereby alleviating the dopamine deficiency that characterizes PD.^[10,11]

Ropinirole binds to central and peripheral dopamine receptors with an order of receptor affinity similar to that of dopamine.^[11] It is ≈20-fold more selective for D₃ than D₂ receptors and ≈50-fold more selective for D₃ than D₄ receptors, with negligible affinity for D₁ receptors.^[11] Ropinirole has little or no affinity for β-adrenoceptors or adrenergic, serotonergic, GABA or benzodiazepine receptors.^[11]

Do its pharmacokinetics differ from those of the immediate-release formulation?

Ropinirole prolonged release 8 mg once daily and ropinirole immediate release 2.5 mg three times daily (i.e. administered at 8-hour intervals with meals) have similar exposure over 24 hours at steady state in patients with early-stage PD.^[3] At steady state, the prolonged- and immediate-release ropinirole formulations had similar values for dose-normalized geometric mean area under the plasma concentration-time curve from 0–24 hours (16.3 vs 16.0 ng • h/mL/mg; ratio 1.02 [90% CI 0.96, 1.09]) and dose-normalized geometric mean minimum plasma concentration (C_{min}; 0.44 vs 0.45 ng/mL/mg; ratio 0.98 [90% CI 0.90, 1.06]).^[3] The 90% confidence intervals for these two parameters were within the limits associated

Adis Evaluation

Key clinical benefits of ropinirole prolonged release in Parkinson's disease (PD)

- Provides continuous dopaminergic stimulation
- Associated with fewer fluctuations in plasma concentrations and better effectiveness than the immediate-release formulation
- Convenient once-daily administration without regard to food
- Has a titration schedule that is simpler and faster than that of the immediate-release formulation
- Reduces hours of 'off' time and increases hours of 'on' time
- Improves other PD-related symptoms, quality of life, sleep, activities of daily living and mood
- Provides control of symptoms during the day and night
- Associated with reductions in concomitant levodopa dosages
- Reduces the risk of developing dyskinesia relative to the use of levodopa

1 Registered as Requip-Modutab®, Requip® LP, Requip® XL, Requip® Depot and Requip® Prolib.

with bioequivalence (0.80–1.25). The dose-normalized geometric mean maximum plasma concentration ($C_{\max}$) was $\approx 12\%$ lower with prolonged-release ropinirole than with immediate-release ropinirole (0.92 vs 1.05 ng/mL/mg; ratio 0.88 [90% CI 0.78, 0.99]).

Importantly, the prolonged-release formulation was associated with fewer fluctuations in plasma ropinirole concentrations than ropinirole immediate release (degree of fluctuation 0.66 vs 0.85).^[3] Moreover, the predicted fluctuation between $C_{\min}$ and $C_{\max}$ plasma concentrations was 2-fold with once-daily ropinirole prolonged release, whereas it was 5-fold with the immediate-release formulation (administered with meals at typical dose intervals of 6, 6 and 12 hours).^[3] Of note, first thing in the morning, when patients are typically akinetic and trying to rise from bed, plasma concentrations of ropinirole with the prolonged-release formulation were twice as high as those with the immediate-release formulation.^[3]

Who should receive the drug?

In the treatment of PD, ropinirole prolonged release is indicated both as initial monotherapy in early disease and then as an adjunct to levodopa (table 1).^[10,12] It may be taken without regard to food.^[10,12]

What is its efficacy in advanced disease compared with placebo ...

The efficacy of ropinirole prolonged release in advanced PD has been assessed in a double-blind trial in patients aged ≥ 30 years with idiopathic PD suboptimally controlled by levodopa.^[2] Patients were randomized to receive once-daily ropinirole prolonged release or placebo ($n = 202$ and 191) for 24 weeks, plus their current levodopa therapy.^[2] Ropinirole prolonged release was initiated at 2 mg/day and titrated until the occurrence of an optimal therapeutic response or adverse effects (minimum dosage of 6 mg/day). At 24 weeks, the mean ropinirole prolonged-release dosage was 18.8 mg/day (median 20 mg/day), with 50% of patients receiving the maximum dosage of 24 mg/day. Efficacy at 24 weeks was assessed in the modified intent-to-treat population using last observation carried forward methodology.^[2] At baseline in the ropinirole and placebo groups, mean total daily 'off' time was 7.0 hours (both groups), 'on' time was 9.0 and 9.1 hours, and 'on' time without troublesome dyskinesia was 8.5 and 8.4 hours.^[2]

Once-daily administration of ropinirole prolonged release was effective in the treatment of patients with advanced PD who experienced suboptimal control with levodopa.^[2] After 24 weeks, the mean reduction from baseline in total daily 'off' time (primary endpoint) was

significantly greater in patients receiving ropinirole prolonged-release than in placebo recipients (figure 1). The adjusted mean treatment difference of -1.7 hours per day (95% CI -2.34 , -1.09 ; $p < 0.0001$) was considered clinically significant,^[2] and equates to the addition of ≈ 12 hours per week that the patients are mobile.

Moreover, 'on' time and 'on' time without troublesome dyskinesia improved from baseline to a significantly ($p < 0.0001$) greater extent with ropinirole prolonged release than with placebo (figure 1); the respective mean between-group differences were 1.7 (95% CI 1.06, 2.33) and 1.5 hours (95% CI 0.85, 2.13).^[2]

Ropinirole prolonged release was also significantly more effective than placebo with regard to mean improvements from baseline in a number of endpoints related to PD symptom control, quality of life and mood, including:

- Unified PD Rating Scale (UPDRS) motor,^[2] activities of daily living (ADL),^[2] tremor,^[15] rigidity^[15] and bradykinesia^[15] scores (all $p \leq 0.0003$);^[2]
- PD Quality-of-Life questionnaire subscales scores for mobility, ADL, emotional well-being, stigma and communication (all $p < 0.02$), but not for social support, cognition or bodily discomfort;^[16]
- Beck Depression Inventory-II total score ($p = 0.01$).

In addition, significantly more ropinirole prolonged-release than placebo recipients were 'very much improved' or 'much improved' on the Clinical Global Impression-Improvement (CGI-I) scale (42% vs 14%; $p < 0.001$) at 24 weeks.^[2]

Ropinirole prolonged release is also associated with improvements in sleep.^[2,16] At 24 weeks in the double-blind trial,^[2] ropinirole prolonged release was significantly more effective than placebo with regard to mean improvements from baseline in PD Sleep Scale (PDSS) total score ($p = 0.02$).^[2] Moreover, in a pooled analysis^[16] of two 24-week trials,^[2,17] ropinirole prolonged release significantly reduced sleep disturbance as assessed by the PDSS in those patients who had significant sleep dysfunction at baseline.

Treatment with ropinirole prolonged-release > 8 mg/day were accompanied by decreases in the dosage of levodopa.^[2] During the placebo-controlled study, the mean levodopa dosage decreased by 278 mg/day in ropinirole prolonged-release recipients and 164 mg/day in placebo recipients.^[2] Levodopa dose reduction occurred in 95% of patients receiving ropinirole prolonged release and 92% of patients receiving placebo; reinstatement of levodopa following dose reduction was necessary in 7% and 28% of patients in the corresponding treatment groups (adjusted odds ratio 0.2; $p < 0.0001$).^[2] Time to reinstatement

Table 1. Features and properties of oral ropinirole prolonged release (PR) in Parkinson's disease (PD)^(1,10,12) a

Approved indications, dosage and availability in the EU⁽¹⁰⁾

Indications	Initial monotherapy in the treatment of early PD In combination with levodopa when the effect of levodopa wears off or becomes inconsistent, and fluctuations in the therapeutic effect occur
Initial dosage	2 mg once daily for 1 wk
Titration (based on symptomatic control)	4 mg once daily from wk 2 Increase daily dosage in 2 mg increments at intervals of ≥ 1 wk up to 8 mg once daily, then by 2–4 mg increments at intervals of ≥ 2 wk (maximum 24 mg/d)
Availability	2, 4 and 8 mg film-coated tablets

Approved indication, dosage and availability in the US⁽¹²⁾

Indication	Treatment of the signs and symptoms of idiopathic PD
Initial dosage	2 mg once daily for 1–2 wk
Titration (based on symptomatic control)	Increase daily dosage by 2 mg increments at intervals of ≥ 1 wk (maximum 24 mg/d)
Availability	2, 4, 8 and 12 mg film-coated tablets

Dosages when switching from other dopaminergic agonists to ropinirole PR

Previously receiving ropinirole immediate release (IR) ^(10,12)	If previous total daily dosage of ropinirole IR was 0.75–2.25, 3–4.5, 6, 7.5–9, 12, 15–18, 21 or 24 mg, switch to ropinirole PR 2, 4, 6, 8, 12, 16, 20 and 24 mg, respectively
Previously receiving oral pramipexole ⁽¹³⁾	Use an initial conversion ratio of 1 mg of pramipexole to 4 mg of ropinirole PR
Previously receiving rotigotine patch ⁽¹⁴⁾	Use an initial conversion ratio of 2 mg of rotigotine to 2 mg of ropinirole PR

Use in special populations

Age ≥ 65 y	Increase dosages gradually and titrate to therapeutic response (ropinirole clearance is decreased)
Patients with renal impairment	Dosage adjustments not required in mild to moderate impairment (has not been studied in severe impairment; use not recommended in EU ⁽¹⁰⁾)
Patients with hepatic impairment	Has not been studied (use not recommended in EU ⁽¹⁰⁾ ; titrate with caution in US ⁽¹²⁾)

Pharmacokinetic profile

Bioavailability	$\approx 50\%$
Maximum plasma concentration (C_{max}) ^b	0.92 ng/mL/mg
Median time to C_{max}	6 h
Minimum plasma concentration ^b	0.44 ng/mL/mg
Volume of distribution	≈ 7 L/kg
Plasma protein binding	10–40%
Metabolism	Primarily by cytochrome P450 (CYP) 1A2, with a minor contribution from CYP3A
Excretion	Primarily as metabolites in urine ($\approx 10\%$ excreted unchanged)
Elimination half-life	≈ 6 h

Situations potentially leading to drug interactions that may require an adjustment in ropinirole dosage

CYP1A2 inhibitors (e.g. ciprofloxacin, enoxacin, fluvoxamine) are introduced or withdrawn
Smoking is started or stopped (smoking induces CYP1A2)
Hormone replacement therapy is started or stopped (high-dose estrogens may increase ropinirole plasma concentrations)
Centrally active dopamine antagonists (e.g. sulpiride, metoclopramide) are co-administered (may reduce the efficacy of ropinirole)

^a Consult local prescribing information for further details.

^b Geometric mean values for dose-normalized steady-state pharmacokinetic parameters of ropinirole prolonged release in patients with PD.

analyses revealed that placebo recipients were ≈ 5 -fold more likely than ropinirole prolonged-release recipients to require levodopa reinstatement following dose reduction at any timepoint ($p < 0.001$).¹²¹ The response rate (defined as the proportion of patients with a $\geq 20\%$ reduction for baseline in both 'off' time and levodopa dosage) was significantly higher in patients receiving ropinirole prolonged release than in patients receiving placebo (52% vs 20%; $p < 0.001$).¹²¹

... or ropinirole immediate release?

The efficacy of ropinirole prolonged release was compared with that of ropinirole immediate release in patients with advanced PD not optimally controlled with levodopa in preliminary results of a randomized, double-blind, 24-week trial.^{117,181} Patients received ropinirole prolonged release 2–24 mg once daily ($n = 177$) or ropinirole immediate release 0.75–24 mg/day in three divided doses ($n = 173$).¹¹⁷¹ At week 24, mean dosages of

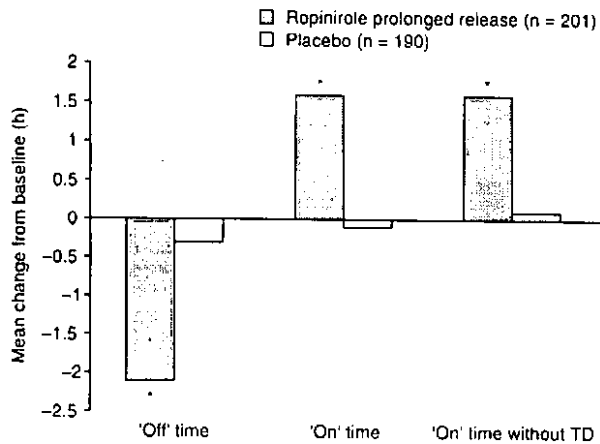


Fig. 1. Efficacy of ropinirole in patients with advanced Parkinson's disease suboptimally controlled by levodopa. Mean change from baseline in 'off' time (primary endpoint), 'on' time and 'on' time without troublesome dyskinesia (TD) in patients randomized to once-daily ropinirole prolonged release (titrated to 6–24 mg/d) or placebo in a double-blind, 24-wk trial. * $p < 0.0001$.

ropinirole prolonged release and immediate release were 18.6 and 10.4 mg/day.^[17]

The prolonged-release formulation of ropinirole was more effective than the immediate-release formulation with regard to the primary endpoint,^[17] with significantly more ropinirole prolonged-release than ropinirole immediate-release recipients maintaining a $\geq 20\%$ reduction from baseline in 'off' time at week 24 (64% vs 51%; $p = 0.009$).^[17]

Secondary endpoints also improved to a greater extent with ropinirole prolonged release than with the immediate-release formulation at 24 weeks. Significantly more ropinirole prolonged-release recipients than ropinirole immediate-release recipients were 'very much improved' or 'much improved' on the CGI-I scale (55% vs 43%).^[18] The UPDRS motor score also improved to a significantly greater extent in patients receiving ropinirole prolonged release than in those receiving ropinirole immediate release ($p = 0.02$), with no significant between-group difference in the change in UPDRS ADL score.^[17] The levodopa dosage was reduced from baseline by a mean 162 mg in ropinirole prolonged-release recipients and 113 mg in ropinirole immediate-release recipients.^[17]

What is its tolerability profile?

