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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Evento : 001
Actuación : 444

Referencia : Expediente No. 03.077.336
Asunto : Solicitud de Patente para **NUEVAS COMPOSICIONES DE MEDICAMENTOS SOBRE LA BASE DE AGENTES ANTICOLINERGICOS E INHIBIDORES DE PDE-IV**
Solicitante : **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG**
Fecha de Solicitud : 4 de Septiembre de 2003

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al oficio número 4348 notificado por fijación en lista de 13 de abril de 2007.
2. Mediante mi memorial de fecha 11 de julio de 2007 solicité un plazo de 30 días para atender el oficio número 4348.
3. Mediante oficio número 4348 se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Atiendo a las observaciones de la manera siguiente:

3.1. CLARIDAD DE LA SOLICITUD:

El Examinador argumenta que la reivindicación 1 pretende proteger composiciones que contienen uno o varios agentes anticolinérgicos con uno o varios inhibidores de PDE IV y resalta que el efecto sinérgico no corresponde a la simple suma aritmética de los efectos que presenta cada uno de los componentes. Así mismo el Examinador dice que a lo largo de la descripción se deberían haber incluido datos de ensayos que demostrarán dicho efecto inesperado en un curva dosis-respuesta que demostraran el efecto sinérgico de esta combinación.

En respuesta a esta objeción, mi representada presenta un estudio realizado por el laboratorio ALTANA PHARMA AG presentado con la solicitud de patente WO 2004/084896 - cuya fecha de prioridad es posterior a la de la presente solicitud de patente - en el cual el efecto sinérgico entre el roflumilast y el bromuro de tiotropio es demostrado.

Como se puede ver en el documento adjunto el efecto de la combinación es evaluada en *conejos de indias* a los que se les indujo artificialmente un broncoespasmo por acción de metacolina y luego se procede a evaluar la respuesta en las vías aéreas de los reactivos biológicos frente a roflumilast y tiotropio individualmente y en combinación.

En las gráficas adjuntas, se observa que el efecto obtenido tras el uso de la combinación de el roflumilast y el tiotropio es mayor al resultado de la suma aritmética del efecto individual producido por los compuestos (figuras 3 y 4).

En este caso es claro que el efecto producido por estos medicamentos en combinación en una sola dosis y su evolución en el tiempo y por la combinación de agentes anticolinérgicos e inhibidores de PDE 4 genera una respuesta sinérgica. De esta manera queda demostrado el efecto sinérgico de las composiciones de roflumilast y tiotropio.

Por otro lado, el Examinador argumenta que se pretende protección para un sinnúmero de mezclas que abarcan compuestos pertenecientes al grupo de los agentes anticolinérgicos y al grupo de los inhibidores de PDE 4.

En respuesta a la anterior objeción, la solicitante presenta un nuevo pliego reivindicatorio en el cual el grupo de agentes anticolinérgicos se ha limitado únicamente a: sales de tiotropio (reivindicación 1), de esta forma el número de composiciones obtenidas al combinar los agentes anticolinérgicos y los inhibidores de PDE 4 es menor que en el pliego presentado inicialmente.

Por otro lado, el Examinador argumenta que no hay claridad en torno a la característica esencial de la invención, a los compuestos activos, excipientes y proporciones que caracterizan el sinergismo sugiriendo una precisión sobre las características esenciales de la formulación para definir el objeto de la invención.

En respuesta a este aspecto, la solicitante argumenta que en la descripción se describen claramente las cantidades de excipientes y principios activos empleados en la obtención de las composiciones de los polvos y aerosoles inhalables reivindicados, es decir, hace parte de la información relevante que debe ser usada para interpretar el alcance de las reivindicaciones .

Asi mismo el Examinador argumenta que el uso de nombres y códigos comerciales no es adecuado en el momento de reivindicar esta composición.

Por esta razón, en el nuevo pliego reivindicatorio se incluyen los nombre comunes, los nombres químicos y en algunos casos los códigos que identifican los compuestos pertenecientes al grupo 2 (inhibidores de PDE 4).

El Examinador además solicita que se precise el verdadero objeto de su invención señalando las características esenciales que lo hacen nuevo e inventivo con respecto al arte previo. Definir el vehículo y el sistema de entrega, teniendo en cuenta que no se puede cobijar bajo una misma invención diferentes sistemas tales como líquidos, heterodispersos y sólidos.

En respuesta a esta objeción, la solicitante argumenta que las composiciones reivindicadas son obtenidas a partir de producto obtenido o reivindicado en las reivindicaciones iniciales, en donde se describe la composición obtenida por la combinación de algunos excipientes con los principios activos allí establecidos y el producto obtenido es pues empleado para la producción de las formas farmacéuticas posteriormente reivindicadas como las soluciones, las suspensiones y los aerosoles.

3.2. USOS

El examinador argumenta que las reivindicaciones 1 a 35 comprenden la utilización de la combinación farmacológica para su administración por vía nasal en un sistema tipo inhalador.

En respuesta a esta objeción, se indica que las reivindicaciones 1 a 31 hacen referencia a composiciones farmacéuticas. Por otro lado, las reivindicaciones 32 a 35 representan el uso de dichas composiciones, razón por la cual la solicitante ha eliminado dichas reivindicaciones del pliego reivindicatorio.

3.3. UNIDAD DE INVENCION

A este respecto el Señor Examinador argumenta que no hay unidad de invención en torno a la combinación de compuestos contemplados dentro de la combinación reivindicada y que además no existe unidad inventiva en relación al sistema de entrega reivindicado.

En respuesta a esta objeción vale destacar que la solicitante limitó el grupo 1 correspondiente a agentes anticolinérgicos a sales de tiotropio. Adicionalmente, los sistemas de entrega descritos poseen un único concepto inventivo porque la composición farmacéuticamente reivindicada inicialmente es usada para la formulación de las siguientes composiciones. De esta manera, las forma líquidas, sólidas y aerosoles son manufacturadas a partir de la composición obtenida que es descrita en las reivindicaciones iniciales.

3.4. NOVEDAD

En este aspecto el Examinador argumenta que D1 revelaba combinaciones entre agentes anticolinérgicos e inhibidores de PDE 4.

En respuesta a esta objeción, la solicitante en el nuevo pliego reivindicatorio solicita el privilegio de patente para la combinación dirigida únicamente a las sales de tiotropio y a un grupo limitado de agentes inhibidores de PDE 4, de tal manera que cualquier indicación general en el estado del arte no podría afectar la novedad de la presente invención.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se conceda la patente solicitada.

Anexos:

1. Nuevo pliego reivindicatorio
2. Formulario para modificaciones
3. Recibo por valor de \$99.000 por concepto de modificaciones en solicitud pendiente

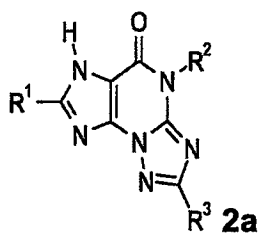
Espacio reservado para el adhesivo de radicación

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES

1	SOLICITUD DE: ☐ Corrección de Error Material ☒ Modificación a una solicitud	
2 SOLICITANTE	Nombre: BOEHRINGER INGELHEIM PHARMA GMBH & CO.KG. Sociedad constituida y existente bajo las leyes de Alemania. Dirección: 55216 Ingelheim am Rhein, Alemania Domicilio: Ingelheim am Rhein, Alemania Teléfono: 546 09 70 Fax: 249 40 70 E-mail: clientes@camyp.com	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: _____
3 REPRESENTANTE O APODERADO	Nombre: Emilio FERRERO Dirección: Carrera 4ª No. 72-35 Teléfono: 347 36 11 Fax: 217 92 11 E-mail: cavelier@cavelier.com	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: <u>438.019 TP 31.929</u>
4	Número de expediente: <u>03.077.336</u>	
5	Descripción de la corrección o modificación solicitada: Se presenta nuevo capítulo reivindicatorio compuesto por 30 reivindicaciones. Para que se efectúe el examen de patentabilidad sobre el mismo.	
6	Comprobante de pago No. <u>07-64.893</u> Fecha: <u>13 de agosto de 2007</u>	
7	Anexos ☒ Comprobante de pago de la tasa por valor de \$99.000.00 ☐ Poderes, si fuere el caso ☐ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.	
8	NOMBRE: EMILIO FERRERO	FIRMA:  C.C. 438.019 de Usaquén T.P.A. 31.929

REIVINDICACIONES

- 5 1) Composición farmacéutica caracterizada por que contiene una o más sales de tiotropio (1) combinada con uno o más inhibidores PDE-IV (2), opcionalmente en la forma de enantiómeros, mezclas de enantiómeros o en la forma de racematos de estos, opcionalmente en la forma de solvatos o hidratos y opcionalmente junto con un excipiente farmacéuticamente aceptable.
- 10 2) Composición farmacéutica de acuerdo con la reivindicación 1, caracterizada por que las sustancias activas 1 y 2 están presentes juntas en una única formulación o en dos formulaciones separadas.
- 15 3) Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 2, caracterizada por que 1 está presente en la forma de cloruro, bromuro, yoduro, metanosulfonato, paratolueno sulfonato o metil sulfato, preferiblemente en la forma de bromuro.
- 20 4) Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 3, caracterizada por que 2 se selecciona entre:
- 25 3-propilxantina (*Enprofilina*), (3-ciclopropilmetoxi-4-difluorometoxi-N-[3,5-di-cloropirid-4-il]-benzamida) (*Roflumilast*), ácido c-4-ciano-4-(3-ciclopentiloxi-4-metoxifenil)-r-l-ciclohexano carboxílico (*ariflo*), ester del ácido 2-(2,4-dicloro-benzoil)-3-ureido-benzofuran-6-il metanosulfónico (*Irimilast*; BAY-198004), 8-ciclopentil-6-etil-3-tiofen-2-il-5,8-dihidro-4H- 1, 2, 3a, 7, 8 -pentaaza-as-indaceno (*tofimilast*; CP-325,366), 4-(9-etoxi-8-metoxi-2-metil-1, 2, 3, 4, 4a, 10b, -exahidrobenczo[c][1,6]naftiridin-6-il)-N, 30 N-diisopropil-benzamida (*Pumafentrina*; BY 343), (3,5-dicloro-1-oxipiridin-4-il)-amida del ácido 8-metoxi-2-trifluorometil-quinolina-5-carboxílico (*D-4396* (*Sch-351591*)), [3-(3-ciclopentiloxi-4-metoxi-benzil)-8-isopropil-3H-purin-6-il]-etil-amino-clorhidrato (*V-11294A*), N-(3,5-dicloro-piridin-4-il)-2-[1-(4-fluorobenzil)-5-hidroxi-1H-indol-3-il]-2-oxo-acetamida (*AWD-12-* 35 281) y los heterociclos de nitrógeno tricíclicos de la fórmula general 2a



en donde

5 R^1 denota alquilo C_1-C_5 , cicloalquilo C_5-C_6 , fenilo, bencilo o un anillo heterocíclico saturado o insaturado de 5 o 6 miembros que puede contener uno o dos heteroátomos seleccionados entre oxígeno y nitrógeno;

10 R^2 denota alquilo C_1-C_5 o alquenilo C_2-C_4

R^3 denota alquilo C_1-C_5 que se puede sustituir opcionalmente por alcoxi C_1-C_4 , cicloalquilo C_5-C_6 , fenoxi o un anillo heterocíclico saturado o insaturado de 5 o 6 miembros que puede contener uno o dos heteroátomos seleccionados entre oxígeno y nitrógeno

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cicloalquilo C_5-C_6 o fenilo o bencilo opcionalmente sustituido por alcoxi C_1-C_4 , opcionalmente en la forma de sus racematos, sus enantiómeros, en la forma de los diastereómeros y las mezclas de estos, opcionalmente en la forma de sus tautómeros y opcionalmente las sales de adición ácida farmacológicamente aceptables de estos.

