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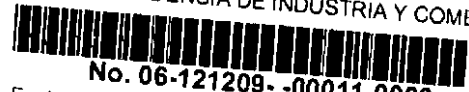
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señor Director

DIRECCION DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Trámite : 011

Evento : 378

Actuación : 444

Referencia : Expediente No. **06.121.209**
Asunto : Solicitud de Patente para:
**COMBINACIONES QUE COMPRENDEN AGENTES
ANTIMUSCARÍNICOS Y CORTICOESTEROIDES**
Solicitante : **ALMIRALL, S.A.**
Clase : A61K 031/058, A61K 031/439, A61K 031/573, A61K 045/000,
A61P 011/000, A61P 011/006, A61P 011/008
Fecha de Solicitud : 30 de Noviembre de 2006

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al Oficio No. **00959** notificado por fijación en lista del 21 de Enero de 2011.

2. Mediante memorial radicado el 13 de Abril de 2011 solicité plazo de treinta (30) días para atender el oficio No. **00959**.

3. Mediante el Oficio No. **00959** se puso en conocimiento del solicitante el informe del examen de fondo que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente.

4. Nivel Inventivo

Para la evaluación de este requisito, el Examinador ha citado las siguientes anterioridades:

- D1: WO 01/04118, "Novel quinuclidine derivatives and medicinal compositions containing the same"
- D2: WO 02/053564, "Novel quinuclidine derivatives and medicinal compositions containing the same"
- D3: WO 03/087094, "New pyrrolidinium derivatives"

La anterioridad D1 enseña los derivados de quinuclidina y su efecto como antagonistas de los receptores muscarínicos M3 para el tratamiento de enfermedades respiratorias. De la misma manera, dicha anterioridad describe de la combinación de los compuestos mencionados en dicha anterioridad, como lo es (3R)-1-fenetil-3-(9H-xanten-9-carbonilo)-1-azoniabicyclo[2.2.2] octano, junto con agonistas β_2 , esteroides, antialérgicos o inhibidores de fosfodiesterasa IV.

Por su parte, el documento D2 describe los derivados de quinuclidina y composiciones que los contienen, como agentes antimuscarínicos de efecto potente y de larga duración, los cuales pueden administrarse en forma simultánea, por separado o en forma secuencial junto con agonistas β_2 , esteroides, antialérgicos, inhibidores de fosfodiesterasa IV y/o antagonistas de leucotrieno D4.

Así mismo, el documento D3 describe la combinación de los derivados de pirrolidina como agentes antimuscarínicos M3, junto con agonistas β_2 , esteroides, antialérgicos, inhibidores de fosfodiesterasa IV y/o antagonistas de leucotrieno D4 para el tratamiento de enfermedades respiratorias.

5. Respuesta a las objeciones

De este modo y con el objeto de atender las objeciones arriba mencionadas, se pone de presente al Despacho las siguientes aclaraciones y argumentos:

5.1 Nivel Inventivo

El Examinador cita los documentos D1 a D3 y manifiesta que estos afectan el nivel inventivo de la presente invención, puesto que, si bien los datos previamente presentados muestran un aumento en la inhibición de la respuesta contráctil cuando se emplean de manera concomitante corticoesteroides junto con 3(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-fenoxipropil)-1-azoniabicyclo[2.2.2] octano, dicho aumento no resulta significativo frente a los resultados cuando se administran los corticoesteroides únicamente. A este respecto solicitamos la reconsideración de la objeción, con base en los siguientes argumentos:

La presente invención surge de la mejora sorprendente en la eficacia observada cuando se combina un corticoesteroide con una sal de 3(R)-(2-hidroxi-2,2-ditien-2-ilacetoxi)-1-(3-

fenoxipropil)-1-azoniabicyclo[2.2.2] octano, asignada internacionalmente bajo el nombre "aclidinio".

Como fue previamente expuesto por mi representada, los resultados experimentales de las especificaciones muestran que el efecto obtenido por la administración de un corticoesteroide sobre la inhibición de un alérgico que induce una respuesta contráctil del anillo traqueal es significativamente mayor cuando dicho medicamento es usado en combinación con aclidinio, en comparación cuando el corticoesteroide es combinado con tiotropio.

Sin embargo, el Señor Examinador concluye que los datos presentes en la tabla 1 de la presente solicitud no demuestran un cambio significativo en la respuesta contráctil entre la combinación de aclidinio y un corticoesteroide, y el corticoesteroide únicamente. A este respecto manifestamos nuestro desacuerdo con el análisis llevado a cabo y con las conclusiones derivadas del mismo como se demuestra a continuación:

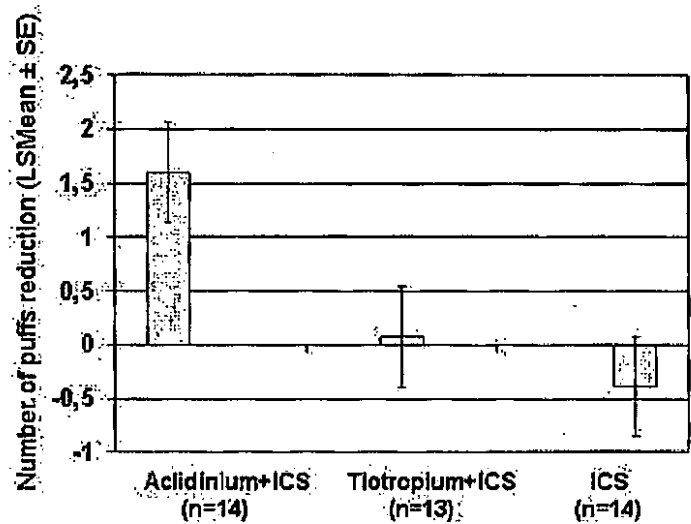
En particular, la inhibición contráctil observada cuando el compuesto 1, correspondiente al aclidinio, es combinado con budesonida es de 63 unidades, mientras que la inhibición observada para la budesonida por separado es de 51 unidades. Contrario a lo afirmado por su Despacho, dicha inhibición del efecto contráctil sí es significativa, puesto que una reducción del 24% en dicho estudio médico representa una respuesta que no puede ser ignorada en los factores de respuesta bajo estudio.

De manera similar, la inhibición observada para la combinación de aclidinio junto con beclometasona es de 46, el cual al ser comparado con un resultado de 12 obtenido para la beclometasona por separado muestra, un cambio del 284%. Evidentemente, el aumento en la inhibición en la respuesta contráctil observada cuando un corticoesteroide es combinado con el aclidinio es significativamente representativo, con un gran potencial terapéutico que beneficia a pacientes que padecen enfermedades respiratorias. Así mismo, resulta evidente a partir de los datos comparativos de la tabla 1, que las mejoras alcanzadas por la administración concomitante de los compuestos arriba mencionados no son observadas cuando otros antagonistas M3, como el tiotropio, son combinados con corticoesteroides.

Con el fin de presentar de una manera más evidente aun los beneficios terapéuticos alcanzados, anexo a este memorial se presenta un reporte experimental adicional, el cual muestra los resultados obtenidos en un ensayo clínico en el que se administraron combinaciones de acuerdo a la invención para compararlos posteriormente con combinaciones análogas en las cuales el antagonista M3 era tiotropio. Con relación a este reporte, deseamos llamar la atención del Señor Examinador específicamente a la figura 2, mostrada a continuación, la cual representa de manera clara la mejora significativa de los síntomas típicos observados en pacientes que padecen de "Enfermedad pulmonar obstructiva

crónica” - EPOC, cuando fueron tratados con la combinación reclamada en la presente solicitud, toda vez que dicha combinación reduce la frecuencia requerida del uso de inhalador para conservar una respiración normal. Nótese que la mejora en la sintomatología no fue observada cuando se administraban las combinaciones que comprenden tiotropio, conocidas en el estado de la técnica, a los pacientes tratados.

Reduction in the average number of daily puffs of relief medication needed by the patient during two weeks of treatment compared to baseline.



LSMean is the Least Squares Mean according to the ANCOVA model for cross-over designs of the changes from baseline in the number of daily puffs during two weeks of treatment

Así mismo, resulta necesario señalar que las mejoras ventajosas en la actividad anti-alérgicas discutidas previamente surgen únicamente a partir de las propiedades del acclidinio. Como es estipulado en la reivindicación 1 de la presente solicitud, el acclidinio es un antagonista M3 de los receptores muscarínicos. Dichos antagonistas corresponden a una clase ampliamente conocida de medicamentos usados activamente como broncodilatadores de los pulmones, ya que estos logran la relajación efectiva de los músculos lisos de los bronquios. Sin embargo, la actividad alcanzada en los receptores muscarínicos M3 no permitiría normalmente que un compuesto farmacológico lograra el bloqueo de una respuesta contráctil de la tráquea mediada por antígenos, puesto que dichos receptores no se encuentran relacionas con las respuestas inflamatorias.

Por el contrario, los corticoesteroides presentan la habilidad de bloquear una respuesta contráctil de la tráquea mediada por un alérgico. Siendo así las cosas, los ejemplos de la presente solicitud muestran como se llevó a cabo una prueba estandarizada para determinar la potencia de un corticoesteroide para inhibir una respuesta contráctil de un anillo traqueal aislado como respuesta a una prueba realizada con un alérgico. Dicha prueba consistía en

sensibilizar conejillos de india frente a la ovoalbumina, de forma tal que se alcanzaba una respuesta alérgica en los animales frente a la proteína suministrada.

La presente invención se basa en el descubrimiento que el aclidio, además de su actividad primaria como bloqueador de los receptores muscarínicos M3, también presenta una actividad similar a la observada para los corticoesteroide de bloquear la contracción traqueal inducida por alérgicos. Los ejemplos presentados en la solicitud inicial evidencian dicha mejora en la aumento en la inhibición de la contracción estudiada.

Como fue previamente demostrado en el memorial de respuesta a la acción oficial No. 04857 del 2010, identificado bajo radicado No. 06-121209-00008-0000, la tabla que se presenta a continuación incluye resultados adicionales del ensayo sobre un anillo traqueal aislado descrito en la página 16 de la presente solicitud.

Compound	Number of Animals Tested	Tracheal Ring's Response to the antigen in mg (mean±sem)	% Inhibition of the contractile response to ovoalbumin
Vehicle	23	886±108	-
Acridinium	15	612±91	31
Tiotropium	14	844±72	5
Budesonide	17	435±68	51
Beclomethasone	6	778±83	12
Acridinium+ Budesonide	9	325±81	63
Acridinium+ Beclomethasone	7	478±61	46
Tiotropium+ Budesonide	8	523±147	41
Tiotropium+ Beclomethasone	6	612±109	31

Compounds tested at 10 µM.

Los anteriores datos confirman que el aclidinio solo puede alcanzar una inhibición hasta del 31% sobre la respuesta contráctil mediada por un alérgico. Siendo un aspecto demostrativo para el análisis de la importancia de la inhibición observada para la combinación reclamada en la presente solicitud, deseamos esclarecerle a su Despacho que, como es del conocimiento de una persona conocedora de enfermedades respiratorias y su tratamiento basado en los antagonistas M3 conocidos en el estado de la técnica, el bloqueo en la respuesta contráctil no es una actividad típica de otros compuestos de esta clase específica de medicamentos. Como prueba de lo anterior, llamamos la atención del Señor Examinador a

la comparación de los valores obtenidos para el aclidinio frente a los valores correspondientes al tiotropio, antagonista M3 predominantemente comercializado en el mercado farmacéutico. La diferencia porcentual observada entre ambos compuestos demuestra una mejora del aclidinio superior al 25%.

De forma similar, la tabla que se presenta a continuación, resume los valores correspondientes a un ensayo separado realizado para evaluar la actividad del enantiomero S de aclidinio. Como se puede observar, los resultados obtenidos no muestran una actividad representativa.

Effect of S-aclidinium* in inhibiting the contraction induced by the antigen in ovalbumin-sensitized guinea-pig isolated tracheal rings

Compound	Number of Animals Tested	Tracheal Ring's Response to the antigen in mg (mean±sem)	% Inhibition of the contractile response to ovalbumin
Vehicle	8	1065±118	—
S-Aclidinium	9	1061±132	0

Compounds tested at 10 µM.

* The term "S-aclidinium" is used to denote 3(S)-(2-hydroxy-2,2-dithien-2-ylacetoxy)-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane.

De este modo, ambas tablas prueban que la actividad similar a un corticoesteroide observada para el compuesto aclidinio no es una respuesta típica y usual que puede ser extrapolada a todos los antagonistas M3, sino que por el contrario, corresponde a un efecto alcanzado únicamente por el aclidinio.