Ropinirole prolonged release 6–24 mg once daily was generally well tolerated in patients with advanced PD suboptimally controlled by levodopa.^[2] Most adverse events were of mild or moderate severity and adverse events were generally typical of non-ergoline dopamine agonists.

Adverse events occurred in 64% of patients receiving ropinirole prolonged release and in 55% of patients

receiving placebo.^[2] The most commonly occurring adverse events are shown in figure 2. Dyskinesia and nausea tended to be reported during the first 4 weeks of the study (i.e. during the titration phase). Study withdrawal because of adverse events occurred in 5% of patients in both treatment groups.

Serious adverse events occurred in 4% of patients receiving ropinirole prolonged release and in 4% of patients receiving placebo.^[2] Three ropinirole prolonged-release recipients experienced a serious adverse event considered to be drug related (syncope [$n = 1$] and hallucinations [$n = 2$]).

What is its effect on dyskinesia compared with levodopa?

Treatment with a long-acting dopaminergic agonist that provides continuous dopaminergic stimulation is less likely to result in the development of dyskinesia than treatment with agents with more pulsative activation of the striatum.^[9] In a 2-year, double-blind flexible-dose study, patients with PD not optimally controlled with up to 600 mg/day of levodopa^[9] were randomized to receive ropinirole prolonged release 2–24 mg once daily ($n = 105$) or levodopa/carbidopa 50–1000 mg/day ($n = 104$).

Ropinirole prolonged release significantly ($p < 0.001$) delayed the onset of dyskinesia (primary endpoint) relative to levodopa/carbidopa.^[9] Dyskinesia occurred in 3% of patients receiving ropinirole prolonged release and 17% of those receiving levodopa/carbidopa.^[9] Importantly, this delay was not at the cost of reduced motor control, as patients in each study arm were equally well controlled (i.e. UPDRS ADL and motor scores were similar in each

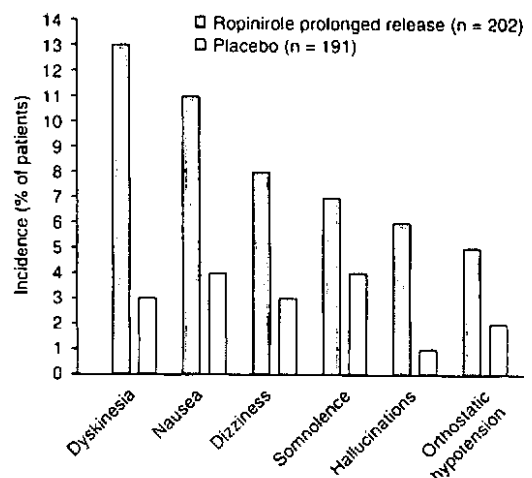


Fig. 2. Tolerability of ropinirole prolonged release in patients with advanced Parkinson's disease suboptimally controlled by levodopa. Treatment-emergent adverse events reported by $\geq 5\%$ of recipients of once-daily ropinirole prolonged release (titrated to 6–24 mg/d) or placebo in a randomized, double-blind 24-wk trial.^[2]

group).^[9] The study was terminated prematurely because of difficulty in recruiting sufficient patients who had been initially treated with levodopa rather than dopamine agonists and because a preliminary blinded review indicated apparent low dyskinesia rates could lead to futility.

What is its current positioning?

Ropinirole prolonged release is a valuable option in the treatment of patients with early PD (as monotherapy) and as an adjunct to levodopa. In patients whose PD is suboptimally controlled by levodopa, it reduces the number of hours of daily 'off' time and improves a number of other PD-related parameters. Moreover, initiating treatment with ropinirole prolonged release rather than increasing the levodopa dosage reduces the likelihood of patients developing subsequent dyskinesias.

The prolonged-release formulation of ropinirole offers advantages over the immediate-release formulation. In addition to the convenience of once-daily administration, it is associated with fewer fluctuation in plasma ropinirole concentrations. Ropinirole prolonged-release recipients were more likely than ropinirole immediate-release recipients to maintain a $\geq 20\%$ reduction from baseline in 'off' time or have improvements in other endpoints. Ropinirole prolonged release was generally well tolerated in patients with advanced PD.

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Ropinirole 24-hour prolonged release

Randomized, controlled study in advanced Parkinson disease

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on behalf of the EASE-PD Adjunct Study Investigators*

Abstract—Objective: To evaluate the efficacy of ropinirole 24-hour prolonged release (ropinirole 24-hour) as an adjunct to levodopa in patients with Parkinson disease (PD) and motor fluctuations. **Methods:** In a double-blind, placebo-controlled, 24-week study, 393 subjects with PD were randomized to ropinirole 24-hour (n = 202) or placebo (n = 191). The primary outcome measure was reduction in hours of daily “off” time. **Results:** At week 24, the mean dose of ropinirole 24-hour was 18.8 mg/day with a mean reduction in daily levodopa of 278 mg. There was a mean reduction in daily “off” time of 2.1 hours in the ropinirole 24-hour group and 0.3 hours with placebo. Secondary outcome measures including change in hours and percent of daily “on” time and “on” time without troublesome dyskinesia, Unified PD Rating Scale motor and activities of daily living subscales, Beck Depression Inventory-II, PDQ-39 subscales of mobility, activities of daily living, emotional well-being, stigma and communication, and PD Sleep Scale were significantly improved at week 24 with ropinirole 24-hour. The most common adverse events (AE) with ropinirole 24-hour were dyskinesia, nausea, dizziness, somnolence, hallucinations, and orthostatic hypotension and AEs led to study withdrawal in 5% of both the active and placebo groups. **Conclusion:** Ropinirole 24-hour was effective and well tolerated as adjunct therapy in patients with Parkinson disease (PD) not optimally controlled with levodopa. Ropinirole 24-hour demonstrated an improvement in both motor and non-motor PD symptoms, while permitting a reduction in adjunctive levodopa dose.

NEUROLOGY 2007;68:1108–1115

Ropinirole is a non-ergot dopamine agonist that has demonstrated efficacy in early and advanced Parkinson disease (PD), when used as monotherapy or as an adjunctive therapy to levodopa.^{1–5} Although ropinirole is well tolerated and effective, an extended titration phase and a need for multiple dosages per day may decrease patient compliance and provide a barrier to optimizing patient function.^{4,6} Therefore, a simple and rapid titration schedule and a reduction in the number of daily doses may improve patient compliance and ultimately improve outcomes. In an effort to address these needs, a prolonged-release ropinirole formulation has been developed as a once-a-day formulation with a simple and faster dose-titration regimen. A prolonged-release formulation that allows a steady rate of absorption and reduces plasma-level fluctuations should produce a smoother pharmacokinetic profile and therefore may improve tolerability and efficacy and may lead to reduction in levodopa dose and motor fluctuations.

To assess the efficacy of prolonged release ropinirole, a Phase III, multicenter, multinational, randomized, double-blind, placebo-controlled study of ropinirole 24-hour prolonged release (ropinirole 24-hour) in patients with PD not optimally controlled by levodopa, the Efficacy And Safety Evaluation in PD-Adjunct (EASE-PD Adjunct) study was conducted. The primary objective of the study was to evaluate the efficacy of ropinirole 24-hour as adjunctive therapy in patients with PD not optimally controlled with levodopa.

Methods. Patients. A total of 393 patients with PD and suboptimal control from levodopa were enrolled in this trial between July 2003 and December 2004 at 67 centers in Belgium, the Czech Republic, France, Hungary, Italy, Poland, Spain, and the United States. Men and women at least 30 years of age with a diagnosis of idiopathic PD and a modified Hoehn & Yahr stage of II to IV with suboptimal control with levodopa therapy (e.g., end-of-dose akinesia, motor fluctuations) were eligible for the study. A stable dose of levodopa for at least 4 weeks prior to screening and a minimum of 3 hours in the “off” state as measured by each of four

*The principal EASE-PD Adjunct Study Investigators are listed in the appendix.

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Disclosures: This study was sponsored by GlaxoSmithKline (GSK) and Skye Pharma. R. Pahwa, S.A. Factor, K.E. Lyons, F. Stocchi, B.P. Hersh, L.W. Elmer, and D. Truong have received research grant support from GSK for research studies not reported in this article. This research support exceeded \$10,000 for R. Pahwa, B.P. Hersh, and D. Truong. R. Pahwa, M.A. Stacy, S.A. Factor, K.E. Lyons, F. Stocchi, B.P. Hersh, and L.W. Elmer have received personal compensation from GSK. This compensation has exceeded \$10,000/year for R. Pahwa, F. Stocchi, and B.P. Hersh. N.L. Earl is an employee of GSK.

Received May 22, 2006. Accepted in final form December 5, 2006.

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patient diaries completed during the placebo run-in period were required. Selegiline, amantadine, anticholinergics, and catechol-O-methyl-transferase (COMT) inhibitors were permitted, provided the dose was stable for at least 4 weeks prior to screening. Neuroleptics and antiemetics were not permitted during the study. Patients with incapacitating peak dose or biphasic dyskinesia; any dopamine agonist use within 4 weeks of screening; significant or uncontrolled psychiatric, neurologic, or other medical disorders; clinically significant laboratory abnormalities at screening; a recent history of severe dizziness or fainting due to postural hypotension; clinical dementia precluding assessment; a recent history or current evidence of drug abuse or alcoholism; or withdrawal, introduction, or dose change of hormone replacement therapy or any drug known to substantially inhibit or induce cytochrome P450 1A2 were not eligible for the study. All patients provided written, informed consent approved by their respective ethics committee or institutional review board and the study was conducted in accordance with good clinical practice, subject privacy requirements, and the guiding principles of the Declaration of Helsinki.

Study design/procedures. This was a multicenter, multinational, randomized, double-blind, parallel-group, placebo-controlled study (EASE-PD Adjunct Study). Eligible subjects entered a 14-day placebo run-in period. Subjects who completed the run-in period and continued to meet the inclusion criteria were randomized 1:1 to receive once-daily, adjunctive treatment with ropinirole 24-hour or placebo for 24 weeks. A computer-generated randomization schedule using the Registration and Medication Ordering System (RAMOS) was used. Investigators or coordinators phoned into this system to register and randomize subjects. To ensure balance in the number of subjects allocated to each group within each center, the allocation schedule was generated in blocks. In order to achieve blinding, dosages were referred to as Levels 1 through 8, placebo subjects were dosed similarly to the ropinirole 24-hour group, and ropinirole 24-hour and placebo tablets were identical in appearance and packaging. Only in the event of an emergency affecting the clinical management or welfare of the subject could the investigator break the blind. In North American sites, the medication bottles were labeled with a two-panel label. The second panel tear-off contained a blackened disclosure panel that, when swabbed with alcohol, revealed the contents of the bottle. For all other centers, emergency unblinding was available via RAMOS.

Subjects were evaluated at baseline and weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24. At the end of the study, or at withdrawal, subjects entered a 7-day down-titration phase. A follow-up safety visit was performed 4 to 14 days after last dose of study medication. Study drug was titrated at a starting dose (Level 1) of 2 mg/day ropinirole 24-hour or matching placebo. Subjects were instructed to take the medication once daily at the same time each day. The following dose titration was used with levels increasing each visit as necessary: Level 1: 2 mg/day; Level 2: 4 mg/day; Level 3: 6 mg/day; Level 4: 8 mg/day; Level 5: 12 mg/day; Level 6: 16 mg/day; Level 7: 20 mg/day; Level 8: 24 mg/day. The dose was titrated until an optimal therapeutic response was achieved or adverse effects occurred. All subjects were titrated to a minimum dose of 6 mg/day ropinirole 24-hour or matching placebo (Level 3). Once an optimal therapeutic dose was achieved, the subject was maintained on that dose for the remainder of the treatment phase unless further titration was required up to a maximum of 24 mg/day.