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5) Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 4, caracterizada por que 2 se selecciona entre 3-propylxanthine (*Enprofilina*), (3-ciclopropilmetoxi-4-difluorometoxi- N-[3,5-di-chloropirid-4-il]-benzamida) (*Roflumilast*), ácido c-4-ciano-4-(3-ciclopentiloxi-4-metoxifenil)-r-l-ciclohexano carboxílico (*ariflo*), N-(3,5-dicloro-piuridin-4-il)-2-[1-(4-fluorobenzil)-5-hidroxi-1H-indol-3-il]-2-oxo-acetamida (*AWD-12-281*) y los heterociclos de nitrógeno tricíclico de la fórmula general 2a.

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6) Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 5, caracterizada por que las proporciones en peso de 1a y 2a están en el rango de 1:300 a 50:1, preferiblemente de 1:250 a 40:1.

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- 5 7) Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 6, caracterizada por que una administración única corresponde a una dosis de la combinación de sustancia activa 1 y 2 de 0.01 a 10000 µg, preferiblemente de 0.1 a 2000p µg.
- 10 8) Composición farmacéutica de acuerdo con una de las reivindicaciones 1 a 7, caracterizado en que está en la forma de una formulación adecuada para inhalación.
- 15 9) Composición farmacéutica de acuerdo con la reivindicación 8, caracterizado en que es una formulación seleccionada entre polvos inhalables, aerosoles medidos que contienen propulsor y soluciones inhalables libres de propulsor o suspensiones.
- 20 10) Composición farmacéutica de acuerdo con la reivindicación 9, caracterizado en que es un polvo inhalable que contiene 1 y 2 en mezcla con excipientes fisiológicamente aceptables adecuados seleccionados entre monosacáridos, disacáridos, oligo- y polisacáridos, polialcoholes, sales o mezclas de estos excipientes con otro.
- 25 11) Polvo inhalable de acuerdo con la reivindicación 10, caracterizado en que el excipiente tiene un tamaño de partícula promedio máximo de hasta 250 µm, preferiblemente entre 10 y 150 µm.
- 30 12) Cápsulas, caracterizadas en que ellas contienen un polvo inhalable de acuerdo con la reivindicación 10 o 11.
- 35 13) Composición farmacéutica de acuerdo con la reivindicación 9, caracterizado en que esta es un polvo inhalable que solo contiene la sustancia activa 1 y 2 como sus ingredientes.
- 14) Composición farmacéutica de acuerdo con la reivindicación 9, caracterizado en que esta es un aerosol inhalable que contiene propulsor que contiene 1 y 2 en forma disuelta o dispersa.

- 5 15) Aerosol inhalable que contiene propulsor de acuerdo con la reivindicación 14, caracterizada por que contiene, como gas propulsor, hidrocarburos tales como n-propano, n-butano o isobutano o halohidrocarburos tal como derivados fluorinados y/o clorinados de metano, etano, propano, butano, ciclopropano o ciclobutano.
- 10 16) Aerosol inhalable que contiene propulsor de acuerdo con la reivindicación 15, caracterizado en que el gas propulsor es TG134a, TG227 o una mezcla de estos.
- 15 17) Aerosol inhalable que contiene propulsor de acuerdo con la reivindicación 14, 15 o 16, caracterizado en que contiene opcionalmente uno o más de otros ingredientes seleccionados entre cosolventes, estabilizadores, tensoactivos, antioxidantes, lubricantes y medios para ajustar el pH.
- 20 18) Aerosol inhalable que contiene propulsor de acuerdo con una de las reivindicaciones 14 a 17, caracterizado en que puede contener hasta 5 por ciento en peso de la sustancia activa 1 y/o 2.
- 25 19) Composición farmacéutica de acuerdo con la reivindicación 9, caracterizada por que es una suspensión o solución inhalable libre de propulsor que contiene agua, etanol o una mezcla de agua y etanol como solvente.
- 30 20) Suspensión o solución inhalable de acuerdo con la reivindicación 19, caracterizada por que el pH es 2 - 7, preferiblemente 2 - 5.
- 21) Suspensión o solución inhalable de acuerdo con la reivindicación 20, caracterizada por que el pH se ajusta por medio de un ácido seleccionado entre ácido clorhídrico, ácido bromhídrico, ácido nítrico, ácido sulfúrico, ácido ascórbico, ácido cítrico, ácido málico, ácido tartárico, ácido maleico, ácido succínico, ácido fumárico, ácido acético, ácido fórmico y ácido propiónico o mezclas de estos.

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22) Suspensión o solución inhalable de acuerdo con una de las reivindicaciones 19 a 21, caracterizada por que contiene opcionalmente otros cosolventes y/o excipientes.

5 23) Suspensión o solución inhalable de acuerdo con la reivindicación 22, caracterizada por que contiene como ingredientes cosolventes que contienen grupos hidroxilo u otros grupos polares, por ejemplo alcoholes - particularmente alcohol isopropílico, glicoles - particularmente propilenglicol, polietilenglicol, polipropilenglicol, glicoléter, glicerol, 10 alcoholes de polioxietileno y ésteres de ácidos grasos de polioxietileno.

24) Suspensión o solución inhalable de acuerdo con una de las reivindicaciones 22 o 23, caracterizada por que contiene como 15 tensoactivos excipientes, estabilizantes, agentes complejantes, antioxidantes y/o preservativos, saborizantes, sales farmacológicamente aceptables y/o vitaminas.

25) Suspensión o solución inhalable de acuerdo con la reivindicación 24, 20 caracterizada por que contiene como agente complejante ácido acético a una sal de ácido edítico, preferiblemente edetato de sodio.

26) Suspensión o solución inhalable de acuerdo con la reivindicación 24 o 25, caracterizada por que contiene, como antioxidantes, compuestos 25 seleccionados entre ácido ascórbico, vitamina A, vitamina E y tocoferoles.

27) Suspensión o solución inhalable de acuerdo con la reivindicación 24, 25 o 26, caracterizada por que contiene como compuestos preservativos 30 seleccionados de cloruro de piridinio cetilo, cloruro de benzalconio, ácido benzoico y benzoatos.

28) Suspensión o solución inhalable de acuerdo con una de las reivindicaciones 22 a 27, caracterizada por que contiene, en adición a la 35 sustancia activa 1 y 2 y el solvente, solo cloruro de benzalconio y edetato de sodio.

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(54) Title: SYNERGISTIC COMBINATION COMPRISING ROFLUMILAST AND AN ANTICHOLINERGIC AGENT
SELECTED FROM IPRATROPIUM, OXITROPIUM AND TIOTROPIUM SALTS FOR THE TREATMENT OF RESPIRATORY
DISEASES

(57) Abstract: The invention relates to the administration of roflumilast and an anticholinergic agent selected from the group of an
ipratropium, oxitropium or tiotropium salt for the treatment of respiratory diseases.

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABogados	CONSIGNACION	BANCO POPULAR	050-00110-6	63769917	13/08/2007	39,640,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
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Novel approaches and targets for treatment of chronic obstructive pulmonary disease.

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Novel Approaches and Targets for Treatment of Chronic Obstructive Pulmonary Disease

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There is a driving need to develop new and effective treatments for COPD. Bronchodilators are now the mainstay of symptomatic therapy and a new long-acting anticholinergic bronchodilator, tiotropium bromide, is now in advanced clinical trials as a once daily dry powder inhaler. Several inflammatory mediators are involved in the chronic neutrophilic inflammation that typifies COPD, including leukotriene B₄ and interleukin 8, for which specific receptor antagonists have been developed. Since the inflammatory process in COPD is essentially steroid resistant, new antiinflammatory treatments are needed. Drugs that may be effective include phosphodiesterase 4 inhibitors, NF- κ B inhibitors, and interleukin 10. Inhibition of proteases is another approach and inhibitors of neutrophil elastase, cathepsins, and matrix metalloproteases are now in clinical development. Supply of endogenous antiproteases, such as α_1 -antitrypsin and secretory leukocyte protease inhibitors as recombinant proteins or by gene transfer, is also being explored. In future drugs that may stimulate alveolar repair might be developed, including retinoid receptor agonists and hepatic growth factor. Future directions will include earlier detection of disease, gene profiling to identify which smokers are at risk of COPD, and the development of noninvasive surrogate markers to monitor disease activity in order to monitor new therapies. Identification of genes that confer a risk for COPD in smokers may identify novel targets for drug development. **Barnes PJ. Novel approaches and targets for treatment of chronic obstructive pulmonary disease.**

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In sharp contrast to the developments in understanding and treating asthma, chronic obstructive pulmonary disease (COPD) has received little attention and there are few new drugs in development for this important disease. There are several possible reasons for the lack of drug development for this disease. First, COPD has been perceived as "untreatable" fixed air-flow obstruction. Second, patients with COPD have been treated with antiasthma therapies, but these drugs may be inappropriate in a disease with a different pathophysiology. Third, since in most patients COPD is the result of long-term heavy cigarette smoking it has been felt to be the "fault" of the patient. Fourth, there has been little interest in investigating the molecular and cell biology of COPD to identify new therapeutic targets, and there are no satisfactory animal models for early drug testing. Last, there are uncertainties about how to test new drugs for COPD, which may require long-term studies in large numbers of patients and surrogate markers (currently lacking) to monitor the short-term efficacy of new treatments. However, some progress is underway and there are several classes of drug that are now in preclinical and clinical development (1, 2).

NEW BRONCHODILATORS

Bronchodilators are the mainstay of current management of COPD, but fail to alter the progression of COPD. The major

advances have been in the development of long-acting bronchodilators. Both long-acting inhaled β_2 agonists (salmeterol and formoterol) and long-acting oral β_2 agonists (bambuterol) are useful for symptom control in COPD. Anticholinergics have been the most effective bronchodilators in COPD and there have been some important developments on this area. With the recognition that there are different subtypes of muscarinic receptor, there has been a search for more selective antagonists that inhibit M₁ receptors, which facilitate cholinergic reflexes, and M₃ receptors, which mediate bronchoconstriction and secretion of mucus, but avoid blockade of M₂ receptors localized to cholinergic nerve terminals that may increase acetylcholine release and therefore enhance cholinergic reflexes. It has been difficult to find selective M₃ antagonists, but drugs selective for M₁ and M₃ receptors, such as revatropate (UK-112,166), are in development for COPD (3). The most interesting anticholinergic drug in development is tiotropium bromide.

