ESCOBAR - URIBE ASOCIADOS

A B O G A D O S

Carrera 11A No. 94-76 Of. 305 - P.O. Box 94948, Bogotá, Colombia, S.A.
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86
92

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00009234 00000002 Folios: 2
Fecha (AMD): 2002-08-21 16:21:14
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2050 DIVISION DE NUEVAS CREACIONES

As. 2306/P.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Ref.: Expediente No. 00-009.234
Solicitud de Patente a nombre de
NOVARTIS AG

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad NOVARTIS AG., domiciliada en Basilea, Suiza, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 02 - 53,300 de agosto 13, 2002, por la suma de $318.000.oo, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,

JIMENA ESCOBAR URIBE
C.C. 39.779.452 de usaquén
T.P. 68.228
Cod. 5376

JEU/ra.

2306

Industria y Comercio

SUPERINTENDENCIA

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00003234 00000002 Folios: 2
Fecha (AMD) : 2002-08-21 16:21:14
Tramite : 002 PATENTES D 1 REGISTRO/ 536 PETICION
Procedencia: 2050 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 02 - 53,300
FECHA : AGOSTO 13 DE 2002

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4796273	13/08/2002	1,988,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	318,000.00
		TOTAL : $	318,000.00

SON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
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Bogotá, D.C., Colombia

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2005-011
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Doctora
JIMENA ESCOBAR URIBE
(Apoderado)

ASUNTO	Radicación	00009234
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	12605
	Folios	032

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

Los textos estudiados fueron la descripción (Folios: 3 a 30) y las reivindicaciones 1 a 19 (Folios: 46 a 48).

La presente solicitud reivindica prioridad británica Nº GB9903759.0 de 18 de febrero de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

Objeto de invención:

La presente solicitud se titula: "Combinaciones de un agonista de beta-2 (formoterol o una sal o un solvato de este) y un esteroide usadas para el tratamiento de enfermedades inflamatorias u obstructivas de las vías aéreas".

El objeto de la presente solicitud se refiere a combinaciones de un agonista de beta-2 y un esteroide, y a su uso para el tratamiento de enfermedades inflamatorias u obstructivas de las vías aéreas.

Según la descripción, el formoterol, particularmente en la forma de su sal de fumarato, es un broncodilatador utilizado en el tratamiento de enfermedades inflamatorias u obstructivas de las vías aéreas. El propionato de fluticasona es un corticosteroide antiinflamatorio. De una manera sorprendente, ahora se ha encontrado que se puede obtener un beneficio terapéutico inesperado significativo, particularmente un beneficio terapéutico sinérgico, en el tratamiento de enfermedades inflamatorias u obstructivas de las vías aéreas, mediante la utilización de una composición que contenga formoterol, o una sal o solvato del mismo, y propionato de fluticasona. Por ejemplo, es posible utilizar esta composición para reducir las dosificaciones de propionato de fluticasona requeridas para un efecto terapéutico dado, considerablemente comparadas con aquellas requeridas utilizando

el tratamiento con propionato de fluticasona solamente, minimizando de esta manera los efectos secundarios posiblemente indeseables. Se ha encontrado que las composiciones que contienen formoterol y propionato de fluticasona inducen una actividad anti-inflamatoria que es significativamente mayor que aquella inducida por formoterol o propionato de fluticasona solo, y que se puede reducir de una manera significativa la cantidad de propionato de fluticasona necesaria para un efecto anti-inflamatorio dado cuando se utiliza mezclado con formoterol, reduciendo de este modo el riesgo de efectos secundarios indeseables por la exposición repedida al esteroide involucrado en el tratamiento de enfermedades inflamatorias u obstructivas de las vías aéreas.

Lo que se revivindica como novedoso es lo siguiente:

Un composición farmacéutica, la cual comprende (A) formoterol o una sal farmacéuticamente aceptable del mismo, o un solvato de formoterol o de dicha sal, y (B) propionato de fluticasona.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/56.

Claridad de la solicitud:

El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción.

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple."

De acuerdo con lo anterior, el título debe estar acorde con lo reivindicado, ya que en el título no se especifica el esteroide nombrado, mientras que en las reivindicaciones se mencionan: formoterol y fluticasona como componentes de la composición.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "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".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 18/02/1999, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma.

Se encontró como anterioridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica prioridad o de la fecha de presentación de esta solicitud) que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	Art. Revista[1]	Combination Therapy	1998
2	Art. Revista[2]	Efficacy of inhaled corticosteroids in asthma	1998
3	Art. Revista[3]	Effects of the long acting β2-agonists Formoterol on asthma control in asthmatic patients using inhaled corticosteroids	1996
4	WO 96/32151	Metered dose inhaler for fluticasone propionate	17 de octubre de 1996
5	WO 95/05805	Process for conditioning substances	2 de marzo de 1995
6	WO 98/34595	Medical aerosol formulations	13 de agosto de 1998
7	WO 98/41193	Preparation of powder agglomerates	24 de septiembre de 1998

Evaluación de los requisitos de Patentabilidad:

El Artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina el cual establece: "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".

Se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de Novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "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".

---

1 "Combination therapy". O'Connor, Pulmonary Pharmacology & Therapeutics, 1998, 11, 397-399.
2 "Efficacy of inhaled corticosteroids in asthma". Barnes, The Journal of Allergy and Clinical Immunology, 1998, Vol. 102(4), page 531-538.
3 "Effects of the long acting β2-agonist Formoterol on asthma control in asthmatic patients using inhaled corticosteroids"-van der Molen et al, Thorax, 1996, 52, pages 535-539.

Esta se evaluó por comparación entre lo solicitado y los documentos encontrados en el estado de la técnica y que se relacionan con el objeto reivindicado y de acuerdo con la definición de novedad del Artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina.

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La Solicitud de Patente Colombiana No. 00009234 menciona una composición farmacéutica, la cual comprende (A) Formoterol o una sal farmacéuticamente aceptable del mismo, o un solvato de formoterol o de dicha sal y (B) propionato de fluticasona.

El documento **WO 96/32151** (folios: 94 a 98) menciona formulaciones de fluticasona propionato empleando un inhalador. La fluticasona propionato puede estar combinada con uno o más principios activos entre los cuales está el formoterol. Por lo tanto, se ve claramente la combinación de fluticasona propionato y formoterol en una composición farmacéutica, tal como está en la presente solicitud.

El documento **WO 98/34595** (folios: 99 y 100) menciona formulaciones en aerosol de un agonista β_2 como el formoterol y que puede estar combinado con un corticosteroide como la fluticasona.

Como se observa, el objeto de esta solicitud puede ser idéntico a lo comprendido en el estado de la técnica, con lo cual se considera que podría no cumplir con el requisito de Novedad.

Evaluación de Nivel Inventivo:

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "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".

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

La Solicitud de Patente Colombiana No. 00009234 menciona una composición farmacéutica, la cual comprende (A) Formoterol o una sal farmacéuticamente aceptable del mismo, o un solvato de formoterol o de dicha sal y (B) propionato de fluticasona.

El **artículo de revista (1)** "Combination Therapy" (folios: 101 a 103) menciona el empleo de agonistas β_2 junto con corticosteroides administrados por inhalación como una alternativa para la administración a altas dosis de corticosteroides inhalados en pacientes con asma aguda (ver folio: 103); el formoterol ha sido mencionado como un agonista β_2 específico y se menciona la fluticasona como corticosteroide. También se dice que al emplearse el agonista β_2 salmeterol con fluticasona, mejora la actividad contra el asma, y se puede disminuir la dosis de fluticasona (ver folio: 102).