Once subjects reached Level 4 (ropinirole 24-hour 8 mg/day or placebo), with each subsequent increase in study medication level, the total daily dose of levodopa was reduced by one half or one full tablet or possibly more if the subject was taking more than six tablets per day. If the subject was taking entacapone and a full dose of levodopa was removed the accompanying entacapone was also eliminated. If loss of symptom control occurred with the reduction in levodopa dose, the dose of study medication was increased to the next dose level, with no adjustment in levodopa dose. If loss of symptom control persisted, the dose of study medication was increased again to the next dose level with no adjustment in levodopa dose. Subjects could return to the clinic at weekly intervals, if necessary, for dose adjustments. Subjects who did not experience improvement in symptoms following up-titration of study medication by two dose levels could have their levodopa dose increased to, but not in excess of, baseline levels.

Subjects were not permitted to switch between controlled-release and immediate-release levodopa formulations.

Outcome measures. The primary outcome measure was mean change from baseline in hours "off" at week 24 as measured by patient diaries. Subjects completed 24-hour diaries at 30-minute intervals indicating if they were in the "off" state, "on" state, "on" state with troublesome dyskinesia, or asleep. "Off" state was when PD medication was not improving PD symptoms resulting in a lack of mobility; "on" state was when PD medication was working and providing benefit; and troublesome dyskinesia were involuntary movements during the "on" state that interfered with function or caused discomfort. Prior to completing any diaries, the investigator or coordinator reviewed the definitions for each motor state with the subject. The subject was required to accurately describe each state to the investigator or coordinator until they were comfortable that the subject could differentiate between motor states. Definitions for each state were also written on each diary form. Each subject completed two 24-hour diaries prior to each study visit and the mean of the two 24-hour periods was used for all analyses. For baseline values, the mean from all four diaries during the 2-week placebo run-in period was used.

Secondary outcome measures included the mean change from baseline in the hours of "on" time; percentage of "on" time; percentage of "off" time; hours of "on" time without troublesome dyskinesia; and percentage of "on" time without troublesome dyskinesia as measured by subject diaries. Mean changes from baseline were also examined for the Unified PD Rating Scale (UPDRS) Motor (Part III) score obtained at least 2 hours after the previous levodopa dose; UPDRS Activities of Daily Living (ADL; Part II) average of "on" and "off" scores; Beck Depression Inventory-II (BDI-II); PD Quality of Life questionnaire (PDQ-39) subscores; Epworth Sleepiness Scale (ESS); and PD Sleep Scale (PDSS). Additional measures included the proportion of subjects "very much improved" or "much improved" according to the Clinical Global Impression-Improvement (CGI-I) scale; the proportion of subjects requiring reinstatement of levodopa following dose reduction; the time to reinstatement of levodopa following dose reduction; and the proportion of responders, defined as those who had at least a 20% reduction from baseline in "off" time and at least a 20% reduction from baseline in levodopa dose.

Safety endpoints included adverse events (AEs), clinical laboratory data, vital signs (blood pressure and heart rate, orthostatic blood pressure, and heart rate), and EKG.

Statistical analyses. Sample size was based on the mean change from baseline to endpoint in hours "off." A difference of 1.2 hours between ropinirole 24-hour and placebo in the reduction in hours "off" was considered clinically relevant based on previous studies.⁷⁻⁹ A total of 133 subjects per treatment group evaluable for the primary analysis (266 overall) were required to detect a difference of 1.2 hours with a SD of 3 hours, for a two-sided test with 90% power and a 5% level of significance. The total number of subjects to be randomized was 368, assuming an attrition rate of 27%.

The primary efficacy measure (change from baseline in hours "off") was analyzed using parametric analysis of covariance. Among the secondary efficacy measures normal, linear models were fitted to each of the continuous variables. Dichotomous variables were analyzed using logistic regression models and time to event data were analyzed using Cox's regression model. For all efficacy measures analyzed at week 24, missing data were imputed using the last observation carried forward (LOCF) method.

Study populations. The safety population consisted of all subjects who received at least one dose of randomized study medication. The primary inferences concerning the safety of ropinirole 24-hour were made using the safety population. The intention-to-treat (ITT) population consisted of all randomized subjects who received at least one dose of study medication and for whom at least one post-baseline efficacy assessment was available. The primary inferences concerning the efficacy of ropinirole 24-hour were made using the ITT population. The per protocol (PP) population consisted of all subjects in the ITT population who had no major protocol deviation with regard to inclusion or exclusion criteria; no major protocol deviation between randomization and completion of the active treatment phase of the study (weeks 1 to 24); and no more than 3 consecutive days of study medication missed throughout active treatment.

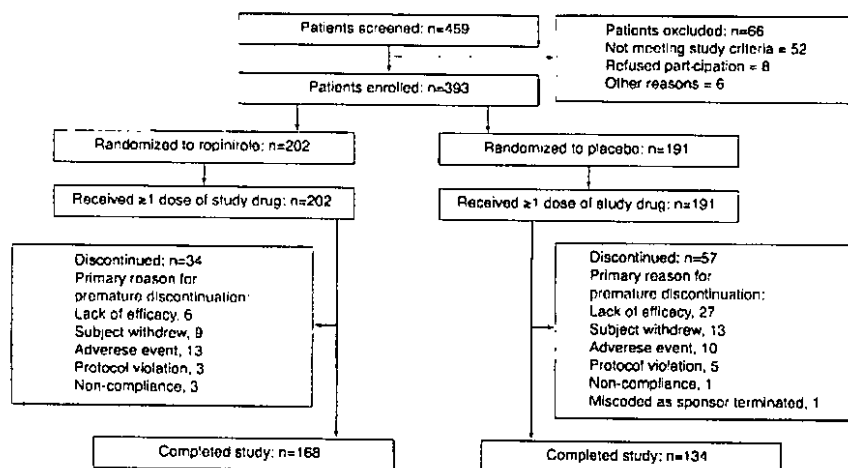


Figure 1. Subject flowchart.

Results. Patients. A total of 393 subjects were randomized and received at least one dose of study medication (safety population): ropinirole 24-hour ($n = 202$), placebo ($n = 191$) (figure 1). The ITT population comprised a total of 391 subjects: ropinirole 24-hour ($n = 201$), placebo ($n = 190$). The PP population comprised 82% (324/393) of all randomized subjects: ropinirole 24-hour ($n = 168$), placebo ($n = 156$). The most common reason for discontinuation was lack of efficacy (ropinirole 24-hour: 6/202 [3%]; placebo 27/191 [14%]).

Baseline demographics are shown in table 1. In the safety population, 189/202 (94%) of the ropinirole 24-hour group and 181/191 (95%) of the placebo group met the definition for overall compliance which required a tablet compliance of $\geq 80\%$ and $\leq 120\%$ and no more than 3 consecutive days of missed study medication. At week 24 the mean dose of ropinirole 24-hour was 18.8 ± 6.26 mg/day and the median dose was 20 mg/day with a range from 2 to 24 mg/day. The mean placebo dose level at week 24 corresponded to 20.0 ± 5.62 mg/day and the median dose level corresponded to 24 mg/day with a range from 2 to 24 mg/day. At week 24, 100/202 (50%) ropinirole 24-hour subjects were receiving the maximum 24 mg/day, compared with 107/191 (56%) subjects in the placebo group receiving the equivalent dose level (Level 8) of matching placebo.

Primary outcome measure. At baseline, mean "off" time was approximately 7 hours in each treatment group (table 1). Mean changes from baseline in "off" time by visit are shown in figure 2. At week 24, mean reduction from baseline in total "off" time was 2.1 hours in the ropinirole 24-hour group and 0.3 hours in the placebo group. The mean treatment difference between ropinirole 24-hour and placebo at week 24 was 1.7 hours (95% CI: $-2.34, -1.09$; $p < 0.0001$) indicating both a clinically relevant and significant benefit of ropinirole 24-hour over placebo. At all visits from week 2 to 24 there was a significant treatment difference for ropinirole 24-hour compared with placebo in change from baseline in "off" time (figure 2). The reduction in "off" time was also significantly reduced in the PP population at week 24 with ropinirole 24-hour compared to placebo.

Secondary outcome measures. Several secondary outcome measures resulted in significant improvement with ropinirole 24-hour compared to placebo including hours of "on" time and "on" time without troublesome dyskinesia;

percent of "off" time, "on" time, and "on" time without troublesome dyskinesia (figure 3); UPDRS motor and ADL scores; BDI-II total score; PDQ-39 subscores of mobility, ADLs, emotional well-being, stigma, and communication; and PDSS total score (table 2). There were no significant differences between ropinirole 24-hour and placebo in PDQ-39 subscores of social support, cognition, or bodily discomfort and ESS total scores (table 2).

More subjects in the ropinirole 24-hour group (83/200, 42%) were classified as responders ("much improved" or "very much improved") on the CGI-I scale at week 24 vs the placebo group (27/189, 14%; OR: 4.4; 95% CI: 2.63, 7.20; $p < 0.001$).

Mean levodopa dose at week 24 was 546 ± 378 mg/day in the ropinirole 24-hour group and 613 ± 349 mg/day in the placebo group. Over the course of the study there was a larger decrease in daily levodopa dose in the ropinirole 24-hour group vs placebo. Mean change from baseline was -278 ± 193 mg/day in the ropinirole 24-hour group and -164 ± 164 mg/day in the placebo group.

Among subjects who had levodopa dose reduction (ropinirole 24-hour: 191/201 subjects [95%]; placebo: 174/190 subjects [92%]), reinstatement of levodopa following dose reduction was required for 7% (14/191) of the ropinirole 24-hour group and 28% (49/174) of the placebo group. The odds of a subject receiving placebo requiring reinstatement with levodopa were five times those of a subject receiving the active drug (adjusted OR: 0.2; 95% CI: 0.09, 0.34; $p < 0.001$). There was also a benefit for ropinirole 24-hour over placebo for time to reinstatement of levodopa following a reduction in dose (adjusted hazard ratio: 0.2; 95% CI: 0.11, 0.37; $p < 0.0001$).

More subjects in the ropinirole 24-hour group (103/200, 52%) were classified as responders based on change in "off" time and levodopa dose (at least a 20% reduction in both from baseline) at week 24 vs the placebo group (38/190, 20%; OR: 4.3; 95% CI: 2.73, 6.78; $p < 0.001$). Thus, the odds of a subject receiving ropinirole 24-hour and achieving a 20% reduction in "off" time and a 20% reduction in levodopa dose was more than four times that of a subject receiving placebo.

Adverse events. AEs were reported by 64% (129/202) of ropinirole 24-hour subjects vs 55% (106/191) of those receiving placebo. The most common AEs (reported by $\geq 5\%$ of the ropinirole 24-hour group) were dyskinesia, nausea,

Table 1 Demographics and baseline characteristics (intention-to-treat population)*

	Ropinirole 24-hour (n = 201)	Placebo (n = 190)
Age, y	66.3 (9.2)	66.0 (9.7)
Women, n (%)	84 (42)	61 (32)
Age at onset of PD, y	57.6 (10.5); 200	57.3 (10.7); 188
Duration of PD, y	8.6 (4.8); 200	8.6 (5.2); 188
Hoehn & Yahr stage	2.7 (0.5); 201	2.7 (0.6); 190
Duration of levodopa, y	6.5 (4.4); 199	6.6 (4.3); 187
Baseline levodopa dose, mg/d	824 (424.4); 199	776 (357.3); 190
Total "off," h	7.0 (2.8)	7.0 (2.6)
Total "on," h	9.0 (2.8)	9.1 (2.7)
Total "on" without dyskinesia, h	8.5 (2.9); 200	8.4 (2.9); 188
UPDRS motor score†	29.8 (12.9); 197	30.7 (14.4); 188
UPDRS ADL score‡	13.9 (6.2); 200	14.2 (6.8); 189
BDI-II total score§	15.9 (9.0); 197	16.1 (8.8); 188
PDQ-39 domain score¶		
Mobility	42.2 (25.6); 194	43.4 (23.6); 183
ADL	42.3 (24.4); 193	45.1 (22.9); 185
Emotional well-being	32.5 (21.7); 190	31.9 (19.4); 181
Stigma	31.2 (23.9); 195	30.3 (24.2); 188
Social support	14.1 (19.9); 194	14.1 (18.3); 187
Cognitive impairment	25.0 (18.0); 197	24.7 (17.3); 188
Communication	24.7 (20.7); 195	25.7 (21.0); 187
Bodily discomfort	37.7 (20.8); 197	39.6 (21.4); 187
ESS total score	7.8 (4.5); 196	7.7 (4.4); 186
PDSS total score**	99.2 (24.6); 198	98.0 (25.9); 189

* Unless noted otherwise, values are expressed as mean (SD); number.

† Range 0–108, where 0 = normal/no symptoms; assessed at least 2 hours after levodopa dose.

‡ Range 0–52, where 0 = normal/no symptoms; average of "on" and "off" scores.

§ Range 0–63 (least–most severe).

¶ Range 0–100 for all domains (no problem–maximum level of problem).

|| Range 0–24 (least–most chance of dozing).

** Range 0–150 (most severe–free from all symptoms).

PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale; ADL = activities of daily living; BDI-II = Beck Depression Inventory II; PDQ-39 = Parkinson's Disease Quality of Life questionnaire; ESS = Epworth Sleepiness Scale; PDSS = Parkinson's Disease Sleep Scale.

dizziness, somnolence, hallucinations, and orthostatic hypotension (table 3). AEs during the down-titration phase did not suggest any rebound or withdrawal symptoms.