Tiotropium Bromide

Tiotropium bromide (Ba 679) is a quaternary ammonium compound similar in structure to ipratropium bromide, but with the unique property of kinetic selectivity, with rapid dissociation from M₂ receptors and slow dissociation from M₁ and M₃ receptors (4). However, its most interesting property is its long duration of action *in vitro* and *in vivo*. A single dose protects against cholinergic challenge for > 72 h and provides bronchodilation for > 24 h in patients with COPD (5). Tiotropium is in Phase III clinical trials as a once-daily dry powder inhalation and is more effective than ipratropium bromide given three times daily.

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SMOKING CESSATION

Quitting smoking is the only strategy that has so far been shown to reduce the rate of decline in lung function in patients with COPD. Less than one-third of patients are able to give up smoking even with support. Nicotine replacement therapy may help some patients and transdermal patches and inhaled nicotine may be the most effective delivery systems, but continued administration of the addictive principle of cigarettes is a poor approach to smoking cessation and nicotine itself theoretically may have adverse cardiovascular effects. Another approach is to develop nicotine receptor antagonists. The novel antidepressant bupropion (Zyban), which enhances central noradrenergic activity, helps smoking cessation. In a study of bupropion given for 7 wk, smoking cessation was 44% compared with only 19% in the placebo group (6).

MEDIATOR ANTAGONISTS

Several inflammatory mediators are likely to be involved in COPD, as many inflammatory cells and structural cells are activated and there is an ongoing inflammatory process, even in patients who have given up smoking. In asthma there are multiple mediators involved (7) and blocking the synthesis or receptors of a single mediator has almost always been unsuccessful in the development of useful therapies. However, some specific inhibitors, notably leukotriene D_4 (LTD_4) antagonists, have had some clinical benefit. It is clear that the profile of mediators of COPD is likely to be different from that of mediators of asthma, so that different drugs may be effective. Since COPD is characterized by a neutrophilic inflammation, attention has focused on mediators involved in recruitment and activation of neutrophils or on reactive oxygen species in view of the oxidative stress in COPD (Table 1).

LTB_4 Inhibitors

LTB_4 is a potent chemoattractant of neutrophils and is increased in the sputum of patients with COPD (8). It is probably derived from alveolar macrophages as well as neutrophils themselves and may be synergistic with interleukin 8 (IL-8). Selective LTB_4 receptor antagonists have now been developed. A potent LTB_4 antagonist (LY 293111) is ineffective against allergen challenge in patients with asthma, although it is interesting that it inhibits neutrophil recruitment into the airways during the late response, indicating the capacity to inhibit neutrophil chemotaxis in the airways (9). Several other potent LTB_4 antagonists are now in development (including SC-53228, CP-105,696, SB 201146, and BIIL284). LTB_4 is synthesized by 5'-lipoxygenase (5-LO), of which there are now several potent inhibitors. 5-LO inhibitors, such as zileuton, are now available in some countries for the treatment of asthma, since they also inhibit the synthesis of cysteinyl-leukotrienes, but it is not certain whether they are effective in COPD.

TABLE 1
MEDIATOR ANTAGONISTS FOR COPD

LTB_4 antagonists (LY 29311, SC-53228, CP-105,696, SB 201146, BIIL284)
5'-Lipoxygenase inhibitors (zileuton, Bay x1005)
Chemokine inhibitors
Interleukin 8 antagonists (SB 225002; CXCR2 antagonist)
MCP-1 antagonists
TNF inhibitors (monoclonal antibodies, soluble receptors, TNF convertase inhibitors)
Antioxidants (stable glutathione analogs, nitrones)
Prostanoid inhibitors (COX-2 inhibitors, thromboxane antagonists, isoprostane receptor antagonists)

Chemokine Inhibitors

Several chemokines are involved in neutrophil chemotaxis (10). These belong to the CXC family of chemokines and the most prominent member is IL-8, which is markedly elevated in the sputum of patients with COPD (11). Blocking antibodies to IL-8 and related chemokines inhibit certain types of neutrophilic inflammation in experimental animals, but may not be suited to long-term therapy in humans, so that there has been a search for IL-8 receptor antagonists. IL-8 attracts neutrophils via a high-affinity G protein-coupled receptor (CXCR1) and a common receptor shared by other members of the CXC family (CXCR2). A nonpeptide inhibitor of CXCR2 (SB225002) has been discovered by screening; it blocks the chemotactic response of neutrophils to IL-8 and other CXC chemokines, such as GRO- α , which are also increased in COPD (12).

Other chemokines may be involved in COPD. The recruitment of large numbers of activated macrophages (presumably from blood monocytes) may be dependent on CC chemokines such as monocyte chemoattractive peptides (MCP-1 to MCP-5), which activate CC receptors (CCR2) on macrophages (10).

Tumor Necrosis Factor α Inhibitors

Tumor necrosis factor α (TNF- α) levels are raised in the sputum of patients with COPD (11) and induces IL-8 in airway cells (13). Humanized TNF antibodies have been developed for clinical use and are effective in other chronic inflammatory disease, such as rheumatoid arthritis and inflammatory bowel disease. Soluble TNF receptors, which sequester released TNF, have also been developed and have entered clinical trials. There may be problems with long-term administration because of the development of blocking antibodies and repeated injections are inconvenient. TNF convertase, which prevents the release of active TNF- α , may be a more attractive target because it is possible to discover small molecule inhibitors, some of which are also matrix metalloprotease inhibitors.

Antioxidants

Oxidative stress is increased in patients with COPD, particularly during exacerbations, and reactive oxygen species contribute to its pathophysiology (14). Oxidants are present in cigarette smoke (10^{14} molecules per puff) and are produced endogenously by activated inflammatory cells, including neutrophils and alveolar macrophages. This suggests that antioxidants may be of use in the therapy of COPD. *N*-Acetylcysteine (NAC) provides cysteine for enhanced production of glutathione (GSH) and has antioxidant effects *in vitro* and *in vivo*. In clinical studies NAC reduces the number of exacerbations of COPD and in an uncontrolled study appeared to reduce the rate of decline in FEV₁ over a 2-yr period (15). Although epidemiological studies have linked COPD to poor intake of dietary antioxidants, such as vitamins C and E, there have been no controlled trials of these vitamins in COPD. It is likely that more effective antioxidants will be developed for clinical use in future. Spin-trap antioxidants, such as α -phenyl-*N*-tert-butyl nitron, are much more potent and inhibit intracellular reactive oxygen species formation by forming stable compounds (16).

Prostanoid Inhibitors

Oxidative stress may result in the nonenzymatic formation of prostanoid mediators, isoprostanes, directly from arachidonic acid without the involvement of cyclooxygenase. There is increased formation of isoprostanes in COPD (17). The most abundant isoprostane, 8-iso-prostaglandin $F_{2\alpha}$, is a potent con-

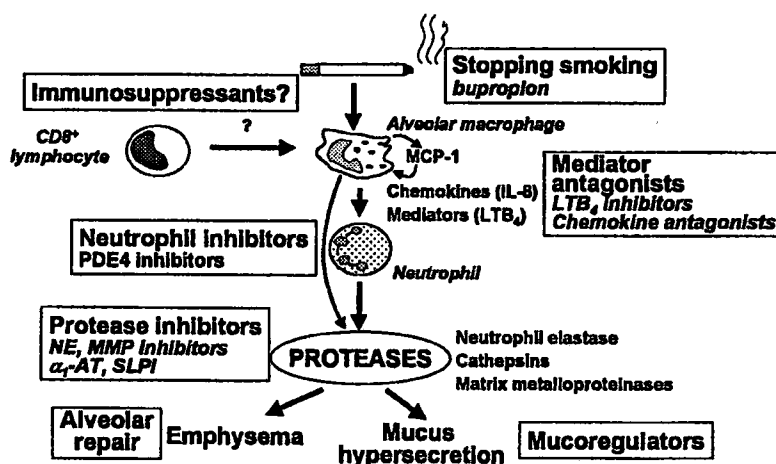


Figure 1. Targets for COPD therapy, based on current understanding of the inflammatory mechanisms. Cigarette smoke (and other irritants) activate macrophages in the respiratory tract that release neutrophil chemotactic factors, including interleukin 8 (IL-8) and leukotriene B₄ (LTB₄). Macrophages may recruit and activate other macrophages via other chemokines such as macrophage chemoattractant peptide 1 (MCP-1). These cells then release proteases, such as neutrophil elastase (NE) and matrix metalloproteinases (MMP), that break down connective tissue in the lung parenchyma, resulting in emphysema, and also stimulate hypersecretion of mucus. These enzymes are normally counteracted by protease inhibitors, including α_1 -antitrypsin (α_1 -AT) and secretory leukoprotease inhibitor (SLPI). Cytotoxic T cells (CD8⁺) may also be involved in the inflammatory cascade.

strictor of human airways *in vitro*, acting partly via stimulation of thromboxane prostanoid (TP) receptors (18). This suggests that thromboxane receptor antagonists, such as seratroast and Bay u3405, might be beneficial in COPD. The role of prostaglandins in COPD is unknown. In patients with bronchiectasis indomethacin has an inhibitory effect on chemotaxis of peripheral neutrophils, but no effect on neutrophils in sputum (19).

NEW ANTIINFLAMMATORY TREATMENTS

COPD is characterized by chronic inflammation of the respiratory tract, even in ex-smokers. Bronchoalveolar lavage and induced sputum in patients with COPD demonstrate increased numbers of neutrophils and macrophages (11). At sites of lung destruction in the lung parenchyma there are increased numbers of macrophages and CD8⁺ (cytotoxic) T lymphocytes and similar changes are seen in the airway walls (20). The mechanisms of the neutrophilic inflammation in COPD are not yet certain, but it is likely that neutrophil chemotactic factors are released into the airways from activated macrophages and possibly from epithelial cells and CD8⁺ T lymphocytes. It is important to elucidate more precisely the molecular and cellular mechanisms of COPD in order to identify novel targets for therapy. Our current superficial understanding of COPD suggests that there may be several approaches (Figure 1).