El **artículo de revista (2)** titulado: "Efficacy of inhaled corticosteroids in asthma" (folios: 104 a 107) menciona la fluticasona propionato en la lista de corticosteroides usados en el tratamiento de enfermedades inflamatorias; asimismo, se menciona que puede ser adicionado a la terapia con corticosteroides compuestos tales como salmeterol o formoterol, ya que se ha reportado que la combinación de corticosteroides con salmeterol o formoterol es más efectiva en el tratamiento del asma que la terapia donde se aumenta la dosis del corticosteroide.

El **artículo de revista (3)** titulado: "Effects of the long acting β agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids" (folios: 108 a 112) menciona, como lo indica el título, el efecto del formoterol en el control del asma en pacientes asmáticos empleando corticosteroides; se dice que el formoterol es un fármaco seguro cuando se emplea por inhalación junto con corticosteroides.

El documento **WO 95/05805** (folios: 113 a 116) menciona un proceso mediante el cual se producen formas cristalinas de sustancias, que se pueden almacenar y usar sin que se pierdan sus propiedades aerodinámicas requeridas para administración por inhalación. Tales sustancias pueden ser: formoterol (por ejemplo fumarato) y fluticasona (por ejemplo el propionato), o mezclas de los mismos, y cuyo vehículo puede ser un azúcar como la lactosa.

El documento **WO 98/41193** (folios: 117 a 119) menciona formas de dosificación donde el agente activo está seleccionado de al menos un miembro de: mometasona furoato, beclometasona dipropionato, budesonida, fluticasona, dexametasona, formoterol, entre otros. Es decir, para una persona medianamente versada en la materia es claro que si se dice "al menos un miembro de" significa que la formulación puede estar compuesta por uno o más agentes de los que aparecen en la lista citada en esta anterioridad. Así que se sugieren formulaciones de fluticasona con formoterol.

Estos documentos citados como anterioridades revelan composiciones farmacéuticas que comprenden un agonista β2 como lo es el formoterol y un corticosteroide como es la fluticasona. De hecho, estas anterioridades muestran las bondades de la utilización de la combinación de estos dos tipos de fármacos y no solamente uno de ellos para terapias contra el asma. Tras la combinación de estos agentes activos se obtiene una mejora en la actividad y se emplea menor dosis en caso que se empleara solo uno de estos agentes en la terapia.

La respuesta al problema técnico que se pretendía resolver, resulta obvia partiendo de las anterioridades en mención.

Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica.

Evaluación de la Aplicación Industrial:

El artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios".

El objeto de la presente solicitud cumple con el requisito de Aplicación Industrial.

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En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	Art. Revista[1]	1 a 19	Nivel Inventivo
2	Art. Revista[2]	1 a 19	Nivel Inventivo
3	Art. Revista[3]	1 a 19	Nivel Inventivo
4	WO 96/32151	1 a 19	Novedad
5	WO 95/05805	1 a 19	Nivel Inventivo
6	WO 98/34595	1 a 19	Novedad
7	WO 98/41193	1 a 19	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

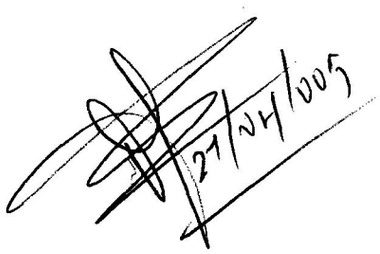
Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 21 ABR. 2005

CONCEPTO TÉCNICO N°: 515	EXAMINADOR TÉCNICO Código N°: 202005	EXAMINADOR JURÍDICO Código N°:

1 "Combination therapy". O'Connor, Pulmonary Pharmacology & Therapeutics, 1998, 11, 397-399.
2 "Efficacy of inhaled corticosteroids in asthma". Barnes, The Journal of Allergy and Clinical Immunology, 1998, Vol. 102(4), page 531-538.
3 "Effects of the long acting β2-agonist Formoterol on asthma control in asthmatic patients using inhaled corticosteroids"-van der Molen et al, Thorax, 1996, 52, pages 535-539.


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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61M 15/00, B65D 83/14, B05D 5/08 — A1

(11) International Publication Number: WO 96/32151

(43) International Publication Date: 17 October 1996 (17.10.96)

(21) International Application Number: PCT/US96/05006

(22) International Filing Date: 10 April 1996 (10.04.96)

(30) Priority Data:

08/422,111	14 April 1995 (14.04.95)	US
08/584,859	5 January 1996 (05.01.96)	US

(60) Parent Applications or Grants
(63) Related by Continuation
US 08/422,111 (CIP)
Filed on 14 April 1995 (14.04.95)
US 08/584,859 (CIP)
Filed on 5 January 1996 (05.01.96)

(71) Applicant *(for all designated States except US)*: GLAXO WELLCOME INC. [US/US]; 5 Moore Drive, Research Triangle Park, NC 27709 (US).

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(74) Agents: LEVY, David, J. et al.; Glaxo Wellcome Holdings plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: METERED DOSE INHALER FOR FLUTICASONE PROPIONATE

(57) Abstract

A metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more nonfluorocarbon polymers, for dispensing an inhalation drug formulation comprising fluticasone propionate, or a physiologically acceptable solvate thereof, and a fluorocarbon propellant, optionally in combination with one or more other pharmacologically active agents or one or more excipients.

Some aerosol drugs tend to adhere to the inner surfaces, i.e., walls of the can, valves, and caps, of the MDI. This can lead to the patient getting significantly less than the prescribed amount of drug upon each activation of the MDI. The problem is particularly acute with hydrofluoroalkane (also known as simply "fluorocarbon") propellant systems, e.g., P134a and P227, under development in recent years to replace chlorofluorocarbons such as P11, P114 and P12.

We have found that coating the interior can surfaces of MDI's with a fluorocarbon polymer significantly reduces or essentially eliminates the problem of adhesion or deposition of fluticasone propionate on the can walls and thus ensures consistent delivery of medication in aerosol from the MDI.

SUMMARY OF THE INVENTION

A metered dose inhaler having part or all of its internal surfaces coated with one or more fluorocarbon polymers, optionally in combination with one or more non-fluorocarbon polymers, for dispensing an inhalation drug formulation comprising fluticasone propionate, or a physiologically acceptable solvate thereof, and a fluorocarbon propellant optionally in combination with one or more other pharmacologically active agents or one or more excipients.

DETAILED DESCRIPTION OF THE INVENTION

The term "metered dose inhaler" or "MDI" means a unit comprising a can, a crimped cap covering the mouth of the can, and a drug metering valve situated in the cap , while the term "MDI system" also includes a suitable channelling device. The terms "MDI can" means the container without the cap and valve. The term "drug metering valve" or "MDI valve" refers to a valve and its associated mechanisms which delivers a predetermined amount of drug formulation from an MDI upon each activation. The channelling device may comprise, for example, an actuating device for the valve and a cylindrical or cone-like passage through which medicament may be delivered from the filled MDI can via the MDI valve to the nose or mouth of a patient, e.g. a mouthpiece actuator. The relation of the

parts of a typical MDI is illustrated in US Patent 5,261,538 incorporated herein by reference.