The number of subjects reporting AEs leading to withdrawal was low and similar in both treatment groups: 11 subjects (5%) in the ropinirole 24-hour group and 10 subjects (5%) in the placebo group. AEs that led to the withdrawal of at least two subjects within a treatment group were hallucinations (ropinirole 24-hour: 4 subjects, 2%;

placebo: 2 subjects, 1%), nausea (ropinirole 24-hour: 2 subjects, <1%; placebo: 1 subject, <1%), and worsening of parkinsonism (ropinirole 24-hour: 0 subjects; placebo: 2 subjects, 1%).

Serious AEs were reported by 4% of subjects in each treatment group (ropinirole 24-hour: 8/202; placebo: 7/191). Only three ropinirole 24-hour subjects reported serious AEs that were considered by the investigator to be related to the study drug (syncope: 1 subject; hallucinations: 2 subjects), and for two of these subjects (syncope and hallucinations) concomitant medications were also considered a possible cause. None of the subjects in the placebo group who reported a serious AE reported an event that was considered by the investigator to be related to the study drug.

Three deaths were reported during the study: one in the ropinirole 24-hour group and two in the placebo group. None was considered related to study drug. In the ropinirole 24-hour group, the serious AE leading to death was pneumonia and in the placebo group, the serious AEs leading to death were hip fracture and pneumonia.

Discussion. We found that ropinirole 24-hour is effective in reducing "off" time compared to placebo in patients with PD not optimally controlled with levodopa. Patients receiving ropinirole 24-hour experienced a reduction in "off" time an average of 2.1 hours (adjusted treatment difference of 1.7 hours), which was both significant and clinically relevant. These benefits for ropinirole 24-hour were observed from week 2 through week 24.

The decrease in "off" time in the ropinirole 24-hour group was accompanied by an average increase in "on" time of 1.6 hours (treatment difference of 1.7 hours). At study end (week 24), there was a significant treatment difference in favor of ropinirole 24-hour for "on" time without troublesome dyskinesia. In contrast, the mean "on" time with troublesome dyskinesia decreased by 0.04 hours in the ropinirole 24-hour group and by 0.23 hours in the placebo group. Thus, the decrease in "off" time and increase in "on" time seen in the ropinirole 24-hour group did not result in an increase in troublesome dyskinesia. The reduction in troublesome dyskinesia is likely secondary to the reduction in levodopa dose in both groups.

The efficacy of ropinirole 24-hour in improving symptom control was supported by several other secondary outcome measures. Significant benefits in favor of ropinirole 24-hour were observed for the change in UPDRS motor score (indicating improvements in motor impairments and disability), UPDRS ADL score (indicating improvements in daily functioning), and in the proportion of patients classified as responders on the CGI-I scale (indicating global improvement).

Ropinirole 24-hour was also associated with significant treatment benefits compared with placebo in terms of mood (change in BDI-II total score) and various aspects of quality of life including PDQ-39 subscores for mobility, ADLs, emotional well-being, stigma, and communication. Furthermore, the lack

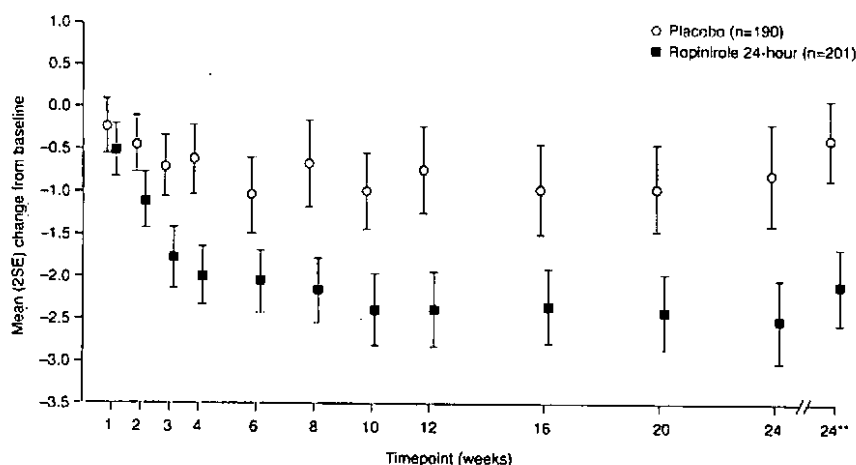


Figure 2. Mean (2 SE) change from baseline in total hours "off" at each visit for ropinirole 24-hour prolonged release and placebo. Adjusted treatment difference (95% CI), ropinirole 24-hour prolonged release vs placebo, for change from baseline in "off" time at each visit: week 1 = -0.3 (-0.73, 0.13; $p = 0.1741$); week 2 = -0.7 (-1.09, -0.23; $p = 0.0029$); week 3 = -1.1 (-1.52, -0.59; $p < 0.0001$); week 4 = -1.3 (-1.80, -0.79; $p < 0.0001$); week 6 = -0.9 (-1.47, -0.39; $p = 0.0008$); week 8 = -1.5 (-2.05, -0.87; $p < 0.0001$); week 10 = -1.4 (-1.93, -0.78; $p < 0.0001$); week 12 = -1.6 (-2.21, -0.96; $p < 0.0001$); week 16 = -1.3 (-1.88, -0.63; $p = 0.0001$); week 20 = -1.3 (-1.99, -0.69; $p < 0.0001$); week 24 = -1.6 (-2.30, -0.85; $p < 0.0001$); ** last observation carried forward.

of a significant treatment difference for the cognition subscore of the PDQ-39 suggests that treatment with ropinirole 24-hour was not associated with an adverse effect on mental function. Although the study dose was administered in the morning, subjects in the ropinirole 24-hour group experienced significant improvements in sleep compared with those receiving placebo as assessed by the PDSS.

The efficacy of ropinirole 24-hour was demonstrated alongside a levodopa-sparing effect. The study design mandated reductions in concomitant levodopa dose for increases in study medication and the decrease in levodopa dose was greater in the ropinirole 24-hour compared to the placebo group (-278 mg/day vs -164 mg/day). Among patients who underwent levodopa dose

reduction, the odds of requiring reinstatement of levodopa after such a reduction were five times greater in the placebo group than in the ropinirole 24-hour group. Furthermore, based on time to reinstatement analyses, at any time point subjects receiving placebo were approximately five times more likely to require levodopa rescue. This study therefore provides evidence that ropinirole 24-hour is effective as an adjunct therapy to levodopa, permitting a substantial reduction in the concomitant dose of levodopa while offering an improvement in motor fluctuations. Indeed, the proportion of subjects achieving both a $\geq 20\%$ reduction in levodopa dose and a $\geq 20\%$ reduction in "off" time was significantly greater in the ropinirole 24-hour group (52%) vs placebo (20%).

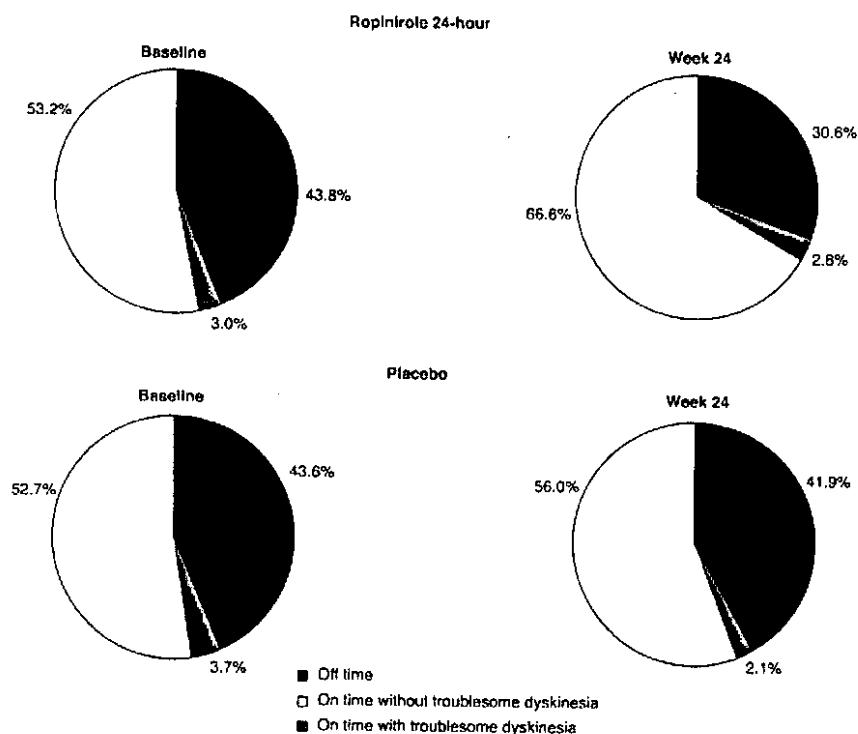


Figure 3. Percentage of "off" time, "on" time, and "on" time with troublesome dyskinesia at baseline and week 24 for ropinirole 24-hour prolonged release and placebo.

Table 2 Mean change from baseline in diary measures, UPDRS motor and ADL scores, BDI-II total score, PDQ-39 domain scores, ESS total score, and PDSS total score at week 24 last observation carried forward for ropinirole 24-hour prolonged release and placebo

	Mean (2 SE); n change from baseline		Adjusted treatment difference (95% CI)	p Value
	Ropinirole 24-hour prolonged release (n = 201)	Placebo (n = 190)		
"Off" time (diary)	-2.1 (0.64); 201	-0.3 (0.64); 190	-1.7 (-2.34, -1.09)	<0.0001
"On" time (diary)	1.6 (0.64); 201	-0.1 (0.64); 190	1.7 (1.06, 2.33)	<0.0001
On without troublesome dyskinesia (diary)	1.6 (0.64); 200	0.1 (0.65); 188	1.5 (0.85, 2.13)	<0.0001
% "Off" time (diary)	-12.1 (4.01); 201	-0.9 (4.05); 190	-11.2 (-15.13, -7.21)	<0.0001
% "On" time (diary)	12.1(4.00); 201	1.0 (4.04); 190	11.1 (7.17, 15.08)	<0.0001
% "On" without troublesome dyskinesia (diary)	12.3 (4.04); 200	2.7 (4.08); 188	9.7 (5.67, 13.69)	<0.0001
UPDRS Motor	-6.5 (1.81);194	-1.7 (1.83); 183	-4.8 (-6.56, -2.98)	<0.0001
UPDRS ADL	-3.5 (0.78); 197	-0.9 (0.79); 184	-2.6 (-3.36, -1.83)	<0.0001
BDI-II total score	-2.1 (1.3); 188	-0.5 (1.3); 179	-1.6 (-2.86, -0.34)	0.0130
PDQ-39 Subscales				
Mobility	-4.9 (3.36); 186	1.9 (3.42); 172	-6.8 (-10.07, -3.53)	<0.0001
Activities of daily living	-5.4 (3.30); 185	1.1 (3.76); 176	-6.5 (-9.71, -3.25)	<0.0001
Emotional well-being	-4.3 (3.06); 182	-0.6 (3.06); 172	-3.7 (-6.68, -0.82)	0.0124
Stigma	-3.3 (3.68); 187	1.2 (3.70); 178	-4.5 (-8.06, -0.87)	0.0150
Social support	-1.5 (2.98); 185	-0.3 (3.0); 177	-1.2 (-4.07, 1.77)	0.4385
Cognition	3.4 (2.68); 188	2.9 (2.68); 178	0.5 (-2.13, 3.09)	0.7176
Communication	-1.4 (3.26); 187	2.4 (3.34); 176	-3.7 (-6.88, -0.61)	0.0193
Bodily discomfort	-3.6 (3.42); 189	-1.5 (3.50); 176	-2.1 (-5.40, 1.26)	0.2224
ESS total score	0.5 (0.78); 188	0.2 (0.82); 173	0.3 (-0.41, 1.09)	0.3692
PDSS total score	1.3 (4.18); 191	-3.3 (4.22); 178	4.7 (0.75, 8.57)	0.0196

UPDRS motor 0–108, 0 = normal/no symptoms, assessed at least 2 hours after levodopa dose; UPDRS ADL 0–52, 0 = normal/no symptoms, average of "on" and "off" scores; BDI-II total score = 0–63; PDQ-39 = 0–100 for each domain; ESS total score = 0–24; PDSS = range 0–150.

UPDRS = Unified Parkinson's Disease Rating Scale; ADL = activities of daily living; BDI-II = Beck Depression Inventory II; PDQ-39 = Parkinson's Disease Quality of Life questionnaire; ESS = Epworth Sleepiness Scale; PDSS = Parkinson's Disease Sleep Scale.