The Disappointment of Corticosteroid Therapy

Because there is chronic inflammation in COPD airways it was argued that inhaled corticosteroids might prevent the progression of the disease. The efficacy of corticosteroids in COPD is still uncertain, but this very uncertainty implied that they are of little benefit (21). There is little evidence that inhaled corticosteroids are beneficial in COPD, although there may be a minority of patients (~10%) who have some response to steroids and these patients should probably be regarded as having concomitant asthma. Several studies of the long-term use of inhaled corticosteroids in slowing disease progression have been reported, confirming that there is no significant

benefit. This might be predicted by the demonstration that neither inhaled nor oral corticosteroids have any significant effect on neutrophil counts, granule proteins, or inflammatory cytokines in induced sputum (22). A trivial inhibitory effect on neutrophil chemotaxis and neutrophil elastase activity has been reported, but in another study there was no effect on proteases or antiproteases in induced sputum. This is in marked contrast to the efficacy of corticosteroids in asthma and their ability to reduce eosinophil counts in induced sputum (22). However, corticosteroids are effective in treating acute exacerbations in COPD, presumably via some as yet undefined antiinflammatory effect (23), but possibly related to the fact that there is an increase in eosinophils in the airways during acute exacerbations of COPD. The disappointing action of corticosteroids in COPD suggests that novel types of nonsteroidal antiinflammatory treatment may be needed. One of the reasons that corticosteroids may be ineffective is that they are usually ineffective in neutrophilic inflammation and prolong the survival of neutrophils by delaying apoptosis. Furthermore, corticosteroids fail to inhibit the elevated IL-8 and TNF- α levels in induced sputum in patients with COPD, although synthesis of these cytokines would be expected (22). This may indicate that there is an element of corticosteroid resistance in COPD that may be a part of the disease process.

TABLE 2
NEW ANTIINFLAMMATORY DRUGS FOR COPD

Phosphodiesterase 4 inhibitors (SB 207499, CP 80633, CDP-840)
NF- κ B inhibitors (I- κ B kinase inhibitors, I- κ B- α gene transfer)
Adhesion molecule inhibitors (anti-CD11/CD18, anti-ICAM-1, E-selectin inhibitors)
Prostaglandin E analogs (misoprostil, butaprost)
Interleukin 10
p38 MAP kinase inhibitors (SB 203580, SB 220025, RWJ 67657)
Colchicine
Macrolide antibiotics (erythromycin, clarithromycin, roxithromycin)

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There are several new approaches to antiinflammatory treatment in COPD (Table 2).

Phosphodiesterase 4 Inhibitors

Inhibition of phosphodiesterases (PDEs) increases cyclic AMP content of neutrophils, resulting in reduced chemotaxis, activation, degranulation, and adherence (24). Theophylline is a weak and nonselective PDE inhibitor and has inhibitory effects on neutrophil function *in vitro*. Unlike corticosteroid treatment in patients with COPD, theophylline reduces neutrophil counts in induced sputum (25). The predominant isoenzyme in inflammatory cells is PDE4, and several PDE4 inhibitors are now in clinical development for asthma. PDE4 inhibitors also inhibit the function of macrophages and CD8⁺ T lymphocytes, which are also involved in the inflammatory process in COPD (Figure 2). Many of the first-generation PDE4 inhibitors have been limited by side effects, particularly nausea. In second-generation PDE4 inhibitors, such as SB 207499, this may be less of a problem and a trial of this drug has shown an improvement in lung function and symptoms of patients with moderate COPD.

NF- κ B Inhibitors

The transcription factor NF- κ B regulates the expression of IL-8 and TNF- α and its inhibition therefore inhibits neutrophilic inflammation (26). There are several possible approaches to inhibition of NF- κ B, including gene transfer of the inhibitor of NF- κ B (I- κ B), a search for inhibitors of I- κ B kinases (IKK), NF- κ B-inducing kinase (NIK), and I- κ B ubiquitin ligase, which regulate the activity of NF- κ B, and the development of drugs that inhibit the degradation of I- κ B (27). One concern about this approach is that effective inhibitors of NF- κ B may result in immune suppression and impair host defenses, since knock-out mice who lack NF- κ B proteins succumb to septicemia.

Adhesion Molecule Blockers

Neutrophil recruitment into the lungs and respiratory tract is dependent on adhesion molecules expressed on neutrophils and endothelial cells in the pulmonary and bronchial circulations. Neutrophil adhesion in response to chemotactic factors is characterized by expression of the β_2 integrins CD11a/CD18 (LFA-1) and CD11b/CD18 (Mac-1) on the surface of the neutrophil and their interaction with their counterreceptors, including intercellular adhesion molecule 1 (ICAM-1), on endothelial cells. E-selectin on endothelial cells also interacts

with sialyl-Lewis^x on neutrophils. Bronchial biopsies of patients with COPD have demonstrated increased expression of E-selectin on vessels and ICAM-1 on epithelial cells (28). Drugs that interfere with these adhesion molecules should therefore inhibit neutrophil inflammation in COPD. Monoclonal antibodies to CD18, ICAM-1, and E-selectin inhibit neutrophil accumulation in animal models of lung inflammation. Small molecule inhibitors of adhesion molecules are now in clinical development. However, there are concerns about this therapeutic approach for a chronic disease, as an impaired neutrophilic response may increase the susceptibility to infection. Indeed, a congenital deficiency of β_2 integrins results in leukocyte adhesion deficiency syndrome, characterized by recurrent septicemia.

Interleukin 10

IL-10 is a cytokine with a wide spectrum of antiinflammatory actions. It inhibits the secretion of TNF- α and IL-8 from macrophages, but tips the balance in favor of antiproteases by decreasing the expression of matrix metalloproteinases, while increasing the expression of tissue inhibitors of matrix metalloproteinases (TIMPs) (29). IL-10 is currently in clinical trials for other chronic inflammatory diseases (inflammatory bowel disease, rheumatoid arthritis, and psoriasis), including patients with steroid resistance. Treatment with daily injections of IL-10 over several weeks has been remarkably well tolerated. IL-10 may have therapeutic potential in COPD, especially if a selective activator of IL-10 receptors or signal transduction pathways can be developed. Some currently available drugs, including theophylline and PDE4 inhibitors, may also increase the secretion of IL-10.

p38 MAP Kinase Inhibitors

Mitogen-activated protein (MAP) kinases play a key role in chronic inflammation and several complex enzyme cascades have not been defined (30). One of the p38 MAP kinase pathways is involved in secretion of cytokines, including IL-8 and TNF- α . Nonpeptide inhibitors of p38 MAP kinase, such as SB 203580, SB 220025, and RWJ 67657, have now been developed and these drugs have a broad range of antiinflammatory effects.

Other Neutrophil Inhibitors

Prostaglandin E₂ (PGE₂) is a potent inhibitor of the oxidative burst in neutrophils and its effects are mediated via EP₂ receptors. Selective EP₂ agonists, such as misoprostil and butaprost, may therefore be effective in suppressing neutrophil activation, but have not been studied in COPD.

Colchicine potently inhibits neutrophil activation, enzyme release, and chemotaxis by disrupting cytoskeletal microtubule structure. A controlled trial of colchicine in COPD showed some reduction in neutrophil elastase activity (31).

PROTEASE INHIBITORS

There is compelling evidence for an imbalance between proteases that digest elastin (and other structural proteins) and antiproteases that protect against this in COPD. This suggests that either inhibiting these proteolytic enzymes or increasing antiproteases may be beneficial and theoretically should prevent the progression of airflow obstruction in COPD (Table 3). Considerable progress has been made in identifying the enzymes involved in elastolytic activity in emphysema and in characterizing the endogenous antiproteases that counteract this activity.

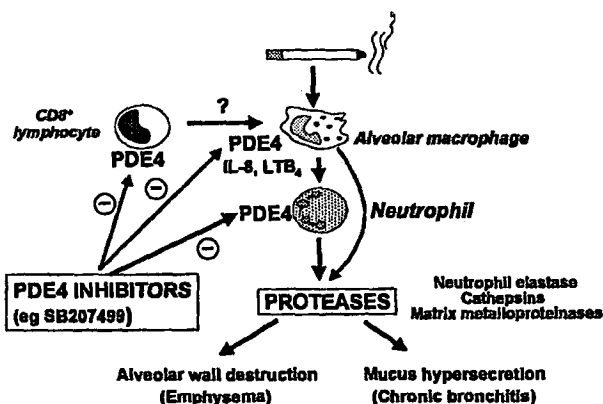


Figure 2. Effect of phosphodiesterase 4 (PDE4) inhibitors on the inflammatory process in COPD. PDE4 inhibitors inhibit the activation of macrophages, neutrophils, and CD8⁺ T lymphocytes.

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TABLE 3
PROTEASE INHIBITORS FOR COPD

Neutrophil elastase inhibitors (ICI 200355, ONO-5046, MR-889, I. 658,758)
Cathepsin inhibitors (suramin)
Matrix metalloproteinase inhibitors (batimastat, marimastat, selective MMP inhibitors)
α_1 -Antitrypsin (purified, human recombinant, gene transfer)
Secretory leukoprotease inhibitor (human recombinant, gene transfer)
Elafin

Neutrophil Elastase Inhibitors

Neutrophil elastase (NE), a neutral serine protease, is a major constituent of lung elastolytic activity. In addition, it potently stimulates secretion of mucus and induces IL-8 release from epithelial cells and therefore may perpetuate the inflammatory state. This has led to a search for neutrophil elastase inhibitors. Peptide NE inhibitors, such as ICI 200355, and non-peptide inhibitors, such as ONO-5046, have been developed and have high potency (32, 33). These drugs inhibit neutrophil elastase-induced lung injury in experimental animals, whether given by inhalation or systemically (32), and inhibit neutrophil elastase-induced secretion of mucus *in vitro*. There are few clinical studies of neutrophil elastase in COPD. A clinical study of oral MR889 administered for 4 wk showed no overall effect on plasma elastin-derived peptides or urinary desmosine (markers of elastolytic activity), but these may not be sensitive markers (34). These inhibitors act extracellularly and may not inhibit the enzyme at the site of release when neutrophils adhere to connective tissue. Intracellular NE inhibitors might therefore be more effective, at least in preventing lung destruction. Although neutrophil elastase is likely to be the major mechanism mediating elastolysis in patients with α_1 -antitrypsin (α_1 -AT) deficiency, it may well not be the major elastolytic enzyme in smoking-related COPD, and it is important to consider other enzymes as targets for inhibition.

Cathepsin Inhibitors

Neutrophil elastase is not the only proteolytic enzyme secreted by neutrophils. Cathepsin G and proteinase 3 have elastolytic activity and may need to be inhibited together with neutrophil elastase. Cathepsins (cathepsins B, L, and S) are also released from macrophages. Suramin, a hexasulfonated naphthylurea that has been used as an antitumor drug, is a potent inhibitor of cathepsin G, proteinase 3, and neutrophil elastase (35). Novel and more specific cathepsin inhibitors and now in development.