The term "fluorocarbon polymers" means a polymer in which one or more of the hydrogen atoms of the hydrocarbon chain have been replaced by fluorine atoms. Thus, "fluorocarbon polymers" include perfluorocarbon, hydrofluorocarbon, chlorofluorocarbon, hydro-chlorofluorocarbon polymers or other halogen substituted derivatives thereof. The "fluorocarbon polymers" may be branched, homo-polymers or co-polymers.

U.S. Patent No. 4,335,121, incorporated herein by reference, teaches an antiinflammatory steroid compound known by the chemical name [(6a, 11b, 16a, 17a)-6, 9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy) androsta-1, 4-diene-17-carbothioic acid, S-fluoromethyl ester and the generic name "fluticasone propionate". Fluticasone propionate in aerosol form, has been accepted by the medical community as useful in the treatment of asthma and is marketed under the trademarks "Flovent " and "Flonase". Fluticasone propionate may also be used in the form of a physiologically acceptable solvate.

The term "drug formulation" means fluticasone propionate (or a physiologically acceptable solvate thereof) optionally in combination with one or more other pharmacologically active agents such as other antiinflammatory agents, analgesic agents or other respiratory drugs and optionally containing one or more excipients, and a fluorocarbon propellant. The term "excipients" as used herein means chemical agents having little or no pharmacological activity (for the quantities used) but which enhance the drug formulation or the performance of the MDI system. For example, excipients include but are not limited to surfactants, preservatives, flavorings, antioxidants, antiaggregating agents, and cosolvents, e.g., ethanol and diethyl ether.

Suitable surfactants are generally known in the art, for example, those surfactants disclosed in European Patent Application No. 0327777. The amount of surfactant employed is desirably in the range of 0.0001% to 50% weight to weight ratio relative to the drug, in particular 0.05 to 5% weight to weight ratio. A

particularly useful surfactant is 1,2-di[7-(F-hexyl) hexanoyl]-glycero-3-phospho-N,N,N-trimethylethanolamine also known as 3, 5, 9-trioxa-4-phosphadocosan-1-aminium, 17, 17, 18, 18, 19, 19, 20, 20, 21, 21, 22, 22, 22-tridecafluoro-7-[(8, 8, 9, 9, 10, 10, 11, 11, 12, 12, 13, 13, 13-tridecafluoro-1-oxotridecyl)oxy]-4-hydroxy-N, N,N-trimethyl-10-oxo-, inner salt, 4-oxide.

A polar cosolvent such as C_{2-6} aliphatic alcohols and polyols e.g. ethanol, isopropanol and propylene glycol, preferably ethanol, may be included in the drug formulation in the desired amount, either as the only excipient or in addition to other excipients such as surfactants. Suitably, the drug formulation may contain 0.01 to 5% w/w based on the propellant of a polar cosolvent e.g. ethanol, preferably 0.1 to 5% w/w e.g. about 0.1 to 1% w/w.

It will be appreciated by those skilled in the art that the drug formulation for use in the invention may, if desired, contain fluticasone propionate (or a physiologically acceptable solvate thereof) in combination with one or more other pharmacologically active agents. Such medicaments may be selected from any suitable drug useful in inhalation therapy. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. beclomethasone (e.g. the dipropionate), flunisolide, budesonide, tipredane or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. salbutamol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, orciprenaline, or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in

the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Particularly preferred drug formulations contain fluticasone propionate (or a physiologically acceptable solvate thereof) in combination with a bronchodilator such as salbutamol (e.g. as the free base or the sulphate salt) or salmeterol (e.g. as the xinafoate salt).

A particularly preferred drug combination is fluticasone propionate and salmeterol xinafoate.

"Propellants" used herein mean pharmacologically inert liquids with boiling points from about room temperature (25°C) to about -25°C which singly or in combination exert a high vapor pressure at room temperature. Upon activation of the MDI system, the high vapor pressure of the propellant in the MDI forces a metered amount of drug formulation out through the metering valve then the propellant very rapidly vaporizes dispersing the drug particles. The propellants used in the present invention are low boiling fluorocarbons; in particular, 1,1,1,2-tetrafluoroethane also known as "propellant 134a" or "P 134a" and 1,1,1,2,3,3,3-heptafluoro-n-propane also known as "propellant 227" or "P 227".

Drug formulations for use in the invention may be free or substantially free of formulation excipients e.g. surfactants and cosolvents etc. Such drug formulations are advantageous since they may be substantially taste and odour free, less irritant and less toxic than excipient-containing formulations. Thus, a preferred drug formulation consists essentially of fluticasone propionate, or a physiologically acceptable salt thereof, optionally in combination with one or more other pharmacologically active agents particularly salmeterol (e.g. in the form of the xinafoate salt), and a fluorocarbon propellant. Preferred propellants are 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or mixtures thereof, and especially 1,1,1,2-tetrafluoroethane.

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(54) **Title:** MEDICAL AEROSOL FORMULATIONS

(54) **Bezeichnung:** MEDIZINISCHE AEROSOLFORMULIERUNGEN

(57) **Abstract**

The invention concerns a pressure–liquified propellant mixture for aerosols, said mixture comprising a fluoridated alkane, in particular 1,1,1,2–tetrafluoroethane and/or 1,1,1,2,3,3,3–heptafluoropropane, and carbon dioxide. This mixture improves the wetting properties for pharmaceutical active substances, whereby existing formulation problems with hydrofluoroalkanes as concerns suspension and solution aerosols can be overcome and hence improved medical aerosol formulations can be obtained. By using carbon dioxide, the pressure and hence the particle size distribution can be influenced in targeted manner, and by removing oxygen from the hydrofluoroalkanes the stability during storage of oxidation–sensitive active substances can be improved.

(57) **Zusammenfassung**

Ein druckverflüssigtes Treibimittelgemisch für Aerosole, umfassend ein fluoriertes Alkan, insbesondere 1,1,1,2–Tetrafluorethan und/oder 1,1,1,2,3,3,3–Heptafluorpropan, und Kohlendioxid, ermöglicht eine Verbesserung der Benetzungseigenschaften für pharmazeutische Wirkstoffe, wobei man die mit Hydrofluoralkanen bestehenden Formulierungsprobleme in Bezug auf Suspensions– als auch Lösungsaerosole überwinden und damit verbesserte medizinische Aerosolformulierungen erhalten kann. Mit Hilfe von Kohlendioxid ist es auch möglich, den Druck und damit die Teilchengrössenverteilung gezielt zu beeinflussen sowie durch Verdrängung von Sauerstoff aus den Hydrofluoralkanen die Lagerstabilität von oxidationsempfindlichen Wirkstoffen zu verbessern.

13. Aerosolformulierung nach einem der Ansprüche 9 bis 12, dadurch gekennzeichnet, dass sie bei 20°C einen Druck von 3 bis 12 bar, vorzugsweise 4 bis 7 bar, aufweist.

14. Aerosolformulierung nach einem der Ansprüche 9 bis 13, dadurch gekennzeichnet, dass der Kohlendioxidgehalt 0,0001 bis 10 Gew.-%, vorzugsweise 0,01 bis 6 Gew.-%, beträgt.

15. Aerosolformulierung nach einem der Ansprüche 9 bis 14, dadurch gekennzeichnet, dass sie zusätzlich ein Cosolvens in einer Menge von 0,1 bis 50 Gew.-%, vorzugsweise 1 bis 30 Gew.-%, enthält.