AEs were typical of non-ergot dopamine agonists. The proportion of patients withdrawn due to AEs or reporting serious AEs was no greater in the ropinirole 24-hour group than in the placebo group. Most

Table 3 Number (%) of subjects reporting any adverse event (AE) and the number (%) of subjects reporting the most common on-treatment AEs: reported by ≥5% of the ropinirole 24-hour prolonged release group

	Ropinirole 24-hour prolonged release (n = 202)	Placebo (n = 191)
Subjects with at least one AE	129 (64)	106 (55)
Dyskinesia	27 (13)	5 (3)
Nausea	23 (11)	7 (4)
Dizziness	16 (8)	6 (3)
Somnolence	14 (7)	7 (4)
Hallucinations	12 (6)	2 (1)
Orthostatic hypotension	11 (5)	3 (2)

patients reported AEs that were mild or moderate. In general, the most common AEs occurring in ≥10% of the ropinirole 24-hour group, dyskinesia (13%) and nausea (11%), were reported during the first 4 weeks of the study. This was during the up-titration phase before the planned reduction in levodopa dose occurred.

Although dyskinesia was the AE reported by the greatest proportion of subjects receiving ropinirole 24-hour, the amount of time spent "on" with troublesome dyskinesia was similar in each treatment group at study end and had decreased slightly over the course of the study. More specifically, 48% of the 27 ropinirole 24-hour subjects reporting dyskinesia as an AE during the study reported dyskinesia at baseline according to the UPDRS Part IV (item 32). The dyskinesia was mildly disabling in 23%, moderately disabling in 31%, and not disabling in 46%. Of the 27 subjects reporting dyskinesia throughout the study, 81% (22/27) reported dyskinesia at week 24. In these subjects, the dyskinesia was mildly disabling in 15%, moderately disabling in 19%, and not

disabling in 65%. The baseline daily dose of levodopa was greater in the ropinirole 24-hour group (824 mg/day) compared to the placebo group (776 mg/day) and the subjects in the ropinirole 24-hour group who reported dyskinesia as an AE had a higher baseline dose of levodopa (975 mg/day) compared to those who did not report dyskinesia as an AE (800 mg/day). The increased dyskinesia in the ropinirole 24-hour group compared to placebo may largely be due to the design of the study. During the titration phase of the study, the study drug was increased by 2 mg/week; however, reductions in levodopa did not occur until a daily dose of 8 mg was achieved. Therefore, the increase in dyskinesia could be due to an increased dopaminergic load in the ropinirole 24-hour group during the first several weeks of the study, which would not have been present in the placebo group. This hypothesis is further supported by the fact that 85% (23/27) of the subjects in the ropinirole 24-hour group who reported dyskinesia did so prior to week 12 of the study.

The proportion of subjects reporting AEs of special interest in terms of dopamine agonists (e.g., hallucinations, unintended sleep episodes) was low. Of the 16 subjects (8%) in the ropinirole 24-hour group who reported AEs of hallucinations, only 4 were discontinued from the study, compared with 2 of the 4 subjects (2%) reporting hallucinations in the placebo group. Only one ropinirole 24-hour subject reported an AE of an unintended sleep episode which was of moderate intensity on the first day of the study and resolved after 1 day. Ropinirole 24-hour was not discontinued as a result of this AE and the subject completed the study. One subject receiving placebo also reported an AE of an unintended sleep episode of moderate intensity 145 days after the first dose, which was resolved on the day of onset. Again, no action was taken with regard to study medication, and the subject completed the study. The proportion of subjects reporting AEs of orthostatic hypotension, hypotension, or blood pressure decreases was also low in both treatment groups and none of these subjects was withdrawn from the study as result of the AE. Syncope was reported for two ropinirole 24-hour recipients (<1%), and for one of these subjects led to withdrawal from the study. Both AEs of syncope were reported as resolved the day after onset. There were no AEs suggestive of fibrosis. Overall, the ropinirole 24-hour regimen was well tolerated in the population studied.

The adjusted mean treatment difference in the reduction in "off" time with ropinirole 24-hour and placebo of 1.7 hours was either comparable or superior to the reduction in hours of "off" time measured by subject diaries reported for other similar studies of adjunctive treatments in PD. A study of pergolide compared to placebo as an adjunct therapy to levodopa reported a treatment difference in the reduction of "off" time of 1.6 hours.¹⁰ Similarly, a study of pramipexole dosed three times daily compared to placebo reported a treatment difference in the reduc-

tion of "off" time of 2.0 hours.¹¹ A study examining both rasagiline 1 mg and entacapone (200 mg per levodopa dose) compared to placebo demonstrated a treatment difference in reduction of "off" time for both drugs of 0.8 hours.¹² Similarly, a study of rasagiline 0.5 mg and rasagiline 1.0 mg compared to placebo reported treatment differences in the reduction in "off" time of 0.49 hours (0.5 mg) and 0.94 hours (1.0 mg).¹³

The results of this study suggest that ropinirole 24-hour is as efficacious but better tolerated when compared to the results of a similar study with immediate release ropinirole.⁴ The percentage of responders ($\geq 20\%$ reduction in levodopa dose and daily "off" time) on active drug in the immediate release ropinirole study was 35% compared to 52% in the current study. AEs with immediate release ropinirole were dyskinesia (34%), worsening of PD (21%), nausea (20%), ataxia (20%), dizziness (20%), somnolence (19%), postural hypotension (17%), and insomnia (14%). The percentages were higher than those for the same AEs in this current ropinirole 24-hour study. Furthermore, 16% of the subjects in the immediate release ropinirole study discontinued the study due to AEs compared with 5% in the present study despite a faster dose titration to 24 mg/day (8 weeks) of ropinirole 24-hour compared to immediate release (13 weeks).

Ropinirole 24-hour was effective and well tolerated as adjunct therapy in patients with PD not optimally controlled with levodopa. Ropinirole 24-hour demonstrated an ability to improve both motor and non-motor PD symptoms, while permitting a reduction in adjunctive levodopa dose.

Appendix

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Adherence Among Patients with Parkinson's Disease Taking Ropinirole Immediate Release At Least Three Times Daily

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Introduction

Medication non-adherence is a serious problem facing current medical practice,^{1,2} and research shows that patients who have a high frequency treatment regimen tend to be less compliant than patients who have a treatment regimen of lower frequency.³ While adherence to medication has been demonstrated across a range of therapeutic areas, much data in Parkinson's disease (PD) are limited. The purpose of this study was to assess self-reported adherence, as well as drivers and consequences of non-adherence among patients with PD taking ropinirole immediate release (IR) at least three times daily (T.I.D.).

Methods

Study Design and Patients

- This survey was carried out on the USA between April and May 2006, in patients with PD who had been taking stable doses of ropinirole IR for at least 4 weeks
- The survey consisted of 15 items to identify patients' adherence and experiences with ropinirole IR, in addition to their reasons for non-adherence. The consequences of non-adherence, and their interest in a once-daily formulation of ropinirole were asked to respond to each question from a multiple choice format
- Patients were eligible for inclusion if they were:
 - aged 18 years or older
 - had a diagnosis of idiopathic PD
 - taking a stable dose of ropinirole IR at least 4 weeks for a minimum of 4 weeks
- Patients were ineligible for inclusion if they were:
 - taking any other dopaminergic agent (including levodopa, amantadine, entacapone, or any other dopaminergic agent)
 - based on the inclusion criteria listed above. Physicians were responsible for identifying and recruiting patients who met the eligibility criteria by reviewing their files and the logbooks of the study.
- Eligible patients were contacted by telephone by their neurologist. After providing informed written consent, participating patients completed the survey at their physician's office and their neurologist completed a case report form.

Statistical Analysis

- Descriptive statistics were computed to summarize the responses to all survey items.
- Some items were collapsed into dichotomous categories and chi-square tests were used to test the association between adherence and other variables.
- Patients were defined as being adherent if they indicated that they never missed a dose of rosiglitazone IR, even if they reported late doses.
- No imputations were made for missing data and statistical inferences were based on the assumption of data being missing at random.

Results

Patients

- A total of 250 patients completed the survey.
- Patients were primarily white men with a mean (SD) age of 65.9 (10.5) years (Table 1).
- The most common dosing regime was t.i.d. (80% of patients) with a mean daily dose of 8.9 mg.

Table 1. Patient demographics and baseline characteristics

[illegible]

PD: Pearson's χ^2 testing SD, standard deviation.

- Participating patients had been taking ropinirole IR for a mean time of 32 months (range 1–120 months) and had been on their current ropinirole IR regimen for a mean time of 11.9 months (range 1–60).

Figure 1. Most commonly reported reasons for non-adherence with enalapril immediate

- Most patients were either on rosiglitazone monotherapy (34%) or concomitant *l*-dopa (55%).
- Cardiovascular and gastrointestinal disorders were the most commonly occurring comorbidities, followed by depression.
- All patients except one reported having some type of health insurance, with more than 51% indicating that their primary health insurance was Medicare. Insurance coverage of prescription medications varied, with approximately 14% of the sample reporting full coverage, 74% reporting partial coverage with some co-payment, and 9% reporting no insurance coverage.

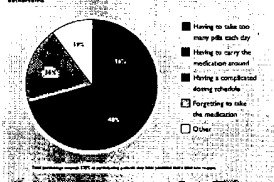
Self-Reported Adherence

- More than two-thirds (57%) of patients indicated that they had missed at least one dose of rosiglitazone IR and were classified as non-adherent. Specifically, in the last 7 days:
 - 24% of patients had missed at least one dose
 - 57% of patients were late with one or more doses.
- Adherence was unrelated to age, gender, employment status, education, dosage and frequency, current use of other PD medications, monotherapy versus combination therapy, dosing assistance strategies used, type of insurance and co-payment requirements, or percentage of "off" periods.

Reasons for Non-Adherence

- The most commonly reported reason for non-adherence included forgetting to take treatment (44%), intending to take their treatment with their meals (11%), and being too busy to take their treatment (11%) (Figure 1).
- In total, 40% of patients reported that taking rifampin IR the prescribed number of times a day was very bothersome or "somewhat bothersome" rather than a little bothersome or "not bothersome at all".
- The most commonly reported reason for finding adherence bothersome was having too many pills to take each day (55%), followed by having to carry the medication around (40%), and having a complicated dosing schedule (17%) (Figure 2).

Figure 2. Reported cases with taking rifampicin immediate release three times daily to behercetam.



Consequences of Non-Adherence

- The proportion of patients reporting a consequence related to missed or late doses of risperidone IR was 75%.
 - The most commonly reported consequences of missed or late doses were increase in tremors (41%), bradykinesia (14%), difficulty concentrating (25%), difficulty moving (24%), and difficulty walking (22%) (Figure 3).
 - The proportion of patients who reported development of a worsening of Parkinson's disease symptoms was 14% and was not statistically significant.
- Approximately half of the patient sample indicated that their current risperidone IR dosing regimen interfered with their social activities (56%) and leisure activities (51%).
- Approximately 40% of patients reported interference with their work (fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, twelfth, thirteenth, fourteenth, fifteenth, sixteenth, seventeenth, eighteenth, nineteenth, twentieth, twenty-first, twenty-second, twenty-third, twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth, twenty-ninth, thirtieth, thirty-first, thirty-second, thirty-third, thirty-fourth, thirty-fifth, thirty-sixth, thirty-seventh, thirty-eighth, thirty-ninth, fortieth, forty-first, forty-second, forty-third, forty-fourth, forty-fifth, forty-sixth, forty-seventh, forty-eighth, forty-ninth, fiftieth, fifty-first, fifty-second, fifty-third, fifty-fourth, fifty-fifth, fifty-sixth, fifty-seventh, fifty-eighth, fifty-ninth, sixtieth, sixty-first, sixty-second, sixty-third, sixty-fourth, sixty-fifth, sixty-sixth, sixty-seventh, sixty-eighth, sixty-ninth, seventieth, seventy-first, seventy-second, seventy-third, seventy-fourth, seventy-fifth, seventy-sixth, seventy-seventh, seventy-eighth, seventy-ninth, eightieth, eighty-first, eighty-second, eighty-third, eighty-fourth, eighty-fifth, eighty-sixth, eighty-seventh, eighty-eighth, eighty-ninth, ninetieth, ninety-first, ninety-second, ninety-third, ninety-fourth, ninety-fifth, ninety-sixth, ninety-seventh, ninety-eighth, ninety-ninth, one hundredth).

- Nearly one-third (30%) reported that their current roxatrolol IR dosing regimen interfered with sexual activity.

Patient Interest in Once-Daily Dosing

- When asked how interested they would be in a once-daily formulation of rolapiride from "very interested" to "very disinterested", the proportion of patients who reported being at least "somewhat interested" was 88%.
 - The most common reasons for interest were: ease of remembering to take a once-daily formulation (86%); not having to carry medication around (11%); currently taking too many medications (17%); and being too busy to take medication more than once a day (14%).

Conclusions

- Pill burden and dosing schedule play an important role in the lack of adherence.
- Lack of adherence may contribute to morbidity and mortality and may be a driver behind repeat visits to the physician's office with unresolved physician complaints and higher healthcare costs.
- Mechanisms to improve adherence to treatment regimens, including physician awareness, patient education, and improved dosing regimens may result in improved patient care and better outcomes.
- The majority of patients taking ropinirole IR in this survey were interested in the prospect of a once-daily dosing schedule.

