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Referencia : Expediente No. **05129157**
Asunto : Solicitud de patente para GABOXADOL PARA EL
TRATAMIENTO DE LA DEPRESIÓN Y OTROS
TRASTORNOS AFECTIVOS
Solicitante : H. LUNDBECK A/S
OPOSITOR : LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

I. ALEGATOS CONTESTACIÓN OPOSICIÓN

Yo, Emilio FERRERO, en mi condición de apoderado de la sociedad solicitante H. LUNDBECK A/S, por el presente escrito doy respuesta a la oposición formulada por el doctor José Luis REYES VILLAMIZAR, apoderado de la sociedad LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A. contra la solicitud de patente para la invención GABOXADOL PARA EL TRATAMIENTO DE LA DEPRESIÓN Y OTROS TRASTORNOS AFECTIVOS que se tramita en el expediente de la referencia.

II. CONTESTACIÓN DENTRO DEL TÉRMINO LEGAL

El oficio N° 10952 que dispone el traslado de la oposición formulada fue notificado por fijación en lista el 7 de septiembre de 2007, por lo que el término inicialmente concedido de 60 días hábiles vence el 5 de diciembre de 2007; sin embargo, teniendo en cuenta que el 30 de noviembre de 2007 solicité una prórroga del término, el término legal para contestar la oposición expira el 3 de marzo de 2008, de tal manera que la oposición está siendo contestada en término legal.

III. RESPUESTA A LA PETICIÓN

Me opongo a las peticiones de la sociedad LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A., y en consecuencia solicito se declare infundada la oposición presentada y se otorgue el privilegio de patente para la invención GABOXADOL PARA EL TRATAMIENTO DE LA DEPRESIÓN Y OTROS TRASTORNOS AFECTIVOS a nombre de mi representada, la sociedad H. LUNDBECK A/S, tramitada bajo el expediente 05.129.157.

IV. FUNDAMENTO FÁCTICO DE LA OPOSICIÓN

Fundamenta el opositor su petición, en los siguientes argumentos principales:

4.1. La invención solicitada consiste en un método terapéutico de prohibido patentamiento, además carece de nivel inventivo "por obra del conocimiento previo de todos los constituyentes que se administran en dicho método."

4.2. Es así como el GABOXADOL se describe en documentos como EP 0000338 B1 y EP 0840601, además los inhibidores de la reabsorción de serotonina SRI y algunas combinaciones que los contienen, han sido revelados en documentos como la solicitud internacional WO 01/41766 A1 del 14 de julio de 2001, "anteriores a la fecha de publicación de la solicitud colombiana en trámite."

4.3. Adicionalmente la patente europea EP 1 254 668 A2 publicada el 6 de noviembre de 2002 revela un método para tratar la depresión o la ansiedad en un mamífero "caracterizado por la administración de un agonista GABA A alfa 2/3 con un SRI, en cantidades adecuadas que permiten tratar la ansiedad o la depresión con una eficacia aumentada."

4.4. En opinión del apoderado del opositor, la patente solicitada en este asunto "busca resolver el mismo problema técnico" que ya había

resuelto la patente antes mencionada, equivalente a la solicitud internacional WO 04/112786 A2, toda vez que ambas hacen referencia a la combinación de GABOXADOL y un SRI (inhibidor de la recaptación de serotonina).

4.5. Igualmente la solicitud internacional WO 01/41766 A1 publicada el 14 de junio de 2001 plantea "la misma finalidad o solución que propone la solicitud colombiana en trámite", en tanto ambas "buscan proporcionar una formulación farmacéutica que comprenda un compuesto bien sea Gaboxadol o Irindalona y un inhibidor de la recaptación de serotonina (SRI) que es capaz de elevar el nivel de serotonina extracelular."

4.6. En opinión del apoderado del opositor, "la solicitud en trámite no está resolviendo un nuevo problema, pues se limita a realizar otra combinación predecible, que al igual que la de la revelada en la solicitud internacional mencionada, puede potenciar la acción de los fármacos."

4.7. Asimismo destaca el apoderado del opositor, la publicación científica PHARMACODYNAMIC EFFECTS AND POSSIBLE THERAPEUTIC USES OF THIP, A SPECIFIC GABA-AGONIST, del 22 de octubre de 1982, la cual revela el uso de Gaboxadol o TPI (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol) y su posible uso con otros fármacos los cuales pueden incrementar la actividad de las composiciones.

4.8. Finalmente se señala que las reivindicaciones 1 a 8 y 9 a 35 no son patentables por referirse a un método de tratamiento y a un uso respectivamente.

4.9. Por los anteriores hechos se concluye que no es procedente otorgar privilegio de patente a la invención solicitada, por infringir lo dispuesto en los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de la Comisión de la Comunidad Andina.

El apoderado de la sociedad opositora solicitó una prórroga del término para sustentar la oposición, de acuerdo con lo previsto en el párrafo 2° artículo 42 de la Decisión 486 de la Comisión de la Comunidad Andina.

Dentro de esta prórroga solicitó al Despacho tener en cuenta la patente americana US 4,278,676 publicada el 14 de julio de 1981 que revela el Gaboxadol "que ha mostrado poseer actividad relacionada con GABA".

De acuerdo con esta anterioridad se señala que "aunque el empleo de gaboxadol en la anterioridad citada no corresponde a la Depresión, no lo es menos que, todas y cada una de las características de dicho principio activo, y aún el hecho de combinar a Gaboxadol con otros compuestos activos no entraña novedad ni nivel inventivo como para acceder a la concesión del privilegio de patente solicitado."

V. RESPUESTA A LOS HECHOS Y ALEGATOS

En primer lugar manifiesto a este Despacho que, de conformidad con la posibilidad prevista en el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, presento a su consideración un nuevo capítulo reivindicatorio conformado por 10 reivindicaciones, sobre las cuales respetuosamente solicito se efectúe el correspondiente estudio de patentabilidad.

En segundo lugar, me permito presentar a consideración de este Despacho, las razones que demuestran que es procedente otorgar privilegio de patente a la invención solicitada por mi representada en este asunto, toda vez que no infringe las normas citadas por el apoderado del opositor como sustento de sus pretensiones, como ninguna otra establecida en nuestro ordenamiento vigente.

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Señala el opositor que la invención solicitada no cumple con los requisitos de novedad y nivel inventivo, presupuestos establecidos en los artículos 14, 16 y 18 de la Decisión 486 de la Comisión de la Comunidad Andina, además que contraviene lo previsto en el artículo 20 literal d) ibidem; estas normas disponen:

Artículo 14.- Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial.

Artículo 16.- Una invención se considerará nueva cuando no está comprendida en el estado de la técnica.

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40.

Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.

Artículo 20.- No serán patentables:

[...]

d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales.

Pues bien, en cuanto al requisito de novedad, es pertinente destacar lo señalado en el Manual Andino de Patentes página 65, en el cual se señala:

"para determinar la novedad de la invención, se debe comprobar si existen anticipaciones del estado de la técnica que contengan explícitamente todas las características técnicas esenciales de la

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invención. El examen de novedad se efectúa comparando elemento por elemento de la invención tal como está definido por las reivindicaciones con los del estado de la técnica." -el subrayado es mío-

Y más adelante en la página 66 señala:

"Un antecedente del estado de la técnica no puede ser interpretado. Solamente lo que está descrito claramente o lo que es directamente derivable de la divulgación de dicho antecedente puede ser usado en contra de la novedad de un objeto reivindicado"

De acuerdo con un análisis de estas disposiciones en concordancia desde luego con lo previsto en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina, se tiene de entrada que no existen argumentos válidos que permitan objetar la patentabilidad de la invención solicitada por mi poderdante por ausencia de NOVEDAD.

En efecto, no ha demostrado el apoderado del opositor que alguna de las anterioridades mencionadas en su escrito contenga todas las características técnicas de la invención.

Es así como la sola afirmación sobre la ausencia de novedad no basta, porque de acuerdo con lo previsto en el artículo 14 de la Decisión 486, es preciso demostrar que la invención solicitada ya estaba comprendida en el estado de la técnica, situación que no es la del presente caso.

En efecto, como bien se señala en el Manual Andino de Patentes, un antecedente del estado de la técnica no puede ser interpretado; así, el hecho que el apoderado del opositor haya puesto en evidencia la existencia de una serie de anterioridades que contienen las composiciones de la presente invención, tal circunstancia no conlleva la aplicación de la prohibición de patentabilidad por ausencia de novedad, pues no se ha demostrado que

la combinación específica que se reivindica con la invención solicitada se haya encontrado en alguna de dichas anterioridades.

Tal y como podrá corroborar este Despacho, las reivindicaciones modificadas que se presentan con este escrito están dirigidas hacia una composición farmacéutica que comprende GABOXADOL y ESCITALOPRAM, cuya combinación no es revelada por ninguna de las anterioridades citadas por el opositor; tal situación permite demostrar sin lugar a dudas el carácter NOVEDOSO de la invención solicitada, respecto a lo encontrado en el estado del arte.

Ahora bien, en cuanto al requisito sobre el NIVEL INVENTIVO ha señalado el Tribunal Andino de Justicia lo siguiente, en la Sentencia de Interpretación del Proceso 129-IP-2007.

"Este requisito, previsto por el artículo 4 de la Decisión 344, que exige que la invención tenga nivel inventivo, presupone que la misma represente un salto cualitativo en relación con la técnica existente y, además de no ser obvia para una persona del oficio normalmente versada en la materia técnica, debe ser siempre el resultado de una actividad creativa del hombre."

Tal y como se ha mencionado con anterioridad, la invención solicitada por mi representada en el expediente de la referencia reivindica una composición farmacéutica que comprende GABOXADOL y ESCITALOPRAM, combinación que soluciona positivamente algunos de los problemas asociados con los antidepresivos actualmente en el mercado, como por ejemplo con el ESCITALOPRAM cuando se usa solo; este hecho evidencia un salto cualitativo en relación con lo existente en el estado de la técnica.

De este modo tenemos, en cuanto a las anterioridades citadas por el opositor más cercanas a la invención solicitada, tenemos que serían los documentos EP 1254668 (D1), además de la publicación "Pharmacodynamic effects and possible therapeutic uses of THIP, a specific GABA-agonist", (Efectos farmacodinámicos y posibles usos terapéuticos de THIP, un agonista GABA específico), Christensen AV

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et al, Pharm. Weekbl. Sci., 1982, 22 Oct., vol 4, no 5, páginas 145-153 (D2), a los cuales me referiré a continuación:

Análisis respecto al documento D1:

Este documento revela el uso de un inhibidor de reabsorción de serotonina en combinación con un agonista GABA-A alfa 2/3, seleccionado entre gaboxadol, ganaxolona, fengabine, 2-(4-metoxifenil)-2,5,6,7,8,9-hexahidro-pirazolo[4,3-c]cinolin-3-ona, 7-ciclobutil-6-(2-metil-2H-1,2,4-triazol-3-ilmetoxi)-3-fenil-1,2,4-triazol[4,3-b]piridazina, (3-fluoro-4-metilfenil)-N-({1-[2-metilfenil]metil}-benzimidazol-2-il} metil)-N-pentilcarboxamida y 3-(aminometil)-5-ácido metilhexanoico. Sin embargo en este documento no se revelan datos respecto a que esta combinación sea efectiva y mucho menos a que el GABOXADOL produce efectos por si solo.