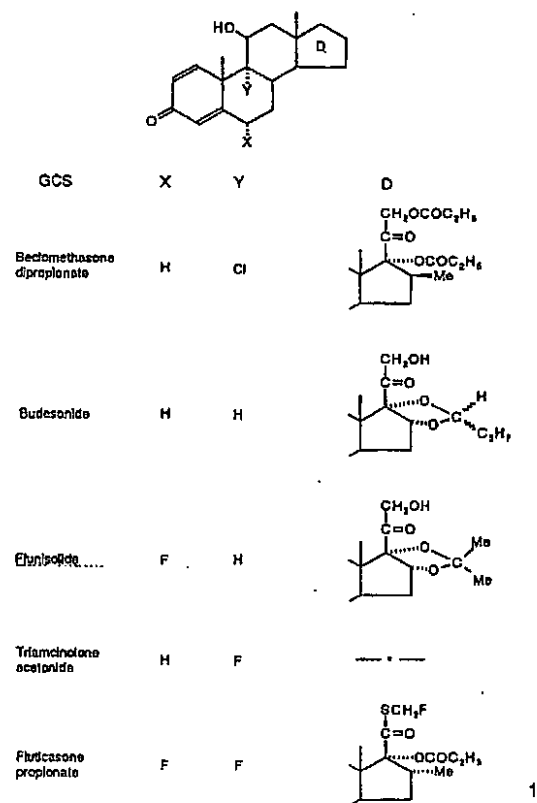
Sin necesidad de discutir el mecanismo específico mediante el cual dicho compuesto presenta propiedades que se traducen en una actividad funcional similar a la de los corticoesteroides, en lineamiento con los argumentos arriba expuestos resulta claro que este compuesto corresponde a un medicamento particularmente apropiado para ser usado en combinación con cualquier corticoesteroide, con el fin de potenciar la actividad alcanzada en los pacientes a los que se les administra, logrando adicionalmente su efecto primario como antagonista M3 de los receptores muscarínicos.

Lo que es más, aunque los resultados presentes en los ejemplos de las especificaciones corresponden únicamente a combinaciones entre el aclidinio con budesonida y beclometasona, estos representan la pruebas necesarias y suficientes mediante las cuales es posible demostrar que el aclidinio resulta particularmente apropiado para combinarse con cualquier corticoesteroide, toda vez que, un antagonista M3 que a su vez presenta actividades

similares a un corticoesteroide será apropiado para ser combinado con cualquier farmacéutico corticoesteroide.

Sin embargo, para una mejor comprensión por parte de una persona versada en la materia, deseamos recordar que los corticoesteroides, también conocidos como glucocorticoides, corresponden a una clase definida de medicamentos que presentan un efecto similar en las vías respiratorias, por lo que comúnmente son utilizados en el tratamiento de enfermedades respiratorias.

Resulta importante traer a colación la figura 11.7 del libro “Murray and Nadel’s Textbook of Respiratory Medicine”, presente a continuación, la cual ilustra las estructuras esenciales de los anillos fusionados presentes en todos los corticoesteroides.



Así mismo, los autores del libro anteriormente citado mencionan en el párrafo 2, columna derecha, página 278 que los receptores glucocorticoides se ligan en el citoplasma y que:

¹ MASON, Robert J. MD; V. BROADDUS, Courtney MD; MARTIN, Thomas; KING, Talmadge Jr. MD; SCHRAUFNAGEL, Dean; MURRAY, John F.; NADEL, Jay A.: “Murray and Nadel’s Textbook of Respiratory Medicine”. Tercera Edición, W. B. Saunders Company. 2000. Página 278.

"...solo existe un tipo de receptor glucocorticoide y no hay evidencia de la presencia de sub-tipos diferentes que puedan mediar diferentes aspectos de la acción esteroide..."²

Por lo tanto, todos los corticoesteroides inhiben la infiltración inflamatoria celular en las vías respiratorias cuando son administrados a un paciente que padece enfermedades respiratorias. Lo anterior lo menciona a su vez el libro *"Integrated Pharmacology"* en la página 6, capítulo 9.³

Por lo tanto, la combinación específica de acuerdo a la invención proporciona una mejora significativa en la eficacia terapéutica frente a las combinaciones de corticoesteroides con otros antagonistas M3. Por las razones arriba expuestas, contrario a las afirmaciones del Señor Examinador, corresponde entonces a un resultado sorprendente y significativo de la presente invención que la combinación bajo estudio muestra mejoras importantes en la eficacia primaria de inhibir la respuesta contráctil y en el tratamiento para contrarrestar la sintomatología.

Es así como las anterioridades citadas no presentan indicio alguno que lleve a una persona versada en la materia a combinar específicamente el compuesto aclidinio junto con cualquier corticoesteroide para lograr ventajosamente actividades de inhibición válida en el tratamiento de enfermedades respiratorias.

En este sentido, el documento D1 a pesar de reclamar varios antagonistas de M3, no hace mención alguna o sugiere dentro de sus especificaciones las propiedades ventajosas específicas alcanzadas por el compuesto aclidinio, o da indicio alguno que lleve a su combinación con un corticoesteroide. Por su parte, los documentos D2 y D3 no incluyen dentro de sus descripciones dicho compuesto y mucho menos discuten la posibilidad de combinarlo con otros compuestos farmacológicos.

Por lo anterior, los documentos citados por el Examinador no resultan anterioridades válidas capaces de afectar el nivel inventivo de la solicitud al no revelar o sugerir la combinación específica de los compuestos tal como se reivindican y los cuales poseen propiedades para su uso en el tratamiento de trastornos respiratorios.

Así las cosas, consideramos que la presente invención goza de nivel inventivo a la luz del arte previo.

² MASON, Robert J. MD; V. BROADDUS, Courtney MD; MARTIN, Thomas; KING, Talmadge Jr. MD; SCHRAUFNAGEL, Dean; MURRAY, John F.; NADEL, Jay A.: *"Murray and Nadel's Textbook of Respiratory Medicine"*. Tercera Edición, W. B. Saunders Company. 2000. Página 278.

³ PAGE, Clive P., MD; HOFFMAN, Brian, MD; CURTIS, Michael, WALKER, Michael PhD: *"Integrated Pharmacology"*. Segunda Edición, Mosby. 2002.

6. Conclusiones

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

Así mismo, manifiesto expresamente a ese Despacho que renuncio al término de 30 días solicitado, teniendo en cuenta que con este escrito presento la información y documentación necesaria para continuar con el trámite de la solicitud de patente de la referencia.

7. Anexos

- Reporte Experimental *"Effect of aclidinium and of tiotropium in COPD patients concomitantly treated with inhaled corticosteroid"*
- Copia de las páginas 267 a 291 del libro en inglés *"Murray and Nadel's Textbook of Respiratory Medicine"*. Tercera Edición, W. B. Saunders Company. 2000.
- Copia de las páginas 1 a 13 del capítulo 9 del libro en inglés *"Integrated Pharmacology"*. Segunda Edición, Mosby. 2002.

Señor Director,


LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

COLO-17153-845-003-1
COLO-06734-845-006-4
COLO-11194-841-014-2
LLGILLGND-191614\WPC17153
No. M-2011-191614\LLG

Effect of acclidinium and of tiotropium in COPD patients concomitantly treated with inhaled corticosteroids

Fourteen patients suffering from moderate to severe Chronic Obstructive Pulmonary Disease (COPD) and who were taking inhaled corticosteroids (ICS) were treated in a randomised double-blind, double-dummy, three-period, cross-over, placebo controlled clinical trial with Acclidinium 400 µg twice-daily (BID) and Tiotropium 18 µg once-daily (QD), administered via a dry powder inhaler. These dosages are the ones known to produce similar bronchodilating effects in COPD patients.

The trial consisted of a run-in period of 5 to 9 days and three periods of 15 days of treatment, separated by a washout period of 9 to 15 days. Thus, the patients received the three following treatments:

- **Acclidinium 400 µg.** (Morning administration: acclidinium 400 µg + placebo of tiotropium; evening administration: acclidinium 400 µg)*
- **Tiotropium 18 µg.** (Morning administration: placebo of acclidinium + tiotropium 18 µg; evening administration: placebo of acclidinium)*
- **Placebo.** (Morning administration: placebo of acclidinium + placebo of tiotropium; evening administration: placebo of acclidinium)*

At day 15 of all the treatments the Forced Expiratory Volume in one second (FEV₁) was measured before dosing and serially during 24 hours post-dose. With these FEV₁ values the Area Under the Curve of the change from baseline of the FEV₁ measured during 24 hours (AUC₀₋₂₄) at day 15 of each treatment was calculated. The patients were also requested to record the number of daily puffs of additional relief medication (e.g salbutamol) they needed in order to treat acute attacks of breathlessness occurred during the two weeks of each treatment.

As Figure 1 shows, when the patients were given only placebo, in addition to their treatment with ICS, there was, as expected, practically no change from baseline in the AUC₀₋₂₄ of FEV₁ after 15 days of treatment. The concomitant treatment of tiotropium with ICS produced an increase (mean ± standard error) from baseline of the FEV₁ AUC₀₋₂₄ of 201.0 ± 137 ml. The increase of the FEV₁ AUC₀₋₂₄ produced by the concomitant treatment of acclidinium with ICS was similar (223.6 ± 137 ml). In both cases the difference between the effect of the ICS alone and the effect of the addition of the anticholinergic was statistically

* The "placebo of tiotropium" was a placebo inhaler designed to resemble the tiotropium inhaler. The "placebo of acclidinium" was a placebo inhaler designed to resemble the acclidinium inhaler.

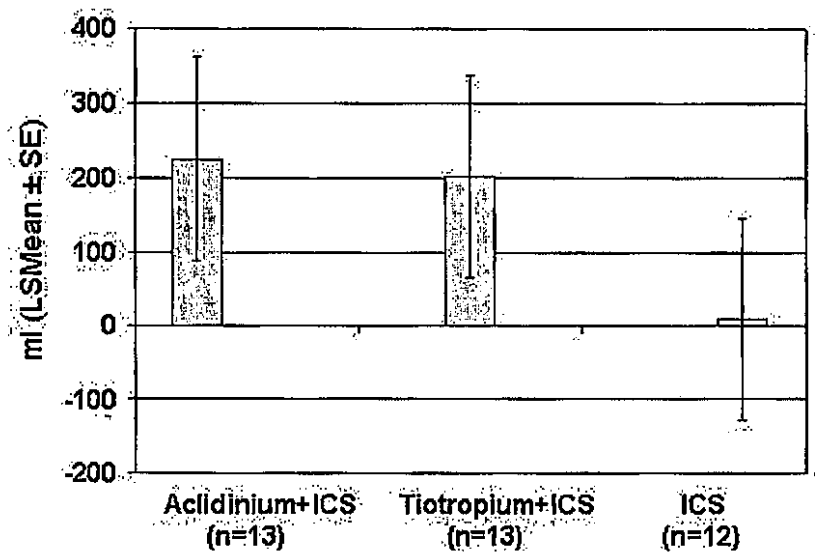
significant with a $p < 0.001$, according to an Analysis of Covariance (ANCOVA) model for crossover design, LSMeans.

Regarding the use of relief medication, figure 2 shows that, again as expected, when patients were given only placebo in addition to ICS there is almost no change in the number of daily puffs needed. In fact, the minor increase which has been observed (0.39 ± 0.46 puffs more than the baseline) can be attributed to biological variability. Strikingly, the concomitant treatment with acclidinium plus ICS produced a much larger reduction in the number of puffs needed (1.60 ± 0.46 puffs less than the baseline) than the concomitant treatment with tiotropium plus ICS (0.07 ± 0.48 puffs less than the baseline). The difference between both treatments is statistically significant ($p = 0.02$). Moreover, whereas no statistically significant difference was observed between the concomitant treatment with tiotropium plus ICS versus the treatment with ICS alone, the comparison between the concomitant treatment of acclidinium plus ICS and the treatment with ICS alone resulted in a statistically significant difference ($p = 0.004$). In all cases the statistical analysis was carried out in accordance with the ANCOVA model for crossover design, LSMeans.

These results show that, although the functional parameters measuring the overall bronchodilating effects produced by the addition of acclidinium to ICS are similar to those observed after the addition of tiotropium to ICS, the actual symptomatology of the patients improved much more when acclidinium was used in a concomitant treatment with ICS, to the extent that the need for additional relief medication diminished drastically. This indicates that there is an unexpected beneficial interaction between acclidinium and corticosteroids, which is not observed with tiotropium, possibly due to a potentiation by acclidinium of the antiinflammatory effects of corticosteroids.

Figure 1

Change from baseline in Normalised FEV₁ AUC₀₋₂₄ (ml) at day 15



LSMean is the Least Squares Mean according to the ANCOVA model for cross-over designs of the changes from baseline in the normalised AUC₀₋₂₄ FEV₁ at Day 15

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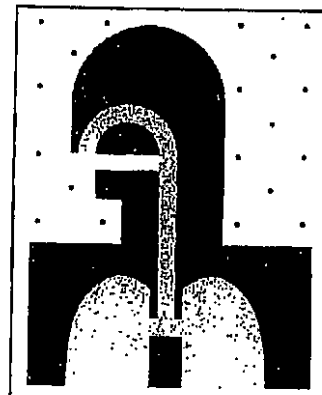
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Textbook of Respiratory Medicine

Third Edition

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TEXTBOOK OF RESPIRATORY MEDICINE

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Airway Pharmacology

PETER J. BARNES, M.A., D.M., D.Sc., F.R.C.P.