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Acknowledgments

Acknowledgments
This study was supported by GlaxoSmithKline. Patient recruitment and data collection were carried out by TNS Healthcare GmbH. Development of the patient survey and data analyses were carried out by 3TI Health Solutions.

Figure 1. Most commonly reported reasons for non-adherence with enalapril immediate

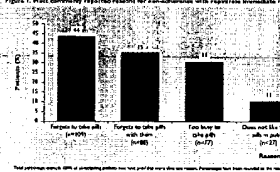
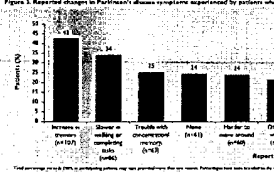


Figure 3. Reported changes in Parkinson's disease symptoms associated with exercise.



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Long-term safety and patient preference for dose frequency in patients receiving ropinirole prolonged release in early or advanced Parkinson's disease

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Introduction

Ropinirole is a non-ergot dopamine agonist used in the treatment of Parkinson's disease (PD), and is available in immediate-release and prolonged-release formulations. Once-daily ropinirole prolonged release has been shown to provide continuous ropinirole delivery with fewer plasma level fluctuations over 24 hours than the immediate-release formulation.¹ The efficacy and tolerability of ropinirole prolonged release have been demonstrated in double-blind clinical trials in patients with early or advanced PD.^{2,3} Here we report the safety and tolerability data for the prolonged-release formulation from two long-term, open-label studies, and the results of an analysis of patient preferred dosing regimen.

Methods

Study design

- Both studies were multicentre, open-label, flexible-dose extension studies (101468/195 and 101468/248).
- Patients received once-daily prolonged-release ropinirole (1–24 mg/day).
- Ropinirole was given as either monotherapy or adjunct therapy.
- The ropinirole dose was up-titrated from 2 mg/day in week 1 to 8 mg/day in week 4 in all patients who had not been receiving 8 mg/day in their feeder study (assuming no tolerability issues).
- Thereafter, the ropinirole dose could be increased at the discretion of the investigator to a maximum of 24 mg/day.
- Following dose titration, safety assessments were conducted every 3 months (study 195) or 6 months (study 248).
- The present analysis is a planned interim update in which data were pooled from the two open-label studies (up to 4.6 years exposure to ropinirole prolonged release).

Patients

- Patients had early or advanced PD, required dopaminergic therapy and had completed a previous clinical trial of ropinirole.
- Patients in study 248 had previously been enrolled in monotherapy studies 165 or 168 in which they received either immediate-release (168) or prolonged-release (165 and 168) ropinirole or the adjunct study 169 (EASE-PD), in which patients received either prolonged-release ropinirole or placebo.
- Patients in study 195 had previously been enrolled in monotherapy studies 164 or 167, in which they received either immediate-release or prolonged-release ropinirole.
- Patients entered the extension study on completion of the feeder study.

Safety and tolerability

- The incidence of treatment-emergent adverse events (TEAEs), serious TEAEs and TEAEs leading to withdrawal were summarised.
- Adverse event data were collected at each clinic visit.
- Routine laboratory assessments were performed every 6 months in study 195.

Preference questionnaire

- Patients enrolled in study 248 who had previously been enrolled in feeder study 168 completed a balanced design questionnaire (Figure 1) regarding their preference for once-daily dosing (in study 248) or three-times-daily dosing (in study 168). The questionnaire was completed at 4 weeks and 36 weeks after enrolment into study 248.

Figure 1. Preference questionnaire.

1) Thinking back to your initial study (168, when you were taking your Parkinson's Disease study medication three times a day, over the past 20 weeks you have been taking your Parkinson's Disease study medication once a day. Please tell us how you feel about your Parkinson's Disease study medication three times a day or once a day by choosing one of the following options. Check ONE box only.

☐ Very much preferred three times a day

☐ Much preferred three times a day

☐ Preferred three times a day

☐ Both are about the same

☐ Preferred once a day

☐ Much preferred once a day

☐ Very much preferred once a day

2) Please tell us the reason or reasons for your preference (check – anything other – until all reasons are given. Use all reasons below).

3) Which dosing schedule of Parkinson's Disease study medication (three per day or once per day) was more convenient? Check ONE box only.

☐ Three times a day

☐ Once a day

☐ Both about the same

☐ Don't know

4) Which dosing schedule of Parkinson's Disease study medication (three per day or once per day) was easier to remember? Check ONE box only.

☐ Once a day

☐ Three times a day

☐ Both about the same

☐ Don't know

- The order of possible responses shown in Figure 1 was reversed for alternate patients to avoid ordering effects.

Results

- A total of 501 patients received prolonged-release ropinirole:
- 194 as monotherapy and 357 as adjunct therapy
- 418 (83%) patients had been exposed for >1 year and 276 (55%) patients were still receiving prolonged-release ropinirole at the data cut.
- 22% of patients had a modal dose of 8 mg/day, 38% had a modal dose of >8–16 mg/day and 40% had a modal dose of >16 mg/day
- mean (SD) ropinirole dose at the last on-treatment visit was 15.9 (6.3) mg/day.

Safety and tolerability

- TEAEs were reported by 404 (80%) patients (Table 1).
- Peripheral oedema was the most commonly reported TEAE (13%).
- Serious TEAEs occurred in 19% of patients, with chest pain (2%) and worsening of PD (2%) reported most frequently; all other serious TEAEs occurred at a frequency of <1%.
- 15% of patients withdrew from ropinirole treatment (14% monotherapy, 13% adjunct therapy) due to a TEAE, most commonly due to hallucination (2.4%).
- There were four deaths, none considered treatment related.

Table 1. TEAEs (% of patients) reported by more than 1% of patients in studies 195 and 248.

Event	Ropinirole therapy		
	Monotherapy	Adjunct therapy	Overall
All events	94	77	80
Peripheral oedema	11	9	12
Back pain	11	10	12
Somnolence	11	7	10
Hallucination	6	7	10
Dizziness	12	6	8
Headache	12	6	8
Insomnia	5	6	7
Pain in extremity	11	3	7
Arthralgia	9	4	6
Depression	9	4	6
Nausea/vomiting	12	2	6
Nausea	9	4	6
Chest pain	5	4	5

Dosing preference

- Of 112 patients enrolled in the preference study, 75 (67%) completed the preference questionnaire at Week 4, and 85 (76%) at Week 36 (Tables 2 and 3).
- At Week 4, 85% of patients preferred once-daily to three-times-daily dosing (very much preferred, much preferred or preferred once a day) while only 15% expressed a neutral or negative opinion (about the same, preferred, much preferred, or very much preferred three times a day) ($p < 0.001$).

Table 2. Patient dosing regimen preferences (n (%)) respondents.

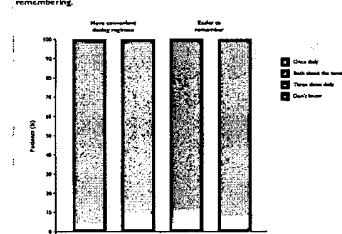
	Week 4 (n=75)	Week 36 (n=85)
Very much preferred three times a day	3 (4)	4 (5)
Much preferred three times a day	0	1 (1)
Preferred three times a day	4 (5)	1 (1)
Both are about the same	4 (5)	5 (6)
Preferred once a day	18 (24)	14 (16)
Much preferred once a day	17 (23)	20 (24)
Very much preferred once a day	29 (39)	39 (46)

Table 3. Spontaneous reasons for preferring once-daily dosing (% reasons – some patients offered more than one reason).

	Week 4 (n=75)	Week 36 (n=85)
Do not forget	37	34
Convenience	30	37
Simplicity	9	13
Effective	5	5
Fewer side-effects	5	7
More comfortable	1	5
Side-effects (bad worse)	2	8
Other	11	11

- At Week 36, 86% of patients preferred once-daily to three-times-daily dosing while only 14% were neutral or preferred three-times-daily dosing ($p < 0.001$).
- Reasons spontaneously offered for preferring once-daily dosing included less likely to forget (34%); more convenient (27%); simplicity (13%); more effective (7%) and fewer side-effects (5%).
- Subsequent, elicited responses indicated 90% of patients thought the once-daily regimen was more convenient and 92% thought it easier to remember than the three-times-daily regimen (Figure 2).

Figure 2. Patient preferences at Week 4 and Week 36 for once-daily versus three-times-daily ropinirole dosing with respect to convenience and ease of remembering.



Conclusion

- Long-term therapy with ropinirole prolonged release is well tolerated by patients with early or advanced PD.
- The TEAEs reported are as expected for non-ergot dopamine agonists.
- Patients preferred once-daily dosing as it is more convenient and less likely to be forgotten than three-times-daily dosing.

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Acknowledgements

Study supported by GlaxoSmithKline (GSK) Research and Development.

Disclosures and conflicts of interest

B Hunter, J Statham, J Kirsch and L Giorgi are employees of GSK. H Reichmann has received honoraria from GSK for advisory board meetings and lectures. A Szczudlik has received honoraria from GSK for lectures.

Accepted 15
Exp. 02-09-153

Medication Adherence and Associated Outcomes in Medicare Health Maintenance Organization-Enrolled Older Adults with Parkinson's Disease

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Abstract: Maintenance of symptom control in Parkinson's disease (PD) requires continuous titration of medication and addition of multiple therapies over the course of the disease. Adherence to medication is vital to symptom control and key to maximizing the efficacy of existing therapies. However, adherence is compromised by a variety of factors, including motor symptoms, complex dosing regimens, multiple medications, and lack of patient/physician awareness of the impact and prevalence of suboptimal adherence. This retrospective, longitudinal cohort study assessed the prevalence of suboptimal adherence [measured as the medication possession ratio (MPR)] to PD medications, and its impact on the worsening of PD symptoms (measured as increase in monotherapy dose, augmentation of therapy, PD-related emergency department

visit, or hospitalization), in a Medicare Health Maintenance Organization population in the United States. Irrespective of the MPR threshold chosen, a high percentage of patients were categorized as suboptimally adherent to their PD medications, and patients with suboptimal adherence to their PD medications had higher risks of worsening of PD symptoms, compared with those who were adherent. Increased awareness of both the magnitude and impact of suboptimal adherence to PD medications, coupled with dosage simplification and a unified effort by healthcare professionals and patients, may improve adherence to PD medications and ultimately improve symptom control. © 2007 Movement Disorder Society

Key words: adherence; prevalence; elderly; medications; Parkinson's disease.

The estimated annual incidence of Parkinson's disease (PD) in the United States is 12.3 per 100,000 population,¹ and the estimated prevalence is 106.9 per 100,000.² Both prevalence and incidence increase with age, and show a marked increase in people older than 60 years, consistent with the usual age of diagnosis, which is between 65 and 70 years.^{1,2} Given that PD is a chronic and progressive neurological disorder, once patients start

medication they will usually continue receiving treatment for the rest of their lives.

Although currently available therapies for PD are effective in treating the motor symptoms of the disease, long-term management of the disorder is complicated by several factors. As the disease progresses, increasing doses or adding other medications are required to manage the worsening motor symptoms. Nonmotor symptoms of PD usually develop some time after diagnosis, and some may require additional therapies. During long-term treatment with certain antiparkinsonian medications, a large proportion of patients, particularly those receiving levodopa, develop motor complications associated with therapy. The resulting motor fluctuations and dyskinesias require careful management, and the treatment regimen may inherently affect the quality of life.

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Received 4 May 2007; Revised 6 August 2007; Accepted 9 October 2007

Published online 11 December 2007 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.21831

The drugs used to treat uncomplicated PD are often taken at least three times daily, but motor progression leads to increasingly complicated titration and dosing schedules, and correlate with reduced medication adherence.³⁻⁷ Furthermore, as mentioned, PD is a disease that typically occurs later in life,^{1,2} and an elderly population is likely to have multiple comorbidities for which they are taking medications. Leoni et al. found that patients with PD took a mean of 2.4 antiparkinsonian medications (correlated with disease duration) plus a mean of 2.4 nonantiparkinsonian medications (correlated with patient's current age), for a total of around 5 medications per patient.⁸ Therefore, patients with PD are often taking several drugs, in complex regimens, and may experience motor symptoms that impair administration and adherence. These factors may increase the risk of suboptimal adherence to medications.

The clinical consequences of suboptimal adherence vary, depending on disease severity and drug potency. The consequences of missed medication dosing include decreased motor function, poor mobility, fluctuations in motor control, dyskinesias, and decline in the quality of life.³ During clinical assessment, a treating physician may mistakenly assume that compliance is not a factor in motor decline. This perspective may result in unnecessary treatment changes in some instances, and may also lead both physician and patient to assume the decline in mobility to be a result of disease progression.^{3,5} The physician may therefore increase the dose of, or switch, medication, whereas addressing the problem of suboptimal adherence may improve treatment efficacy. Thus, patients will experience treatment changes (which may in turn contribute to further suboptimal adherence) and medications may be used inefficiently in the long term. In addition, intermittent use of certain antiparkinsonian medications may have serious acute and long-term consequences, such as neuroleptic malignant syndrome.^{9,10} These changes may also inadvertently lead to intermittent treatment with dopaminergic medications, and may predispose patients to the development of motor complications of therapy, particularly dyskinesias.¹¹⁻¹³

Considering the possible clinical impact of suboptimal adherence to PD medications, assessment of patient adherence in this disease is warranted. The purpose of this study was to assess the prevalence of poor medication adherence in PD and its effect on worsening of symptoms in a Medicare population.