Adicionalmente, se debe tener en cuenta que para la fecha de prioridad de la presente invención se conocía que el GABOXADOL era un agonista del receptor GABA-A y más específicamente un agonista selectivo del receptor GABAA extrasináptico que mostraba selectividad funcional para receptores distintos a los receptores que contenían $\alpha 2/\alpha 3$, por lo que la inclusión de GABOXADOL en la serie de compuestos mencionados en el documento D1 sería considerada por el técnico en la materia como errónea.

Problema a ser resuelto:

El problema a ser resuelto por la presente invención es proporcionar un tratamiento nuevo y mejorado para la depresión. Una de las mejoras que se desean es que los estudios clínicos de trastornos depresivos indican que la falta de respuesta a los SSRI (Inhibidores Selectivos de la Reabsorción de Serotonina, por sus siglas en inglés) es significativa, hasta de un 30%. Otro factor que es a menudo pasado por alto en el tratamiento antidepresivo es el cumplimiento, lo cual tiene un profundo efecto en la motivación del

paciente para continuar con la farmacoterapia. En algunas circunstancias, la falta de respuesta a los SSRI puede estar ligada al cumplimiento de la prescripción. Otra mejora deseada en un nuevo tratamiento antidepresivo es que tenga un inicio rápido de acción lo que significa que el paciente responderá al tratamiento en un periodo corto de tiempo. Otro problema a ser resuelto por la presente invención es proporcionar un tratamiento que, comparado con algunos compuestos antidepresivos, tiene un perfil más benéfico de efectos secundarios.

En la solicitud de que trata el presente caso se presenta el resultado de la administración de 2.5 mg/kg de gaboxadol a ratas sujetas a una prueba de estrés leve crónico. Se considera que la prueba de estrés leve crónico es una prueba pre-clínica del potencial de un antidepresivo muy predecible, cuando no la más predecible.

A continuación se presentan datos de otras pruebas de GABOXADOL en combinación con ESCITALOPRAM en pruebas de estrés leve moderado. Las pruebas que constituyen los fundamentos para estos datos experimentales presentados fueron realizadas tal como se describe en la presente solicitud.

Los resultados de estas pruebas muestran un sorprendente efecto, el cual por consiguiente no es obvio, de GABOXADOL en combinación con ESCITALOPRAM en la prueba de estrés leve crónico, los cuales son altamente indicativos de que el uso de GABOXADOL en combinación con ESCITALOPRAM en el tratamiento de la depresión puede solucionar algunos de los problemas asociados con los actuales tratamientos para la depresión. En los resultados que se muestran a continuación, uno de los antidepresivos más ampliamente recetados, ESCITALOPRAM, se toma tanto como prueba del modelo, así como parámetro de los resultados obtenidos en el modelo con GABOXADOL en combinación con ESCITALOPRAM.

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Los resultados demuestran (de acuerdo con la Tabla 1 a continuación) que cuando a las ratas estresadas se les da GABOXADOL en combinación con ESCITALOPRAM, un alto porcentaje de ratas experimentarán una reversión de su fenotipo y se tornarán "normales" en comparación con las ratas estresadas a las que se les ha dado una dosis óptima de ESCITALOPRAM. Se puede concluir por consiguiente que el GABOXADOL en combinación con ESCITALOPRAM en el modelo preclínico puede tratar a un porcentaje más grande de individuos afectados - produciendo más respuestas al tratamiento. Por consiguiente el GABOXADOL en combinación con ESCITALOPRAM tiene el potencial de resolver el problema asociado con la falta de respuesta al tratamiento con los SSRI.

Tabla 1. Resultados de la prueba de estrés leve crónico con GABOXADOL en combinación con ESCITALOPRAM y con ESCITALOPRAM solo:

	Dosis	Nivel de respuesta
Gaboxadol + escitalopram	5 + 5 mg/kg IP	69% (11/16)
Escitalopram	5 mg/kg IP	05% (8/16)

Los datos experimentales anteriores demuestran que la combinación de GABOXADOL con ESCITALOPRAM como lo comprueba el modelo preclínico de estrés leve crónico para el potencial de un antidepresivo puede tratar porcentajes más grandes (una tasa más alta de respuesta) que el ESCITALOPRAM solo y por lo tanto resuelve el problema de la falta de respuesta a los SSRI. Adicionalmente, lo anterior indica que puede haber un mejor cumplimiento del tratamiento con GABOXADOL en combinación con ESCITALOPRAM en comparación con los SSRI actualmente usados.

La solución al problema

Al proporcionar una composición farmacéutica que comprende GABOXADOL y ESCITALOPRAM como se especifica en las reivindicaciones

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modificadas de la presente invención resuelve los problemas anteriormente descritos. No existe ningún indicio en el documento D1 respecto a que el GABOXADOL en combinación con ESCITALOPRAM podría resolver los problemas anteriormente descritos, como tampoco el documento D2 o ninguna de las referencias citadas por el opositor proporciona indicio alguno de que GABOXADOL en combinación con ESCITALOPRAM podría resolver el problema.

Análisis respecto al documento D2:

Este documento revela una larga lista de indicaciones en donde se señala que GABOXADOL podría tener valor benéfico, uno de estos es para la depresión. El técnico en la materia al leer el documento D2 en la fecha de prioridad de la presente invención estaría al tanto que para la mayoría de las indicaciones mencionadas en el documento D2 en donde se señala que el GABOXADOL podría tener beneficios, que las pruebas clínicas han demostrado que el GABOXADOL de hecho no tiene ningún valor benéfico, esto con respecto por ejemplo a la epilepsia (D3), disquinesia tardía (D4), enfermedad de Alzheimer (D5) y enfermedad de Huntington (D6). Como prueba del hecho que GABOXADOL ha fallado en muchas de las enfermedades mencionadas en el documento D2, se presentan como prueba los siguientes documentos:

- D3: Petersen et al., 1983, Acta Neurol Scand., 67 :114-117, "THIP: A single-blind controlled trial in patients with epilepsy" (Estudio controlado de ciego sencillo en pacientes con epilepsia).
- D4: Korsgaard et al., 1982, Arch Gen Psychiatry, 39 :1017-1021, "The effect of tetrahydroisoxazopyridinol (THIP) in Tardive Diskinesia" (El efecto de tetrahydroisoxasolopiridinol (THIP) en Disquinesia Tardía).
- D5: Mohr et al., 1986, Clinical Neuropharmacology, 9(3):25-63, "GABA-Agonist therapy for Alzheimer's disease". (Terapia de Agonista GABA para la enfermedad de Alzheimer).

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- D6: Foster et al., 1983, Neurology, 33 :637-639, "THIP treatment of Huntingdon's disease" (Tratamiento con THIP de la enfermedad de Huntingdon).

Problema a ser resuelto

El problema a ser resuelto por la presente invención respecto al documento D2 es el mismo que cuando del documento D1 es la anterioridad más cercana; por consiguiente resultan aplicables a este respecto, las mismas consideraciones analizadas respecto al Documento D1 en mención.

La solución al problema

Al proporcionar una composición farmacéutica que comprende GABOXADOL y ESCITALOPRAM como se especifica en las reivindicaciones modificadas, la presente invención resuelve los problemas anteriormente descritos. No hay indicio alguno en el documento D2 respecto a que el GABOXADOL en combinación con el ESCITALOPRAM pueda resolver los problemas mencionados anteriormente.

Por el contrario se considera que el técnico versado en la materia después de leer el documento D2 habría estado renuente a tener en cuenta la proposición de que el GABOXADOL podría tener valor benéfico dado que la persona versada en el arte conocería que el GABOXADOL había fallado en muchas de las otras indicaciones del documento D2 señalando que el GABOXADOL podría tener efectos benéficos.

Sin embargo, aún si se deja esto de lado, no existe indicio alguno en el documento D2 que cuando el GABOXADOL se combina con el ESCITALOPRAM de acuerdo con la presente invención, como se especifica en las reivindicaciones modificadas, sería posible resolver el problema que soluciona la presente invención.

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Es más, ni el documento D1 ni ninguna de las otras referencias citadas por el opositor, proporcionan tal indicio.

En resumen, el técnico versado en la materia al enfrentar el anterior problema y después de leer el documento D1 y/o el documento D2 o cualquiera de las otras referencias citadas por el opositor - no llegaría a la presente invención como se especifica en las reivindicaciones modificadas.

Finalmente, en cuanto a la anterioridad citada por el opositor dentro de la prórroga solicitada, esto es, la patente americana US 4,278,676 publicada el 14 de julio de 1981, me permito respetuosamente llamar la atención del Despacho sobre el hecho que la misma no podrá ser considerada como fundamento de la oposición presentada, de conformidad con lo previsto en el párrafo 2 del artículo 42 de la Decisión 486 de la Comisión de la Comunidad Andina, según el cual:

"A solicitud de parte, la oficina nacional competente otorgará, por una sola vez, un plazo adicional de sesenta días para sustentar la oposición." -el subrayado es mío-

Como se advierte claramente de acuerdo con esta disposición, es evidente que no es posible presentar a consideración hechos nuevos dentro del término de la prórroga solicitada, pues esta solo procede para efectos de sustentar la oposición.

Por tanto, solicito a este Despacho no considerar la anterioridad en mención como fundamento de la oposición formulada a nombre de la sociedad LABORATORIO FRANBCO COLOMBIANO LAFRANCOL S.A., la cual, si en gracia de discusión fuera tenida en cuenta por este Despacho, es de considerar en todo caso que no constituiría fundamento válido para impedir la patentabilidad de la invención de mí representada, por los mismos hechos a que he tenido oportunidad de referirme con anterioridad.

En efecto, la patente americana US 4,278,676 no revela la misma combinación que reivindica la invención solicitada en el presente asunto, que representa un salto cualitativo en relación con el tratamiento de la depresión.

En consecuencia, y siendo como se ha demostrado que la invención de mi representada es el resultado un proceso de experimentación, de tal manera que no se habría derivado de manera obvia ni evidente del estado de la técnica por parte de una persona del oficio normalmente versada en la materia, y al presentar un salto cualitativo frente a lo existente en el estado del arte, se tiene que la misma cumple el requisito de NIVEL INVENTIVO, contrario a lo afirmado por el opositor en su escrito.

En consecuencia, de conformidad con todos los anteriores hechos se demuestra como es que sí procede otorgar el privilegio de patente a la invención solicitada por mi representada en este asunto, ya que cumple con los presupuestos exigidos para el efecto por el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina, toda vez que se trata de una invención de producto que goza de los requisitos de NOVEDAD, NIVEL INVENTIVO y APLICACION INDUSTRIAL.