Introduction

Bronchodilators

- Beta₂-Adrenergic Agonists
- Theophylline
- Anticholinergics
- New Bronchodilators

Controller Drugs

- Corticosteroids
- Cromones

Mediator Antagonists

- Antihistamines
- Anti-Leukotrienes

Steroid-Sparing Therapies

- Methotrexate
- Gold
- Cyclosporine
- Intravenous Immunoglobulin
- Immunotherapy

New Drugs for Asthma and Chronic Obstructive Pulmonary Disease

- Mediator Antagonists
- Anti-Cytokines
- Phosphodiesterase Inhibitors
- Adhesion Molecule Blockers
- Immunomodulators
- Furosemide
- Neuromodulators
- Enzyme Inhibitors
- Transcription Factor Blockers
- Impact of Molecular Genetics

Other Drugs

- Mucoregulators
- Antitussives
- Drugs for Breathlessness
- Ventilatory Stimulants

Drugs Contraindicated in Airway Disease

- Sedatives
- Beta-Blockers
- Aspirin and Other Cyclooxygenase Inhibitors
- Angiotensin-Converting Enzyme Inhibitors
- Local Anesthetics

INTRODUCTION

The pharmacology of the airways is largely concerned with the treatment of airway obstruction, particularly asthma. Important advances in the understanding of asthma as an inflammatory disease of the airways have resulted in a shift of emphasis from bronchodilator to anti-inflammatory therapy. Chronic obstructive pulmonary disease (COPD) has received less attention but appears also to be an inflammatory disease, although the inflammatory response differs from that in asthma and is largely unresponsive to currently available anti-inflammatory treatments.¹ This chapter discusses the pharmacology of the drugs used in the treatment of obstructive airway disease, including bronchodilators, which act mainly by reversing airway smooth muscle contraction, and anti-inflammatory drugs, which suppress inflammatory responses in the airways. Drugs that play a less important role include mediator antagonists, mucolytics, antitussives, and respiratory stimulants. Antibiotics, antituberculosis therapy, and oxygen are considered elsewhere.

BRONCHODILATORS

Bronchodilator drugs have an "anti-bronchoconstrictor" effect, which may be demonstrated directly in vitro by a relaxant effect on precontracted airways. Bronchodilators cause rapid reversal of airway obstruction in asthma in vivo, and this is believed to result from an effect on airway smooth muscle, although additional pharmacologic effects on other airway cells (such as reduced microvascular leakage and reduced release of bronchoconstrictor mediators from inflammatory cells) may contribute to the reduction in airway narrowing.

Three classes of bronchodilators are in current clinical use: beta-adrenergic agonists (sympathomimetics), theophylline (methylxanthines), and anticholinergic drugs.

Drugs such as cromolyn sodium, which prevent bronchoconstriction, have no direct bronchodilator action and are ineffective once bronchoconstriction has occurred. Anti-leukotrienes (leukotriene receptor antagonists and 5-lipoxygenase inhibitors) have a small bronchodilator effect in some patients. Corticosteroids, although they gradually improve airway obstruction, have no direct effect on contraction of airway smooth muscle and therefore are not considered to be bronchodilators.

Beta₂-Adrenergic Agonists

Inhaled beta₂-agonists are the bronchodilator treatment of choice in asthma, because they are the most effective bronchodilators and have minimal side effects when used correctly.² There is no place for short-acting and nonselective beta-agonists such as isoproterenol or metaproterenol.

Chemistry

Beta₂-agonists were developed logically by substitutions in the catecholamine structure of norepinephrine. The catechol-ring consists of hydroxyl-groups in the 3- and 4-positions of the benzene ring (Fig. 11.1). Norepinephrine differs from epinephrine only in the terminal amine group, which therefore indicates that modification at this site confers beta-receptor selectivity. Further substitution of the terminal amine resulted in beta₂-receptor selectivity, as in albuterol and terbutaline. Catecholamines are rapidly metabolized by the enzyme catechol-*o*-methyl transferase (COMT), which methylates in the 3-hydroxyl position and accounts for the short duration of action of catecholamines. Modification of the catechol ring, as in albuterol and terbutaline, prevents this degradation and therefore prolongs the drugs' effect. Catecholamines are also broken down by monoamine oxidase (MAO) in sympathetic nerve terminals and in the gastrointestinal tract through cleavage of the side chain of catecholamines. Isoproterenol, which is a substrate for MAO, is therefore metabolized in the gut, making absorption variable. Substitution in the amine group confers resistance to MAO and ensures reliable absorption. Many other beta₂-selective agonists have now been introduced and, although there may be differences in potency, there are no clinically significant differences in selectivity.

Inhaled beta₂-selective drugs in current clinical use (apart from rimeterol, which is broken down by COMT) have a similar duration of action of 3 to 6 hours. Inhaled beta₂-selective drugs that have a much longer duration of effect (more than 12 hours), such as salmeterol and formoterol, have been developed. Formoterol has a bulky

substitution in the aliphatic chain and has a high lipophilicity, which keeps the drug within the membrane, close to the receptor.³ Salmeterol has a long aliphatic chain, and its long duration of action may be a result of binding within the receptor binding cleft ("exosite") that anchors the drug in the binding cleft.⁴

Mode of Action

Beta-agonists produce bronchodilatation by directly stimulating beta₂-receptors in airway smooth muscle, which leads to relaxation.⁵ This can be demonstrated *in vitro* by the relaxant effect of isoproterenol on human bronchi and lung strips (indicating an effect on peripheral airways) and *in vivo* by a rapid decrease in airway resistance. Beta-receptors have been demonstrated in airway smooth muscle by direct receptor binding techniques, and autoradiographic studies indicate that beta-receptors are located in smooth muscle of all airways from the trachea to terminal bronchioles.⁵ The molecular mechanisms by which beta-agonists induce relaxation of airway smooth muscle have been extensively investigated.

Occupation of beta₂-receptors by agonists results in the activation of adenylyl cyclase via the stimulatory G protein (G_s). This increases intracellular cyclic 3',5'-adenosine monophosphate (cAMP), leading to activation of a specific kinase (protein kinase A); this kinase then phosphorylates several target proteins within the cell, leading to relaxation⁶ (Fig. 11.2).

These processes include lowering of intracellular calcium ion (Ca²⁺) concentration by active removal of Ca²⁺ from the cell and into intracellular stores; an inhibitory effect on phosphoinositide hydrolysis; direct inhibition of myosin light chain kinase; and opening of a large-conductance calcium-activated potassium channel (K_{Ca}), which repolarizes the smooth muscle cell and may stimulate the sequestration of Ca²⁺ into intracellular stores.^{7,8} Beta₂-receptors are directly coupled to K_{Ca} via G_s, so that relaxation of airway smooth muscle may occur independently of an increase in cAMP.⁷

Beta₂-agonists act as *functional antagonists* and reverse

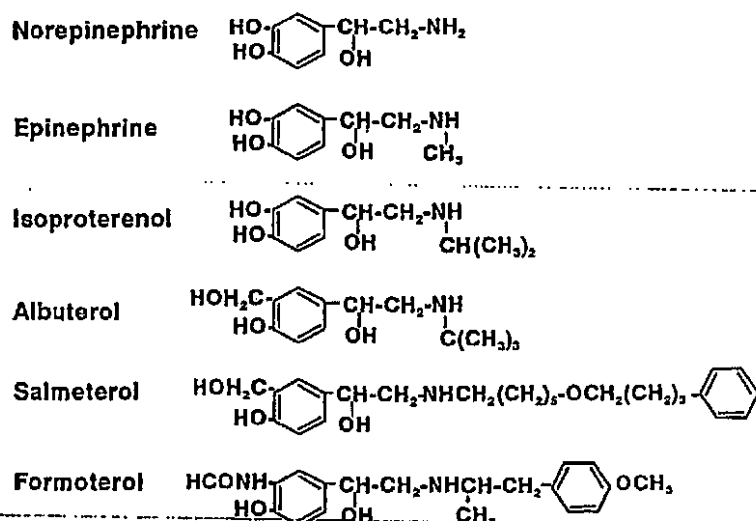
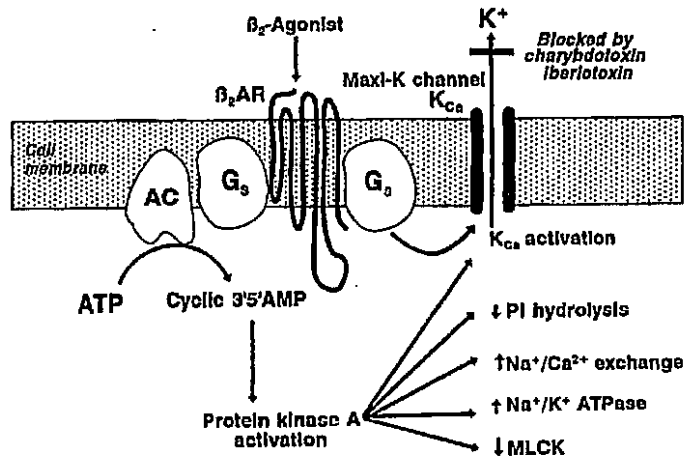


Figure 11.1 Chemical structures of some adrenergic agonists, showing development from catecholamines, are presented.

Figure 11.2 Molecular mechanism of action of beta₂-agonists on airway smooth muscle cells is presented. Activation of beta₂-receptors (β₂AR) results in activation of adenylyl cyclase (AC) via a stimulatory G protein (G_s) and increase in cyclic 3'5'-adenosine monophosphate (AMP). This activates protein kinase A, which then phosphorylates several target proteins, resulting in opening of calcium-activated potassium channels (K_{Ca}) or maxi-K channels, decreased phosphoinositide (PI) hydrolysis, increased sodium/calcium ion (Na⁺/Ca²⁺) exchange, increased sodium-potassium adenosine triphosphatase (Na⁺/K⁺ATPase) production, and decreased myosin light chain kinase (MLCK) activity. In addition, beta₂-receptors may be coupled directly via G_s to K_{Ca}.



bronchoconstriction regardless of the contractile agent. This is an important property, because many bronchoconstrictor mechanisms (neural and mediator) are likely to be contributory in asthma.

Beta₂-agonists have additional effects on airways, and beta-receptors are located in several different types of airway cells (Table 11.1). Beta₂-agonists can cause bronchodilation by a direct action on airway smooth muscle, but also indirectly by inhibiting the release of bronchoconstrictor mediators from inflammatory cells and of bronchoconstrictor neurotransmitters from airway nerves (Fig. 11.3). Other effects of beta₂-agonists include

- Prevention of mediator release from isolated human lung mast cells (via beta₂-receptors)
- Prevention of microvascular leakage and thus the development of bronchial mucosal edema after exposure to mediators such as histamine and leukotriene D₄
- Increase in mucus secretion from submucosal glands and ion transport across airway epithelium; these effects may enhance mucociliary clearance and therefore reverse the defect in clearance found in asthma. Beta₂-agonists appear to selectively stimulate mucous rather than serous cells, which may result in a more viscous mucus secretion, although the clinical significance of this is uncertain.
- Reduction in neurotransmission in human airway cholinergic nerves by an action at prejunctional beta₂-receptors to inhibit acetylcholine release. This

may contribute to their bronchodilator effect by reducing cholinergic reflex bronchoconstriction. In animal studies, beta₂-receptors act on sensory nerves to inhibit the release of bronchoconstrictor and inflammatory peptides such as substance P.

Although these additional effects of beta₂-agonists may be relevant to the prophylactic use of these drugs against various challenges, their rapid bronchodilator action can probably be attributed to a direct effect on airway smooth muscle.