PATIENTS AND METHODS

This was a retrospective, longitudinal cohort study comprising patients aged 65 years and older, enrolled continuously for 1 to 5 years (1996-2000) in a Medicare

Health Maintenance Organization (HMO) in the southeastern United States. The managed care plan was the sole provider of medical care to the enrollees.

This study was restricted to patients with PD, who were using pharmacotherapy for disease control. Patients were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 332 and 332.0 for PD and the concomitant receipt of a PD medication, identified using the National Drug Code, a universal product identifier.

Demographic and clinical variables were retrieved from the administrative claims data of the HMO. Claims paid by the HMO for all healthcare services were used to calculate the costs associated with each enrollee. A discount program became available to patients when filling prescriptions after the monthly coverage limit was exhausted; this program enabled researchers to obtain the prescription refill rates with reasonable certainty. Thus, use of PD medication was obtained regardless of whether the refill was covered by the prescription benefit.

Prescription refill patterns were used to derive measures of adherence under the assumption that a prescription filled was a prescription taken. Pharmacy records have been demonstrated to have predictive validity as measures of cumulative exposure and gaps in medication supply.¹⁴ An index of PD medication utilization was computed for each patient, based on the Med-Total approach by Steiner et al.¹⁵ The medication possession ratio (MPR) was calculated as the days of PD prescription supply dispensed divided by the number of days between prescription refills. The observation period began with the first date of dispensing within each year and ended as the dispensing date of the last prescription. The number of days a person was in a hospital was subtracted from the denominator because any drug taken during this time was provided by the hospital and was not entered in the pharmacy records. When calculating the MPR for PD medications, double-counting of any PD medications used concomitantly by the patients was avoided. Random checks were also performed on the days of prescription supply, recorded with the number of units of medication dispensed, to ensure a reasonable fit with the figure entered.

An MPR of 80% was considered a reasonable threshold for persistence, as it suggests very few days without drug on hand and, consequently, fairly continuous medication usage.¹⁶ For our study, patients with an MPR score of less than 0.8 were considered to be suboptimally adherent to their PD medications. As this threshold has not been validated for PD, a sensitivity analysis was also performed with different thresholds of the MPR scores implying suboptimal adherence. The thresholds chosen

were MPR scores less than 0.60, 0.40, and 0.20 implying suboptimal adherence to PD medications.

An index for worsening of PD was developed, based on assessing treatment patterns for this disorder and disease-related events. Patients who had an increase in their dose of monotherapy or had another treatment added were considered to have worsening of PD symptoms. Hospitalization or emergency department visits specifically for PD were also identified as markers for experiencing worsening of PD symptoms.

Studies have suggested large variations in adherence levels within the elderly population.^{17,18} Our study therefore grouped the population according to age in two categories: younger adults (65–75 years of age) and older adults (76 years of age and older), as is often recommended.¹⁹

A severity-of-comorbidity index was also developed, based on the approach of Charlson et al.²⁰ but adapted for use in database studies and with *ICD-9-CM* codes as per the approach of Deyo et al.²¹ The index assigned was weighted for a number of major conditions (ranging from 1 to 6). The index severity score was calculated for each patient by totaling the assigned weight for each of the patient's comorbidities.

Statistical Analysis

Using the MPR scores as a proxy for medication adherence, prevalence of suboptimal adherence to PD medication was evaluated using the following formula:

Prevalence

$$= \frac{\text{Number of people not adherent to their PD medications}}{\text{Population at risk of being nonadherent to their PD medications in that year}}$$

To assess the impact of poor medication adherence on worsening of PD, logistic multiple regression was used with worsening of PD symptoms (1 = worsening of PD symptoms; 0 = no worsening of PD symptoms) as the dependent variable and adherence to PD medications as the risk factor.

First, univariate analyses were conducted to identify variables that have a significant association with health-care costs. Predictor variables that were significant ($P \leq 0.05$) in the univariate analyses were added to the model as covariates.

The independent variables included in the model were demographic factors (age, sex, number of outpatient visits), medication-related factors (adherence to PD medications), and the dummy variables for the years. As the

MPR threshold of 0.8 has not been validated in PD to define suboptimal adherence, a total of four logistic regression analyses were run using MPR thresholds of 0.8, 0.6, 0.4, and 0.2 as risk factor variables.

RESULTS

The final study sample consisted of 104 patients with PD who were aged 65 years and older and who were enrolled continuously in an HMO for 1 to 5 years (total of 468 patient-years). The unit of analysis was patient-years. The attrition of the sample, especially in the fifth year ($n = 60$), was a manifestation of the decreased Medicare HMO enrollment over the study period. This limited the number of patients whose follow-up information was available for longer periods of time. The descriptive analysis of the study sample indicated an average age of 80 years (Table 1). There was an almost even distribution of men and women in the study population in all the 5 years. The population under study had severe comorbidities, as shown by an average Charlson index of 3.7 in all the 5 years. Adherence to PD therapy was low, with average MPR ranging from as low as 0.42 (± 0.37) in the fifth year to as high as 0.55 (± 0.37) in the second year.

There was a high prevalence of suboptimal adherence among patients, irrespective of the MPR threshold chosen to define adherence to PD medications. When MPR scores of less than 0.8 were used to define suboptimal adherence, almost 67% of patients were found to be suboptimally adherent to their PD medications (see Fig. 1). The high prevalence of suboptimal adherence to PD medication was also observed for the other MPR thresholds. When an MPR threshold as low as 0.2 was chosen, almost 35% of the study population were suboptimally adherent to their PD medications (see Fig. 2).

Irrespective of the threshold of MPR chosen to define suboptimal adherence to PD medication, logistic regression analysis indicated that there was a strong negative association between adherence and worsening of PD symptoms (Table 2). When suboptimal adherence was defined as MPR scores less than 0.8, the odds of patients adherent to PD medications experiencing a worsening of PD symptoms was 0.33 (67% less), compared with the odds of patients suboptimally adherent to medications (odds ratio: 0.33; confidence interval: 0.13–0.85). When the threshold used to define suboptimal adherence was reduced to 0.4, the odds of patients adherent to their PD medications experiencing a worsening of PD symptoms was 0.03 (97% less) compared with the odds of patients who were suboptimally adherent to their PD medications (odds ratio: 0.03; confidence interval: 0.004–0.28). All patients who were suboptimally adherent to their PD

TABLE 1. Characteristics of the study population across 5 years

Variable	Year				
	1 (n = 104)	2 (n = 103)	3 (n = 101)	4 (n = 100)	5 (n = 60)
Age (years)	78.08 (±7.43)	78.90 (±6.71)	80.20 (±7.14)	80.50 (±6.78)	82.70 (±5.73)
Charlson comorbidity index	3.31 (±2.87)	3.59 (±3.04)	3.72 (±3.03)	3.82 (±2.79)	3.98 (±2.78)
PD-specific emergency department visits	0.07 (±0.29)	0.10 (±0.43)	0.21 (±0.68)	0.31 (±1.01)	0.18 (±0.70)
PD-specific hospitalization	0.91 (±2.19)	0.96 (±2.01)	1.28 (±2.58)	1.02 (±2.58)	1.40 (±3.74)
PD-specific outpatient visits	15.20 (±9.72)	15.10 (±10.23)	14.97 (±11.03)	12.70 (±7.21)	13.10 (±13.39)
PD-specific refills	8.34 (±7.69)	8.20 (±7.12)	7.55 (±7.83)	6.68 (±6.95)	6.58 (±6.95)
Number of PD medications	1.39 (±0.96)	1.32 (±0.94)	1.28 (±1.08)	1.27 (±0.90)	1.38 (±1.05)
PD-specific prescription costs (\$)	233.36 (±243.98)	164.02 (±187.95)	188.26 (±343.15)	65.54 (±172.11)	15.38 (±80.43)
PD-specific healthcare costs (\$)	327.09 (±713.71)	285.48 (±547.45)	685.46 (±3038.20)	100.23 (±297.72)	455.04 (±2515.70)
Total healthcare costs (\$)	6054.89 (±6583.20)	7703.66 (±16179.09)	8066.9 (±11283.90)	6154.04 (±9215.72)	6920.5 (±10314.60)
Medication possession ratio	0.52 (±0.35)	0.55 (±0.37)	0.49 (±0.41)	0.45 (±0.37)	0.42 (±0.37)
Men	47.3	48.1	55.4	48.7	56.2
Worsening of PD symptoms	49	47	53.9	46	51.6

All the values are given as Mean ± SD or percentage.
PD, Parkinson's disease; SD, standard deviation.

medications, as defined by MPR scores less than 0.2, experienced worsening of PD symptoms. Hence, a logistic regression analysis could not be carried out for this group of patients.

DISCUSSION

Suboptimal adherence to medications is a serious problem facing current medical practice,^{22,23} and has several ramifications, including higher healthcare costs to patients and society.²⁴ Drug regimens in PD can be complicated, involving titration and addition of multiple agents over time.³ However, adherence to antiparkinsonian medications is important, particularly because physicians modify dosing schedules depending on the clinical response of the patients to the drugs.⁶ Suboptimal adherence to PD medications may lead to suboptimal efficacy, premature treatment modifications, increased symptomatology, and poor outcomes, including, possibly, an increased risk of dyskinesias.^{3,6}

We found rates of suboptimal adherence (MPR < 0.8) ranging between almost 60 and 70% over the 5-year

study period, indicating that suboptimal adherence to PD medications is a serious problem.

People suffering from PD are mostly receiving multiple medications and formulations where tablet size does not equate to unit doses.³ Titrations of doses and multiple agents complicate medication regimens in PD.³ Previous studies have highlighted the relationship between complexity of dosing regimens and adherence to PD medications,⁵⁻⁷ and have suggested that simplifying dosing regimens may enhance adherence to PD medications. Grosset et al.⁵ suggested that the development of long-acting PD drugs might improve medication adherence. They found that patients receiving once-daily dosing regimens had better adherence rates than did those taking regimens requiring multiple daily doses. Thus, dosage simplification may be one simple answer to the complex issue of medication adherence.

The physician-patient relationship has been documented as an important variable in understanding medication adherence.²⁵ Lack of or poor communication between patient and physician may result in a patient

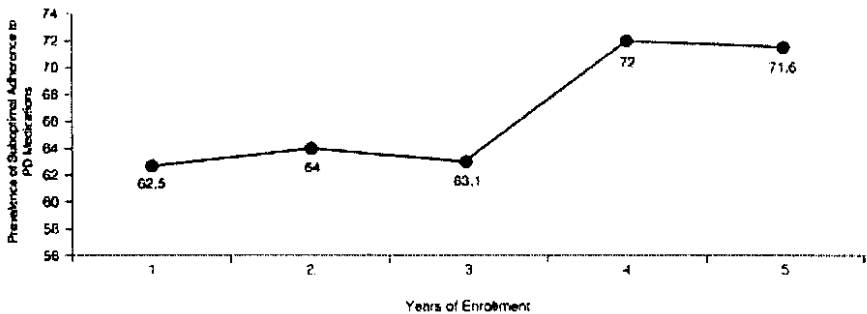


FIG. 1. Prevalence of suboptimal adherence to Parkinson's disease medications (medication possession ratio < 0.8 implying suboptimal adherence).

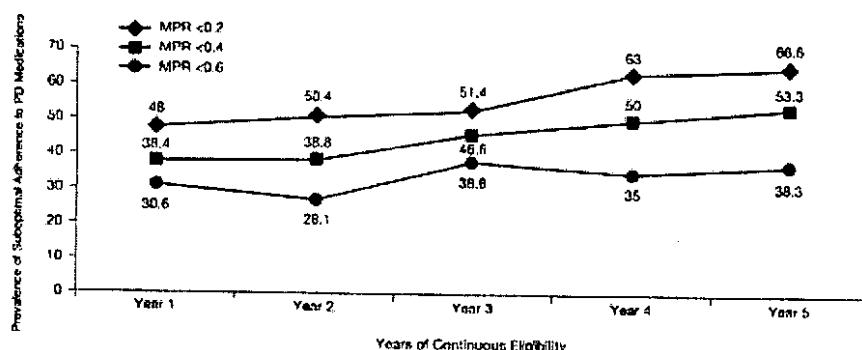


FIG. 2. Prevalence of suboptimal adherence to Parkinson's disease (PD) medication by medication possession ratio (MPR).

failing to recall instructions given by the physician.²⁶ This is particularly true in elderly patients and those with PD, who may also be experiencing a loss of cognitive functioning and/or memory.²⁵ Quality of clinical communication has been shown to be related to positive health outcomes, and all such clinical communications with elderly patients should take into consideration cognitive and memory functioning.²⁵

Patients tend to seek treatments that are effective, have minimal side effects, and do not disrupt their everyday activities.²⁷ This poses a problem with the elderly, who have more concomitant diseases and medications to take, all of which may produce side effects and/or interfere with activities of daily living.²⁵ Therefore, although physicians expect patients to be adherent to their therapy, patients' beliefs and their experience of their medications may preclude this.²⁸

Pharmacists, who have direct contact with the patients, can also play a very important role in encouraging medication adherence.²⁹ Pharmacists with access to the pa-

tient's medicine-taking history and demographics may work with other members of the healthcare team to improve patient's adherence²⁹ and thus may greatly improve a patient's care plan.