Finalmente, en relación con los alegatos del opositor en cuanto a solicitar la aplicación de lo dispuesto en el artículo 20 literal d) de la Decisión 486, me permito manifestar que las reivindicaciones de método han sido eliminadas del capítulo reivindicatorio que se presenta a consideración de este Despacho con el presente memorial, de tal manera que el mismo no resulta aplicable al presente caso por haber sido superada la objeción.

VI. PETICIONES

Por los anteriores hechos, solicito respetuosamente a este Despacho proceder a:

- 6.1. Declarar infundada la oposición presentada por la sociedad LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
- 6.2. Otorgar el privilegio de patente para la invención denominada GABOXADOL PARA EL TRATAMIENTO DE LA DEPRESIÓN Y OTROS TRASTORNOS AFECTIVOS a nombre de mi representada, la sociedad H. LUNDBECK A/S, que se tramita en el expediente de la referencia.

Atentamente manifiesto a este Despacho que, de conformidad con lo previsto en el artículo 36 de la Decisión 486 de la Comisión de la Comunidad Andina, mi representada se reserva el derecho a presentar solicitudes divisionales de la presente invención.

VII. PRUEBAS

Comedidamente solicito se tengan como pruebas en este asunto, todos y cada uno de los documentos que obran en el expediente de la referencia, y adicionalmente las siguientes publicaciones:

- 7.1. Petersen et al., 1983, Acta Neurol Scandi., 67 :114-117, "THIP: A single-blind controlled trial in patients with epilepsy" (Estudio controlado de ciego sencillo en pacientes con epilepsia).
- 7.2. Korsgaard et al., 1982, Arch Gen Psychiatry, 39 :1017-1021, "The effect of tetrahydroisoxazopyridinol (THIP) in Tardive Dyskinesia" (El efecto de tetrahydroisoxasolopiridinol (THIP) en Disquinesia Tardía).
- 7.3. Mohr et al., 1986, Clinical Neuropharmacology, 9(3):25-63, "GABA-Agonist therapy for Alzheimer's disease". (Terapia de Agonista GABA para la enfermedad de Alzheimer).

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1-71

7.4. Foster et al., 1983, Neurology, 33 :637-639, "THIP treatment of Huntingdon's disease" (Tratamiento con THIP de la enfermedad de Huntingdon).

VIII. ANEXOS

Presento junto con este memorial los siguientes documentos:

8.1. Formulario de modificaciones debidamente diligenciado, por el cual se presenta un nuevo capítulo reivindicatorio con un total de 10 reivindicaciones.

8.2. Fotocopia simple de la publicación "THIP: A single-blind controlled trial in patients with epilepsy" (Estudio controlado de ciego sencillo en pacientes con epilepsia).

8.3. Fotocopia simple de la publicación "The effect of tetrahydroisoxazopyridinol (THIP) in Tardive Diskinesia" (El efecto de tetrahydroisoxasolopiridinol (THIP) en Disquinesia Tardía).

8.4. Fotocopia simple de la publicación "GABA-Agonist therapy for Amzheimer's disease". (Terapia de Agonista GABA para la enfermedad de Alzaheimer).

8.5. Fotocopia simple de la publicación "THIP treatment of Huntingdon's disease" (Tratamiento con THIP de la enfermedad de Huntingdon).

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : OS - 16,460
FECHA : FEBRERO 25 DE 2008

CONSIGNACION

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2808482	25/02/2008	40,274,000.00

CONCEPTO

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICADA	
12		MARCAS Y LEÑAS COMERCIALES	103,000.00
		TOTAL :	\$ 103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Cdo 03003-264-003-6

virus recovered from tissue cultures of human adenoids. *Proc Soc Exp Biol Med* 1956;92:418-24.

16. Acute Conditions: Incidence and associated disability, United States, July 1977-June 1978. Hyattsville, MD, US Department of Health, Education, and Welfare, Public Health

Service, National Center for Health Statistics. DHEW publication No. (PHS) 79-1560, series 10, No. 132, 1979:14, 33.

17. Centers for Disease Control. National survey of public attitudes towards A/New Jersey/76 influenza vaccination. Report no. 6, January 1977.

THIP treatment of Huntington's disease

Article abstract—We evaluated the therapeutic efficacy of gamma aminobutyric acid (GABA) system stimulation in four patients with classical Huntington's disease and one with the hypokinetic-rigid form. Orally administered THIP (4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridin-3-ol), a novel GABA receptor agonist, failed to improve motor or cognitive function during a 2-week trial. At maximum levels, THIP mimicked another putative GABA agonist, muscimol, in causing unsteadiness of gait, diminished attention to sensory stimuli, and somnolence. These effects suggest that central GABA systems participate in the regulation of some human and behavioral functions. CSF content of homovanillic acid, a major metabolite of dopamine, increased during high-dose THIP therapy, suggesting that augmentation of dopaminergic function may have contributed to the drug's lack of efficacy.

NEUROLOGY (Cleveland) 1983;33:637-9

Norman L. Foster, Thomas N. Chase, Alessandro Denaro, Theodore A. Hara, and Carol A. Tamminga

The basal ganglia content of gamma aminobutyric acid (GABA) is reduced in patients with Huntington's disease.¹ Striatal application of drugs that antagonize GABA can induce involuntary movements,² and pharmacologic agents that stimulate GABA-mediated synaptic function tend to suppress naturally occurring or drug-induced hyperkinetic disorders.^{3,4} Although previous attempts to treat Huntington's disease with drugs that enhance central GABA activity have been unsuccessful, the recent development of THIP (4,5,6,7-tetrahydroisoxazolo-[5,4-c]pyridin-3-ol) provided an opportunity to test the therapeutic efficacy of a relatively more specific and presumably less toxic GABA analog.

Patients and methods. Five patients (two men and three women aged 25 to 59 years) with Huntington's disease gave informed consent. Four had the classical form with chorea and dementia (one mild, one moderate, and two severe); the fifth had dementia with mild rigidity and tremor (hypokinetic-rigid form). All had a family history of Huntington's disease and CT evidence of caudate atrophy. There was no evidence of other significant illness, and none of the subjects received other medications during this clinical trial. Two patients who had been taking phenothiazines were drug-

free for 2 weeks before entering the study.

A double-blind crossover design was used with initial and terminal placebo phases of random length. Each patient received four identical capsules containing either THIP or an inert placebo (supplied by H. Lundbeck and Co., Copenhagen, Denmark) four times daily for 30 days. THIP was begun at a daily dose of 15 mg, and was gradually increased to a maximum of 60 to 120 mg. The duration of placebo averaged 10 days, and that of active drug therapy 14 days.

Motor and behavioral function was assessed periodically at the bedside by one or more blinded observers. One hour after the first morning THIP dose, extrapyramidal function was evaluated using the Abnormal Involuntary Movement Scale (AIMS) and the modified Columbia rating scale.^{5,6} Videotaped records provided a subsequent opportunity to validate these ratings. Memory was evaluated by a word-learning test consisting of an eight-noun list recited in five trials; a different set of words was given in each assessment. Reaction time was measured by the time necessary to depress a telegraph key after an auditory cue. The Brief Psychiatric Rating Scale (BPRS)⁷ was used to evaluate behavioral changes.

CSF was obtained by lumbar puncture before treatment was initiated and again at the highest

tolerated dose of THIP. The timing of the CSF examination was unknown to the blinded observers. Fluid was collected on ice; 1-ml aliquots of the first 13 ml were frozen at 70 °F within 1 hour for later analysis. GABA was assayed, using an ion-exchange fluorometric technique, after being deproteinized by adding 1/3 volume of 20% aqueous sulfosalicylic acid.⁶ Homovanillic acid (HVA), a metabolite of dopamine, was determined by high-performance liquid chromatography with an electrochemical detector.⁹

Results. There was no clinically significant improvement in abnormal involuntary movements during THIP treatment. Although AIMS scores indicated that chorea was somewhat reduced in several patients at moderate THIP dose levels, for the group as a whole this change failed to reach statistical significance (table 1). Parkinsonian signs remained unchanged by the Columbia rating scale in the rigid patient. Behavioral testing revealed no consistent alteration at less than maximal doses in word learning (5.2 ± 0.6 words recalled on placebo and 5.2 ± 0.4 during treatment), reaction time (0.416 ± 0.09 msec versus 0.401 ± 0.04), or

BPRS scores (25 ± 1.7 versus 24 ± 0.6).

The GABA content of plasma (231 ± 3 pmol per milliliter before and 224 ± 21 during treatment) or CSF (table 2) showed no significant change, but CSF HVA increased by an average of 25% ($p < 0.05$).

At maximum THIP doses (60 to 120 mg per day), all patients evidenced temporary unsteadiness of gait, and four of five had some worsening of involuntary movements. In addition, there was a transitory alteration in consciousness in every patient. All manifested periods of mild somnolence, and during alert periods all developed a dissociative state with slow responses to external stimuli. Amnesia for events during the dissociative state was common. One individual also reported hypnagogic hallucinations. Vital signs and routine tests of renal, hepatic, and hematologic function remained within normal limits.

Discussion. Attempts to provide symptomatic relief to patients with Huntington's disease through pharmacologic stimulation of the GABA system have proved disappointing. An initial report of a response to isoniazid, which inhibits GABA degradation by GABA transaminase (GABA-T), was not confirmed by controlled investigations.¹⁰⁻¹² Other inhibitors of GABA-T, including gamma-vinyl GABA¹³ and amino-oxyacetic acid,¹⁴ have also been ineffective. Similarly, GABA agonists such as imidazole-4-acetic acid¹⁵ and muscimol¹⁶ have lacked therapeutic activity or induced significant toxicity. Finally, THIP also failed to provide clinical improvement during our brief study, although effects of long-term treatment must await other trials.

THIP was selected because of several potentially favorable pharmacokinetic and pharmacologic properties. THIP is completely absorbed when given orally, crosses the blood-brain barrier more completely than muscimol, and is primarily excreted unchanged.^{17,18} Moreover, the binding character-

Table 1. Effect of THIP on AIMS* score

Pt no.	Placebo	60 mg per day	% improvement
1	10	8	20
2	33	32	3
3	34	30	12
4	21	21	0
5	6	5	17
Mean $\pm$ SEM	21 ± 5.7	19 ± 5.5	10 ± 3.9

* The Abnormal Involuntary Movement Scale (AIMS) was used to assess motor function.

Table 2. Effect of THIP on CSF GABA and HVA

Pt no.	GABA			HVA		
	Baseline (pmol/ml)	Treatment (pmol/ml)	% increase	Baseline (ng/ml)	Treatment (ng/ml)	% increase
2	103	133	29	18	21	17
3	169	193	21	12	18	50
4	111	135	22	18	21	17
5	113	100	-11	31	38	18
Mean $\pm$ SEM	122 ± 13	140 ± 19	15 ± 8.9	20 ± 4.0	24 ± 4.1	$25 \pm 8^*$

Treatment values obtained at an average daily THIP dose of 100 mg.
* $p < 0.05$ t-test for paired data.

istics of THIP differ from those of muscimol or other GABA agonists currently available for study.^{18,20}

The motor and behavioral changes during THIP therapy suggest that the drug is capable of penetrating the human brain. Moreover, some of the transient effects induced by high doses of THIP resembled those observed with another potent GABA agonist, muscimol.^{18,21,22} These effects included unsteadiness and an altered state of consciousness characterized by a peculiar inattentiveness to external stimuli or by somnolence, suggesting that GABA-containing neuronal systems may contribute to the regulation of some human psychomotor functions.