Anti-Inflammatory Effects

Whether beta₂-agonists have anti-inflammatory effects in asthma has become an important issue, particularly with their increasing use and the introduction of long-acting inhaled beta₂-agonists. The inhibitory effects of beta₂-agonists on mast cell mediator release and microvascular leakage are clearly anti-inflammatory, suggesting that beta₂-agonists may modify acute inflammation. However beta₂-agonists do not appear to have a significant inhibitory effect on the chronic inflammation of asthmatic airways, which is controlled by corticosteroids. This has been confirmed by biopsy and bronchoalveolar lavage studies in patients with asthma who were taking beta₂-agonists regularly; no significant reduction in the number or activation in inflammatory cells in the airways was demonstrated, in contrast to resolution of the inflammation that occurs with inhaled corticosteroids.⁹⁻¹¹ This finding is likely to be related to the fact that beta₂-agonists do not have an important inhibitory effect on macrophages, eosinophils, or lymphocytes.^{12, 13}

Clinical Use

Inhaled beta₂-agonists are the most widely used and effective bronchodilators in the treatment of asthma.² When inhaled as an aerosol from a metered-dose inhaler (MDI), they are convenient, easy to use, rapid in onset, and without significant side effects. In addition to having an acute bronchodilator effect, they are effective in protecting against various challenges, such as exercise, cold air, and allergens. They are the bronchodilators of choice

Table 11.1 EFFECTS OF BETA-ADRENERGIC AGONISTS ON AIRWAYS

Relaxation of airway smooth muscle (proximal and distal airways)
Inhibition of mast cell mediator release
Inhibition of plasma exudation and airway edema
Increased mucociliary clearance
Increased mucus secretion
Decreased cough
No effect on chronic inflammation

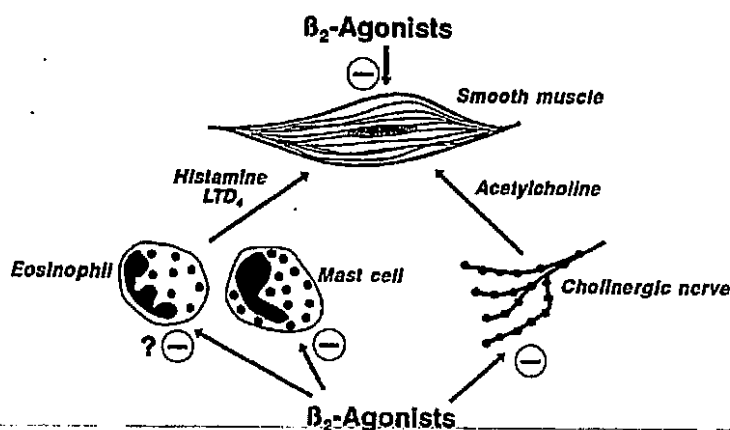


Figure 11.3 Direct and indirect effects of beta₂-agonists are shown. Beta₂-agonists relax airway smooth muscle cells directly but may also cause bronchodilation indirectly by inhibiting the release of mediators from inflammatory cells or neurotransmitters from cholinergic nerves. LTD₄ = leukotriene D₄.

for the treatment of acute severe asthma when the nebulized route of administration is as effective as and easier than intravenous use. The inhaled route is preferable to the oral route because side effects are less and also because it may be more effective. Short-acting inhaled beta₂-agonists, such as albuterol and terbutaline, should not be used on a regular basis in the treatment of mild asthma but should be used "as required" by symptoms, because increased usage serves as an indicator for the need for more anti-inflammatory therapy.

Oral beta₂-agonists are indicated as an additional bronchodilator. Slow-release preparations (such as slow-release albuterol or bambuterol) may be indicated for nocturnal asthma but are less useful than inhaled beta₂-agonists because of an increased risk of side effects.

Therapeutic Choices

Several beta₂-selective agonists are now available. These drugs are as effective as nonselective agonists in their bronchodilator action, because beneficial airway effects are mediated only by beta₂-receptors. However, they are less likely to produce cardiac stimulation than isoproterenol because beta₁-receptors are stimulated relatively less. With the exception of rimeterol (which retains the catechol ring structure and is therefore susceptible to rapid enzymatic degradation), they have a longer duration of action because they are resistant to uptake and enzymatic degradation by COMT and MAO. There is little to choose among the various short-acting beta₂-agonists currently available; all are usable by inhalation and orally, have a similar duration of action (usually 3 to 4 hours but less in severe asthma), and have similar side effects. Differences in beta₂-selectivity have been claimed but are not clinically important. Drugs in clinical use include *albuterol*, *terbutaline*, *fenoterol*, *tulobuterol*, *rimeterol*, and *pirbuterol*. It has been claimed that fenoterol is less beta₂-selective than albuterol and terbutaline, resulting in increased cardiovascular side effects,¹⁴ but this evidence is controversial, because all of these effects are mediated via beta₂-receptors.¹⁵ The increased incidence of cardiovascular effects is more likely to be related to the greater effective dose of fenoterol that is used and perhaps to more rapid absorption into the circulation.

Long-Acting Inhaled Beta₂-Agonists

The long-acting inhaled beta₂-agonists salmeterol and formoterol have been a major advance in asthma therapy. Both drugs have a bronchodilator action of longer than 12 hours and also protect against bronchoconstriction for a similar period.^{16, 17} They are particularly useful in treating nocturnal asthma. Both improve asthma control (when given twice daily), compared with regular treatment with short-acting beta₂-agonists four times daily. Both drugs are well tolerated. Tolerance to the bronchodilator effect of formoterol and to the bronchoprotective effects of formoterol and salmeterol has been demonstrated,¹⁸⁻²¹ but this is not a loss of protection, does not appear to be progressive, and is of doubtful clinical significance. Although both drugs have a similar duration of effect in clinical studies, there are some differences. Formoterol has a more rapid onset of action and is a fuller agonist than salmeterol. This might confer a theoretical advantage in more severe asthma, but it might also make it more likely to induce tolerance. Studies comparing the clinical efficacy of both drugs in mild and severe asthmatic patients are now needed.

Studies have suggested that an inhaled long-acting beta₂-agonist might be introduced earlier in therapy. In patients with asthma not controlled by either 400 or 800 µg of inhaled corticosteroids, the addition of salmeterol gave better control than did increasing the dose of inhaled steroid.^{22, 23} A similar result was found with formoterol, which also reduces the frequency of asthma attacks.²⁴ This suggests that a long-acting inhaled beta₂-agonist may be added to low-dose inhaled steroids if asthma is not controlled, as an alternative (and perhaps in preference) to increasing the dose of inhaled corticosteroids. Long-acting inhaled beta₂-agonists have also been shown to help patients with COPD.²⁵

At present it is recommended that long-acting inhaled beta₂-agonists should be used only in patients who are also prescribed inhaled steroids. In the future, long-acting inhaled beta₂-agonists may be used in fixed-combination inhalers (salmeterol + fluticasone, formoterol + budesonide), to improve compliance and to reduce the risk of patients' using these drugs as sole long-term treatment.

Table 11.2. SIDE EFFECTS OF BETA ₂ -AGONISTS
Muscle tremor (direct effect on skeletal muscle beta ₂ -receptors)
Tachycardia (direct effect on atrial beta ₂ -receptors; reflex effect from increased peripheral vasodilation on baroreceptor)
Hypokalemia (direct effect on skeletal muscle uptake of K ⁺ via beta ₂ -receptors)
Resistant asthma (reflex increased ventilation-perfusion mismatch due to pulmonary vasodilation)
Worsening of asthma (control of bronchodilation)

Side Effects

Unwanted effects are dose-related and are caused by stimulation of extrapulmonary beta-receptors (Table 11.2). Side effects are not common with inhaled therapy but are more common with oral or intravenous administration.

- *Muscle tremor* is caused by stimulation of beta₂-receptors in skeletal muscle and is the most common side effect. It may be more troublesome with elderly patients.
- *Tachycardia and palpitations* are caused by reflex cardiac stimulation secondary to peripheral vasodilation, by direct stimulation of atrial beta₂-receptors (the human heart is unusual in having a relatively high proportion of beta₂-receptors), and possibly also by stimulation of myocardial beta₁-receptors as the doses of beta₂-agonist are increased. These side effects tend to disappear with continued use of the drug, reflecting the development of tolerance.
- *Metabolic effects* (increase in free fatty acids, insulin, glucose, pyruvate, and lactate) are usually seen only after large systemic doses.
- *Hypokalemia* is a potentially more serious side effect. It is caused by beta₂-receptor stimulation of potassium entry into skeletal muscle, which may be secondary to a rise in insulin secretion. Hypokalemia might be serious in the presence of hypoxia, as in acute asthma, when there may be a predisposition to cardiac dysrhythmias. However, in practice, significant arrhythmias after use of nebulized beta₂-agonist have not been reported in acute asthma.
- *Ventilation-perfusion mismatching* is caused by pulmonary vasodilation in blood vessels previously constricted by hypoxia, resulting in the shunting of blood to poorly ventilated areas and a fall in arterial PO₂. Although in practice the effect of beta₂-agonists on arterial PO₂ is usually very small (a fall of less than 5 mm Hg), occasionally in severe chronic airway obstruction it is large, although it may be prevented by giving additional inspired oxygen.

Desensitization

Continuous treatment with an agonist often leads to desensitization (tolerance, subsensitivity), perhaps because of down-regulation of the receptor. For this reason, there have been many studies of bronchial beta-receptor function after prolonged therapy with beta-agonists.²⁶ Tolerance of nonairway beta₂-receptor mediated responses,

such as tremor and cardiovascular and metabolic responses, is readily induced in normal and asthmatic subjects. Tolerance of human airway smooth muscle to beta₂-agonists has been demonstrated *in vitro*,⁵ although the concentration of agonist necessary is high and the degree of desensitization is variable. Animal studies suggest that airway smooth muscle beta₂-receptors may be more resistant to desensitization than beta₂-receptors elsewhere owing to a high receptor reserve.⁵ In normal subjects, bronchodilator tolerance was demonstrated in some studies after high-dose inhaled albuterol, but not in others. In asthmatic patients, tolerance to the bronchodilator effects of beta₂-agonists has not usually been found.²⁶ However, tolerance develops to the bronchoprotective effects of beta₂-agonists, and this is more marked with indirect constrictors such as adenosine, allergen, and exercise (which activate mast cells) than with direct constrictors such as histamine and methacholine.^{27, 28} The reason for the relative resistance of airway smooth muscle beta₂-receptors to desensitization remains uncertain, but it may reflect the fact that there is a large receptor reserve, so that more than 90% of beta₂-receptors may be lost without any reduction in the relaxation response. The high level of beta₂-receptor gene expression in airway smooth muscle compared with peripheral lung²⁹ may also contribute to the resistance to tolerance, because there is likely to be a high rate of beta₂-receptor synthesis. Another possibility is that the expression of the enzyme beta-adrenergic receptor kinase (βARK), which phosphorylates and inactivates the occupied beta₂-receptor, is very low in airway smooth muscle.³⁰ By contrast, there is no receptor reserve in inflammatory cells and βARK expression is high, so that indirect effects of beta₂-agonists are more readily lost. However, tolerance to the bronchodilator effects of the long-acting beta₂-agonist formoterol has been reported.^{19, 21}

Experimental studies have shown that corticosteroids prevent the development of tolerance in airway smooth muscle and prevent and reverse the fall in pulmonary beta-receptor density.³¹ However, inhaled corticosteroids do not appear to prevent the tolerance to the bronchoprotective effect of inhaled beta₂-agonists, possibly because they do not reach airway smooth muscle in a sufficient concentration.^{32, 33}

Long-Term Safety

Because of a possible relationship between adrenergic drug therapy and the rise in asthma deaths in several countries during the early 1960s, doubts were cast on the

safety of beta-agonists. A causal relationship between beta-agonist use and mortality has never been firmly established, although in retrospective studies this would not be possible. A particular beta₂-agonist, fenoterol, was linked to the more recent rise in asthma deaths in New Zealand, because significantly more of the patients who died than case-matched control patients were prescribed fenoterol. This association was strengthened by two subsequent studies, and since fenoterol has not been available the asthma mortality has fallen dramatically.³⁴ An epidemiologic study based in Saskatchewan, Canada, examined the links between drugs prescribed for asthma and death or near-death from asthma attacks, based on computerized records of prescriptions. There was a marked increase in the risk of death with high doses of all inhaled beta₂-agonists.³⁵ The risk was greater with fenoterol, but when the dose was adjusted to the equivalent dose for albuterol there was no significant difference in risk for these two drugs. The link between high beta₂-agonist usage and increased asthma mortality does not prove a causal association, because patients with more severe and poorly controlled asthma, who are more likely to have an increased risk of fatal attacks, are also more likely to use higher doses of beta₂-agonist inhalers and less likely to use effective anti-inflammatory treatment. Among the patients who used regular inhaled steroids, there was a significant reduction in risk of death.

Regular use of inhaled beta₂-agonists has also been linked to increased asthma morbidity. In a study carried out in New Zealand, the regular use of fenoterol was associated with poorer control and with a small increase in airway responsiveness compared with patients using fenoterol "on demand" for symptom control over a 6-month period.³⁶ However, this association was not found in studies with albuterol.^{37,38} There is some evidence that regular use of inhaled albuterol may increase exercise-induced asthma³⁹ and increase inflammation in asthmatic airways. One possible mechanism is that beta-agonists may inhibit the anti-inflammatory action of glucocorticoids.⁴⁰

Although it is unlikely that normally recommended doses of beta₂-agonists worsen asthma, it is possible that this could occur with larger doses. Furthermore, some patients may be more susceptible if they have polymorphic forms of the beta₂-receptor that more rapidly down-regulate.⁴¹ Short-acting inhaled beta₂-agonists should be used only "on demand" for symptom control; if they are required frequently (more than three times weekly), then an inhaled anti-inflammatory drug is needed. There is an association between increased risk of death from asthma and use of high doses of inhaled beta₂-agonists; although this may reflect severity, it is also possible that high doses of beta₂-agonists have a deleterious effect on asthma. High concentrations of beta₂-agonists interfere with the anti-inflammatory action of steroids.⁴² Patients receiving high doses of beta₂-agonists (more than 1 canister per month) should be treated with effective anti-inflammatory treatments, and attempts should be made to reduce the daily dose of inhaled beta₂-agonist.