Matrix Metalloproteinase Inhibitors

Matrix metalloproteinases (MMPs) are a group of more than 20 closely related endopeptidases that are capable of degrading all of the components of the extracellular matrix of lung parenchyma, including elastin, collagen, proteoglycans, laminin, and fibronectin. They are produced by neutrophils, alveolar macrophages, and airway epithelial cells. Increased levels of collagenase (MMP-1) and gelatinase B (MMP-9) have been detected in bronchoalveolar lavage fluid of patients with emphysema. Lavaged macrophages from patients with emphysema express more MMP-9 and MMP-1 than do cells from control subjects, suggesting that these cells, rather than neutrophils, may be the major cellular source (36). Alveolar macrophages also express a unique MMP, macrophage metalloelastase (MMP-12) (37). MMP-12 knockout mice do not develop emphysema and do not show the expected increases in lung macrophages after long-term exposure to cigarette smoke

(38). Tissue inhibitors of metalloproteinases (TIMPs) are endogenous inhibitors of these potent enzymes and several TIMPs have now been characterized. There are several approaches to inhibiting MMPs (39). One approach is to enhance the secretion of TIMPs and another is to inhibit the induction of MMPs in COPD. MMPs may show increased expression with cigarette smoking through induction in response to inflammatory cytokines, oxidants, and other enzymes, such as neutrophil elastase. It may be possible to prevent this induction with specific transcription inhibitors. Another approach is to develop specific enzyme inhibitors. Tetracyclines and hydroxamates, such as batimastat (BB-94) and the orally active marimastat (BB-2516), are nonselective MMP inhibitors. Side effects of such drugs may be a problem in long-term use, however. More selective inhibitors of individual MMPs, such as MMP-9 and MMP-12, are now in development and are likely to be better tolerated in chronic therapy. However, it is still not clear whether there is one predominant MMP in COPD or whether a broad-spectrum inhibitor will be necessary.

α_1 -Antitrypsin

The association of α_1 -AT deficiency with early onset emphysema suggested that this endogenous inhibitor of NE may be of therapeutic benefit in COPD. Cigarette smoking inactivates α_1 -AT, resulting in unopposed activity of NE and cathepsins. Extraction of α_1 -AT from human plasma is expensive and extracted α_1 -antitrypsin is available only in a few countries. This treatment must be given intravenously and has a half-life of only 5 d. This has led to the development of inhaled formulations, but these are inefficient and expensive (40). Recombinant α_1 -AT with amino acid substitutions to increase stability may result in a more stable product. Gene therapy is another possibility, using an adenovirus vector or liposomes, but there have been major problems in developing efficient delivery systems. There is a particular problem with gene transfer in α_1 -AT deficiency in that large amounts of protein (1–2 g) need to be synthesized each day. Human α_1 -AT has now been available for more than 10 yr, but even in patients with severe α_1 -AT deficiency and emphysema there is only a marginal effect on the rate of decline in FEV₁ (41). There is no evidence that α_1 -AT treatment would halt the progression of COPD and emphysema in patients who have normal plasma concentrations.

Serpins

Other serum protease inhibitors (serpins), such as elafin, may also be important in counteracting elastolytic activity in the lung. Elafin, an elastase-specific inhibitor, is found in bronchoalveolar lavage and is synthesized by epithelial cells in response to inflammatory stimuli (42). Serpins may not be able to inhibit NE at the sites of elastin destruction, owing to tight adherence of the inflammatory cell to connective tissue. Furthermore, these proteins may become inactivated by the inflammatory process and the action of oxidants, so that they may not be able to adequately counteract elastolytic activity in the lung unless used in conjunction with other therapies.

Secretory Leukoprotease Inhibitor

Secretory leukoprotease inhibitor (SLPI) is a 12-kD serpin that appears to be a major inhibitor of elastase activity in the airways. It is secreted by epithelial cells (42) and its secretion is increased by corticosteroids *in vitro* (43). *In vitro* recombinant human SLPI is more effective at inhibiting neutrophil-mediated proteolysis than α_1 -AT (44). Recombinant human SLPI given by aerosolization increases anti-neutrophil elastase

activity in epithelial lining fluid for more than 12 h, indicating potential therapeutic use (45).

MUCOREGULATORS

Increased secretion of mucus is found in all patients who smoke heavily, irrespective of airflow obstruction. However, epidemiological data suggest that hypersecretion of mucus is significantly associated with a more rapid decline in FEV₁ and increased hospitalization of patients with COPD (46). This suggests that it may be important to develop drugs that inhibit the hypersecretion of mucus, although it is important to find drugs that do not suppress normal mucous secretion or impair mucociliary clearance. There are several types of mucoregulatory drug in development.

Tachykinin Antagonists

Tachykinins are potent stimulants of mucous secretion from submucosal glands and goblet cells in human and animal airways and act via NK₁ receptors. In animal studies cigarette smoke induces airway secretion of mucus via release of tachykinins from sensory nerves through a local axon reflex mechanism (47). NK₁ antagonists markedly inhibit neurogenic secretion of mucus and may therefore have potential as mucoregulators in cigarette smoke-induced chronic bronchitis. Several potent nonpeptide NK₁ receptor antagonists, such as CP-99,994 and SR 140333, are now in clinical development, and while it is unlikely that they will be useful in asthma, they might have a role as regulators of hypersecretion of mucus in COPD.

Sensory Neuropeptide Release Inhibitors

Another approach to blocking tachykinin-mediated effects is to inhibit the release of tachykinins from sensory nerve endings, via activation of prejunctional receptors (48). Of these receptors, μ -opioid receptors are most effective and the μ -opioid agonist morphine potentially inhibits cigarette smoke-induced secretion of mucus in animal airways. In human airways *in vitro* morphine inhibits secretion of mucus activated via stimulation of sensory nerves. While morphine itself may not be useful as a therapeutic agent because of addiction, peripherally acting opioid agonists that do not cross the blood-brain barrier, such as BW443, might be of use.

Many prejunctional receptors appear to operate via the opening of a common potassium (K⁺) channel, suggesting that K⁺ channel openers may be useful in blocking the secretion of mucus. Openers of ATP-dependent K⁺ channels, such as levromakalim, have an inhibitory effect on cigarette smoke-induced secretion of mucus in animals.

Mediator and Enzyme Inhibitors

Many mediators stimulate secretion of mucus from submucosal glands and/or goblet cells and may therefore contribute to increased secretion of mucus in COPD. It is unlikely, however, that any mediator antagonists (e.g., anti-leukotrienes) would have a major effect on secretion of mucus. NE and other proteases are potent stimulants of submucosal gland and goblet cell secretion, suggesting that protease inhibitors may have inhibitory effects on secretion of mucus, as well as inhibiting lung destruction. Inhalation of the cyclooxygenase inhibitor indomethacin is reported to reduce hypersecretion of mucus in patients with COPD (49), but long-term trials of COX inhibitors have not yet been undertaken.

MUC Gene Suppressors

Nine MUC genes that encode mucin proteins have already been cloned and many are expressed in human airways. MUC5AC

(particularly in goblet cells), MUC5B (particularly in submucosal glands), MUC4, and MUC8 appear to be important in airway mucus. MUC5AC may be upregulated by inflammatory cytokines and inhibited by glucocorticoids (50). It is possible that drugs may be developed that inhibit the abnormally increased expression of MUC genes in COPD, while preserving baseline secretion of MUC2. Such drugs, other than corticosteroids, have not yet been developed.

Mucolytic Agents

Several drugs were developed to reduce viscosity of mucus, thus aiding clearance from the respiratory tract. These drugs include cysteine derivatives such as N-acetylcysteine, methylecysteine, and carbocysteine, which are effective in reducing the viscosity of mucus *in vitro*, but there is little convincing evidence that they increase clearance of mucus in patients with COPD. DNase also reduces sputum viscosity, particularly when sputum is infected, as DNA is a major determinant of sputum viscosity. Although nebulized recombinant human DNase (dornase alfa) appears to improve the rheological properties of mucus in patients with cystic fibrosis, this has not been reported in COPD. It is possible that more effective mucolytic agents will be developed in future.

Macrolide Antibiotics

Erythromycin inhibits mucin secretion from human airways *in vitro* and appears to be interactive with corticosteroids (51). This property does not appear to be related to its antibiotic activity and is consistent with other studies demonstrating an inhibitory action of erythromycin on cell secretion. The molecular mechanisms involved in these effects need to be defined and controlled studies in COPD may be indicated.

ALVEOLAR REPAIR

Since a major mechanism of airway obstruction in COPD is loss of elastic recoil due to proteolytic destruction of lung parenchyma, it seems unlikely that this could be reversible by drug therapy, although it might be possible to reduce the rate of progression by preventing the inflammatory and enzymatic disease process. It is even possible that drugs might be developed that will stimulate regrowth of alveoli. Retinoic acid increases the number of alveoli in rats and, remarkably, reverses the histological and physiological changes induced by elastase treatment (52). It is not certain whether such alveolar proliferation is possible in adult human lungs, however. Retinoic acid activates intracellular retinoic acid receptors, which act as transcription factors to regulate the expression of many genes. The molecular mechanisms involved, and whether this can be extrapolated to humans, are not yet known. Several retinoic acid receptor subtype agonists have now been developed that may have a greater selectivity for this effect.

Hepatocyte growth factor (HGF, scatter factor) has a major effect on the growth of alveoli in fetal lung (53) and it is possible that in future drugs might be developed that switch on responsiveness to HGF in adult lung or mimic the action of HGF.

ROUTE OF DELIVERY

Bronchodilators are currently given via inhalers, either metered dose inhalers or dry powder inhalers, that have been optimized to deliver drugs to the respiratory tract in asthma. But in emphysema the inflammatory process takes place in the lung parenchyma. This implies that if a drug is to be delivered by inhalation it should have a lower mass median diameter, so that there is preferential deposition in the lung periphery. It

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may be more appropriate to give therapy parenterally, as it will need to reach the lung parenchyma via the pulmonary circulation, but parenteral administration may increase the risk of systemic side effects.

FUTURE DIRECTIONS

New drugs for the treatment of COPD are needed. While preventing and quitting smoking is the obvious preferred approach, this has proved to be difficult in the majority of patients. In addition, it is likely that the inflammatory process initiated by cigarette smoking may continue even when smoking has ceased. Furthermore, approximately 10% of patients with COPD are nonsmokers. COPD may be due to other environmental factors (pollutants, passive smoking, other inhaled toxins) or due to developmental changes in the lungs.

Genetic Risk Factors for COPD

It is important to identify the factors that determine why only 10–20% of smokers develop COPD. So far this is little understood, although it is likely that genetic factors are important (54). A clearly established genetic risk factor for COPD is the ZZ allele of the α_1 -antitrypsin gene, although heterozygotes may be at slightly increased risk. There is also an association with a polymorphism of the TNF- α gene (*TNF2*) that is associated with greater inducibility of TNF- α . There are also weak associations with α_1 -antichymotrypsin, α_2 -macroglobulin, and vitamin D-binding protein. A polymorphism in the gene for an enzyme, microsomal epoxide hydrolase, that is responsible for metabolism of reactive epoxide intermediates, which may be generated in tobacco smoke, has been associated with a four- to fivefold increased risk of COPD and emphysema. It is likely that many other genetic polymorphisms will be discovered that will confer risk on smokers for the development of COPD and emphysema, so that it will eventually be possible to identify at-risk patients and focus more effective therapies on these patients before lung function becomes too impaired.