It is notable that the highest values of HVA seen among our patients were found in the person with hypokinetic-rigid features. So far, no consistent difference in HVA concentration has been documented in this as compared with the more typical form of Huntington's disease.

Although examined only in four patients, the finding of increased CSF HVA levels may indicate that THIP augments central dopaminergic function. In rats, THIP elevated striatal and limbic HVA concentrations and nigral and ventral tegmental dopamine neuron firing rates.^{23,24} Since drugs that potentiate dopamine-mediated synaptic transmission characteristically aggravate chorea, the lack of effectiveness of THIP in Huntington's disease may be attributed to direct or indirect actions on the dopamine system. Whether this or some other possibility, such as a loss of GABA receptors or the multiplicity of transmitter systems that degenerate, accounts for the inability of THIP to ameliorate symptoms of Huntington's disease remains to be determined.

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Acta Neurol Scand., 1986;67:114-117

Key words: Antiepileptic drugs; GABA agonists; THIP.

THIP: A single-blind controlled trial in patients with epilepsy

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ABSTRACT - In an early phase-2 study, THIP (4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol) was investigated in a single-blind controlled trial comprising 9 outpatients suffering from epilepsy.

THIP was added to the concomitant antiepileptic treatment with increasing doses (15 to 120 mg/day) based on therapeutic effect or side-effects. The blood levels of concomitant therapy were kept constant.

No significant difference was established between the number of seizures during treatment with maximal doses of THIP and placebo. A trend was observed for lower seizure frequency during a period on submaximal dose of THIP.

Accepted for publication November 4, 1985

Since the discovery of gamma-aminobutyric acid (GABA), there has been increasing evidence to indicate that it is a major inhibitory transmitter in many areas of the brain (1). Indirect evidence suggests disturbances in GABA neurotransmission in epilepsy. The concentration of GABA in the cerebrospinal fluid of medicated epileptic patients is lower than normal (2). GABA antagonists such as bicuculline and picrotoxin can induce seizures in experimental animals (3). In seizure patients, a diffuse low concentration of GABA in cerebral cortex has been observed (4). Similarly it has been shown that valproate, an effective antiepileptic drug, increases the cerebral GABA content in animals (5), al-

though the doses used exceeded the usual clinical doses (6).

THIP (4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol) is a compound with a selective action on GABA receptors. At low doses it is active as an anticonvulsant against bicuculline- and metrazol-induced convulsions, and audiogenic seizures in mice, and at higher doses it antagonizes the effects of strychnine and picrotoxin. THIP is, however, inactive against bicuculline-lethality or electroshock seizures (7).

The aim of this placebo-controlled single-blind study was to investigate whether THIP has an antiepileptic effect and to evaluate possible side-effects.

Material and methods

9 outpatients (4 female, 5 male) average age 41 years (range 20-59 years) were included in the study. 4 suffered from primary generalized seizures, 5 from partial seizures with secondary generalization. The average duration of the epilepsy was 23 years (range 4-51 years). All patients continued their antiepileptic drug therapy. 8 patients were treated with two, 1 with only one drug. 8 were treated with carbamazepine, 7 with valproate, 1 with primidone and 1 with phenytoin. The blood levels of concomitant treatment were kept constant during the trial.

Only patients with 4 seizures per month or more were included. Excluded from the study were patients under 17 and above 70 years of age, pregnant women and patients suffering from other somatic diseases.

The study was designed as a placebo-controlled single-blind trial running for 26 weeks. During the first 2 weeks, the patients were treated with placebo. Thereafter treatment with THIP, 5 mg, 3 times a day, was initiated. The dose was then increased every second week with the dose administered 3 times a day as follows: 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg. The fixing of the dose was based on therapeutic effect or side-effects. Where satisfactory therapeutic effect was registered, the dose was kept constant for at least 1 month. The patients were seen every 2 weeks; seizures as well as side-effects were recorded. The latter included tremor, sedation, ataxia, hypotonia, dizziness, myoclonic jerks, insomnia, loss of appetite, changed taste and pruritus.

Hemoglobin value, red and white blood cell count, aspartate aminotransferase, alkaline phosphatases, bilirubine, creatinine, blood sugar and plasma levels of concomitant drug treatment were also determined biweekly.

Results

The results are shown in Fig. 1. The frequency of seizures during the placebo period was compared with the average frequency during a 14-day period on maximal THIP dose (30-120 mg). No significant difference was found between the placebo period and the period on maximal THIP dose ($P = 0.54$ (Wilcoxon)).

When the frequency of seizures during the placebo period was compared with a 2-week period in which the patient had the lowest number of seizures, there seemed to be a tendency towards fewer seizures during this period on submaximal dose of THIP (20-75

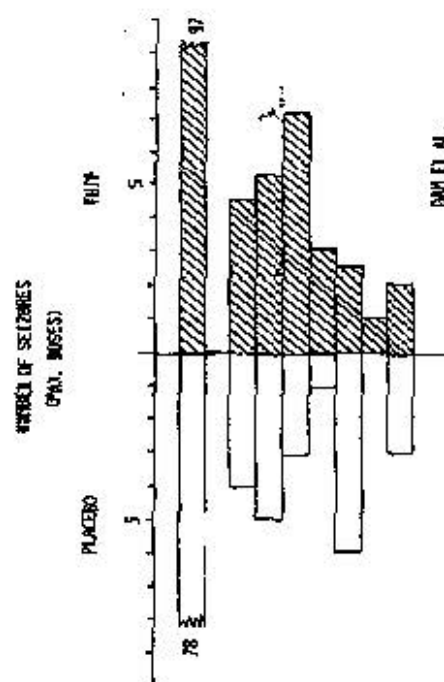


Fig. 1. The total number of seizures in the individual patients on maximal dose compared with the placebo period.

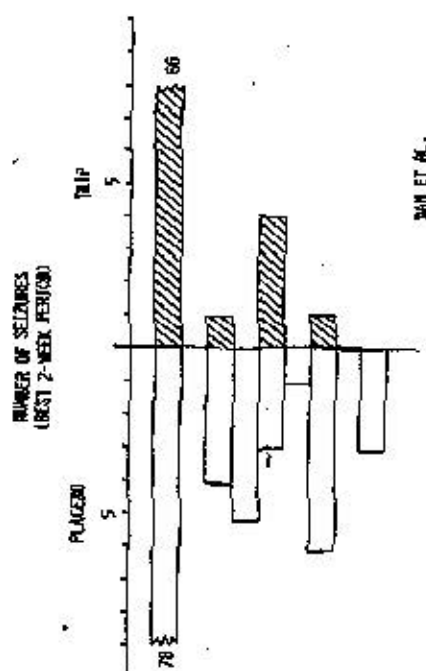


Fig. 2. The total number of seizures in the individual patients on submaximal dose compared with the placebo period.

Table 2
Side-effects on maximal tolerated dose of THFV

Side effects	Number of Patients
Tremor	5
Sedation	4
Ataxia	3
Hypotonia with tendency to fall	3
Dizziness	3
Myoclonic jerks	1
Insomnia	1
Loss of appetite	1
Changed taste	1
Pruritus	2

mg) (Fig. 2). However, this difference was not statistically significant either ($P = 0.08$) (Wilcoxon).

The side-effects were relatively frequent (Table 1) and prevented all the patients except for 2 from reaching the maximal dose of 120 mg daily. However, adverse reactions were few and insignificant when the patients were on the submaximal dose, which gave a tendency for seizure reduction.

1 patient had to be withdrawn from the trial after 18 weeks of treatment because of hypertension which was found to be without relation to the present investigation.

Discussion

The present study was unable to discover any significant antiepileptic effect on THIP when used in maximal tolerated doses. There was, however, a non-significant trend toward a reduction in seizure frequency during a period on submaximal dose when comparing a selected 2-week period with the placebo period.

The side-effects were relatively frequent and prevented all patients, except for 2 from reaching maximal dose. However, few adverse reactions were recorded when the patients were treated with the lowest dose, which gave a tendency for seizure reduction. Although the concept of a GABA-mediated mechanism of action of antiepileptic drugs seems attractive, many aspects remain contradictory or unsolved. For example some GABA agonists like muscimol and THIP have been shown to possess convulsant properties when tested in primates, although they have shown anticonvulsant effects in rodent screening tests (8). Similarly we were unable to verify the supposed antiepileptic effect of Progabide, another GABA agonist, in a randomized double-blind cross-over trial in patients with partial complex seizures, although this compound

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in several animal models has shown marked activity in inhibiting both chemically and electrically induced seizures (9).

The diffuse activation of GABA receptors by GABA agonists may be unphysiological and not necessarily associated with an antiepileptic effect in man, as this diffuse activation may inhibit the GABA synthesis through a feedback mechanism.

However, a recent single-blind study of gamma-vinyl-GABA, a catalytic irreversible inhibitor of GABA transaminase which is chiefly responsible for the GABA metabolism showed that this compound had a marked antiepileptic effect in patients (10). These recent findings await further verification in double-blind controlled trials.

Acknowledgements

THIP was kindly supplied by Lundbeck Ltd., Copenhagen.

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The Effect of Tetrahydroisoxazolopyridinol (THIP) in Tardive Dyskinesia

A New γ -Aminobutyric Acid Agonist

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γ -Aminobutyric acid (GABA) agonists have been proposed for the treatment of tardive dyskinesia, but their therapeutic potential has been limited by side effects and toxicity. To elucidate further the role of GABA in neuroleptic-induced dyskinesias, we evaluated tetrahydroisoxazolopyridinol (THIP), a new, less toxic GABA analog and GABA receptor agonist, in both a dose-finding (single-dose) pilot study with five patients and a longer (four-week) placebo-controlled study with 13 patients. The patients were videotaped during a standardized examination; tardive dyskinesia, parkinsonian symptoms, and eye-blinking rates were rated blindly and randomly. The maximal short-term dose of THIP was 10 to 25 mg, whereas in the longer-term study the highest daily dose ranged from 20 to 120 mg. Tardive dyskinesia was unchanged during THIP treatment, but preexisting parkinsonism increased significantly and eye-blinking rates decreased. Psychiatric symptoms showed no significant changes, although tension and depression lessened. Side effects included sedation, confusion, dizziness, vomiting, and myoclonic jerks. Although THIP is not an effective new treatment for tardive dyskinesia, more specific GABA agonists should be evaluated in future studies of this syndrome.