Future Trends

Beta₂-agonists will continue to be the bronchodilators of choice for the foreseeable future, because they are effective

in all patients and have few or no side effects when used in low doses. It will be very difficult to find a bronchodilator that improves on the efficacy and safety of inhaled beta₂-agonists. Although some concerns have been expressed about the long-term effects of inhaled beta₂-agonists, the evidence suggests that they are safe when used as required for symptom control. If patients are using large doses, their asthma should be assessed; an appropriate anti-inflammatory treatment should be given, and attempts should be made to reduce the dose. Long-acting inhaled beta₂-agonists are a very useful addition for long-term control in asthma and COPD. In the future, these drugs may also be useful for treatment of acute exacerbations. Improvement in inhaled beta₂-agonists might include an increased selectivity for beta₂-receptors and a longer duration of action. There is little advantage to be gained by improving beta₂-receptor selectivity, because most of the side effects of beta-agonists are caused by beta₂-receptor stimulation (muscle tremor, tachycardia, hypokalemia). It may be possible to develop once-daily inhaled beta₂-agonists in the future. *R*-albuterol is the active enantiomer of albuterol; it was developed because of animal studies showing that the *S*-albuterol in the normal racemic (*RS*) mixture that is used clinically could induce airway hyperresponsiveness in guinea pigs.⁴³ In single doses, inhaled *R*-albuterol has an equivalent effect to *RS*-albuterol, whereas *S*-albuterol has a weak effect, providing little indication that the *R*-enantiomer will have any clinical advantage.⁴⁴

Theophylline

Methylxanthines such as theophylline, which are related to caffeine, have been used in the treatment of asthma since 1930. Theophylline is still the most widely used antiasthma therapy worldwide because it is inexpensive. Theophylline became more useful with the availability of rapid plasma assays and the introduction of reliable slow-release preparations.⁴⁵ However, the frequency of side effects and the relatively low efficacy of theophylline have led to reduced usage; inhaled beta₂-agonists are far more effective as bronchodilators, and inhaled steroids have a greater anti-inflammatory effect. However, in patients with severe asthma, theophylline still remains a very useful drug. There is increasing evidence that theophylline has an anti-inflammatory or immunomodulatory effect.⁴⁶

Chemistry

Theophylline is a methylxanthine similar in structure to the common dietary xanthines caffeine and theobromine. Several substituted derivatives have been synthesized, but none has any advantage over theophylline,⁴⁷ apart from the 3-propyl derivative, enprofylline, which is more potent as a bronchodilator and may have fewer toxic effects. Many salts of theophylline have also been marketed, the most common being aminophylline, which is the ethylenediamine salt used to increase solubility at neutral pH. Other salts, such as choline theophyllinate, do not have any advantage, and some, such as acepihylline, are virtually inactive.⁴⁸

Table 11.3. MECHANISMS OF ACTION OF THEOPHYLLINE

• Inhibition of phosphodiesterases
• Adenosine receptor antagonism, especially A_{2B}
• Stimulation of epinephrine release
• Inhibition of histamine release
• Inhibition of interleukin-10 release

Mode of Action

Although theophylline has been in clinical use for more than 50 years, its mechanism of action is still uncertain and several modes of action have been proposed (Table 11.3). In addition to its bronchodilator action, theophylline has many other actions that may be relevant to its antiasthma effect (Fig. 11.4):

- **Inhibition of phosphodiesterases.** Phosphodiesterases (PDEs) break down cyclic nucleotides in the cell, thereby leading to an increase in intracellular cAMP and cyclic 3'5'-guanosine monophosphate (cGMP) concentrations (Fig. 11.5). Theophylline is a nonselective PDE inhibitor, but the degree of inhibition is minor at concentrations of theophylline that are within the "therapeutic range." PDE inhibition almost certainly accounts for the bronchodilator action of theophylline,⁴⁸ but it may not account for the nonbronchodilator effects of theophylline that are seen at subbronchodilator doses. Inhibition of PDEs should lead to synergistic interaction with beta-agonists, but this has not been convincingly demonstrated in vivo. Several isoenzyme families of PDEs have now been recognized,⁴⁹ and some are more important in smooth muscle relaxation.
- **Adenosine receptor antagonism.** Theophylline inhibits adenosine receptors at therapeutic concentrations.⁵⁰ Of particular importance may be the adenosine A_{2B} receptor on mast cells, which is activated by adenosine in asthmatic patients. In vitro adeno-

sine has little direct effect on human airway smooth muscle, but it causes bronchoconstriction by releasing histamine and leukotrienes.⁵¹ Enprofylline, another methylxanthine that has a similar antiasthma profile to theophylline, also inhibits A_{2B} receptors.⁵²

- **Secretion of epinephrine.** Theophylline increases the secretion of epinephrine from the adrenal medulla, although the increase in plasma concentration is small and insufficient to account for any significant bronchodilator effect.⁵³
- **Increased secretion of interleukin-10 (IL-10).** Theophylline increases IL-10 secretion from human blood mononuclear cells.⁵⁴ IL-10 is a potent inhibitor of allergic inflammation, and its secretion may be defective in asthma.
- **Nonbronchodilator mechanisms.** Despite extensive study, it has been difficult to elucidate the molecular mechanism for the nonbronchodilator antiasthma actions of theophylline. It is possible that any beneficial effect in asthma is related to its action on other cells (e.g., platelets, T lymphocytes, macrophages) or on airway microvascular leak and edema in addition to airway smooth muscle relaxation. Indeed, theophylline is a rather ineffective bronchodilator and its antiasthma effect is more likely to be explained by other effects. It may be relevant that theophylline is ineffective when given by inhalation but is effective when a critical plasma concentration is reached⁵⁵; this may indicate that it has important effects on cells other than those in the airway. It is possible that theophylline acts as an immunomodulator and has effects on T-lymphocyte function in vitro. A placebo-controlled theophylline withdrawal study indicated that theophylline has an immunomodulatory effect and decreases the number of activated T cells in the airways, probably by blocking their trafficking from the circulation.⁵⁶ Theophylline inhibits the late response to allergen challenge more effectively than the early response⁵⁷ and inhibits the influx of eosinophils into the airways.⁵⁸

Pharmacokinetics

There is a close relationship between improvement in airway function and serum theophylline concentration.

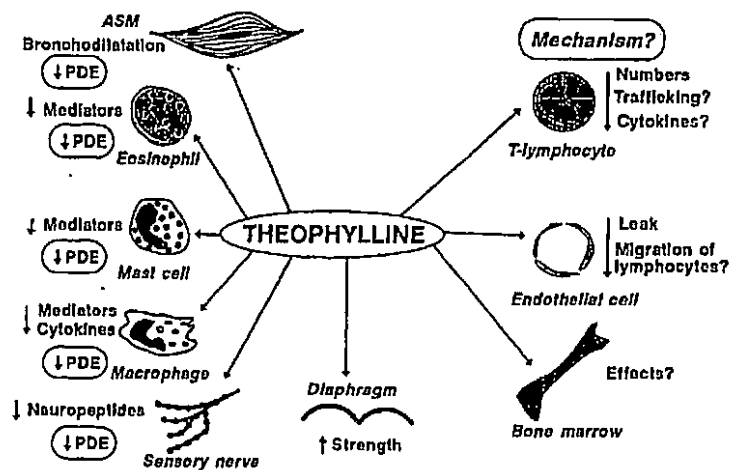


Figure 11.4 Theophylline has effects on several other cells in addition to airway smooth muscle. Some these effects are mediated via inhibition of phosphodiesterases (PDE).

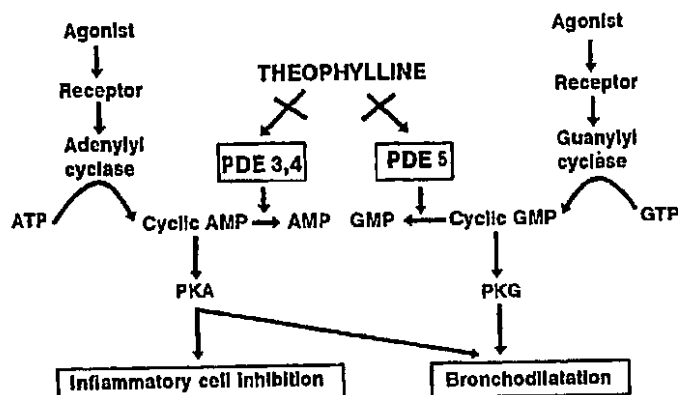


Figure 11.5 The inhibitory effect of theophylline on phosphodiesterases (PDE) may result in bronchodilatation and inhibition of inflammatory cells. ATP = adenosine triphosphate; AMP = adenosine monophosphate; PKA = protein kinase A; GTP = guanosine triphosphate; GMP = guanosine monophosphate; PKG = protein kinase G.

Below 10 mg/L the therapeutic effects (at least in terms of bronchodilatation) are small and above 25 mg/L additional benefits are outweighed by side effects, so the therapeutic range is usually taken as 10 to 20 mg/L. It is now clear that theophylline has antiasthma effects other than bronchodilatation and that these may be seen at concentrations lower than 10 mg/L. A more useful therapeutic range is 5 to 15 mg/L. The dose of theophylline required to yield these therapeutic concentrations varies among subjects, largely because of differences in clearance. In addition, there may be differences in bronchodilator response to theophylline and, with acute bronchoconstriction, higher concentrations may be required to produce bronchodilatation. Theophylline is rapidly and completely absorbed, but there are large interindividual variations in clearance owing to differences in hepatic metabolism (Table 11.4). Theophylline is metabolized in the liver by the cytochrome P-450 microsomal enzyme system (mainly CYP1A2), and a large number of factors may influence hepatic metabolism.

Increased clearance is seen in children (1 to 16 years) and in cigarette and marijuana smokers. Concurrent administration of phenytoin and phenobarbitone increases

activity of P-450, resulting in increased metabolic breakdown, so higher doses may be required.

Reduced clearance is found in liver disease, pneumonia, and heart failure, and doses need to be reduced to half and plasma levels monitored carefully. Reduced clearance is also seen with certain drugs, including erythromycin, certain quinolone antibiotics (ciprofloxacin, but not ofloxacin), allopurinol, cimetidine (but not ranitidine) and zafirlukast, which interfere with cytochrome P-450 function. Thus, if a patient on maintenance theophylline requires a course of erythromycin, the dose of theophylline should be halved. Viral infections and vaccination may also reduce clearance, and this may be particularly important in children. Because of these variations in clearance, individualization of theophylline dosage is required. With slow-release preparations, plasma concentrations should be measured 4 hours after the last dose, when a steady state has usually been achieved. There is no significant circadian variation in theophylline metabolism; there may be delayed absorption at night, which may relate to the supine posture.

Routes of Administration

Intravenous aminophylline has been used for many years in the treatment of acute, severe asthma. The recommended dose is now 6 mg/kg given intravenously over 20 to 30 minutes, followed by a maintenance dose of 0.5 mg/kg/hr. If the patient is already taking theophylline or there are any factors that decrease clearance, these doses should be halved and the plasma level checked more frequently.

Oral plain theophylline tablets or elixir, which are rapidly absorbed, cause wide fluctuations in plasma levels and are not recommended. Several effective sustained-release preparations are now available. They are absorbed at a constant rate and provide steady plasma concentrations over a 12- to 24-hour period. Although there are differences among preparations, they are relatively minor and of no clinical significance. Both slow-release aminophylline and theophylline are available and are equally effective (although the ethylene diamine component of aminophylline has very occasionally been implicated in allergic reactions). For continuous treatment, approximately 8 mg/kg twice daily is needed, although some preparations are designed for once-daily administration.

Table 11.4 FACTORS AFFECTING CLEARANCE OF THEOPHYLLINE

Increased clearance

Enzyme induction (rifampicin, phenobarbitone, ethionel)
Smoking (tobacco, marijuana)
High-protein, low-carbohydrate diet
Barbecued meat
Childhood

Decreased clearance

Enzyme inhibition (cimetidine, erythromycin, ciprofloxacin, allopurinol, zileuton, zafirlukast)
Congestive heart failure
Liver disease
Pneumonia
Viral infection and vaccination
High-carbohydrate diet
Old age

For nocturnal asthma, a single dose of slow-release theophylline at night is often effective, and often more effective than an oral slow-release β_2 -agonist preparation. Once optimal doses have been determined, plasma concentrations usually remain stable, provided no factors that alter clearance change.