The healthcare system itself has a vital role to play in promoting health in the general population, particularly in the elderly. Strategies introduced to minimize cost to healthcare providers can sometimes come at a high price. For example, cost-saving strategies, such as prescription-drug benefit caps, can force patients to take inappropriate, "self-initiated" cost-saving measures, such as taking fewer medications than prescribed.³⁰ Indeed, "cost-saving strategies" have resulted in a decline in adherence to medications and increased hospitalization and emergency department visits.³¹ Therefore, it is important that members of the healthcare team and patients take into account benefit plans when deciding on treatment strategies.

Despite the strong associations between suboptimal adherence to medication and patient outcomes that we

TABLE 2. Logistic regression analysis of the association between worsening of Parkinson's disease symptoms and adherence to Parkinson's disease medications across 5 years

	Worsening of Parkinson's disease symptoms		
	MPR > 0.8	MPR > 0.6	MPR > 0.4
Odds ratio* (95% confidence interval)			
Adherence	0.33 (0.13–0.85) ^a	0.12 (0.03–0.39) ^a	0.03 (0.004–0.28) ^a
Number of outpatient visits	1.30 (1.00–1.70) ^a	1.37 (1.04–1.80) ^a	1.42 (1.08–1.86) ^b
Patients aged < 75 years	0.96 (0.34–2.72)	1.04 (0.36–3.02)	1.15 (0.39–3.37)
Men	0.49 (0.19–1.28)	0.48 (0.18–1.27)	0.42 (0.15–1.12)
Year 1 dummy	1.03 (0.21–5.09)	1.31 (0.25–6.68)	1.28 (0.24–6.61)
Year 2 dummy	0.77 (0.17–3.40)	0.95 (0.21–4.32)	1.04 (0.22–4.81)
Year 3 dummy	2.88 (0.45–18.39)	3.53 (0.53–23.27)	3.33 (0.49–22.35)
Year 4 dummy	0.78 (0.18–3.38)	0.80 (0.18–3.59)	0.77 (0.16–3.53)

MPR, medication possession ratio.

*Reference groups were women, patients aged ≤ 75 years, and Year 5.

^aSignificance at the 0.01 level.

^bSignificance at the 0.05 level.

had observed, these findings should be considered as an initial exploration of this issue and should be interpreted in the light of some limitations of the study. For instance, the observational nature of the study does not permit causal inferences. The definition of worsening of PD symptoms is not standard and was developed in consultation with a neurologist, keeping in mind the variables available in the dataset to allow for such a definition. The study used pharmacy records to infer medication adherence. Although this method has been shown to be reliable, it cannot safeguard from undetected adherence. If hospitalized patients received medications from the hospital or were discharged with a generous amount of medication, the study methods would have erroneously recorded a period of suboptimal adherence. In addition, other variables, such as socioeconomic status and physician-patient interactions, could not be assessed, as these data were not available in the database used for the study.

Despite these limitations, the study potentially has strong policy implications that merit further investigation. Research needs to be conducted in larger populations, particularly using adherence-enhancing interventions, to fully explore the relation between suboptimal adherence to PD medication and worsening of symptoms, with an emphasis on identifying factors that lead to suboptimal adherence and recommending effective strategies to overcome these.

CONCLUSION

There was a high prevalence of suboptimal adherence to PD medications in this population. Irrespective of the threshold of MPR chosen, there was a strong association between worsening of PD symptoms and suboptimal adherence to antiparkinsonian medications. Identifying and remedying suboptimal adherence to PD medications may improve symptom control and clinical outcomes.

Acknowledgments: This study was funded by a research grant from GlaxoSmithKline and was conducted as part of Dr. Kulkarni's dissertation under the direction of Dr. Balkrishnan. The article does not discuss any specific products of the company. We like to acknowledge the programming assistance provided by Fabian Camacho, as well as critical comments and suggestions provided by Drs. Milap C. Nahata and Sharon Schweikhart from The Ohio State University on the article. Dr. Stacy has received compensation from GlaxoSmithKline as a consultant and for honoraria related to lectures on Parkinson's disease and restless legs syndrome. Dr. Balkrishnan has received compensation from GlaxoSmithKline as a consultant in epilepsy. Dr. Anderson has received compensation from GlaxoSmithKline as a consultant. Dr. Kulkarni completed a summer internship with GlaxoSmithKline. Ms. Edin and Dr. Kirsch are employees of GlaxoSmithKline.

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Maintained increase in "on" time with ropinirole prolonged release in advanced Parkinson's disease

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Introduction

Patients with Parkinson's disease (PD) who are treated with L-dopa experience "on" time, when symptoms are controlled, and "off" time, during which the effects of L-dopa wear off and symptoms return. An aim of adjunctive therapy is to reduce the amount of "off" time and increase the amount of "on" time while receiving L-dopa therapy.

The efficacy of adjunctive therapy with ropinirole prolonged release compared with placebo was investigated in the EASE-PD (Efficacy And Safety Evaluation in Parkinson's Disease) Adjunct study (101468/159). The primary endpoint for the study was the mean change from baseline in the amount of awake time spent "on" at Week 24 (last observation carried forward [LOCF]). The proportions of patients achieving sustained increases in "on" time were analysed post hoc.

Methods

Patients

- Patients were aged ≥30 years, and had idiopathic PD (Hoehn & Yahr stage II-IV). All had been receiving L-dopa at a stable dose for ≥4 weeks, with suboptimal control of symptoms.
- Patients were required to have at least 3 waking hours "off" time per day during a baseline period.

Study design

- The EASE-PD Adjunct study was a Phase III, randomized, double-blind, placebo-controlled study.
- Patients were randomized (1:1) to receive ropinirole prolonged release or placebo for 24 weeks. The initial dose of ropinirole prolonged release was 2 mg/day, and doses were titrated to between 6 and 24 mg/day to achieve an optimal therapeutic response for each patient.
- The dose of L-dopa was reduced when the dose of study medication reached 8 mg/day, and at each subsequent dose increase.
- If symptom control was lost, the dose of study medication was increased to the next dose level.
- Patients whose symptoms did not improve after two up-titrations could have their L-dopa dose increased up to (but not above) their baseline dose.
- The primary endpoint was the mean change in daily awake time spent "on" from baseline to Week 24 (LOCF). In addition, a post-hoc analysis investigated the proportion of patients with increases in "on" time of ≥0.75, ≥1, ≥1.2 and ≥1.5 hours from baseline, which were present at a minimum of two consecutive visits and were maintained to the end of the study.

Results

Baseline characteristics and treatment

- A total of 391 patients were included in the intent-to-treat (ITT) population in the study, of whom 201 received ropinirole prolonged release and 190 received placebo. Baseline characteristics are summarized in Table 1.
- The mean (standard deviation [SD]) dose of ropinirole prolonged release at Week 24 LOCF was 18.8 (6.3) mg/day.

Table 1. Baseline demographic characteristics (intent-to-treat population).

	Ropinirole prolonged release (N=201)	Placebo (N=190)
Age, years	64.3 (9.1)	66.0 (9.7)
Women, n (%)	84 (42)	61 (32)
Age at onset of PD, years	57.6 (10.5) ^a	57.3 (10.7) ^a
Duration of PD, years	8.6 (4.8) ^a	8.6 (5.7) ^a
Duration of L-dopa treatment, years	6.5 (4.4) ^a	6.6 (4.3) ^a
L-dopa dose, mg/day	814 (234) ^a	776 (257) ^a
Total daily awake time spent "on", hours	9.0 (2.8)	9.1 (2.7)

n=200; n=188; n=190; n=187.

PD, Parkinson's disease.

All values are mean (standard deviation) unless stated otherwise.

- The adjusted mean reduction (adjusted for country and baseline dose) in L-dopa dose was 242 mg/day with ropinirole prolonged release and 137 mg/day with placebo at Week 24 LOCF. The adjusted mean treatment difference was -105.4 mg/day (95% confidence interval [CI]: -137.8, -73.0; p<0.0001).

Maintained increases in "on" time

- Overall, treatment with ropinirole prolonged release produced a significantly greater increase in "on" time from baseline to Week 24 LOCF than placebo. The mean treatment difference, adjusted for country and baseline score, was 1.7 hours (95% CI: 1.06, 2.33; p<0.0001).
- Greater proportions of patients attained increases from baseline in "on" time at Week 2 (observed case) which were maintained to study endpoint with ropinirole prolonged release than with placebo (Figure 1).
- More patients achieved sustained increases in "on" time of ≥0.75, ≥1, ≥1.2 and ≥1.5 hours with ropinirole prolonged release than with placebo at all measured timepoints, from Week 1 through to Week 24 (Figure 2).

Figure 1. Proportions of patients achieving maintained increases in "on" time at Week 2 (observed case analysis, intent-to-treat population).

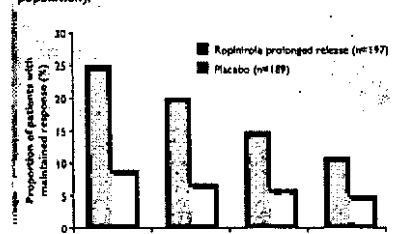
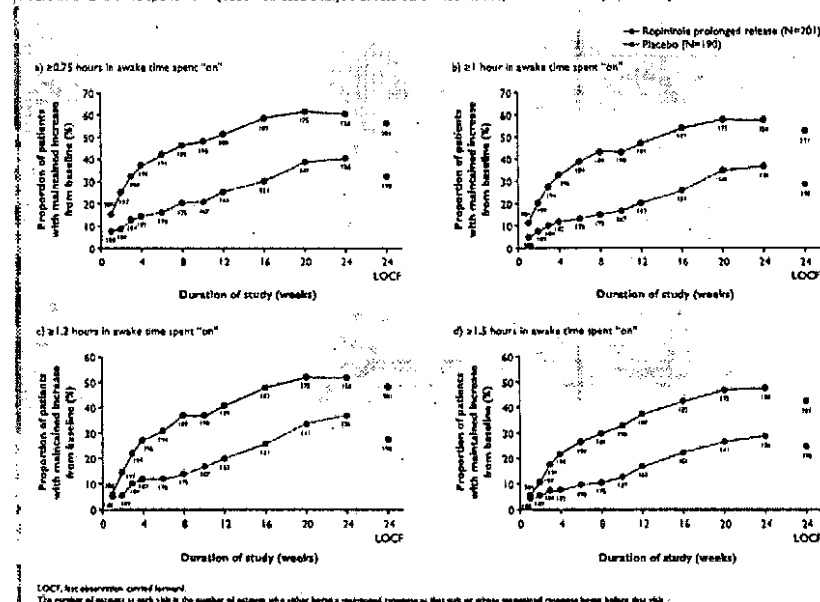


Figure 2. Proportion of patients achieving maintained increases from baseline of a) ≥0.75 hours, b) ≥1 hour, c) ≥1.2 hours and d) ≥1.5 hours in awake time spent "on" (observed case analysis unless otherwise stated; intent-to-treat population).



LOCF, last observation carried forward.

The number of patients at each visit is the number of patients who either had a maintained response at that visit or whose maintained response began before that visit.

Conclusions

- In this study in patients with advanced PD not optimally controlled with L-dopa, a larger proportion of patients treated with ropinirole prolonged release compared with placebo achieved sustained increases in "on" time at all measured timepoints.
- More patients treated with ropinirole prolonged release (43%) compared with placebo (23%) achieved a sustained increase in "on" time of at least 1.5 hours at Week 24 LOCF.
- The increases in "on" time achieved with ropinirole prolonged release were seen as early as 1 week after the start of treatment.

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Acknowledgements

Study supported by GlaxoSmithKline (GSK) Research and Development and StrykePharma.

Disclosures and conflicts of interest

E Růžicka is a member of a GSK advisory board and has received honoraria or consulting fees from Allergan, Boehringer Ingelheim, GSK and Medtronic. L Giorgi is an employee of GSK. B Hersh has received honoraria or consulting fees from Allergan, Boehringer Ingelheim, GSK, Novartis, Teva and Valeant Pharmaceuticals, research support from GSK and StrykePharma, Essi Ltd, Solway, Valeant and Acadia Pharmaceuticals, and grant funding from Teva Pharmaceuticals.