(*Arch Gen Psychiatry* 1992;39:1017-1021)

Tardive dyskinesia is a hyperkinetic movement disorder characterized by abnormal involuntary orofacial movements and may include hyperkinesias in limbs and trunk. It occurs during or at the cessation of prolonged neuroleptic treatment and may be irreversible. The exact pathogenesis of the syndrome is still unknown, but dopa-

minergic hypersensitivity and a disturbed balance between the dopaminergic and cholinergic systems have been proposed to be primarily involved.^{1,2} The discovery of a γ -aminobutyric acid (GABA)-mediated feedback system between striatal cholinergic and nigral dopaminergic neurons³ and demonstration of GABA-dopamine interactions⁴⁻¹⁰ suggest that a complete understanding of movement disorders may include a role for GABA in tardive dyskinesia.

Clinical trials in tardive dyskinesia with agents thought to increase GABA activity in the brain have produced conflicting results. Muscimol suppressed tardive dyskinesia, but produced undesirable side effects.¹¹ γ -Acetylenic GABA had modest antihyperkinetic and parkinsonism-aggravating effects, especially in patients receiving potent antidopaminergic neuroleptic treatment.¹² Valproate sodium, which may increase brain GABA by inhibition of GABA transaminase,^{13,14} reduced tardive dyskinesia in the initial report,¹⁵ but subsequent evaluations noted only modest improvement^{16,17} or no effect.¹⁸ Baclofen, a structural analog of GABA, with unclear effects on GABA mechanisms,¹⁹ has produced divergent effects in tardive dyskinesia, varying from improvement^{20,21} to no effect,^{22,23} and this treatment often produced side effects of sedation, confusion, and increased parkinsonism.²⁴ In summary, the currently available drugs affecting GABA have been either too nonspecific or too toxic for clinical use.

Tetrahydroisoxazolopyridinol (THIP; 4,5,6,7-tetrahydroisoxazole [5,4-c]-pyridin-3-ol), a rigid bicyclic isoxazole derivative of GABA, is a new direct GABA receptor agonist^{25,26} that is less toxic than muscimol. It penetrates the blood-brain barrier readily and is approximately one third as potent as muscimol after systemic administration.^{27,28}

Against this background, it was important to investigate the effects of THIP in tardive dyskinesia and neuroleptic-induced parkinsonism. In addition, eye-blinking rates were assessed, as disturbances in eye blinking have been associated with dopaminergic functions and various dyskinesias²⁹ and may be influenced by GABA drugs.³⁰

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Reprint requests to Department H, Sol Hans Mental Hospital, DK-4000 Roskilde, Denmark (Dr Korsgaard).

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Table 1.—Patient Data

Patient/ Sex/ Age, yr	Diagnosis	Duration of Illness, yr	Duration of Neuroleptic Treatment, yr	Duration of Tardive Dyskinesia, yr	Concurrent Neuroleptic Treatment		Other Drugs	Maximum THIP ^a Dose, mg/Day ^b
					Drug	Duration, yr		
1/M/68	Schizophrenia, paranoid type	13	3	1.5	Flupentixol decanoate, 200 mg/2 wk Methotrimiprazine, 50 mg/day	0.5 0.5	...	20
2/F/70	Schizophrenia, paranoid type	35	25	4.0	...	...	...	20
3/M/73	Cardiac neurosis Senile dementia	60 4	10	3.0	Pinazide, 4 mg/day Chlorprothixene, 50 mg/day	1.5 1.5	...	35
4/F/71	Manic-depressive	3	3	1.0	Flupentixol, 10 mg/day	0.25	...	45
5/M/28	Schizophrenia, hebephrenic type	8	7	1.0	Clozapine, 450 mg/day	1.25	...	25
6/M/52	Schizophrenia, hebephrenic type	31	26	7.0	Clophenithol decanoate, 100 mg/2 wk	1.0	...	60
7/M/57	Schizophrenia, hebephrenic type	28	22	10.0	Clozapine, 350 mg/day	5.0	Epiphen hydrochloride, 5 mg/day	51
8/M/81	Schizophrenia, paranoid type	27	22	5.0	...	...	Procypridine hydrochloride, 15 mg/day	55
9/M/84	Presenile dementia	5	5	1.0	Methotrimiprazine, 25 mg/day	0.25	...	60
10/M/67	Schizophrenia, undifferentiated type	31	18	7.0	Methotrimiprazine, 25 mg/day	0.25	...	60
11/M/53	Alcoholic dementia	7	2	0.5	Pipolazine palmitate, 100 mg/3 wk	1.0	...	120
12/M/59	Schizophrenia, paranoid type	27	25	11.0	Pipolazine palmitate, 200 mg/3 wk Chlorprothixene, 200 mg/day	0.5 0.5	Orphenadrine hydrochloride, 100 mg/day	123
13/M/83	Manic-depressive	27	16	2.0	Haloperidol 2 mg/day	1.0	Lithium carbonate, 1,350 mg/day	120
14/F/80	Schizophrenia, hebephrenic type	52	24	5.0	Pinazide, 5 mg/day	0.5	...	...
Mean values (age, 51 yr)	...	23.2	14.7	4.3	...	...	...	88*

*THIP indicates tetrahydrocannabinol.
†Only patients from the longer-term study.

SUBJECTS AND METHODS

Subjects

Fourteen psychiatric inpatients with tardive dyskinesia, all physically healthy, gave informed consent to participate in this placebo-controlled trial. Since this was the first clinical trial with THIP, five patients (No. 3, 8, 11, 12, and 14) were included in a preliminary dose-finding single-dose study, whereas 13 (four of whom were involved in the single-dose study) took part in the following longer-term study. They all met the following criteria: (1) neuroleptic treatment for more than two years; (2) stable tardive dyskinesia for at least six months; and (3) unchanged neuroleptic or anticholinergic treatment during the last three months. Patient data are presented in Table 1.

Medications

Medication, if any, taken at the beginning of the study was continued during the entire evaluation. During the single-dose study, the patients received placebo and THIP in identical capsules, starting with placebo followed by THIP. The initial dose of 5 mg was increased by 5 mg per test day to a maximum of 25 mg unless side effects occurred. Although the elimination half-life in

humans is estimated to be less than two hours,¹⁰ the single doses were administered twice weekly to avoid accumulation.

In the longer-term study, patients 1 through 13 followed a schedule of one week of placebo three times a day, and four weeks of THIP, beginning with 5 mg three times a day, increasing twice weekly by 5 mg three times a day to a maximum of 120 mg/day or until disturbing side effects appeared. After the THIP dose was gradually reduced over a period of one week, placebo was given for two weeks. When side effects developed, the dose was reduced to the former level.

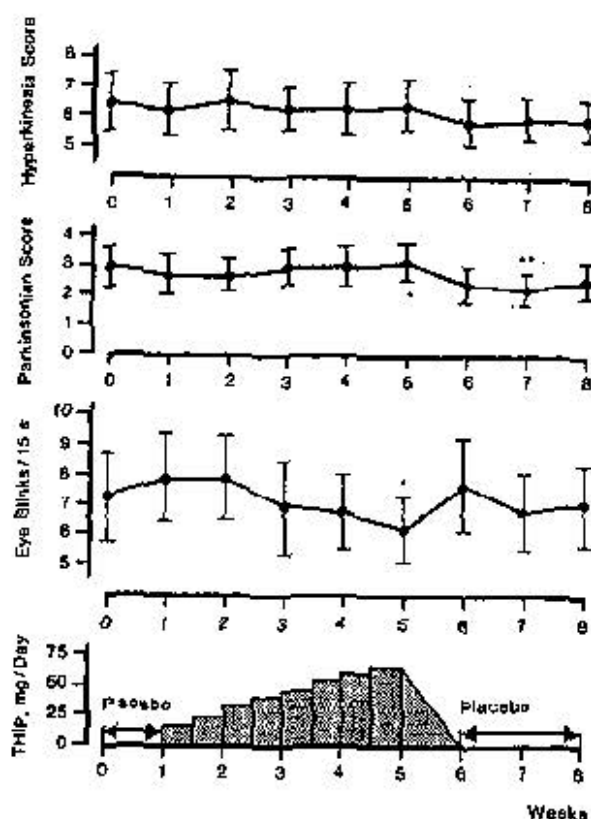
Evaluations

Tardive dyskinesia, parkinsonian symptoms, and eye-blinking rates were evaluated from videotapes prepared before and 1, 2, and 4 hours after the single doses. During the longer-term study, video recordings were made weekly at the same time each day. The standardized recording sessions of approximately five minutes' duration included sitting, standing, walking, distraction by conversation, and performing voluntary movements of unaffected muscle groups such as writing. The rating scale for tardive dyskinesia included evaluations of eight body regions: jaw, tongue, lips, face, head, trunk, and upper and lower extremities, scored from 0 to 6 (absent to severe), whereas the rating scale for

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Table 2.—Total Scores (Mean ± SEM) of Tardive Dyskinesia, Parkinsonism, and Eye-Blinking Rates in Single-Dose Study (N = 5)										
	Hours After Placebo			Hours After THIP,* 10 mg			Hours After Maximum THIP Dose (20 ± 5 mg)			
	0	2	4	0	2	4	0	2	4	
Tardive dyskinesia	5.00 ± 0.93	5.00 ± 1.05	4.90 ± 0.91	4.80 ± 0.70	4.70 ± 0.80	4.50 ± 0.71	4.30 ± 0.83	4.30 ± 1.08	4.20 ± 1.59	
Parkinsonism	2.90 ± 0.79	2.40 ± 0.76	3.00 ± 0.77	2.20 ± 0.58	2.80 ± 0.93	2.80 ± 0.68	3.00 ± 1.04	4.60 ± 1.53	4.00 ± 1.30	
Eye blinks/15 s	3.40 ± 1.77	3.40 ± 1.72	3.80 ± 1.82	4.00 ± 1.70	4.40 ± 1.82	4.80 ± 1.98	4.60 ± 2.27	3.80 ± 2.80	5.60 ± 2.40	

*THIP indicates tetrahydroisoxazopyridinol.



Effect of increasing doses of tetrahydroisoxazopyridinol (THIP) on mean scores. Brackets indicate SEM; asterisks, $P < .05$ compared with pretreatment scores; double asterisk, $P < .05$ compared with score at highest THIP dose.

parkinsonism consisted of eight items: facial expression, bradykinesia, tremor, posture, arm swing, gait, rigidity, and salivation, scored from 0 to 3 (absent to severe).¹ Eye-blinking rates were determined for 15-s epochs during the standardized examinations. The videotapes were randomly sequenced and scored blindly by one rater experienced in evaluating movement disorders. Psychiatric symptoms were rated weekly under single-blind conditions by means of the Brief Psychiatric Rating Scale (BPRS).² Side effects were registered whenever they occurred. Blood pressure and pulse rate were measured every second day. Extensive laboratory tests, including hematologic, hepatologic, and nephrologic functions, electrolyte values, and ECGs, were performed weekly during both the single-dose and longer-term trials. Electroencephalograms were recorded in the initial placebo period and at the highest THIP dose in the longer-term study.