Aminophylline may be given as a suppository, but rectal absorption is unreliable and proctitis may occur, so this route is best avoided. Inhalation of theophylline is irritant and ineffective. Intramuscular injections of theophylline are very painful and should never be given.

Clinical Use

In patients with acute asthma, intravenous aminophylline is less effective than nebulized β_2 -agonists and should therefore be reserved for those patients who fail to respond to β_2 -agonists. Theophylline should not be added routinely to nebulized β_2 -agonists, because it does not increase the bronchodilator response⁵⁹ and may only increase their side effects.⁶⁰

Theophylline has little or no effect on bronchomotor tone in normal airways but reverses bronchoconstriction in asthma, although it is less effective than inhaled β_2 -agonists and is more likely to have unwanted effects. In fact, any role of theophylline in the management of asthma has been questioned. There is good evidence that theophylline and β_2 -agonists have additive effects, even if true synergy is not seen, and there is evidence that theophylline may provide an additional bronchodilator effect even when maximally effective doses of β_2 -agonist have been given.⁶¹ This means that, if adequate bronchodilatation is not achieved by a β_2 -agonist alone, theophylline may be added to the maintenance therapy with benefit. Controlled trials have demonstrated that the addition of low-dose theophylline to either high or low doses of inhaled corticosteroids in patients whose asthma is not adequately controlled provides better symptom control and lung function than does doubling of the dose of inhaled steroid.^{62, 63} Theophylline may be useful in some patients with nocturnal asthma, because slow-release preparations are able to provide therapeutic concentrations overnight and are more effective than slow-release oral β_2 -agonists.⁶⁴ Although theophylline is less effective than a β_2 -agonist and corticosteroids, there are a minority of asthmatic patients who appear to derive unexpected benefit, and even patients receiving oral steroids may show a deterioration in lung function when theophylline is withdrawn.⁶⁵

Theophylline may also benefit patients with COPD, increasing exercise tolerance, although without any improvement in spirometry tests unless it is combined with an inhaled β_2 -agonist.⁶⁶ However, theophylline may reduce trapped gas volume, suggesting an effect on peripheral airways, and this may explain why some patients obtain considerable symptomatic improvement.⁶⁷

Side Effects

Unwanted effects of theophylline are usually related to plasma concentration and tend to occur when plasma levels exceed 20 mg/L. However, some patients develop

side effects even at low plasma concentrations. To some extent, side effects may be reduced by gradually increasing the dose until therapeutic concentrations are achieved.

The most common side effects are headache, nausea and vomiting, abdominal discomfort, and restlessness (Table 11.5). There may also be increased acid secretion and diuresis. There has been concern that theophylline, even at therapeutic concentrations, might lead to behavioral disturbance and learning difficulties in school children,⁶⁸ although it is difficult to design adequate controls for such studies.

At high concentrations, convulsions and cardiac arrhythmias may occur. Some of the side effects (central stimulation, gastric secretion, diuresis, and arrhythmias) may be caused by adenosine receptor antagonism and may therefore be avoided by drugs such as enprofylline, which has less adenosine antagonism at the adenosine receptors involved.

Future Use

Theophylline use has been declining, partly because of the problems with side effects, but mainly because more effective therapy with inhaled corticosteroids has been introduced. Oral theophylline is still a very useful treatment in some patients with difficult asthma and appears to have effects beyond those provided by steroids. Rapid-release theophylline preparations are cheap and are the only affordable antiasthma medication in some developing countries. There is increasing evidence that theophylline has some antiasthma effect at doses that are lower than those needed for bronchodilatation, and plasma levels of 5 to 15 mg/L are recommended, instead of the previously recommended 10 to 20 mg/L. Low-dose theophylline gives better control than does doubling of the dose of inhaled steroids in patients whose asthma is not controlled with a dose of 800 μ g daily,⁶² so it may be a less expensive alternative to the addition of a long-acting β_2 -agonist or anti-leukotriene.

Anticholinergics

Datura plants, which contain the muscarinic antagonist stramonium, were smoked for relief from asthma two centuries ago. Atropine, a related naturally occurring compound, was also introduced for treatment of asthma but, because these compounds produced side effects, particularly drying of secretions, less soluble quaternary compounds, such as atropine methylnitrate and ipratropium bromide, were introduced. These compounds are topically active and are not significantly absorbed from the respiratory or gastrointestinal tract.

Table 11.5 SIDE EFFECTS OF THEOPHYLLINE

Nausea and vomiting	Behavioral disturbance (?)
Headaches	Cardiac arrhythmias
Gastric discomfort	Epileptic seizures
Diuresis	

Mode of Action

Anticholinergics are specific antagonists of muscarinic receptors and, in therapeutic use, have no other significant pharmacologic effects. In animals and humans, there is a small degree of resting bronchomotor tone that is probably a result of tonic vagal nerve impulses that release acetylcholine in the vicinity of airway smooth muscle, since it can be blocked by anticholinergic drugs. Evidence suggests that acetylcholine may be released from other airway cells, including epithelial cells.⁶⁹ There is considerable evidence that cholinergic pathways may play an important role in regulating acute bronchomotor responses in animals, and there are a wide variety of mechanical, chemical, and immunologic stimuli that are capable of eliciting reflex bronchoconstriction via vagal pathways. This suggests that cholinergic mechanisms might underlie airway hyperresponsiveness and acute bronchoconstrictor responses in asthma, with the implication that anticholinergic drugs would be effective bronchodilators in asthma. Many controlled studies have now been performed.⁷⁰ In general, although these drugs may afford protection against acute challenge by sulfur dioxide, inert dusts, cold air, and emotional factors, they are less effective against antigen challenge, exercise, and fog. This is not surprising, because anticholinergic drugs only inhibit reflex cholinergic bronchoconstriction and could have no significant blocking effect on the *direct* effects of inflammatory mediators such as histamine and leukotrienes on bronchial smooth muscle. Furthermore, cholinergic antagonists probably have little or no effect on mast cells, microvascular leak, or the chronic inflammatory response.

Theoretically, anticholinergics may reduce airway mucus secretion and reduce mucus clearance, but this does not occur in clinical studies. Oxitropium bromide has been shown to reduce mucus secretion in patients with COPD.⁷¹

Clinical Use

In asthmatic subjects, anticholinergic drugs are less effective than beta-agonists as bronchodilators⁷⁰ and offer less efficient protection against various bronchial challenges, although their duration of action is longer. These drugs may be more effective in older patients with asthma in whom there is an element of fixed airway obstruction. Nebulized anticholinergic drugs are effective in acute severe asthma, although they are less effective than beta-agonists in this situation. Nevertheless, in the acute and chronic treatment of asthma, anticholinergic drugs may have an additive effect with beta-agonists and should therefore be considered when control of asthma is not adequate with beta-agonists,⁷² particularly if there are problems with theophylline or if inhaled beta-agonists give troublesome tremor in elderly patients. The time course of bronchodilatation with anticholinergic drugs is slower than with beta-agonists, reaching a peak only 1 hour after inhalation but persisting for longer than 6 hours.

In COPD, anticholinergic drugs may be as effective as, or even superior to, beta-agonists.^{73, 74} Their relatively

greater effect in COPD than in asthma may be explained by an inhibitory effect on vagal tone which, although not necessarily increased in COPD, may be the only reversible element of airway obstruction that is exaggerated by geometric factors in a narrowed airway (Fig. 11.6).

Therapeutic Choices

Ipratropium bromide is the most widely used anticholinergic inhaler and is available in MDI and nebulized preparations.⁷⁵ The onset of bronchodilatation is relatively slow and is usually maximal 30 to 60 minutes after inhalation, but it may persist for up to 8 hours. This drug usually is given by MDI four times daily on a regular basis, rather than intermittently for symptom relief, in view of its slow onset of action.

Oxitropium bromide is a quaternary anticholinergic bronchodilator that is similar to ipratropium bromide in terms of receptor blockade.⁷⁶ It is available in higher doses by inhalation and therefore may have a more prolonged effect. For this reason, it may be useful in some patients with nocturnal asthma.⁷⁷

Fixed-combination inhalers of an anticholinergic and a beta₂-agonist are popular, particularly in patients with COPD. Several studies have demonstrated additive effects of these two drugs, providing an advantage over increased doses of beta₂-agonist in patients who have side effects.

Side Effects

Inhaled anticholinergic drugs are usually well tolerated, and there is no evidence for a decline in responsiveness

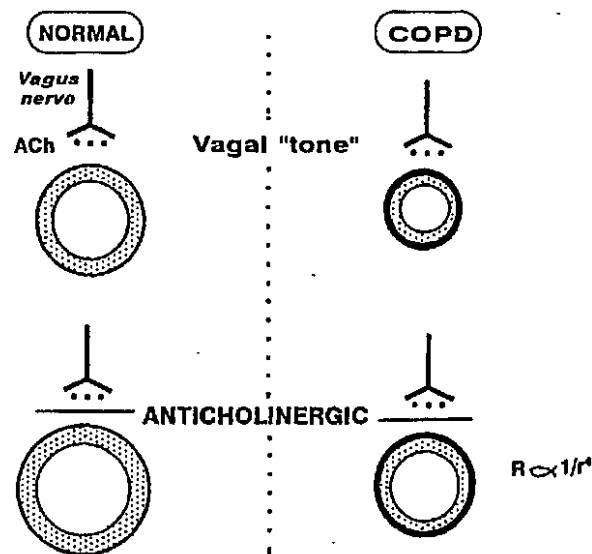


Figure 11.6 Anticholinergic drugs inhibit vagally mediated airway tone, leading to bronchodilatation. This effect is small in normal airways but is greater in airways of patients with chronic obstructive pulmonary disease (COPD), which are structurally narrowed. Airway resistance (R) is inversely proportional to the fourth power of the airway radius (r). ACh = acetylcholine.

with continued use. On stopping inhaled anticholinergics, a small rebound increase in responsiveness has been described,⁷⁸ but the clinical relevance of this effect is uncertain. Atropine has side effects that are dose-related; they are caused by cholinergic antagonism in other systems that may lead to dryness of the mouth, blurred vision, and urinary retention. Systemic side effects after ipratropium bromide are very uncommon, because there is virtually no systemic absorption.⁷⁹ Because cholinergic agonists stimulate *mucus secretion*, there have been several studies of mucus secretion with anticholinergic drugs, because of concern that they may reduce secretion and lead to more viscous mucus. Atropine reduces mucociliary clearance in normal subjects and in patients with asthma and chronic bronchitis, but ipratropium bromide, even in high doses, has no detectable effect in either normal subjects or in patients with airway disease. A significant unwanted effect is the unpleasant, *bitter taste* of inhaled ipratropium, which may contribute to poor compliance with this drug. Nebulized ipratropium bromide may precipitate *glaucoma* in elderly patients due to a direct effect of the nebulized drug on the eye. This may be prevented by nebulization with a mouthpiece rather than a face mask. Reports of *paradoxical bronchoconstriction* with ipratropium bromide, particularly when given by nebulizer, were largely explained by the hypotonicity of the nebulizer solution and by antibacterial additives such as benzalkonium chloride and ethylenediamine tetraacetic acid (EDTA). Nebulizer solutions free of these problems are less likely to cause bronchoconstriction. Occasionally, bronchoconstriction may occur with ipratropium bromide given by MDI. It is possible that this is a result of blockade of prejunctional M_2 -receptors on airway cholinergic nerves that normally inhibit acetylcholine release.

Future Developments

Anticholinergics are the bronchodilators of choice in COPD and therefore have a large market. There has been a search for selective muscarinic antagonists. Ipratropium bromide and oxitropium bromide are nonselective; in addition to blocking M_3 -receptors in airway smooth muscle and M_1 receptors in ganglia, they also block prejunctional M_2 -receptors and may therefore increase the release of acetylcholine from airway cholinergic nerves.^{79, 80} This suggests that selective M_3 or mixed M_1/M_3 antagonists may have an advantage over nonselective antagonists. However, it has been difficult to develop such drugs, and antagonists such as darifenacin (M_3 -selective) and

revatropate do not have a high degree of selectivity.⁸¹ The most important development is the discovery of *tiotropium bromide*, a quaternary ammonium compound similar to ipratropium that has a unique kinetic selectivity and dissociates very slowly from M_1 and M_3 receptors but rapidly from M_2 receptors.⁸² Tiotropium has a very long duration of action and protects against cholinergic challenge for more than 3 days after a single dose.⁸³ It is effective as a bronchodilator in patients with COPD⁸⁴ and is suitable as a once-daily inhaled treatment that is very well tolerated.

New Bronchodilators

Several new classes of bronchodilator are under development (Table 11.6), but it is difficult to envisage a more effective bronchodilator than inhaled β_2 -agonists for asthma and the long-acting anticholinergic tiotropium bromide for COPD. It has been difficult to find new classes of bronchodilators, and several new potential drugs have had problems with vasodilator side effects.