16. Aerosolformulierung nach Anspruch 15, dadurch gekennzeichnet, dass sie als Cosolvens Wasser, Ethanol, Propanol, Ethylenglykol, Propylenglykol, Propan, Butan, Isobutan, Pentan, Dimethylether oder Diethylether enthält.

17. Aerosolformulierung nach einem der Ansprüche 9 bis 16, dadurch gekennzeichnet, dass sie als Wirkstoff ein Betamimetikum, vorzugsweise Salbutamol, Formoterol, Salmeterol, Salbutamol, Fenoterol, Clenbuterol, Terbutalin, Bambuterol, Broxaterol, Epinephrin, Isoprenalin, Orciprenalin, Hexoprenalin, Tulobuterol, Reproterol oder Bamethan, enthält.

18. Aerosolformulierung nach einem der Ansprüche 9 bis 16, dadurch gekennzeichnet, dass sie als Wirkstoff ein Corticoid, vorzugsweise Beclomethason, Betamethason, Ciclomethason, Dexamethason, Triamcinolon, Budesonid, Butixocort, Ciclesonid, Fluticason, Flunisolid, Icomethason Mometason, Tixocortol oder Loteprednol, enthält.

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PULMONARY PHARMACOLOGY & THERAPEUTICS

Combination Therapy

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INTRODUCTION

It has been known for many years that asthma is associated with airway inflammation.[1] Until the early 1980s, regular short-acting inhaled β_2-agonists were regarded as mainstay therapy for mild to moderate disease.[2] Additional treatment with oral theophylline, cromolyn and, to a lesser extent, inhaled steroids was given to those patients with more severe disease. The important role of inflammation was implicitly recognized by the use of maintenance and oral steroid therapy in patients with very advanced disease.[3]

Since the mid 1980s, our research endeavours have been directed towards clarifying and elucidating the inflammatory mechanisms that underlie asthma.[4] As a consequence of this research, the first major international guidelines were drafted towards the end of the last decade. These guidelines quite rightly focused on the need for inhaled steroid therapy as first-line treatment for the majority of patients with mild to moderate asthma.[5]

BACKGROUND TO COMBINATION THERAPY

There was a common consensus in Europe, Australia and Canada that inhaled steroids be prescribed in increasing doses up to a maximum of 2000 µg per day of beclomethasone dipropionate or equivalent. Inhaled short-acting β-agonists were only to be used for symptom relief. The USA was reluctant to use such high doses of inhaled steroids and in some cases oral theophylline and/or cromolyn were advocated as first-line therapy.[3,6]

Moreover, in Europe, the guidelines suggested that combination therapy should only be used in those patients with on-going symptoms despite high-dose inhaled steroids. Before the advent of long-acting β-agonists, the guidelines suggested that add-on treatment with theophylline and/or anti-cholinergics be given to those patients with severe disease already taking high-dose inhaled steroids.[5]

The widespread exposure and adherence to the guidelines by the early 1990s has led to an increased use of inhaled steroids amongst physicians and allied health care professionals across many countries.[7,8] Indeed, the average dose of inhaled steroids has increased several fold over the past 10–15 years. This poses the question of what is an appropriate use for inhaled steroids. Several authors have indicated that the majority of patients do not derive any benefit from increasing the dose of inhaled steroids above 1000 µg, as they have reached the plateau of their steroid dose-response curve. Moreover, systemic absorption of inhaled steroids increases exponentially once the daily dose is increased beyond 1000 µg. Thus the benefit risk ratio of inhaled steroids appears to be altered once the total daily dose exceeds 1000 µg.[9] This leaves clinicians with the dilemma of what to do with those patients with persistent symptoms, despite high doses of inhaled steroids.

Salmeterol and formoterol became available in the early 1990s. There was a reluctance to embrace these drugs for use on a regular basis except in patients with severe disease. This is indeed reflected in revised guidelines of the early 1990s.[10] These drugs were regarded as being useful at step 4 (i.e. patients with symptoms despite high doses of inhaled steroids). Much concern had been expressed about the use of regular β-agonists. Firstly, several asthma experts feared that patients, already reluctant to take inhaled steroids, may opt to use long-acting β-agonists as mono-therapy. Moreover, several studies have suggested that the regular use of β-agonists may be detrimental to asthma control.[11–13]

STUDIES ON COMBINATION THERAPY

More recently, several studies have shown that, in uncontrolled asthma, the addition of long-acting β-agonists to low-dose inhaled steroids provides equivalent control to increasing the dose of inhaled steroids. The first study of Greening and Ind enrolled 450 patients with symptomatic asthma despite regular maintenance by beclomethasone dipropionate 400 µg

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daily.[14] After a 2-week run-in period on this low-dose inhaled steroid, patients with significant asthma symptoms, diurnal variations in peak flow and increased use of short-acting β-agents were randomized in double-blind parallel group fashion to receive either the same dose of beclomethasone dipropionate plus salmeterol 50 μg BD or increased dose of beclomethasone dipropionate 1000 μg daily. These subjects were followed for 6 months, during which time clinic lung function, twice daily morning and evening home peak flow rates, symptom scores and use of rescue medication were recorded. In all parameters measured, the group taking low-dose beclomethasone dipropionate plus added salmeterol did at least as well, if not better, than the high beclomethasone dipropionate group. Furthermore, on retrospective evaluation of the exacerbation rates over the course of the study, there was no difference between either group.

There were a number of criticisms of this study. Firstly, there was no true placebo limb. The data from this study does not address the question whether or not these patients might improve on low-dose beclomethasone dipropionate alone. Secondly, the study measured lung function or surrogates of lung function, parameters likely to improve with a potent long-acting bronchodilator, but did not measure any direct or surrogate markers of airway inflammation. Thirdly, a 6-month study may not have been long enough to evaluate the potential detrimental effect of inhaled β-agonists.

In a similar study with more severe patients, Woolcock et al enrolled patients with symptomatic asthma despite regular beclomethasone dipropionate 1000 μg daily.[15] These subjects were also studied for 6 months in a randomized parallel group trial involving three treatment limbs: beclomethasone dipropionate 1000 μg plus salmeterol 50 μg BD; BDP 1000 μg daily plus added salmeterol 100 μg BD and double-dose beclomethasone dipropionate 2000 μg daily. The same end-points were used. Indeed, their results were similar showing equivalent or greater control of asthma with added salmeterol to lower-dose beclomethasone dipropionate. Retrospective evaluation of acute exacerbation also showed no difference between all three treatment limbs.

Subsequently, in moderate to severe asthmatics, Ind et al showed that addition of salmeterol to 50 μg daily fluticasone produced a greater improvement in asthma control than increasing the dose of fluticasone in symptomatic patients.[16] In this 6-month study, patients suboptimally controlled during run-in on fluticasone 500 μg daily, showed equivalent improvement maintained on this dose throughout the clinical trial compared to increasing doses to 1000 μg daily. This study suggests that these patients have reached the plateau of the dose response to inhaled steroids and are unlikely to achieve any benefit from increasing their dose. With this study, it is readily apparent that added salmeterol provides improvement in asthma control. Despite this, the criticisms of previous studies also apply; this study was only of 6-month duration and the primary end-points were improvement in symptoms and improvement in lung function.