Scores for tardive dyskinesia, parkinsonism, and eye-blinking

Table 3.—Side Effects of THIP* During Longer-Term Study†					
Patient	Maximum THIP dose, mg/Day	Sedation	Dizziness	Confusion	Vomiting
1	20	++	—	—	—
2	20	—	++	—	++
3	35	+	++	—	—
4	45	—	++	—	+
5	60	+	—	—	—
6	60	—	+	—	—
7	60	—	++	—	—
8	60	+	—	—	++
9	60	+	—	++	—
10	90	—	—	++	—
11	120	—	—	—	—
12	120	—	—	—	—
13	120	—	—	—	—

*THIP indicates tetrahydroisoxazopyridinol.
†Minus sign indicates effect absent; plus sign, present; and double plus sign, present and severe.

rates from each video recording and the BPRS scores from interviews were analyzed by Wilcoxon's test for paired differences.

RESULTS

In the single-dose trial, two patients (No. 8 and 14) were treated with doses up to 15 mg; one patient (No. 8), up to 20 mg; and two patients (No. 11 and 13), up to 25 mg. The scores for tardive dyskinesia, parkinsonism, and eye-blinking rates at placebo, 10 mg, and the highest dose of THIP are shown in Table 2. Although there was a trend toward a decrease in tardive dyskinesia scores, with 10 mg two hours after drug administration, and an aggravation of parkinsonian symptoms at 10 and 25 mg, no consistent changes were found. Two patients (No. 11 and 13) experienced no side effects, but two others (No. 8 and 14) vomited and obviously became more parkinsonian, with increased tremor and bradykinesia (15 and 20 mg). One patient (No. 13) had ataxia and reported dizziness and nausea after 15 mg of THIP.

In the longer-term study, the maximum dose varied from 20 to 120 mg/day because of individual differences in tolerance. Only three patients received 120 mg/day without side effects. The average dose is shown in the Figure.

The effect of THIP on tardive dyskinesia, parkinsonism, and eye-blinking rates (range, 1 to 17 blinks per 15 s) was not striking (Figure). Tardive dyskinesia scores were very stable. Statistically significant but clinically modest changes were increased parkinsonism and decreased eye-blinking rates (range, 1 to 12 blinks per 15 s) at the highest THIP dose level, and an amelioration of the parkinsonian

symptoms after cessation of THIP medication. No differences were found between patients taking moderate or low doses of neuroleptics, between different diagnostic groups, or between younger or elderly patients.

The BPRS scores decreased moderately in item 6 (tension, from 1.1 to 0.8) and item 9 (depressive mood, from 1.4 to 0.9), but neither reached statistical significance. Other BPRS items and BPRS total scores were unchanged.

Side effects limiting THIP use in ten patients are summarized in Table 3. Sedation, dizziness, and vomiting, all rather long lasting (three to four days after cessation or reduction of THIP therapy), were prominent, and two patients became severely confused. Patient 10 (90 mg/day) remained in a confusional state for three hours, followed by amnesia for the episode, and patient 9 (60 mg/day) was confused for several days and had myoclonic jerks. Patient 1 had an increase in BP from 155/90 to 180/120 mm Hg at the end of the last week of THIP treatment (20 mg/day), but BP returned to pretreatment values three days after stopping THIP administration.

Laboratory values remained within normal limits. Patient 10's EEG, which was abnormal before and after THIP therapy, showed an increased amount of low-frequency activity (2 to 8 Hz) during treatment with THIP (80 mg/day).

COMMENT

While other clinical studies have found that GABA agonists have some antihyperkinetic or neuroleptic-potentiating effect in tardive dyskinesia, this trial suggests that THIP has no antihyperkinetic effect, only a weak parkinsonism-aggravating effect, and slightly decreases eye-blinking rates. This discrepancy may be accounted for by a number of considerations.

Although the THIP dose used in this study was increased to a maximum of 120 mg/day or until disturbing side effects became evident, the dose may have been too low to produce antihyperkinetic effects. Animal studies have shown that only high doses of THIP (> 10 mg/kg) inhibited apomorphine-induced contralateral turning in rats with unilateral lesions of the nigrostriatal dopamine system induced by 6-OH-dopamine, and that 20 mg/kg of THIP was needed to increase levels of the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in striatal and limbic tissue or to potentiate haloperidol-induced increases of DOPAC and HVA.²⁰ Compared with such doses, those used in this study (approximately 0.1 to 2.0 mg/kg) appear to be low. However, it does not seem to be possible to use THIP in doses above 120 mg/day in most patients.

Studies in tardive dyskinesia with the GABA transaminase inhibitors valproate sodium and γ -acetylenic GABA have shown that these presumed GABA agonists exert more pronounced antihyperkinetic effects in patients concurrently receiving moderate to high doses of neuroleptic drugs.^{11,21} If THIP should interact in a similar way, the lack of antihyperkinetic effect seen in this study may be due to the relatively small doses of concurrent neuroleptic treatment (Table 1). The indirect or secondary role of GABA in modulating dopaminergic effects is also supported by the data from a study of the interaction of dopamine agonists and GABA drugs on behavior of nonhuman primates. Low doses of γ -acetylenic GABA or muscimol had no effect on apomorphine-induced locomotor activity, stereotypy, and oral hyperkinesias, whereas high doses of these drugs moderately reduced but did not suppress these behaviors.¹⁰ Additional considerations for the lack of antihyperkinetic

effect or dose intolerance with THIP include the possibility of unknown drug interactions, though no consistent pattern was evident.

Clinical heterogeneity may also be an explanation for the limited effect of a drug. Although this study included both young and elderly patients with psychoses or dementia, no differences in the effect of THIP on dyskinesias or mental state were found across age or diagnostic groups. The absence of obvious changes does not exclude the possibility that THIP might influence certain psychiatric symptoms or diseases. For example, it would be of interest to evaluate THIP administration in patients with depression or anxiety, as these two symptoms showed a trend toward improvement in our study.

The absence of a correlation between changes in eye-blinking rate and tardive dyskinesia or psychosis does not clarify the proposed relationship between blinking and dopaminergic/GABAergic functions in schizophrenia or tardive dyskinesia.²² These results are consistent, however, with the previous observations of a wide range of blinking rates in patients with tardive dyskinesia.^{11,23} The concomitantly decreased blinking rates and increased parkinsonism at high THIP doses suggest that these may be measures of similar symptoms, such as bradykinesia. In non-human primates, moderate to high doses of both muscimol and γ -acetylenic GABA partially suppressed increased eye-blinking rates induced by apomorphine,¹⁶ and muscimol increased haloperidol-induced dystonia and parkinsonism.²⁴ Since disturbances in eye blinking or eye movement are involved in a number of dyskinetic syndromes (parkinsonism, levodopa- and other dopamine agonist-induced dyskinesias, tardive dyskinesia, spontaneous blepharospasm, orofacial dyskinesias, etc), further investigations with the purported GABA drugs in these disorders may be worthwhile.

Side effects, especially toxic reactions on the CNS, have been limiting factors in research on GABA drugs. It was also the case in this study, although to a lesser degree than with other GABA agonists such as muscimol. It is not clear whether such side effects (sedation, confusion, dizziness, nausea, vomiting, and myoclonic jerks) will inevitably be associated with all GABA agonist treatments.

γ -Aminobutyric acid is a ubiquitous neurotransmitter in the brain, with a variety of purported receptor subtypes, some of which perhaps mediate either inhibition or facilitation of hyperkinetic movements.^{25,26} By systemic administration of GABA drugs, these receptor subtypes may be diversely affected, with the combined effect resulting in no functionally significant influence on tardive dyskinesia. This proposal is consistent with several behavioral and biochemical observations. Bilateral intranigral administration of bicuculline methiodide, a GABA antagonist, induces biting behavior in rats, which is antagonized by concomitant injections of THIP or muscimol into the substantia nigra. After systemic administration, however, THIP was without effect on this biting behavior, while γ -acetylenic GABA was most effective and muscimol partially effective.²⁷ The varied effects of these GABA agonists might be due to differences in their affinities to different subtypes of GABA receptors. Recent studies have demonstrated the existence of two types of bicuculline-sensitive GABA receptor sites, one of which is linked to the benzodiazepine receptor.^{28,29} While GABA and muscimol activate benzodiazepine receptor binding, THIP is almost inactive in this respect,^{17,30} and it has been hypothesized that THIP may be only a partial GABA agonist for this site, or a selective agonist for GABA receptors not linked

to the benzodiazepine system.⁴ Thus, the mechanisms mediating the behavioral expression of GABA influences are highly complex and incompletely understood. Only if more specific GABA drugs can be developed that selectively affect these different, partly counteracting GABA influences will it be possible to offer therapeutically useful GABA drugs for movement disorders.

In conclusion, although modestly influencing parkinsonism and eye-blinking rates, THIP did not appear to affect tardive dyskinesia when added to relatively low doses of concurrent antipsychotic treatment. This observation, together with the inconsistent efficacy of other GABA agonists in tardive dyskinesia and the severity of their side effects, makes it questionable whether GABA agonists will

prove to be of value in the treatment of tardive dyskinesia. On the other hand, if GABA agonists with more selective affinity to specific GABA receptors are developed, new opportunities will be available for research with GABA drugs in tardive dyskinesia and other disorders.

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The Effect of Tetrahydroisoxazolopyridinol (THIP) in Tardive Dyskinesia

A New γ -Aminobutyric Acid Agonist

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γ -Aminobutyric acid (GABA) agonists have been proposed for the treatment of tardive dyskinesia, but their therapeutic potential has been limited by side effects and toxicity. To elucidate further the role of GABA in neuroleptic-induced dyskinesias, we evaluated tetrahydroisoxazolopyridinol (THIP), a new, less toxic GABA analog and GABA receptor agonist, in both a dose-finding (single-dose) pilot study with five patients and a longer (four-week) placebo-controlled study with 13 patients. The patients were videotaped during a standardized examination; tardive dyskinesia, parkinsonian symptoms, and eye-blinking rates were rated blindly and randomly. The maximal short-term dose of THIP was 10 to 25 mg, whereas in the longer-term study the highest daily dose ranged from 20 to 120 mg. Tardive dyskinesia was unchanged during THIP treatment, but preexisting parkinsonism increased significantly and eye-blinking rates decreased. Psychiatric symptoms showed no significant changes, although tension and depression lessened. Side effects included sedation, confusion, dizziness, vomiting, and myoclonic jerks. Although THIP is not an effective new treatment for tardive dyskinesia, more specific GABA agonists should be evaluated in future studies of this syndrome.

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Tardive dyskinesia is a hyperkinetic movement disorder characterized by abnormal involuntary orofacial movements and may include hyperkinesias in limbs and trunk. It occurs during or at the cessation of prolonged neuroleptic treatment and may be irreversible. The exact pathogenesis of the syndrome is still unknown, but dopa-

minergic hypersensitivity and a disturbed balance between the dopaminergic and cholinergic systems have been proposed to be primarily involved.^{1,2} The discovery of a γ -aminobutyric acid (GABA)-mediated feedback system between striatal cholinergic and nigral dopaminergic neurons³ and demonstration of GABA-dopamine interactions⁴⁻¹⁰ suggest that a complete understanding of movement disorders may include a role for GABA in tardive dyskinesia.