Identification of Novel Therapeutic Targets

Identification of genes that predispose to the development of COPD in smokers may identify novel therapeutic targets. Powerful techniques, including high-density oligonucleotide arrays (gene chips), are able to identify multiple polymorphisms; differential display may identify the expression of novel genes and proteomics of novel proteins expressed.

Early Detection of Disease

Since at the moment COPD is irreversible and slowly progressive it will become ever more important, as effective therapies emerge, to identify early cases before symptoms develop.

Surrogate Markers

Several drugs now in development may be useful in COPD. These include LTB₄ antagonists and 5-LO inhibitors, PDE4 inhibitors, new antioxidants, and NE and MMP inhibitors. It will be difficult to demonstrate the efficacy of such treatments, as determination of the effect of any drug on the rate of decline in lung function will require large studies over at least 2 yr. There is an urgent need to develop surrogate markers, such as in the analysis of sputum parameters (cells, mediators, enzymes), that may predict the clinical usefulness of such drugs. More research on the basic cellular and molecular mechanism of COPD and emphysema is urgently needed to aid the logical development of new therapies for this common and important disease for which no effective preventative treatments currently exist.

References

- Barnes, P. J. 1998. New therapies for chronic obstructive pulmonary disease. *Thorax* 53:137–147.
- Barnes, P. J. 1998. Chronic obstructive pulmonary disease: new opportunities for drug development. *Trends Pharmacol. Sci.* 19:415–423.
- Alabaster, V. A. 1997. Discovery and development of selective M₃ antagonists for clinical use. *Life Sci.* 60:1053–1060.
- Barnes, P. J., M. G. Belvisi, J. C. W. Mak, E. Haddad, and B. O'Connor. 1995. Tiotropium bromide (Ba 679 BR), a novel long-acting muscarinic antagonist for the treatment of obstructive airways disease. *Life Sci.* 56:853–859.
- Maesen, F. P. V., J. J. Smeets, T. J. M. Sledsers, F. D. M. Wald, and J. P. G. Cornelissen. 1995. Tiotropium bromide, a new long-acting antimuscarinic bronchodilator: a pharmacodynamic study in patients with chronic obstructive pulmonary disease (COPD). *Eur. Respir. J.* 8: 1506–1513.
- Hurt, R. D., D. P. L. Sachs, E. D. Glover, K. P. Offord, J. A. Johnston, L. C. Dale, M. A. Khayrallah, R. Schroeder, P. N. Glover, C. R. Sullivan, I. T. Croghan, and P. M. Sullivan. 1997. A comparison of sustained-release bupropion and placebo for smoking cessation. *N. Engl. J. Med.* 337:1195–1202.
- Barnes, P. J., K. F. Chung, and C. P. Page. 1998. Inflammatory mediators of asthma: an update. *Pharmacol. Rev.* 50:515–596.
- Zakrzewski, J. T., N. C. Barnes, J. F. Costello, and P. J. Piper. 1987. Lipid mediators in cystic fibrosis and chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 136:779–782.
- Evans, D. J., P. J. Barnes, L. J. Couliby, S. M. Spaethe, E. C. van Alstyne, P. A. Pechous, M. I. Mitchell, and B. J. O'Connor. 1996. The effect of a leukotriene B₄ antagonist LY293111 on allergen-induced responses in asthma. *Thorax* 51:1178–1184.
- Luster, A. D. 1998. Chemokines—chemotactic cytokines that mediate inflammation. *N. Engl. J. Med.* 338:436–445.
- Keatings, V. M., P. D. Collins, D. M. Scott, and P. J. Barnes. 1996. Differences in interleukin-8 and tumor necrosis factor- α in induced sputum from patients with chronic obstructive pulmonary disease or asthma. *Am. J. Respir. Crit. Care Med.* 153:530–534.
- White, J. R., J. M. Lee, P. R. Young, R. P. Hertzberg, A. J. Jurewicz, M. A. Chaikin, K. Widdowson, J. J. Foley, L. D. Martin, D. E. Griswold, and H. M. Sarau. 1998. Identification of a potent, selective non-peptide CXCR2 antagonist that inhibits interleukin-8-induced neutrophil migration. *J. Biol. Chem.* 273:10095–10098.
- Kwon, O. J., B. T. Au, P. D. Collins, I. M. Adcock, J. C. Mak, R. A. Robins, J. M. Baranluk, K. F. Chung, and P. J. Barnes. 1994. Tumor necrosis factor-induced interleukin 8 expression in cultured human epithelial cells. *Am. J. Physiol.* 11:L398–L405.
- Repine, J. E., A. Bast, and I. Lankhorst. 1997. Oxidative stress in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* 156:341–357.
- Lundback, B., M. Lindstrom, E. Jonsson, S. Anderson, and C. van Herwaarden. 1995. Effect of N-acetylcysteine on the decline in lung function in patients with COPD. *Eur. Respir. J.* 5(Suppl. 15):895.
- Thomas, C. E., D. F. Ohlweiler, A. A. Carr, T. R. Nieduzak, D. A. Hay, G. Adams, R. Vaz, and R. C. Bernotas. 1996. Characterization of the radical trapping activity of a novel series of cyclic nitron spin traps. *J. Biol. Chem.* 271:3097–3104.
- Pratico, D., S. Basili, M. Vieri, C. Cordova, F. Violi, and G. A. Fitzgerald. 1998. Chronic obstructive pulmonary disease is associated with an increase in urinary levels of isoprostane F_{2a}-III, an index of oxidant stress. *Am. J. Respir. Crit. Care Med.* 158:1709–1714.
- Kawikova, I., P. J. Barnes, T. Takahashi, S. Tadjkarimi, M. H. Yacoub, and M. G. Belvisi. 1996. 8-Epiprostaglandin F_{2a}, a novel non-cyclooxygenase derived prostaglandin, is a potent constrictor of guinea-pig and human airways. *Am. J. Respir. Crit. Care Med.* 153:590–596.
- Llewellyn Jones, C. G., M. M. Johnson, J. L. Mitchell, A. Pye, V. C. Okafor, S. L. Hill, and R. A. Stockley. 1995. In vivo study of indomethacin in bronchiectasis: effect on neutrophil function and lung secretion. *Eur. Respir. J.* 8:1479–1487.
- Jeffery, P. K. 1998. Structural and inflammatory changes in COPD: a comparison with asthma. *Thorax* 53:129–136.
- McEvoy, C. E., and D. E. Niewoehner. 1997. Adverse effects of corticosteroid therapy for COPD: a critical review. *Chest* 111:732–743.
- Keatings, V. M., A. Jatakanon, Y. M. Worsdell, and P. J. Barnes. 1997. Effects of inhaled and oral glucocorticoids on inflammatory inducers in asthma and COPD. *Am. J. Respir. Crit. Care Med.* 155:542–548.
- Thompson, W. H., C. P. Nielson, P. Carvalho, N. B. Charan, and J. J. Crowley. 1998. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am. J. Respir. Crit. Care Med.* 154:407–412.

165
165

24. Nielson, C. P., R. E. Vestal, R. J. Sturm, and P. R. Heasli. 1990. Effect of selective phosphodiesterase inhibitors on the polymorphonuclear leukocyte respiratory burst. *J. Allergy Clin. Immunol.* 86:801-808.
25. Culpitt, S., W. Maziak, S. Loukides, A. Keller, and P. J. Barnes. 1997. Effect of theophylline on induced sputum inflammatory indices in COPD patients (abstract). *Am. J. Respir. Crit. Care Med.* 157:A797.
26. Barnes, P. J., and M. Karin. 1997. Nuclear factor- κ B: a pivotal transcription factor in chronic inflammatory diseases. *N. Engl. J. Med.* 336:1066-1071.
27. Barnes, P. J., and I. M. Adcock. 1997. NF- κ B: a pivotal role in asthma and a new target for therapy. *Trends Pharmacol. Sci.* 18:46-50.
28. Di Stefano, A., P. Maestrelli, A. Roggeri, G. Turato, S. Calabro, A. Potena, C. E. Mapp, A. Ciaccia, L. Covacev, and L. M. Fabbri. 1994. Up-regulation of adhesion molecules in the bronchial mucosa of subjects with chronic obstructive bronchitis. *Am. J. Respir. Crit. Care Med.* 149:803-810.
29. Lacraz, S., L. P. Nicod, R. Chicheportiche, H. G. Welgus, and J. M. Dayer. 1995. IL-10 inhibits metalloproteinase and stimulated TIMP-1 production in human mononuclear phagocytes. *J. Clin. Invest.* 96:2304-2310.
30. Karin, M. 1998. Mitogen-activated protein kinase cascades as regulators of stress responses. *Ann. N.Y. Acad. Sci.* 851:139-146.
31. Cohen, A. B., W. Girard, J. McLarty, B. Starcher, M. Stevens, D. S. Fair, D. Davis, H. James, J. Rosenbloom, and U. Kuch. 1990. A controlled trial of colchicine to reduce the elastase load in the lungs of cigarette smokers with chronic obstructive pulmonary disease. *Am. Rev. Respir. Dis.* 142:63-72.
32. Williams, J. C., R. C. Falcone, C. Knee, R. L. Stein, A. M. Strimpler, B. Reaves, R. E. Giles, and R. D. Krell. 1991. Biologic characterization of ICI 200,880 and ICI 200,355, novel inhibitors of human neutrophil elastase. *Am. Rev. Respir. Dis.* 144:875-883.
33. Kawabata, K., M. Suzuki, M. Sugitani, K. Imaki, M. Toda, and T. Miyamoto. 1991. ONO-5046, a novel inhibitor of human neutrophil elastase. *Biochem. Biophys. Res. Commun.* 177:814-820.
34. Luisetti, M., C. Sturani, D. Sella, E. Madonini, V. Galavotti, G. Bruno, V. Peona, U. Kuch, G. Dagnino, J. Rosenbloom, B. Starcher, and C. Grassi. 1996. MR889, a neutrophil elastase inhibitor, in patients with chronic obstructive pulmonary disease: a double-blind, randomized, placebo-controlled clinical trial. *Eur. Respir. J.* 9:1482-1486.
35. Cadene, M., J. Duranton, A. North, M. Si Tahar, M. Chignard, and J. G. Bleth. 1997. Inhibition of neutrophil serine proteinases by suramin. *J. Biol. Chem.* 272:9950-9955.
36. Finlay, G. A., L. R. O'Driscoll, K. J. Russell, E. M. D'Arcy, J. B. Master-son, M. X. FitzGerald, and C. M. O'Connor. 1997. Matrix metalloproteinase expression and production by alveolar macrophages in emphysema. *Am. J. Respir. Crit. Care Med.* 156:240-247.
37. Shapiro, S. G., D. K. Kobayashi, and T. J. Ley. 1993. Cloning and characterization of a unique elastolytic metalloproteinase produced by human alveolar macrophages. *J. Biol. Chem.* 268:23824-23829.
38. Hautamaki, R. D., D. K. Kobayashi, R. M. Senior, and S. D. Shapiro. 1997. Requirement for macrophage metalloelastase for cigarette smoke-induced emphysema in mice. *Science* 277:2002-2004.
39. Cawston, T. E. 1996. Metalloproteinase inhibitors and the prevention of connective tissue breakdown. *Pharmacol. Ther.* 70:163-182.
40. Hubbard, R. C., and R. G. Crystal. 1990. Strategies for aerosol therapy of alpha 1-antitrypsin deficiency by the aerosol route. *Lung* 168(Suppl.): 565-578.
41. Seersholm, N., M. Wencker, N. Banik, K. Viskum, A. Dirksen, A. Kok-Jensen, and N. Konietzko. 1997. Does antitrypsin augmentation therapy slow the annual decline in FEV₁ in patients with severe hereditary antitrypsin deficiency. *Eur. Respir. J.* 10:2260-2263.
42. Sallenave, J. M., J. Shulmann, J. Crossley, M. Jordana, and J. Gauldie. 1994. Regulation of secretory leukocyte proteinase inhibitor (SLPI) and elastase-specific inhibitor (ESI/elafin) in human airway epithelial cells by cytokines and neutrophilic enzymes. *Am. J. Respir. Cell Mol. Biol.* 11:733-741.
43. Abbinante-Nissen, J. M., L. G. Simpson, and G. D. Leikauf. 1995. Corticosteroids increase secretory leukocyte protease inhibitor transcript levels in airway epithelial cells. *Am. J. Physiol.* 12:L601-L606.
44. Llewellyn Jones, C. G., D. A. Lomas, and R. A. Stockley. 1994. Potential role of recombinant secretory leukoprotease inhibitor in the prevention of neutrophil mediated matrix degradation. *Thorax* 49:567-572.
45. McElvaney, N. G., B. Doujaji, M. J. Moan, M. R. Burnham, M. C. Wu, and R. G. Crystal. 1993. Pharmacokinetics of recombinant secretory leukoprotease inhibitor aerosolized to normals and individuals with cystic fibrosis. *Am. Rev. Respir. Dis.* 148:1056-1060.
46. Vestbo, J., E. Prescott, and P. Lange. 1996. Association of chronic mucus hypersecretion with FEV₁ decline and chronic obstructive pulmonary disease morbidity: Copenhagen City Heart Study Group. *Am. J. Respir. Crit. Care Med.* 153:1530-1535.
47. Kuo, H., P. J. Barnes, and D. F. Rogers. 1992. Cigarette smoke-induced airway goblet cell secretion: dose dependent differential nerve activation. *Am. J. Physiol.* 7:L161-L167.
48. Barnes, P. J., M. G. Belvisi, and D. F. Rogers. 1990. Modulation of neurogenic inflammation: novel approaches to inflammatory diseases. *Trends Pharmacol. Sci.* 11:185-189.
49. Tamaoki, J., A. Chiyotani, S. Kobayashi, T. Noritaka, T. Kanemura, and T. Takizawa. 1992. Effect of indomethacin on bronchorrhea with chronic bronchitis, diffuse panbronchiolitis or bronchiectasis. *Am. Rev. Respir. Dis.* 145:548-552.
50. Kai, H., K. Yoshitake, A. Hisatsune, T. Kido, Y. Isohama, K. Takahama, and T. Miyata. 1996. Dexamethasone suppresses mucus production and MUC-2 and MUC-5AC gene expression by NCI-H292 cells. *Am. J. Physiol.* 271:L484-L488.
51. Goswami, S. K., S. Kivity, and Z. Marom. 1990. Erythromycin inhibits respiratory glycoconjugate secretion from human airways *in vitro*. *Am. Rev. Respir. Dis.* 141:72-78.
52. Massaro, G., and D. Massaro. 1997. Retinoic acid treatment abrogates elastase-induced pulmonary emphysema in rats. *Nature Med.* 3:675-677.
53. Ohmichi, H., U. Koshimizu, K. Matsumoto, and T. Nakamura. 1998. Hepatocyte growth factor (HGF) acts as a mesenchyme-derived morphogenic factor during fetal lung development. *Development* 125: 1315-1324.
54. Barnes, P. J. 1999. Molecular genetics of COPD. *Thorax* 54:245-252.