The much quoted FACET Study, in contrast to previous studies of add-on β-agonist treatment, prospectively evaluated the effect of two doses of budesonide with or without formeterol on asthma exacerbations.[17] This study was for 1 year, all patients had moderate asthma and were rendered symptom-free before the random study. During run-in, budesonide 1000 μg was given to each subject in order to achieve stability of lung function and asthma symptoms. Subjects allocated to a four limb treatment parallel group study of budesonide 100 μg BD, budesonide 100 μg and formeterol 12 μg BD, budesonide 400 μg BD, budesonide 400 μg and formeterol 12 μg BD. The combination of high-dose budesonide and formeterol achieved optimal control for both mild to severe exacerbations, whereas budesonide 100 μg and formeterol 12 μg BD was equal to budesonide 400 μg for mild exacerbations. For severe exacerbations, the higher dose of budesonide alone was marginally superior to low-dose budesonide and formeterol. In summary, this study demonstrated the added value of long-acting β-agonists in preventing exacerbations.

Although combination therapy has enhancing effects, a recent study using theophylline, when added to either low-dose or high-dose inhaled steroids, produced a satisfactory control of asthma.[18,19] As with long-acting β-agonists, added theophylline was at least equivalent to the doubling dose of inhaled steroids in controlling asthma.

Several studies showing the benefit of add-on treatment for patients suboptimally controlled asthma with medium doses of inhaled corticosteroids. We have a number of options at step 3 guidelines. The data for long-acting β-agonists is very convincing. Indeed, oral theophylline when added to low-inhaled steroids also provides a very good asthma control. The recent arrival and capability of leukotriene antagonists may provide us with further alternatives with the management of patients with the disease. This also suggests that leukotriene receptor antagonists when added to inhaled steroids improved asthma when compared to doubling the dose of inhaled steroids.[20,21]

SUMMARY

For the future, the likelihood is that combination therapy will become the cornerstone of treatment for those patients with troublesome asthma, prone to frequent symptoms and acute exacerbations receiving

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maintenance prophylactic therapy. The most recent British Thoracic Society guidelines are now advocating the addition of long-acting β-agonists to inhaled corticosteroids as an alternative to increasing the dose of inhaled corticosteroids in patients with acute asthma.[22]

A drawback to this is the need for patients to use a separate inhaler on a regular basis. This has cost implications and may affect compliance. Ideally, a single inhaler combining a long-acting β-agonist and corticosteroids would circumvent these problems. Preferably, such a combination inhaler should be available at three different dose levels for corticosteroids, whilst maintaining a fixed dose of long-acting β-agonists. The aim of combination therapy should be to simplify asthma treatment for patients with moderate to severe disease.

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Efficacy of inhaled corticosteroids in asthma

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Inhaled corticosteroids have now become established as first-line therapy for patients with persistent asthma. Corticosteroids are the only currently available asthma therapy that suppress inflammation in asthmatic airways, and they inhibit almost every aspect of the inflammatory process in asthma. Inhaled corticosteroids are effective in most patients with asthma, irrespective of age or asthma severity. They not only control asthma symptoms and improve lung function but also prevent exacerbations and may reduce asthma mortality and the irreversible changes in airway function that occur in some patients. The dose-response curve to inhaled corticosteroids is relatively flat, and there is increasing evidence that addition of another class of therapy (long-acting inhaled β_2-agonists, low-dose theophylline, or antileukotrienes) may be preferable to increasing the dose of inhaled corticosteroids in patients with moderate-to-severe asthma. Inhaled corticosteroids are convenient to use and are the most cost-effective treatment currently available for long-term asthma control. A small proportion of patients are resistant to the antiinflammatory effects of corticosteroids. Future developments may include inhaled corticosteroids with even fewer systemic effects or more specific anti-inflammatory drugs. (J Allergy Clin Immunol 1998;102:531-8.)

Key words: Asthma, corticosteroids, airway hyperresponsiveness, inflammation

Corticosteroids are by far the most effective therapy currently available for asthma, and a response to steroids is one of the characteristic clinical features of asthma. Inhaled corticosteroids have revolutionized asthma management and have now become the mainstay of therapy for patients with persistent asthma.[1] There has recently been an enormous increase in our understanding of the molecular and cellular mechanisms whereby corticosteroids suppress inflammation in asthma, and this has led to changes in the way corticosteroids are used and may point the way to the development of more specific therapies in the future.[2] Inhaled corticosteroids are the most carefully studied drugs that are in current clinical use.

Abbreviations used
AHR: Airway hyperresponsiveness
AP-1: Activator protein-1
BDP: Beclomethasone dipropionate
FP: Fluticasone propionate
GR: Glucocorticoid receptor
NF-κB: Nuclear factor-κB
PEF: Peak expiratory flow

ANTIINFLAMMATORY MECHANISMS

Corticosteroids are very effective at suppressing the eosinophilic inflammation in the airways of patients with asthma. This antiinflammatory effect is through increased transcription and expression of antiinflammatory proteins, such as IL-1 receptor antagonist, IL-10, and neutral endopeptidase. More importantly, this effect is through repression of inflammatory genes, such as cytokines involved in the inflammatory response in asthma (eg, IL-4, IL-5, and chemokines involved in eosinophil recruitment).[2] Corticosteroids are probably so effective in asthma because they inhibit many components of the inflammatory response in asthma (Fig 1). They inhibit the activation and recruitment of inflammatory cells, particularly eosinophils, T lymphocytes, macrophages, and dendritic cells. Although they do not block mast cell activation, they inhibit the survival of mast cells at the airway surface, thus preventing their activation in challenges such as exercise and fog. Increasingly, it is also recognized that corticosteroids also inhibit the release of mediators from structural cells in the airways, such as epithelial, smooth muscle, and endothelial cells and fibroblasts. Indeed, an inhibitory effect on epithelial cells may be one of the major actions of inhaled corticosteroids (Fig 2).[3]

Many studies have now documented the suppressive effect of inhaled corticosteroids on inflammation in asthmatic airways. This is reflected by a reduced number of inflammatory cells (particularly eosinophils, surface mast cells, and macrophages), and to a lesser extent T lymphocytes, in bronchial biopsy specimens of asthmatic patients. Similar results have been reported in the bronchoalveolar lavage fluid of asthmatic patients. There is also a reduction in other markers of airway inflammation, including eosinophils in induced sputum and in exhaled nitric oxide (NO), a reflection of increased expression of the inflammatory enzyme–inducible NO synthase, which is suppressed by corticosteroids.

Effects on airway hyperresponsiveness

By reducing airway inflammation, inhaled corticosteroids consistently reduce airway hyperresponsiveness (AHR) in asthmatic adults and children.[4] Chronic treatment with inhaled corticosteroids reduces responsiveness to histamine, cholinergic agonists, allergen (early and late responses), exercise, fog, cold air, bradykinin, adenosine, and irritants (eg, sulfur dioxide and metabisulfite). The reduction in AHR takes place over several weeks and may not be maximal until after several months of therapy. The magnitude of reduction is variable between patients and is in the order of 1 to 2 doubling dilutions for most challenges; it often fails to return to the normal range. This may reflect suppression of the inflammation but persistence of structural changes that cannot be reversed by corticosteroids. Inhaled corticosteroids not only make the airways less sensitive to spasmogens, but they also limit the maximal airway narrowing in response to spasmogens.