Clinical trials in tardive dyskinesia with agents thought to increase GABA activity in the brain have produced conflicting results. Mucimol suppressed tardive dyskinesia, but produced undesirable side effects.¹¹ γ -Acetylenic GABA had modest antihyperkinetic and parkinsonism-aggravating effects, especially in patients receiving potent antidopaminergic neuroleptic treatment.¹² Valproate sodium, which may increase brain GABA by inhibition of GABA transaminase,^{13,14} reduced tardive dyskinesia in the initial report,¹⁵ but subsequent evaluations noted only modest improvement^{16,17} or no effect.¹⁸ Baclofen, a structural analog of GABA, with unclear effects on GABA mechanisms,¹⁹ has produced divergent effects in tardive dyskinesia, varying from improvement^{20,21} to no effect,²² and this treatment often produced side effects of sedation, confusion, and increased parkinsonism.²³ In summary, the currently available drugs affecting GABA have been either too nonspecific or too toxic for clinical use.

Tetrahydroisoxazolopyridinol (THIP; 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol), a rigid bicyclic isoxazole derivative of GABA, is a new direct GABA receptor agonist^{24,25} that is less toxic than muscimol. It penetrates the blood-brain barrier readily and is approximately one third as potent as muscimol after systemic administration.^{26,27}

Against this background, it was important to investigate the effects of THIP in tardive dyskinesia and neuroleptic-induced parkinsonism. In addition, eye-blinking rates were assessed, as disturbances in eye blinking have been associated with dopaminergic functions and various dyskinesias²⁸ and may be influenced by GABA drugs.²⁹

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Patient/ Sex/ Age, yr	Diagnosis	Duration of Illness, yr	Duration of Neuroleptic Treatment, yr	Duration of Tardive Dyskinesia, yr	Concurrent Neuroleptic Treatment		Other Drugs	Maximum THIP* Dose, mg/Day†
					Drug	Duration, yr		
1/M/66	Schizophrenia, paranoid type	13	3	1.6	Flupenthixol decanoate, 200 mg/2 wk Methotrimeprazine, 60 mg/day	0.5 0.5	...	20
2/F/70	Schizophrenia, paranoid type	35	25	4.0	...	...	...	20
3/M/73	Cardiac neurosis Senile dementia	60 4	10	3.0	Pimozide, 4 mg/day Chlorpromazine, 50 mg/day	1.5 1.5	...	35
4/F/71	Manic-depressive	3	3	1.5	Thioridazine, 75 mg/day	0.25	...	45
5/M/68	Schizophrenia, hebephrenic type	6	7	1.0	Clozapine, 450 mg/day	1.25	...	60
6/M/52	Schizophrenia, hebephrenic type	31	28	7.0	Clonazepam decanoate, 100 mg/2 wk	1.0	...	60
7/M/67	Schizophrenia, hebephrenic type	28	22	10.0	Clozapine, 350 mg/day	8.0	Biperiden hydrochloride, 6 mg/day	60
8/M/51	Schizophrenia, paranoid type	27	22	5.0	...	...	Prochlorperazine hydrochloride, 15 mg/day	60
9/M/64	Presenile dementia	5	5	1.0	Methotrimeprazine, 25 mg/day	0.25	...	60
10/M/67	Schizophrenia, undifferentiated type	31	16	7.0	Methotrimeprazine, 25 mg/day	0.25	...	60
11/M/63	Alcoholic dementia	7	2	0.5	Pipolizine palmitate, 100 mg/3 wk	1.0	...	120
12/M/69	Schizophrenia, paranoid type	27	25	11.0	Pipolizine palmitate, 200 mg/3 wk Chlorpromazine, 200 mg/day	0.5 0.5	Oxphenadine hydrochloride, 100 mg/day	120
13/M/63	Manic-depressive	27	15	2.0	Haloperidol, 2 mg/day	1.0	Lithium carbonate, 1,350 mg/day	120
14/F/80	Schizophrenia, hebephrenic type	52	24	5.0	Pimozide, 8 mg/day	0.5	...	65.9
Mean values (age, 51 yr)	...	23.2	14.7	4.3	...	...	...	65.9

*THIP indicates triethylhydroxydiazolopyridinol.

†Only patients from the longer-term study.

SUBJECTS AND METHODS

Subjects

Fourteen psychiatric inpatients with tardive dyskinesia, all physically healthy, gave informed consent to participate in this placebo-controlled trial. Since this was the first clinical trial with THIP, five patients (Nos. 3, 8, 11, 13, and 14) were included in a preliminary dose-finding single-dose study, whereas 13 (four of whom were involved in the single-dose study) took part in the following longer-term study. They all met the following criteria: (1) neuroleptic treatment for more than two years; (2) stable tardive dyskinesia for at least six months; and (3) unchanged neuroleptic or anticholinergic treatment during the last three months. Patient data are presented in Table 1.

Medications

Medication, if any, taken at the beginning of the study was continued during the entire evaluation. During the single-dose study, the patients received placebo and THIP in identical capsules, starting with placebo followed by THIP. The initial dose of 5 mg was increased by 5 mg per test day to a maximum of 25 mg unless side effects occurred. Although the elimination half-life in

humans is estimated to be less than two hours,¹⁰ the single doses were administered twice weekly to avoid accumulation.

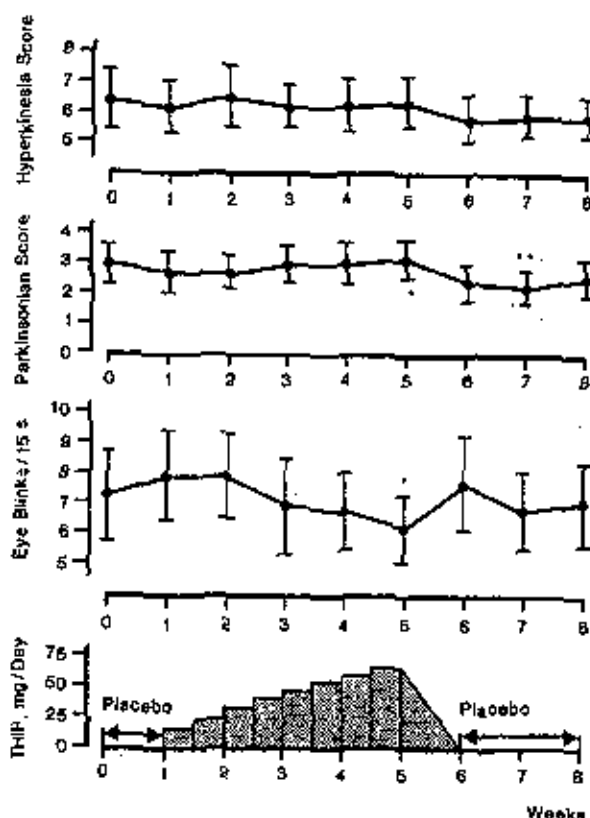
In the longer-term study, patients 1 through 13 followed a schedule of one week of placebo three times a day, and four weeks of THIP, beginning with 5 mg three times a day, increasing twice weekly by 5 mg three times a day to a maximum of 120 mg/day or until disturbing side effects appeared. After the THIP dose was gradually reduced over a period of one week, placebo was given for two weeks. When side effects developed, the dose was reduced to the former level.

Evaluations

Tardive dyskinesia, parkinsonian symptoms, and eye-blinking rates were evaluated from videotapes prepared before and 1, 2, and 4 hours after the single doses. During the longer-term study, video recordings were made weekly at the same time each day. The standardized recording sessions of approximately five minutes' duration included sitting, standing, walking, distraction by conversation, and performing voluntary movements of nonaffected muscle groups such as writing. The rating scale for tardive dyskinesia included evaluations of eight body regions: jaw, tongue, lips, face, head, trunk, and upper and lower extremities, scored from 0 to 5 (absent to severe), whereas the rating scale for

	Hours After Placebo			Hours After THIP, 10 mg			Hours After Maximum THIP Dose (20 $\pm$ 5 mg)		
	0	2	4	0	2	4	0	2	4
Tardive dyskinesia	6.00 $\pm$ 0.63	5.00 $\pm$ 1.05	4.90 $\pm$ 0.91	4.90 $\pm$ 0.70	4.20 $\pm$ 0.60	4.80 $\pm$ 0.71	4.10 $\pm$ 0.63	4.30 $\pm$ 1.08	4.70 $\pm$ 1.28
Parkinsonism	2.80 $\pm$ 0.74	2.60 $\pm$ 0.75	3.00 $\pm$ 0.77	2.20 $\pm$ 0.58	2.80 $\pm$ 0.39	2.80 $\pm$ 0.68	3.00 $\pm$ 1.04	4.80 $\pm$ 1.53	4.00 $\pm$ 1.30
Eye blinks/15 s	3.40 $\pm$ 1.27	3.40 $\pm$ 1.72	3.80 $\pm$ 1.92	4.00 $\pm$ 1.70	4.40 $\pm$ 1.80	4.80 $\pm$ 1.98	4.80 $\pm$ 2.27	3.80 $\pm$ 2.80	5.60 $\pm$ 2.40

*THIP indicates tetrahydroisoazolo[4,5-b]pyridinol.



Effect of increasing doses of tetrahydroisoazolo[4,5-b]pyridinol (THIP) on mean scores. Brackets indicate SEM; asterisks, $P < .05$ compared with pretreatment scores; double asterisk, $P < .05$ compared with score at highest THIP dose.

parkinsonism consisted of eight items: facial expression, bradykinesia, tremor, posture, arm swing, gait, rigidity, and salivation, scored from 0 to 3 (absent to severe).¹ Eye-blinking rates were determined for 15-s epochs during the standardized examinations. The videotapes were randomly sequenced and scored blindly by one rater experienced in evaluating movement disorders. Psychiatric symptoms were rated weekly under single-blind conditions by means of the Brief Psychiatric Rating Scale (BPRS).²¹ Side effects were registered whenever they occurred. Blood pressure and pulse rate were measured every second day. Extensive laboratory tests, including hematologic, hepatologic, and nephrologic functions, electrolyte values, and ECGs, were performed weekly during both the single-dose and longer-term trials. Electroencephalograms were recorded in the initial placebo period and at the highest THIP dose in the longer-term study.

Scores for tardive dyskinesia, parkinsonism, and eye-blinking

Patient	Maximum THIP dose, mg/Day	Sedation	Dizziness	Confusion	Vomiting
1	20	++	—	—	—
2	20	—	++	—	++
3	35	+	++	—	—
4	45	—	++	—	+
5	60	+	—	—	—
6	60	—	+	—	—
7	60	—	++	—	—
8	60	+	—	—	++
9	60	+	—	++	—
10	60	—	—	++	—
11	120	—	—	—	—
12	120	—	—	—	—
13	120	—	—	—	—

*THIP indicates tetrahydroisoazolo[4,5-b]pyridinol.
†Minus sign indicates effect absent; plus sign, present; and double plus sign, present and severe.

rates from each video recording and the BPRS scores from interviews were analyzed by Wilcoxon's test for paired differences.