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Thorax**Effects of theophylline and ipratropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease.****Tsukino M, Nishimura K, Ikeda A, Hajiro T, Koyama H, Izumi T.**

Chest Disease Research Institute, Kyoto University, Japan.

BACKGROUND: The effects of theophylline or anticholinergic agents on exercise capacity in patients with chronic obstructive pulmonary disease (COPD) remain controversial. The aim of the present study was to compare the effect of an oral theophylline with an inhaled anticholinergic agent and to examine the effects of combined therapy on exercise performance using progressive cycle ergometry. **METHODS:** Twenty one men with stable COPD and a mean (SD) forced expiratory volume in one second (FEV1) of 1.00 (0.40) l were studied. Theophylline (600 or 800 mg daily), ipratropium bromide (160 micrograms), a combination of both drugs, and placebo were given in a randomised, double blind, four period crossover design study. Spirometric data, pulse rate, and blood pressure were assessed before and at 90 and 120 minutes after inhalation. Symptom limited progressive cycle ergometer exercise tests (20 watts/min) were performed 90 minutes after each inhalation, and dyspnoea was measured during exercise using the Borg scale. **RESULTS:** The mean (SD) serum theophylline concentration was 18.3 (6.3) micrograms/ml, and seven patients had side effects during treatment with theophylline. Theophylline and ipratropium bromide produced greater increases in FEV1, maximal oxygen consumption, maximal minute ventilation, and several dyspnoea ratios than placebo. There were no differences between theophylline and ipratropium bromide except in maximal heart rate. A combination of both drugs produced greater improvements in pulmonary function and exercise capacity than either drug alone. **CONCLUSIONS:** Both high dose theophylline and high dose ipratropium bromide improved exercise capacity in patients with stable COPD. Although data based on short term effects cannot be directly applied to long term therapy, theophylline added to an inhaled anticholinergic agent may have beneficial effects on exercise capacity in patients with COPD.

PMID: 9741369 [PubMed - Indexed for MEDLINE]

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Chest

The effects of the combination of inhaled ipratropium and oral theophylline in asthma.

Burki NK.

Division of Pulmonary and Critical Care Medicine, University of Kentucky Medical Center, Lexington 40536, USA.

BACKGROUND: In comparison to beta-agonist drugs, which are the primary bronchodilator drugs in current use in asthma, both oral theophylline and inhaled ipratropium have a weaker bronchodilating action in asthma. Although a number of studies have shown an additive effect of ipratropium in combination with beta-agonist bronchodilator drugs in asthmatics, to our knowledge, the effects of combined treatment with ipratropium and theophylline have not been assessed. **STUDY OBJECTIVE:** To assess whether the combination of oral theophylline and inhaled ipratropium has an additive bronchodilator effect in asthmatics. **DESIGN:** Double-blind, placebo-controlled, crossover study. **SUBJECTS:** Nineteen patients (8 male, 11 female) with mild-to-moderate stable asthma. **METHODS:** Initially the optimal single oral dose of theophylline required to achieve therapeutic blood levels (10 to 20 microg/mL) was established in each patient. They then returned at varying intervals on 4 subsequent days. On each day, they received, in a random, placebo-controlled, double-blind, crossover design, one of four different therapies: oral and inhaled placebo; oral theophylline at the established optimal dose (range, 300 to 700 mg) plus inhaled placebo; oral placebo plus inhaled (40 microg) ipratropium; and the combination of theophylline and ipratropium. Spirometry was performed at baseline and at 15 min, 30 min, and hourly intervals for 6 h after therapy. **RESULTS:** Each drug regimen resulted in a significant ($p < 0.05$) increase in FEV₁, but the combined regimen resulted in a significantly greater bronchodilation ($p < 0.05$) over either ipratropium or theophylline alone (FEV₁ = 3.00 +/- 0.75 L vs 2.48 +/- 0.77 L vs 2.61 +/- 0.72 L, respectively, at 3 h postdrug). **CONCLUSIONS:** There was a significant, early, sustained additive bronchodilator effect of the combination therapy; there were no untoward side effects. These findings indicate that the addition of inhaled ipratropium to oral theophylline provides greater bronchodilation than either drug alone and may be a useful therapeutic modality in asthma.

PMID: 9187165 [PubMed - indexed for MEDLINE]

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DIVISIÓN DE NUEVAS CREACIONES**

2020
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		Cap. II	☒

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:

1. Documentos estudiados

- 1.1. Descripción: Folios: 55 a 79
- 1.2. Reivindicaciones: Folios: 80 a 83
Folios: 143 a 148 Memorial de 24/08/2007
- 1.3. Dibujos: Folios: 84 a 86
- 1.4. Datos PCT:

Solicitud Internacional:	PCT/EP02/01988
Capítulo II	
Fecha Sol. Internacional:	26/02/2002
Publicación. Internacional:	WO02/069945
Fecha Pub. Internacional:	12/09/2002
Fecha Inicio Fase Nacional:	07/10/2003
Solicitud Nacional:	CO 03 77336
Fecha Sol. Nacional:	04/09/2003
- 1.5. Prioridad: DE10110772.2 de 07/03/2001
- 1.6. Respuesta del solicitante: Folios: 136 a 1546 Memorial de 24/08/2007

2. Objeto de la invención

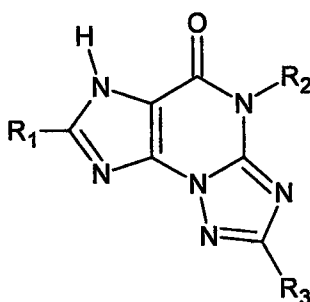
Título de la solicitud

"Nuevas composiciones de medicamentos sobre la base de agentes anticolinérgicos e inhibidores de PDE-IV"

Reivindicaciones

Reivindicaciones 1 a 10, 13, 14 y 19: Se reivindica una composición caracterizada porque contiene una o más sales de tiotropio (1) combinada con uno o más inhibidores de PDE-IV (2)

El compuesto (1) se encuentra en forma de cloruro, bromuro, yoduro, metano-sulfonato, sulfato o p-toluen-sulfonato. El compuesto (2) se selecciona del grupo que consiste en: enprofilina, roflumilast, ariflo, Bay-198004, CP-325,366, BY343, D-4396 (Sch-351591), V-11294A, AWD-12-281, así como los heterocíclicos nitrogenados de la fórmula general (2a):



Reivindicaciones 11 y 12: Se reivindica un polvo inhalable y las cápsulas caracterizadas porque el polvo inhalable tiene un tamaño de partícula de 250µm

Reivindicaciones 15 a 18: Se reivindica un aerosol inhalable que contiene propulsor

Reivindicaciones 20 a 30: Se reivindica una suspensión para inhalación caracterizada porque el valor de pH es de 2 a 7 y preferiblemente 2 a 5.

Sustento Descriptivo

La invención se refiere a composiciones medicamentosas sobre la base de agentes anticolinérgicos e inhibidores PDEIV, procedimientos para su preparación y su utilización en la terapia de enfermedades de las vías respiratorias.