CLINICAL EFFICACY

Inhaled corticosteroids are very effective in controlling asthma symptoms to asthmatic patients of all ages with asthma of all severities (Table I).[1,5,6] Inhaled corticosteroids improve the quality of life of patients with asthma and may allow patients to lead normal lives, improve lung function, reduce the frequency of exacerbations, and possibly prevent irreversible airway changes. They were first introduced to reduce the requirement for oral corticosteroids in patients with severe asthma, and many studies have confirmed that the majority of patients can be weaned off oral corticosteroids.[6]

Studies in adults

As experience has been gained with inhaled corticosteroids, they have been introduced in patients with milder asthma, with the recognition that inflammation is

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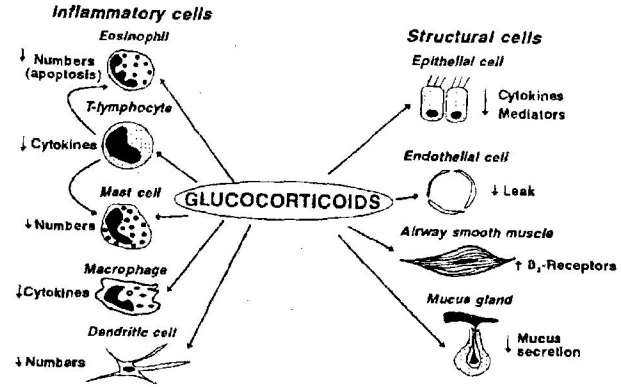


FIG 1. Inhaled corticosteroids have effects on many inflammatory and structural cells that are involved in asthmatic inflammation.

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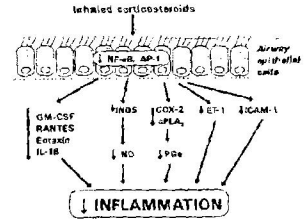


FIG 2. Inhaled corticosteroids may inhibit transcription of several inflammatory genes in airway epithelial cells and thus reduce inflammation in airway wall. iNOS, Inducible NO synthase; COX-2, inducible cyclooxygenase; cPLA2, cytosolic phospholipase A2; ET1, endothelin-1; ICAM-1, intercellular adhesion molecule-1.

present even in patients with mild asthma. Inhaled anti-inflammatory drugs have now become first-line therapy in any patient who needs to use a β_2-agonist inhaler more than once a day, and this is reflected in national and international guidelines for the management of chronic asthma.[7-9] In patients with newly diagnosed asthma, inhaled corticosteroids (budesonide 600 μg twice daily) reduced symptoms and β_2-agonist inhaler use and improved peak expiratory flows (PEFs). These effects persisted over the 2 years of the study, whereas in a parallel group treated with inhaled β_2-agonists alone there was no significant change in symptoms or lung function.[10] In another study patients with mild asthma treated with a low dose of inhaled corticosteroid (budesonide 200 μg twice daily) showed less symptoms and a progressive improvement in lung function over several months, and many patients became completely asymptomatic.[11] There was also a significant reduction in the number of exacerbations. Although the effects of inhaled corticosteroids on AHR may take several months to reach a plateau, the reduction in asthma symptoms occurs more rapidly.[12]

High-dose inhaled corticosteroids have now been introduced in many countries for the control of more severe asthma. This markedly reduces the need for maintenance oral corticosteroids and has revolutionized the management of more severe and unstable asthma. Inhaled corticosteroids are the treatment of choice in nocturnal asthma, which is a manifestation of inflamed airways, reducing nighttime awakening and reducing the diurnal variation in airway function.

High doses of inhaled corticosteroids may also substitute for a course of oral steroids in controlling acute exacerbations of asthma. High-dose fluticasone propionate (FP) (2000 μg daily) was as effective as a course of oral prednisolone in controlling acute exacerbations of asthma in general practice.[13]

Inhaled corticosteroids effectively control asthmatic inflammation but must be taken regularly. When inhaled

TABLE I. Effects of inhaled corticosteroids in asthma

- Control symptoms
- Improve quality of life
- Improve lung function
- Prevent exacerbations
- Reduce mortality (probably)
- Prevent irreversible airway changes
- Alter natural history of asthma (?)

corticosteroids are discontinued, there is usually a gradual increase in symptoms and airway responsiveness back to pretreatment values,[12] although symptoms may not recur in some patients with mild asthma who have been treated with inhaled corticosteroids for a long time.[14]

Studies in children

Inhaled corticosteroids are equally effective in children. In an extensive study of children aged 7 to 17 years, there was a significant improvement in symptoms, peak flow variability, and lung function compared with a regular inhaled β_2-agonist, which was maintained over the 22 months of the study.[15] However, asthma deteriorated when the inhaled corticosteroids were withdrawn.[16] There was a high proportion of drop-outs (45%) in the group treated with inhaled β_2-agonist alone. Inhaled corticosteroids are also effective in younger children. Nebulized budesonide reduces the need for oral corticosteroids and also improved lung function in children under the age of 3 years.[17] Inhaled corticosteroids given by means of a large volume spacer improve asthma symptoms and reduce the number of exacerbations in preschool children and in infants.

Dose-response studies

Surprisingly, the dose-response curve for the clinical efficacy of inhaled corticosteroids is relatively flat, and although all studies have demonstrated a clinical benefit of inhaled corticosteroids, it has been difficult to demonstrate differences between doses, with most benefit obtained at the lowest doses used.[6] This is in contrast to the steeper dose-response for systemic effects, implying that although there is little clinical benefit from increasing doses of inhaled corticosteroids, the risk of adverse effects is increased. However, the dose-response effect of inhaled corticosteroids may depend on the parameters measured, and although it is difficult to discern a dose-response effect when traditional lung function parameters are measured, there may be a dose-response effect in prevention of asthma exacerbations. Thus in a recent study there was a significantly greater effect of budesonide 800 μg daily compared with 200 μg daily in preventing severe and mild asthma exacerbations.[18] Normally, a 4-fold or greater difference in dose has been required to detect a statistically significant (but often small) difference in effect on commonly measured outcomes, such as symptoms, PEF, use of rescue β_2-agonist, and lung function, and even such large differences in dose are not always associated with significant differences in response. These

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findings suggest that pulmonary function tests or symptoms may have a rather low sensitivity in the assessment of the effects of inhaled corticosteroids. This is obviously important for the interpretation of clinical comparisons between different inhaled corticosteroids or inhalers. It is also important to consider the type of patient included in clinical studies. Patients with relatively mild asthma may have relatively little room for improvement with inhaled corticosteroids, and therefore maximal improvement is obtained with relatively low doses. Patients with more severe asthma or with unstable asthma may have more room for improvement and may therefore show a greater response to increasing doses, but it is often difficult to include such patients in controlled clinical trials.

More studies are needed to assess whether other outcome measures, such as AHR, or more direct measurements of inflammation, such as sputum eosinophils or exhaled NO, may be more sensitive than traditional outcome measures, such as symptoms or lung function tests.