Potassium Channel Openers

Potassium (K^+) channels are involved in recovery of excitable cells after depolarization and therefore are important in stabilization of cells. K^+ channel openers such as cromakalim or levcromakalim (the *levo*-isomer of cromakalim) open adenosine triphosphate (ATP)-dependent K^+ channels in smooth muscle and therefore relax airway smooth muscle.⁸⁵ This suggests that K^+ channel activators may be a novel class of bronchodilators.^{86, 87} Clinical studies in asthma have been disappointing, with no bronchodilation or protection against bronchoconstrictor challenges.⁸⁸ However, the cardiovascular side effects of these drugs (postural hypotension, flushing) limit the oral dose. Inhaled K^+ channel openers also have had problems, but new developments include K^+ channel openers that open K_{Ca} channels that are also opened by β_2 -agonists; these drugs may be better tolerated.⁸⁹

Phosphodiesterase Inhibitors

PDEs break down cAMP and, if inhibited, causes cAMP to increase, leading to bronchodilation. There are at least nine isoenzyme families of PDEs, some of which may be selectively inhibited.⁴⁹ In human airway smooth muscle, PDE3 and PDE4 isoenzymes are important in relaxation, and therefore selective inhibitors may be use-

Table 11.6 NEW BRONCHODILATORS

Long-acting inhaled β_2 -agonists (e.g., salmeterol, formoterol, [A2001])
Selective/long-acting muscarinic antagonists (M_1/M_3 antagonists) under development (e.g., tiotropium)
Potassium channel activators (e.g., levcromakalim)
Phosphodiesterase 3/4 inhibitors
Nitrovasodilators
Vasoactive intestinal peptide and analogs
Atrial natriuretic peptide and analogs (urodilatin)

ful bronchodilators.⁹⁰ Combined PDE3/4 inhibitors have been developed but have proved to be ineffective because of side effects such as nausea (associated with PDE4 inhibition).

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) activates guanylyl cyclase and increases cGMP, leading to bronchodilation. ANP is a bronchodilator in asthma⁹¹ and gives comparable effects to β_2 -agonists.^{92, 93} Because it works via a different mechanism from β_2 -agonist, it may provide useful additional bronchodilation and may be useful in acute, severe asthma when β_2 -receptor function may be impaired.

CONTROLLER DRUGS

Inflammation underlies several airway diseases, although the type of inflammatory responses may differ among diseases. Anti-inflammatory drugs suppress the inflammatory response by inhibiting components of the inflammation, such as inflammatory cell infiltration and activation or release, synthesis, and effects of inflammatory mediators. Only corticosteroids are truly anti-inflammatory; other drugs improve control of asthma without acute bronchodilator effects. These drugs are now termed *controllers*.

Corticosteroids

Corticosteroids are used in the treatment of several lung diseases. They were introduced for the treatment of asthma shortly after their discovery in the 1950s and remain the most effective therapy available for asthma. However, side effects and fear of adverse effects have limited their use, and there has been considerable research into discovering new or related agents that retain the beneficial action on airways without unwanted effects. The introduction of inhaled corticosteroids, initially as a way of reducing the requirement for oral steroids, has revolutionized the treatment of chronic asthma.⁹⁴ Now, asthma is viewed as a chronic inflammatory disease, and inhaled steroids may even be considered as first-line therapy in all but the mildest of cases. Oral steroids are indicated in the treatment of several other pulmonary diseases, such as sarcoidosis, interstitial lung diseases, and pulmonary eosinophilic syndromes.

Chemistry

The adrenal cortex secretes cortisol (hydrocortisone) and, by modification of its structure, it was possible to develop derivatives such as prednisolone and dexamethasone with enhanced corticosteroid effects but reduced mineralocorticoid activity. These derivatives with potent glucocorticoid actions were effective in asthma when given systemically but had no antiasthmatic activity when given by inhalation. Further substitution in the 17 α -ester position resulted in steroids with high topical activity, such as beclomethasone dipropionate (BDP), triamcinolone, flunisolide, budesonide, and fluticasone propionate, which were po-

tent in the skin (dermal blanching test) and were later found to have significant antiasthma effects when given by inhalation (Fig. 11.7).

Mode of Action

Corticosteroids enter target cells and bind to glucocorticoid receptors in the cytoplasm. There is only one type of glucocorticoid receptor and no evidence for different subtypes that might mediate different aspects of steroid action.^{95, 96} The steroid-receptor complex is transported to the nucleus, where it binds to specific sequences on the upstream regulatory element of certain target genes, resulting in increased or decreased transcription of the gene, which leads to increased or decreased protein synthesis. Glucocorticoid receptors may also interact *directly* with protein transcription factors in the cytoplasm and nucleus and thereby influence the synthesis of certain proteins independently of an interaction with DNA in the cell nucleus.⁹⁵ The direct repression of transcription factors such as activator protein-1 (AP-1) and nuclear factor-kappa B (NF- κ B) is likely to account for many of the

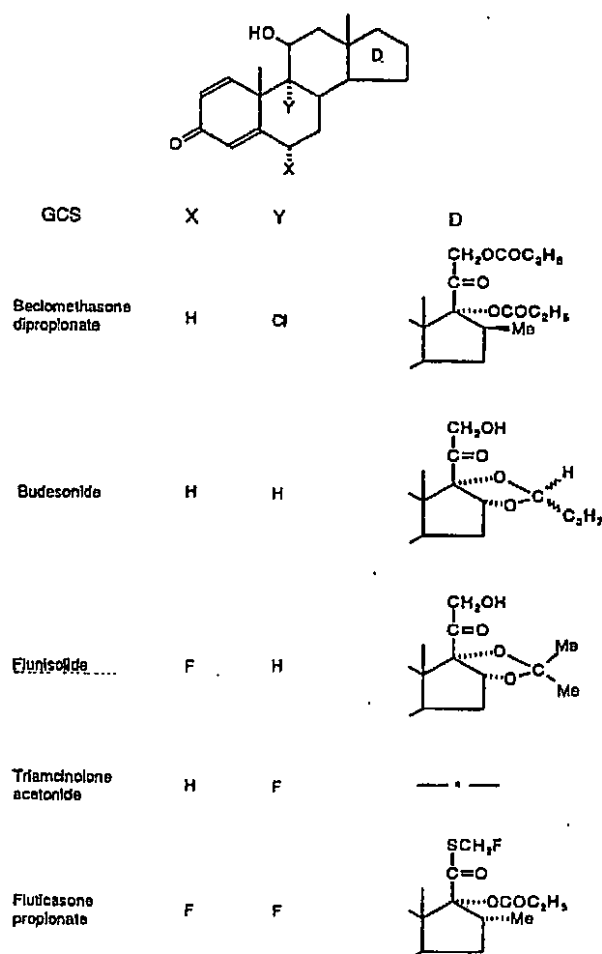


Figure 11.7 Structures of inhaled glucocorticosteroids (GCS) are shown.

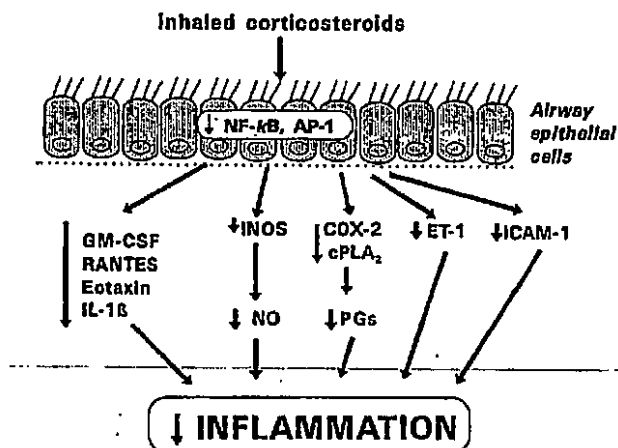


Figure 11.9 Inhaled steroids may inhibit the transcription of several "inflammatory" genes in airway epithelial cells and thereby reduce inflammation in the airway wall. NF- κ B = nuclear factor κ B; AP-1 = activator protein-1; GM-CSF = granulocyte-macrophage colony-stimulating factor; IL-1 = interleukin-1; INOS = inducible nitric oxide synthase; NO = nitric oxide; COX-2 = inducible cyclooxygenase; cPLA₂ = cytoplasmic phospholipase A₂; PGs = prostaglandins; ET = endothelin; ICAM = intercellular adhesion molecule.

whether this is relevant to their effect in asthma is uncertain. Steroids potentiate the effects of beta-agonists on bronchial smooth muscle and prevent and reverse beta-receptor desensitization in airways in vitro and in vivo. At a molecular level, steroids increase the gene transcription of beta₂-receptors in human lung,¹⁰² and systemic glucocorticoids prevent down-regulation of beta₂-receptors in animal lungs.³¹ However, inhaled steroids do not appear to prevent the development of tolerance to inhaled beta₂-agonists in human airways.³²

Pharmacokinetics

Prednisolone is readily and consistently absorbed after oral administration, with little interindividual variation. Enteric coatings to reduce the incidence of dyspepsia delay absorption but not the total amount of drug absorbed. Prednisolone is metabolized in the liver, and drugs such as rifampicin, phenobarbitone, or phenytoin, which induce hepatic enzymes, lower the plasma half-life of prednisolone.¹⁰³ The plasma half-life is 2 to 3 hours, although its biologic half-life is approximately 24 hours, so it is suitable for daily dosing. There is no evidence that previous exposure to steroids changes their subsequent metabolism. Prednisolone is approximately 92% protein bound, the majority to a specific protein transcortin and the remainder to albumin; it is the unbound fraction that is biologically active.

Some patients, usually with severe asthma, apparently fail to respond to corticosteroids.¹⁰⁴ "Steroid-resistant" asthma is not caused by impaired absorption or metabolism of steroids but by a reduced anti-inflammatory action of corticosteroids.

The pharmacokinetics of inhaled corticosteroids is important in relation to systemic effects.¹⁰⁵ The fraction of steroid that is inhaled into the lungs acts locally on the airway mucosa; it may be absorbed from the airway and alveolar surface and thereby reach the systemic circulation. The fraction of inhaled steroid that is deposited in the oropharynx is swallowed and absorbed from the gut. The absorbed fraction may be metabolized in the liver before reaching the systemic circulation (Fig. 11.10). Budesonide and fluticasone propionate have a greater first-pass metabolism than BDP and are therefore less likely to produce systemic effects at high inhaled doses. The use of a large-volume spacer chamber reduces oropharyngeal deposition and therefore reduces systemic absorption of corticosteroids.¹¹¹ Rinsing the mouth and discarding the rinse has a similar effect¹⁰⁶; this procedure should be used with high-dose dry-powder steroid inhalers, because spacer chambers cannot be used with these devices.

Routes of Administration

Oral. Prednisolone and prednisone are the most commonly used steroids. Prednisone is converted to prednisolone in the liver. Clinical improvement with oral steroids may take several days, and the maximal beneficial effect is usually achieved with 30 to 40 mg prednisone daily, although a few patients may need 60 to 80 mg daily to achieve control of symptoms. The usual maintenance dose is on the order of 10 to 15 mg/day. Oral steroids are usually given as a single dose in the morning; this coincides with the normal diurnal increase in plasma cortisol and therefore results in less adrenal suppression than if it is given in divided doses or at night. However, the anti-inflammatory effect of steroids may be greater if it is given in the afternoon, presumably because of increased steroid responsiveness. It may therefore be worth switching to afternoon doses if a patient does not show a good response to oral steroids. The amount of steroid bound to transcortin is less during the day, resulting in higher free concentrations, and this might contribute to the greater functional effect. Alternate-day treatment has the advantage of less adrenal suppression, although in many patients control of asthma is not optimal with this regimen.

Intravenous. Parenteral steroids are indicated in acute severe exacerbations of asthma. Hydrocortisone is the steroid of choice, because it has the most rapid onset (5 to 6 hours after administration), being more rapid than prednisolone (8 hours). The dose required is still uncertain, but it is common to give hydrocortisone 4 mg/kg initially, followed by a maintenance dose of 3 mg/kg every 6 hours. These doses are based on the argument that it is necessary to maintain "stress" levels of plasma cortisol. Although intravenous hydrocortisone is traditionally used for the treatment of acute severe asthma, oral prednisolone is just as effective and is easier to administer.¹⁰⁷

Inhaled. Inhaled topical steroids have been a great advance in the management of chronic asthma, because they make it possible to control symptoms without adre-

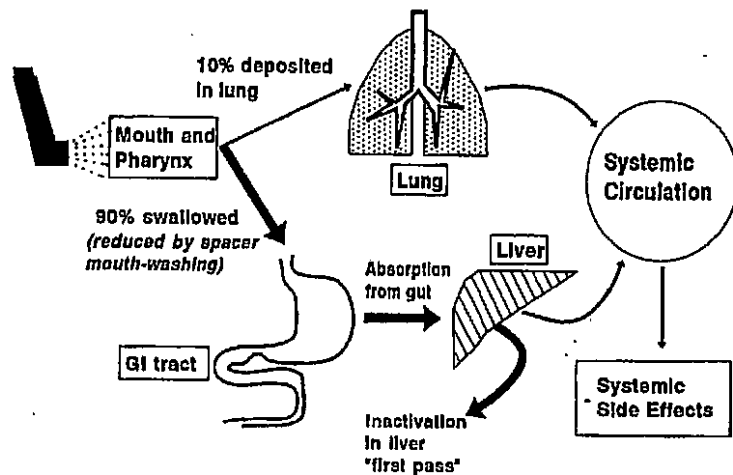


Figure 11.10 The pharmacokinetics of inhaled corticosteroids is depicted. GI = gastrointestinal.

nal suppression or side effects and allow a reduction in the dose of oral maintenance steroids.⁹⁴ The high topical activity of inhaled steroids means that only small doses are required, and any swallowed drug is metabolized by the liver. Only when much larger doses are inhaled is sufficient steroid absorbed (from the gastrointestinal tract and across the alveolar surface) to cause adrenal suppression.