RESULTS

In the single-dose trial, two patients (No. 3 and 14) were treated with doses up to 15 mg; one patient (No. 8), up to 20 mg; and two patients (No. 11 and 13), up to 25 mg. The scores for tardive dyskinesia, parkinsonism, and eye-blinking rates at placebo, 10 mg, and the highest dose of THIP are shown in Table 2. Although there was a trend toward a decrease in tardive dyskinesia scores, with 10 mg two hours after drug administration, and an aggravation of parkinsonian symptoms at 10 and 25 mg, no consistent changes were found. Two patients (No. 11 and 13) experienced no side effects, but two others (No. 8 and 14) vomited and obviously became more parkinsonian, with increased tremor and bradykinesia (15 and 20 mg). One patient (No. 13) had ataxia and reported dizziness and nausea after 15 mg of THIP.

In the longer-term study, the maximum dose varied from 20 to 120 mg/day because of individual differences in tolerance. Only three patients received 120 mg/day without side effects. The average dose is shown in the Figure.

The effect of THIP on tardive dyskinesia, parkinsonism, and eye-blinking rates (range, 1 to 17 blinks per 15 s) was not striking (Figure). Tardive dyskinesia scores were very stable. Statistically significant but clinically modest changes were increased parkinsonism and decreased eye-blinking rates (range, 1 to 12 blinks per 15 s) at the highest THIP dose level, and an amelioration of the parkinsonian

to the benzodiazepine system.* Thus, the mechanisms mediating the behavioral expression of GABA influences are highly complex and incompletely understood. Only if more specific GABA drugs can be developed that selectively affect these different, partly counteracting GABA influences will it be possible to offer therapeutically useful GABA drugs for movement disorders.

In conclusion, although modestly influencing parkinsonism and eye-blinking rates, THIP did not appear to affect tardive dyskinesia when added to relatively low doses of concurrent antipsychotic treatment. This observation, together with the inconsistent efficacy of other GABA agonists in tardive dyskinesia and the severity of their side effects, makes it questionable whether GABA agonists will

prove to be of value in the treatment of tardive dyskinesia. On the other hand, if GABA agonists with more selective affinity to specific GABA receptors are developed, new opportunities will be available for research with GABA drugs in tardive dyskinesia and other disorders.

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GABA-Agonist Therapy for Alzheimer's Disease

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Summary: Evidence suggesting a reduction of cerebral γ -aminobutyric acid (GABA) neurons in Alzheimer's disease has been reported. To evaluate the possible contribution of GABA system dysfunction to the intellectual decline associated with this disorder, a controlled therapeutic trial of a potent and specific GABA agonist, THIP [4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol], was undertaken. Six Alzheimer patients with mild to moderately severe dementia and low spinal-fluid GABA levels received THIP at maximum individually tolerated dosage. No significant change in cognitive function could be discerned, despite attainment of dose levels that produced centrally mediated adverse effects similar to those of other GABA agonists. The results support the views that pharmacologic attempts to stimulate central GABA-mediated synaptic function may not confer therapeutic benefit to patients with Alzheimer's disease and that a GABA system deficit may not serve as a critical determinant of the dementia that characterizes this disorder. **Key Words:** GABA—Alzheimer's disease—GABA agonist therapy—Dementia.

Considerable biochemical evidence suggests that an abnormality in γ -aminobutyric acid (GABA)-containing neurons occurs in patients with Alzheimer's disease. Spinal fluid GABA levels are characteristically reduced (1-4), and several studies of postmortem cortical tissues have shown a decrement in GABA concentrations as well as in the activity of the GABA synthesizing enzyme, glutamic acid decarboxylase (5-7). Recently, it has been suggested that cortical GABA interneurons receive terminals from acetylcholine-containing cells originating in the basal forebrain nuclei (8), a neural system that characteristically degenerates

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in Alzheimer's disease (9). A loss of GABA neurons situated postsynaptic to these cholinergic projections might thus contribute to the cognitive decline that occurs in Alzheimer patients and account for the limited ability of cholinomimetics to ameliorate the dementia. The foregoing considerations support the view that pharmacologic stimulation of GABA-mediated synaptic function might confer symptomatic benefit to individuals with Alzheimer's disease. To evaluate this possibility, a controlled clinical trial of the potent and selective GABA agonist (10,11) THIP [4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol] has been carried out in patients with mild to moderately advanced symptoms of this disorder.

METHODS

Six men with clinically diagnosed Alzheimer's disease (mean $\pm$ SEM age 58 ± 2.0 years, range 50–64) consented to participate in this study after full disclosure of its risks and potential benefits. Each had a history of gradually progressive intellectual deterioration, documented by longitudinal neuropsychological test results, in the absence of focal motor or sensory signs. None had clinical or laboratory evidence of other causes of dementia (Hachinski ischemic scores all 4 or less). Symptom duration averaged 4.5 years and severity ranged from mild to moderately advanced (mean $\pm$ SEM Wechsler Memory Quotient 75 ± 4.5 ; Mattis Dementia Rating Scale 111 ± 4.9). All had reduced spinal fluid GABA levels (Table 1). None received any other centrally active medications for at least 2 weeks before or at any time during this clinical trial.

In order to document cognitive performance decrements in the Alzheimer patients, neuropsychological tests were also carried out in eight untreated, age-matched (61 ± 1.8 years, range 55–68) normal controls. Normative spinal fluid data for GABA were obtained from 17 healthy control individuals (eight men, nine women; age 57 ± 1.8 years, range 45–69) and for somatostatin from 20 normal controls (13 men, seven women; age 59 ± 4.3 years, range 30–74). For comparative purposes, spinal fluid GABA determinations were also made on 22

TABLE 1. Effect of GABA agonist treatment on spinal fluid GABA and somatostatin (SRIF) levels^a

	GABA (pmol/ml)		SRIF (pg/ml)	
	Placebo	THIP	Placebo	THIP
Normal controls	167 ± 16 (17)	—	54 ± 3.7 (20)	—
Alzheimer patients	38 ± 6.3^b (6)	39 ± 8.5 (5)	38 ± 6.4^c (6)	50 ± 16 (3)

GABA, γ -aminobutyric acid; THIP, 4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol.

^a Values are the means $\pm$ SEM for the number of patients given in parentheses.

^b $p < 0.001$ for difference from normal control values.

^c $p < 0.05$ for difference from normal control values.

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otherwise unselected individuals with Alzheimer's disease (13 men, nine women; age 60 ± 1.4 years, range 48-70).

THIP was administered orally in a double-blind, placebo-controlled, crossover design. After 1 week of baseline testing, all patients began a dose-finding phase. An initial THIP dose of 20 mg/day was gradually increased until clinically significant adverse effects were observed; these occurred at an average daily dose of 116 mg (range 40-160 mg) given in four equally divided doses. Patients were then randomly assigned to either a THIP-placebo treatment sequence or the reverse. An equal number of identical-appearing capsules containing either placebo or THIP was administered four times daily during the therapeutic evaluation phase. THIP dosage for each patient was fixed at the highest tolerated level. A 3-day washout period separated the drug and placebo treatment periods, each of which lasted 5 days.

Spinal fluid from patients was obtained by lumbar puncture on the 2nd and 5th days of both placebo and drug therapy. The first 13 ml of fluid was collected and immediately placed on ice. Specimens were then pooled and frozen at -70°C in 1 ml aliquots within 1 h for subsequent analysis. Spinal fluid from normal individuals who were not receiving any centrally active medications was collected and processed in a similar manner. GABA analysis was performed using an ion-exchange fluorometric technique (12). Somatostatin was determined by a double antibody radioimmunoassay (13) with antiserum obtained from Dr. Cass Terry (Ann Arbor, MI, U.S.A.) and a ^{125}I -Tyr-somatostatin tracer (Hazelton Laboratories, Vienna, VA, U.S.A.). All patients also received periodic laboratory tests to detect evidence of drug toxicity.

Alternative forms of the following neuropsychological tests, each lasting approximately 45 min, were administered before and after the treatment phase (two baseline measures) and on the 2nd and 5th days of both placebo and drug therapy.

Story Recall

Patients were read a short passage and then asked to recall verbatim the story's content. The stories were variations of the original Wechsler Memory Scale subtest (14) and followed the same format and length as those used in an earlier study (15).

Word Learning

A list of eight unrelated, concrete nouns was presented over five trials. Immediate free recall was recorded after each trial (15).

Visual Discrimination

Patients were instructed to draw designs from the Visual Form Discrimination Test (16). After removal of the original, patients were asked to recognize it among four designs. The copy and recognition memory versions had eight trials each.

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Pictorial Memory

In the naming portion of this test, patients were presented with a grid containing nine color photographs of common objects for 45 s and asked to recall the objects after removal of the display. Spatial memory was tested by presenting patients with a blank grid and asking for the original location of each object (15).

Recurring Figures

Eight geometric shapes were presented, each for 5 s (15). The original stimuli were then mixed with eight similar patterns, and the patients were asked to identify the target design; five trials were used.

Reaction Time

Reaction time to a tone stimulus was measured by recording the time needed for the release of a telegraph key after stimulus presentation (15). Variable foreperiods for alerting the patient to stimulus delivery were utilized (2, 4, and 10 s in a fixed and variable order) (17).

RESULTS

Baseline neuropsychological testing revealed a significant overall performance deficit in the Alzheimer patient group when compared with the normal age-matched controls (Table 2; MANOVA $p < 0.003$). THIP, when administered at maximum tolerated doses (mean 65 mg/day, range 30–140 mg/day), failed to have a consistent effect on any of these measures (Table 2). Although some verbal tests improved slightly, others showed virtually no change or even a small decline. Reaction time, used here as a measure of attention, also changed insignificantly from 353 ± 60 to 393 ± 63 ms. Informal observations recorded by the ward staff

TABLE 2. Effect of GABA agonist treatment on cognitive function^a

Test	Theoretical maximum	Baseline normal controls (8)	Baseline ^b Alzheimer patients (6)	Placebo Alzheimer patients (6)	THIP Alzheimer patients (6)
Verbal cognition					
Story recall	23	8.9 ± 0.60	2.3 ± 0.70	1.5 ± 0.26	1.6 ± 0.60
Word learning	8	7.3 ± 0.18	3.9 ± 0.64	3.1 ± 0.56	3.2 ± 0.36
Visuospatial cognition					
Visual Form					
Discrimination (match)	8	7.6 ± 0.18	6.5 ± 0.71	5.9 ± 1.0	5.0 ± 1.0
Pictorial memory (object naming)	9	8.6 ± 0.12	3.8 ± 1.1	4.5 ± 1.3	4.1 ± 1.3
Pictorial memory (object placement)	9	9.0 ± 0.00	6.3 ± 0.95	4.5 ± 1.3	4.0 ± 1.3
Recurring figures	80	76 ± 0.76	65 ± 3.9	58 ± 4.1	57 ± 3.6

THIP, 4,5,6,7-tetrahydroisoxalo(5,4-c)pyridin-3-ol.

^a Mean $\pm$ SEM scores are for the number of patients and age-matched controls given in parentheses.

^b $p < 0.003$ for multivariate overall difference from baseline normal control scores.