Se ha encontrado que se puede observar un efecto inesperado de orden sinérgico al realizar el tratamiento de enfermedades inflamatorias u obstructivas de las vías respiratorias cuando uno o varios agentes anticolinérgicos pasan a utilizarse en común con uno o varios inhibidores PDE IV. Por causa del efecto sinérgico las combinaciones de medicamentos conformes al invento se pueden emplear con una dosificación menor que la que se presenta en el caso de una monoterapia.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/4439** de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D. 486)

Nuevamente esta dependencia se permite señalar al señor solicitante que se pretende protección para una generalidad de mezclas, amparadas todas bajo las categorías farmacológicas que se producen cuando se discriminan los compuestos por el mecanismo de acción. De esta forma cuando se habla de agentes Inhibidores PDE IV en combinación con sales de tiotropio se hace alusión a una gran variedad de sinergismos farmacológicos derivados todos de la gran variedad de mezclas que se pueden obtener de combinar las sales con todos los inhibidores PDE IV que relaciona el solicitante en las cláusulas 4 y 5.

Como ya se señaló el sinergismo debido el comportamiento farmacológico y farmacodinámico de un compuesto depende única y exclusivamente del compuesto que produce la acción, de su mecanismo y obviamente de sus propiedades químicas y físicas, de esta forma una interpretación inequívoca del alcance de las combinaciones solo puede producirse si se conoce con exactitud los compuestos que fueron objeto de comprobación e investigación científica, hecho éste que no ocurrió como ya se había mencionado en el requerimiento técnico anterior.

Se reitera que una invención de producto debe definirse en términos de sus características esenciales que para el presente caso corresponde a los compuestos químicos que al ser combinados generan un efecto terapéutico sinérgico. Pero dada la manera como se reclaman, esto es, haciendo alusión al mecanismo de acción como inhibidores PDEIV, el objeto se reivindica en términos del resultado a alcanzar es decir, la reivindicación incluye no sólo la solución propuesta por el solicitante sino todas las alternativas terapéuticas comprobadas o no que puedan eventualmente llegar a tal resultado, motivo por el cual continúa siendo inaceptable la manera como se define el objeto y por tanto se configura el incumplimiento del artículo 30 del ordenamiento jurídico andino.

3.2. Descripción (artículo 28 D. 486)

Como se había señalado en la oportunidad jurídica anterior, si bien es cierto se establece en la cláusula (1) que se pretende protección para las composiciones que contengan sales de tiotropio con uno o varios inhibidores de PDE IV, resulta claro para una persona versada en el arte que el efecto inesperado y sorprendente de las combinaciones farmacológicas no reside en la actividad terapéutica individual de los fármacos ni en la suma aritmética de sus efectos, por el contrario la ventaja comparativa y el salto en la regla técnica tiene su asiento en el hecho resultante de combinar los principios activos el cual genera un incremento sustancial de la respuesta terapéutica que no corresponde precisamente a la suma de los efectos individuales, lo que se conoce en farmacodinamia como sinergismo.

Este hecho debía encontrarse suficientemente divulgado en el aparte descriptivo de la solicitud desde el momento en que se presentó a trámite ante la oficina competente, de tal suerte que fuese posible comprobar estadísticamente la ventaja comparativa frente a la administración individual de los activos y mediante la medición de parámetros farmacodinámicos se evidenciara el efecto inesperado en una curva dosis- respuesta de la potencia relativa de los activos combinados.

La presentación extemporánea de dichos estudios amplía la divulgación inicial que había hecho el señor solicitante de su invento y por tanto no pueden aceptarse las pruebas técnicas aportadas con el memorial de fecha 24/08/2007, dado que nunca se mencionaron los resultados encontrados a lo largo del capítulo descriptivo y como bien se interpreta del alcance del artículo 28 debió ser objeto de presentación al

momento de la radicación de la solicitud en estudio de tal suerte que fuese posible evidenciar las diferencias y eventuales ventajas con respecto al arte previo.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 07/03/2001, se procedió a efectuar la búsqueda de documentos relacionados en el estado de la técnica con fecha de publicación anterior a ésta.

Nº	Documento	Título	Fecha de Publicación*
D1	Artículo 1	"Novel approaches and targets for treatment of chronic obstructive pulmonary disease"	Nov 1999
D2	Artículo 2	"Effects of theophylline and ipratropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease"	Apr 1998
D3	Artículo 3	"The effects of the combination of inhaled ipratropium and oral theophylline in asthma"	Jun 1997

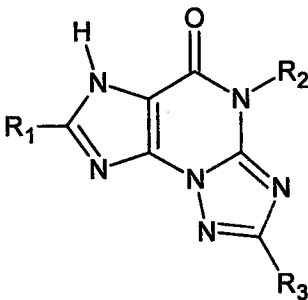
Anterioridades D1 a D3 en los folios 157 a 167

5. Análisis de patentabilidad (artículo 14 D. 486)

5.1 Nivel inventivo (artículo 18 D. 486)

Se reivindica una composición caracterizada porque contiene una o más sales de tiotropio (1) combinada con uno o más inhibidores de PDE-IV (2)

El compuesto (1) se encuentra en forma de cloruro, bromuro, yoduro, metano-sulfonato, sulfato o p-toluen-sulfonato. El compuesto (2) se selecciona del grupo que consiste en: enprofilina, roflumilast, ariflo, Bay-198004, CP-325,366, BY343, D-4396 (Sch-351591), V-11294A, AWD-12-281, así como los heterocíclicos nitrogenados de la fórmula general (2a):



El estado del arte más próximo a la invención hace referencia a la necesidad creciente hacia 1999 de desarrollar tratamientos efectivos para la enfermedad pulmonar obstructiva crónica (EPOC). El documento D1 señala que en particular se han utilizado broncodilatadores como bromuro de tiotropio y una serie de anti-inflamatorios para el control de mediadores de la inflamación crónica que incluye leucotrienos e interleuquina 8. Señala además el documento que la resistencia

generada frente a los corticosteroides ha generado la necesidad de utilizar otra clase de agentes anti-inflamatorios como los inhibidores de fosfodiesterasa PDEIV.

Sobre el tiotropio el documento D1 señala que resulta más efectivo el polvo para inhalación que la administración de bromuro de ipratropio y sobre la terapia anti-inflamatoria señala que una alternativa terapéutica consiste en la administración de inhibidores PDEIV como SB207499, CP 80633 y CDP-840, no obstante, en dicho documento no hace mención alguna a la administración combinada de dichos activos.

El estado de la técnica revela en la publicación D2 que se ha comprobado el efecto benéfico de combinar teofilina (un inhibidor de PDE) y bromuro de ipratropio (análogo de tiotropio) en pacientes que sufren enfermedad pulmonar obstructiva crónica (EPOC). Señala el documento se comparó el efecto de la administración oral de teofilina con un agente anticolinérgico con el fin de determinar el efecto que causa la administración combinada de los activos en la capacidad física de los pacientes. Dentro de los resultados se menciona que dosis elevadas de teofilina y de bromuro de ipratropio mejoran la capacidad física de los pacientes con EPOC, es decir que la adición de teofilina a la solución para inhalación de un agente anticolinérgico puede generar resultados alentadores en el tratamiento de dicha patología.

El documento del estado del arte D3 hace referencia al efecto que causa la administración combinada de ipratropio y teofilina en el tratamiento del asma. En la publicación se señala que ya en diversos estudios se había demostrado el efecto aditivo que se generaba cuando se combinaba un broncodilatador agonista Beta 2 con ipratropio, pero hasta ese momento no se había demostrado el efecto causado por la administración combinada de ipratropio (análogo de tiotropio) con teofilina (un inhibidor PDE) en el control del asma bronquial. El estudio demuestra que se genera un efecto superior a través de la terapia combinada y que la adición de ipratropio por vía nasal a la administración por vía oral de teofilina causa mayor broncodilatación que cuando se administra uno solo de los activos.

De esta manera, dadas las anticipaciones que el estado del arte hacía sobre el objeto de la invención es posible que al combinar las enseñanzas del documento D1 con cualquiera de los documentos D2 o D3 se proponga una solución como la reivindicada por el señor solicitante para el tratamiento de enfermedades inflamatorias y obstructivas de las vías respiratorias (denominadas: asma y EPOC) al combinar uno o varios agentes anticolinérgicos (como bromuro de ipratropio o tiotropio) con uno o varios inhibidores PDEIV (como teofilina, enprofilina, roflumilast, ariflo, irimilast, tofomilast, pumafentrina, entre otros).

En la divulgación efectuada, señala el solicitante cómo se ha encontrado de manera inesperada que se puede observar un efecto inesperado de orden sinérgico al realizar el tratamiento de enfermedades inflamatorias u obstructivas de las vías respiratorias cuando uno o varios agentes anticolinérgicos pasan a utilizarse en común con uno o varios inhibidores PDE IV y que por causa del efecto sinérgico las combinaciones de medicamentos conformes al invento se pueden emplear con una dosificación menor que la que se presenta en el caso de una monoterapia. Sin embargo, el estado del arte anticipaba el objeto de la combinación que reclama el señor solicitante y resuelve el mismo problema técnico, por tanto la materia tal como se encuentra reclamada no es inventiva y por tanto incumple con las disposiciones contempladas en el artículo 18 de la norma andina, en cuanto a que se deriva evidentemente del estado del arte y la solución propuesta resulta obvia para un conocedor de la materia dadas las enseñanzas que revela el estado del arte.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

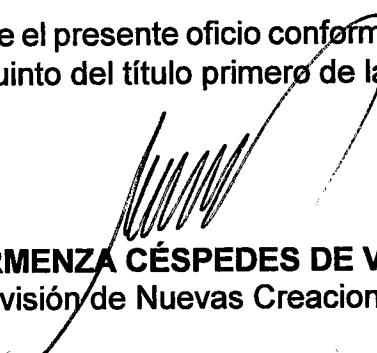
N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	Artículo 1	1 a 30	Nivel Inventivo
D2	Artículo 2	1 a 30	Nivel Inventivo
D3	Artículo 3	1 a 30	Nivel Inventivo

7. Respuesta a los argumentos del solicitante:

Conforme a la respuesta que presenta el solicitante mediante memorial de fecha 24/08/2007 esta Dependencia se permite señalar que no es posible aceptar el estudio realizado acerca del efecto sinérgico que obra cuando se administra concomitantemente un inhibidor PDEIV como roflumilast y bromuro de tiotropio, dado que el mismo no forma parte de la divulgación inicialmente presentada ante este Despacho y con motivo del inicio del trámite de la solicitud de patente. No es posible aceptar dicho documento como parte del sustento descriptivo de la solicitud, por cuanto su incorporación al documento constituiría ampliación de la materia inicialmente divulgada y por tanto incumplimiento de las disposiciones que contempla el artículo 34 de la Decisión 486.

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 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 División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha

11.08.2008

CONCEPTO TÉCNICO No. 2764	EXAMINADOR TÉCNICO Código No. 202044
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