Prevention of irreversible airway changes

Some patients with asthma experience an element of irreversible airflow obstruction, but the pathophysiologic basis of these changes is not yet understood. It is likely that they are the result of chronic airway inflammation and that they may be prevented by treatment with inhaled corticosteroids. There is some evidence that the annual decline in lung function may be slowed by the introduction of inhaled corticosteroids.[19] Increasing evidence also suggests that delay in starting inhaled corticosteroids may result in less overall improvement in lung function in both adults and children.[20-22] These studies suggest that introduction of inhaled corticosteroids at the time of diagnosis is likely to have the greatest effect.[21,22] Several large studies are now underway to assess the benefit of very early introduction of inhaled corticosteroids in children and adults. So far there is no evidence that early use of inhaled corticosteroids is curative, and even when inhaled corticosteroids are introduced at the time of diagnosis, symptoms and lung function revert to pretreatment levels when corticosteroids are withdrawn.[20]

Reduction in mortality

Inhaled corticosteroids may reduce the mortality from asthma, but prospective studies are almost impossible to conduct. In a retrospective review of the risk of mortality and prescribed antiasthma medication, there was a significant apparent protection provided by regular inhaled beclomethasone dipropionate (BDP) therapy (adjusted odds ratio of 0.11, although numbers were small.[23]

Comparison between inhaled corticosteroids

Several inhaled corticosteroids are currently prescribable in asthma, although their availability varies between countries. There have been relatively few studies comparing efficacy of the different inhaled corticosteroids, and it is important to take into account the delivery system and the type of patient under investigation when such comparisons are made. Because of the relatively flat dose-response curve for the clinical parameters normally used in comparing doses of inhaled corticosteroids, it may be difficult to see differences in efficacy of inhaled corticosteroids. Furthermore, most comparisons have concentrated on differences in systemic effects at equally efficacious doses, although it has often proved difficult to establish true clinical efficacy. In the UK, BDP, budesonide, and FP are available, whereas in the US, BDP, flunisolide, triamcinolone, FP, and budesonide are available. There are few studies comparing different doses of inhaled corticosteroids in asthmatic patients. Budesonide has been compared with BDP, and it appears to have comparable antiasthma effects at equal doses in adults and children, whereas FP appears to be approximately twice as potent as BDP and budesonide. There do appear to be some differences between inhaled corticosteroids in terms of their systemic effects at comparable antiasthma doses, however, but these are beyond the scope of this review.

CLINICAL USE OF INHALED CORTICOSTEROIDS

Inhaled corticosteroids are now recommended as first-line therapy for all patients with persistent symptoms.[1] Inhaled corticosteroids should be started in any patient who needs to use a β_2-agonist inhaler for symptom control more than once daily (or possibly 3 times weekly). It is conventional to start with a low dose of inhaled corticosteroid and to increase the dose until asthma control is achieved. However, this may take time, and a preferable approach is to start with a dose of corticosteroids in the middle of the dose range (400 μg twice daily) to establish control of asthma more rapidly.[24] Once control is achieved (defined as normal or best possible lung function and infrequent need to use an inhaled β_2-agonist), the dose of inhaled corticosteroid should be reduced in a step-wise manner to the lowest dose needed for optimal control. It may take as long as 3 months to reach a plateau in response, and any changes in dose should be made at intervals of 3 months or more. This strategy ("start high - go low") is emphasized in the most recent US and UK guidelines.[8,9] When daily doses of 800 μg or greater are needed, a large volume spacer device should be used with a metered-dose inhaler and mouth washing with a dry powder inhaler to reduce local and systemic side effects. Inhaled corticosteroids are usually given as a twice daily dose to increase compliance. When asthma is more unstable, 4 times daily dosage is preferable.[25] For patients who require 400 μg or less daily, once daily dosing appears to be as effective as twice daily dosing, at least for budesonide.[26]

The dose of inhaled corticosteroid should be increased to 2000 μg daily if necessary, but higher doses may result in systemic effects, and it may be preferable to add a low dose of oral corticosteroid because higher doses of inhaled corticosteroids are expensive and have a high incidence of local side effects. Nebulized budesonide has been advocated to

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give an increased dose of inhaled corticosteroid and to reduce the requirement for oral corticosteroids,[27] but this treatment is expensive and may achieve its effects largely by means of systemic absorption.

Additional bronchodilators

Conventional advice was to increase the dose of inhaled corticosteroids if asthma was not controlled on the assumption that there was residual inflammation of the airways. However, it is now apparent that the dose-response effect of inhaled corticosteroids is relatively flat, so that there is little improvement in lung function after doubling the dose of inhaled corticosteroids. An alternative strategy is to add some other class of controller drug. In patients in general practice whose symptoms were not controlled by BDP 200 μg twice daily, addition of salmeterol 50 μg twice daily was more effective than increasing the dose of inhaled corticosteroid to 500 μg twice daily in terms of lung function improvement, rescue β_2-agonist use, and symptom control.[28] This surprising result was confirmed in a group of patients with more severe asthma whose symptoms were not controlled on 800 to 1000 μg BDP daily.[29] Similar results have been found with another long-acting inhaled β_2-agonist, formoterol, which in addition reduced the frequency of mild and severe asthma exacerbations.[15] Recent studies have also shown that addition of low doses of theophylline (giving plasma concentrations of <10 mg/L) were more effective than doubling the dose of inhaled budesonide, either in mild or severe asthma.[30,31] Similar data are now emerging with antileukotrienes.[32] The reason why these alternative treatments are more effective than higher doses of inhaled corticosteroids remains to be elucidated, but it does suggest that there is a reversible component of asthma that may not be steroid-sensitive inflammation. It is possible that this may be an abnormality in airway smooth muscle itself (as a result of remodeling), edematous swelling of the airway, or production of cysteinyl-leukotrienes that is not sensitive to inhibition by inhaled corticosteroids.[33]

Cost effectiveness

Although inhaled corticosteroids may be more expensive than short-acting inhaled β_2 agonists, they are the most cost effective way of controlling asthma because reducing the frequency of asthma attacks will save on total costs.[34] Inhaled corticosteroids also improve the quality of life of patients with asthma and allow many patients a normal lifestyle, thus saving costs indirectly.[35]

Oral corticosteroid–sparing therapy

In patients who have serious side effects with maintenance oral corticosteroid therapy, there are several treatments that have been shown to reduce corticosteroid requirements.[36] These treatments are commonly termed corticosteroid-sparing, although this is a misleading description that could be applied to any additional asthma therapy (including bronchodilators). The amount of corticosteroid sparing with these therapies is not impressive.

Several immunosuppressive agents have been shown to have oral corticosteroid–sparing effects, including methotrexate, oral gold, and cyclosporin A. These therapies all have side effects that may be more troublesome than those of oral corticosteroids and are therefore only indicated as an additional therapy to reduce the requirement of oral corticosteroids. None of these treatments is uniformly effective in all patients, but there are occasional patients who appear to show a good response. Because of side effects, these treatments cannot be considered as a way to reduce the requirement for inhaled corticosteroids. Several other therapies, including azathioprine, dapsone, and hydroxychloroquine, have not been found to be beneficial. The macrolide antibiotic troleandomycin is also reported to have corticosteroid-sparing effects, but this is only seen with methylprednisolone and is due to reduced metabolism of this corticosteroid. Therefore there is little therapeutic gain.[37]

CORTICOSTEROID-RESISTANT ASTHMA

Although glucocorticoids are highly effective in the control of asthma and other chronic inflammatory or immune diseases, a small proportion of patients with asthma fail to respond even to high doses of oral glucocorticoids.[38,39] Resistance to the therapeutic effects of glucocorticoids is also recognized in other inflammatory and immune diseases, including rheumatoid arthritis and inflammatory bowel disease. Corticosteroid-resistant patients, although uncommon, present considerable management problems. Recently, new insights into the mechanisms whereby corticosteroids suppress chronic inflammation has shed new light on the molecular basis of corticosteroid-resistant asthma.

Corticosteroid-resistant asthma is defined as a failure to improve FEV_1 or PEF by greater then 15% after treatment with oral prednisolone 30 to 40 mg daily for 2 weeks, providing the oral steroid is taken (verified by plasma prednisolone level or a reduction in early morning cortisol level). These patients do not have Addison's disease, and they do not have the abnormalities in sex hormones described in the very rare familial glucocorticoid resistance. Plasma cortisol and adrenal suppression in response to exogenous cortisol is normal in these patients, and therefore they experience the side effects of corticosteroids.

Complete corticosteroid resistance in asthma is very rare, with a prevalence of less than 1 in 1000 asthmatic patients. Much more common is a reduced responsiveness to corticosteroids, such that large inhaled or oral doses are needed to control asthma adequately (corticosteroid-dependent asthma). It is likely that there is a range of responsiveness to corticosteroids and that corticosteroid resistance is at one extreme of this range.

It is important to establish that the patient has asthma, rather than chronic obstructive pulmonary disease, "pseudoasthma" (a hysterical conversion syndrome involving vocal cord dysfunction), left ventricular failure, or cystic fibrosis, which do not respond to corticosteroids. Asthmatic patients are characterized by a variability in PEF and, in particular, a diurnal variability of greater than 15% with episodic symptoms. It is also important to identify provoking factors (allergens, drugs, or psychologic problems) that may increase the severity of asthma and its resistance to therapy. Biopsy studies have demonstrated the typical eosinophilic inflammation of asthma in these patients.[39]

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Mechanisms of corticosteroid resistance

There may be several mechanisms for resistance to the effects of glucocorticoids. Certain cytokines (particularly IL-2, IL-4, and IL-13) may induce a reduction in affinity of glucocorticoid receptors in inflammatory cells, such as T lymphocytes and monocytes, by increasing expression of glucocorticoid receptor-β, an endogenous inhibitor of corticosteroid action, resulting in local resistance to the antiinflammatory actions of corticosteroids.[39,40] Another mechanism is an increased activation of the transcription factor activator protein (AP)-1 by inflammatory cytokines, such that AP-1 may consume activated glucocorticoid receptors and thus reduce their availability for suppression of inflammation at inflamed sites.[41] The reasons for this excessive activation of AP-1 by activating enzymes is currently unknown but might be genetically determined.

FUTURE DIRECTIONS

Inhaled corticosteroids are now used as first-line therapy for the treatment of persistent asthma in adults and children in many countries because they are the most effective treatments for asthma currently available. The recent trend to start with a relatively high dose of inhaled corticosteroids to achieve more rapid control of asthma before the dose is reduced to the minimum needed to maintain control may lead to lower overall maintenance doses.[5] Although many patients, particularly those with more severe asthma, remain undertreated, there is also a danger of overtreatment, and many patients with mild asthma who may require very low doses of inhaled corticosteroids are inappropriately treated with high doses. It is essential that inhaled corticosteroids are slowly reduced to the minimal dose required to control asthma, and this dose should then be maintained. An important clinical development is the recognition that asthma is better controlled by addition of an alternative class of treatment (long-acting inhaled β_2-agonists, low dose theophylline, and antileukotrienes) than by increasing the dose of inhaled steroid. Although there may be some patients who are better treated with a higher dose of inhaled corticosteroid, at present it is not possible to identify such patients clinically. Improvement in techniques for the noninvasive monitoring of airway inflammation may be valuable in the future for assessing the requirement for inhaled corticosteroids.[42]

New corticosteroids

Budesonide and FP have been important advances in inhaled corticosteroid therapy. They have reduced systemic effects because of greater first-pass hepatic metabolism than BDP. There are other inhaled corticosteroids in development, such as mometasone, that show a similar improved profile. However, all currently available corticosteroids are absorbed from the lungs into the systemic circulation and therefore inevitably have some systemic component. A class of steroids was developed that was metabolized in the lung, but such so called *soft* steroids, such as tipredane and butixocort, did not prove to be clinically effective, probably because they were metabolized too rapidly in the airways. Steroids that are metabolized by enzymes in the circulation may be the safest type of inhaled corticosteroid. However, it is still not certain whether the antiinflammatory effects of inhaled corticosteroids in asthma are mediated entirely by local antiinflammatory effects in the airways, and it is possible that there is a systemic component (eg, on bone marrow eosinophil precursors). Furthermore, it is not clear whether inhaled corticosteroids are distributed from their point of deposition in the airways to more peripheral airways by means of the local circulation. If this is the case, then corticosteroids that are degraded by enzymes in the circulation may not reach small airways, which are known to be inflamed in asthma.

Understanding the molecular mechanisms of action of corticosteroids has led to the development of a new generation of corticosteroids. As discussed above, a major mechanism of the antiinflammatory effect of corticosteroids appears to be direct inhibition of transcription factors, such as nuclear factor (NF)-κB and AP-1, that are activated by proinflammatory cytokines (transrepression). By contrast, the endocrine and metabolic effects of steroids, which are responsible for the systemic side effects of corticosteroids, are likely to be mediated by means of DNA binding (transactivation). This has led to a search for novel corticosteroids that selectively transrepress, thus reducing the potential risk of systemic side effects. Because corticosteroids bind to the same glucocorticoid receptor (GR), this seems at first to be an unlikely possibility, but although DNA binding involved a GR homodimer, interaction with transcription factors AP-1 and NF-κB involves only a single GR. A separation of transactivation and transrepression has been demonstrated by using reporter gene constructs in transfected cells with selective mutations of the glucocorticoid receptor. Furthermore, some steroids, such as the antagonist RU486, have a greater transrepression than transactivation effect. Indeed, the topical steroids used in asthma therapy today, such as FP and budesonide, appear to have more potent transrepression than transactivation effects, which may account for their selection as potent antiinflammatory agents.[43] Recently, a novel class of steroids has been described in which there is potent transrepression with relatively little transactivation. These *dissociated* steroids, including RU24858 and RU40066, have antiinflammatory effects in vivo.[44] This suggests that the

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development of steroids with a greater margin of safety is possible and may even lead to the development of oral steroids that do not have significant adverse effects.

New antiinflammatory drugs

There has been a concerted effort to find novel antiinflammatory drugs that might replace corticosteroids in the future.[45] However, it has proved very difficult to find classes of drug that are as safe and efficacious as inhaled corticosteroids. More specific antiinflammatory drugs that selectively inhibit eosinophilic inflammation, such as anti-IL-5 drugs, chemokine receptor (CCR3) inhibitors, and adhesion molecule blockers (such as very late antigen-4 inhibitors), are currently in clinical development, but whether these more specific drugs will have the efficacy of corticosteroids is not yet known. Drugs that inhibit NF-κB are also in early development but may prove to be too toxic for use in asthma. More generalized antiinflammatory drugs, such as phosphodiesterase 4 inhibitors, have proved to be disappointing because of side effects, and immunomodulators, such as cyclosporin A, lack uniform clinical efficacy and have a high degree of toxicity. Thus it is likely that inhaled corticosteroids will remain the mainstay of asthma therapy for many years to come.

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