Many patients get a maximal response at a dose of 400 to 500 µg/day, but some patients may benefit from higher doses (up to 2000 µg/day), and high-dose inhalers have therefore been introduced. Traditionally steroid inhalers are used twice daily, but four-times-daily administration may be more effective in severe disease.¹⁰³ Once-daily administration of some steroids, such as budesonide, is effective when doses of 400 µg or less are needed.¹⁰⁹

Clinical Use

Hydrocortisone is given intravenously in *acute asthma*. Although the value of corticosteroids in acute severe asthma has been questioned by some, others have found that they speed the resolution of attacks. There is no apparent advantage in giving very high doses of intravenous steroids (e.g., methylprednisolone 1 g). Intravenous steroids are indicated in acute asthma if lung function is less than 30% of the predicted value and there is no significant improvement with nebulized beta₂-agonist. Intravenous therapy is usually given until a satisfactory response is obtained, and then oral prednisolone may be substituted. Oral prednisolone (40 to 60 mg) has a similar effect to intravenous hydrocortisone and is easier to administer.¹⁰⁷ Inhaled steroids have no proven effect in acute asthma, but trials are underway.

Inhaled steroids are now recommended as first-line therapy in all but the mildest of asthma cases.⁹⁴ Inhaled steroids should be started for any patient who needs to use a beta₂-agonist inhaler for symptom control more than three times a week. Oral steroids are reserved for patients whose asthma cannot be controlled with other therapy, the dose being titrated to the lowest that provides acceptable control of symptoms. For any patient taking regular oral steroids, objective evidence of steroid responsiveness

should be obtained before maintenance therapy is instituted.

Short courses of oral steroids (30 to 40 mg prednisolone daily for 1 to 2 weeks) are indicated for exacerbations of asthma, and the dose may be tailed off over 1 week once the exacerbation is resolved (although the tail-off period is not strictly necessary, patients find it reassuring). Nebulized steroids (budesonide, 2 to 8 mg twice daily) may have a steroid-sparing effect in patients with more severe asthma who are receiving maintenance oral steroids.¹¹⁰

For most patients, inhaled steroids should be used twice daily, which improves compliance once control of asthma has been achieved (which may require four-times-daily dosing initially or a course of oral steroids if symptoms are severe). If a dose of more than 800 µg via MDI daily is used, a spacer device should be used; this reduces the risk of oropharyngeal side effects. Inhaled steroids may be used in children in the same way as in adults, and at doses of 400 µg daily or less there is no evidence of growth suppression.

Nebulized steroids have now been introduced. Nebulized budesonide has been found to be effective in controlling asthma in infants and in adults with severe asthma.^{110, 112} It is very expensive and may work by providing systemic levels that could be much more cheaply achieved by supplementary oral steroids. Local side effects include ulceration of the mouth and lips.

Some patients, usually with severe asthma, apparently fail to respond to corticosteroids.^{104, 113, 114} Steroid-resistant asthma is likely to be a result of an increase in binding of the glucocorticoid receptor to the transcription factor AP-1, due to increased activation of AP-1.¹¹⁵

COPD patients occasionally respond to steroids; these patients are likely to be undiagnosed asthmatics. Steroids have no objective short-term benefit on airway function in patients with true COPD, although they may often produce subjective benefit because of their euphoric effect. There is no convincing evidence that use of inhaled corticosteroids delays the progressive fall in lung function seen in patients with COPD,¹¹⁶ and the prevention of acute exacerbations is not impressive.¹¹⁷

Therapeutic Choices

Several inhaled corticosteroids are now available, including *beclomethasone dipropionate (BDP)*, *triamcinolone*, *flutisolid*, *budesonide*, and *fluticasone propionate (FP)*. All are equally effective as antiasthma drugs, but there are differences in pharmacokinetics, in that budesonide and FP have a lower oral bioavailability due to a greater first-pass hepatic metabolism, resulting in reduced systemic absorption from the fraction of the inhaled drug that is swallowed.^{105, 118} At high doses (more than 1000 µg) budesonide and FP have less systemic effects than BDP, and they are recommended in patients who need high doses of inhaled corticosteroids. The type of delivery system is important in the comparison of inhaled steroids: when doses of inhaled steroid exceed 800 µg daily, a large-volume spacer is recommended; this reduces oropharyngeal deposition and hence gastrointestinal absorption, thus reducing differences between BDP and budesonide. All currently available inhaled corticosteroids are absorbed from the lung into the systemic circulation, so some systemic absorption is inevitable. However, the amount of drug absorbed does not appear to have clinical effects in doses of 1000 µg or less.

Side Effects

Steroids inhibit corticotropin and cortisol secretion by a negative feedback effect on the pituitary gland. Hypothalamic-pituitary-adrenal (HPA) axis suppression is dependent on dose and usually occurs only when a dose of prednisolone greater than 7.5 to 10 mg daily is used. Significant suppression after short courses of steroid therapy is not usually a problem, but prolonged suppression may occur after several months or years of treatment. Steroid doses after prolonged oral therapy must therefore be reduced slowly. Symptoms of "steroid withdrawal syndrome" include lassitude, musculoskeletal pains, and occasionally fever. HPA suppression with inhaled steroids is seen only when the daily inhaled dose exceeds 2000 µg.

Side effects of long-term oral corticosteroid therapy are well described and include fluid retention, increased appetite, weight gain, osteoporosis, capillary fragility, hypertension, peptic ulceration, diabetes, cataracts, and psychosis. Their frequency tends to increase with age. Very occasionally, adverse reactions (such as anaphylaxis) to intravenous hydrocortisone have been described, particularly in aspirin-sensitive asthmatics.

The incidence of systemic side effects after inhaled steroids is an important consideration¹⁰⁵ (Table 11.8). Initial studies suggested that adrenal suppression occurred only when inhaled doses of more than 1500 to 2000 µg daily were used. More sensitive measurements of systemic effects include indices of bone metabolism, such as serum osteocalcin and urinary pyridinium cross-links, and in children knemometry, which may be increased with inhaled doses as low as 800 µg in some patients. However, the clinical relevance of these measurements is not yet clear. Nevertheless, it is important to reduce the likelihood of systemic effects by using the lowest dose of inhaled steroid needed to control the asthma and by using

Table 11.8 SIDE EFFECTS OF INHALED CORTICOSTEROIDS

Local side effects
Dysphonia
Oropharyngeal candidiasis
Cough
Systemic side effects
Adrenal suppression
Growth suppression
Bruising
Osteoporosis
Cataracts
Glaucoma
Metabolic abnormalities (glucose, insulin, triglycerides)
Psychiatric disturbances

a large-volume spacer to reduce oropharyngeal deposition.

Several systemic effects of inhaled steroids have been described and include dermal thinning and skin capillary fragility, which is relatively common in elderly patients after use of high-dose inhaled steroids. There has been particular concern about the use of inhaled steroids in children because of growth suppression.¹¹⁹ Most studies have been reassuring in that doses of 400 µg or less have not been associated with impaired growth, and there may even be a growth spurt as asthma is better controlled. A meta-analysis of more than 20 studies with inhaled BDP showed no effect on growth or overall height of children,¹²⁰ and a more recent study showed no difference in overall final height between children with asthma treated with inhaled steroids and normal control subjects.¹²¹ There is some evidence that use of high-dose inhaled corticosteroids is associated with cataract¹²² and glaucoma,¹²³ but it is difficult to dissociate the effects of inhaled corticosteroids from the effects of courses of oral steroids that these patients usually require.

Inhaled steroids may have *local side effects* due to the deposition of inhaled steroid in the oropharynx. The most common problem is hoarseness and weakness of the voice (dysphonia), which is caused by laryngeal deposition. It occurs in up to 40% of patients and is noticed particularly by patients who need to use their voices during their work (e.g., lecturers, teachers, singers).¹²⁴ It may be a result of atrophy of the vocal cords. Throat irritation and coughing after inhalation are common with MDIs and appear to be caused by the additives, because these problems are not usually seen if the patient switches to a dry-powder inhaler.¹²⁵ Oropharyngeal candidiasis occurs in 5% of patients. The incidence of local side effects may be related to the local concentration of steroid deposited and may be reduced by the use of large-volume spacers, which markedly reduce oropharyngeal deposition. Local side effects are also less likely when inhaled steroids are used twice daily rather than four times daily. There is no evidence for atrophy of the lining of the airway or for an increase in lung infections (including tuberculosis) after use of inhaled steroids.

Future Developments

There has been a dramatic increase in the use of inhaled corticosteroids in asthma treatment. This has occurred because of the recognition that asthma is an inflammatory condition and the introduction of treatment guidelines that emphasize early use of inhaled corticosteroids. There is also increasing recognition that there are no systemic effects at the doses of inhaled steroids needed to control asthma in most patients. However, there is increasing recognition that there may be systemic effects when inhaled corticosteroids are used for long periods in high doses.¹²⁶ It is also apparent that the dose-response curve for inhaled corticosteroids is relatively flat, so that relatively little clinical improvement is obtained with high doses, whereas the risk of systemic effects is increased. This has led to the use of alternative add-on therapies (long-acting inhaled β_2 -agonists, theophylline, anti-leukotrienes) in patients whose symptoms are not controlled by 400 to 800 μg of inhaled steroids daily.

Early treatment with inhaled steroids in both adults and children results in a greater improvement in lung function than if treatment with inhaled steroids is delayed (and other treatments such as bronchodilators are used).¹²⁷⁻¹²⁹ This may reflect the fact that steroids are able to modify the underlying inflammatory process and prevent structural changes (e.g., fibrosis, smooth muscle hyperplasia) in the airway resulting from chronic inflammation. It is not yet certain how early inhaled steroids should be introduced. There is evidence for inflammation in the airways, even when patients have episodic asthma, but at present it is recommended that inhaled steroids be introduced when there are chronic symptoms.

There has been a search for new corticosteroids that have fewer systemic effects. Corticosteroids that are metabolized in the airways (e.g., butixocort, tipredane) proved disappointing in clinical trials because they are probably broken down too rapidly, before they are able to exert anti-inflammatory effects. There is also a search for corticosteroids that are metabolized rapidly in the circulation after absorption from the lungs. The anti-inflammatory actions of corticosteroids may be mediated via different molecular mechanisms from those associated with side effects (which are endocrine and metabolic actions of corticosteroids). It has been possible to develop corticosteroids that dissociate the DNA-binding effect of corticosteroids (which mediates most of the adverse effects) from the transcription factor-binding action (which mediates much of the anti-inflammatory effect).¹³⁰ These "dissociated steroids" should retain anti-inflammatory activity but have a reduced risk of adverse effects.

Cromones

Cromolyn sodium is a derivative of khellin, an Egyptian herbal remedy that was found to protect against allergen challenge without bronchodilator effect. A structurally related drug, nedocromil sodium, which has an identical mode of action, was subsequently developed.¹³¹⁻¹³³

Mode of Action

Initial investigations indicated that cromolyn inhibited the release of mediators by allergen in passively sensitized

human and animal lung and inhibited passive cutaneous anaphylaxis in rats, although it was without effect in guinea pigs. This activity was attributed to stabilization of the mast cell membrane, and therefore cromolyn was classified as a mast cell stabilizer. However, cromolyn has a rather low potency in stabilizing human lung mast cells, and other drugs that are more potent in this respect have little or no effect in clinical asthma. This has raised doubts about mast cell stabilization as the mode of action of cromolyn.

Cromolyn and nedocromil potentially inhibit bronchoconstriction induced by sulfur dioxide, metabisulfite, and bradykinin, which are believed to act through activation of sensory nerves in the airways. In dogs, "cromones" suppress firing of unmyelinated C-fiber nerve endings, reinforcing the view that it might be acting to suppress sensory nerve activation and thus neurogenic inflammation. Cromones have variable inhibitory actions on other inflammatory cells that may participate in allergic inflammation, including macrophages and eosinophils. In vivo, cromolyn is capable of blocking not only the early response to allergen (which may be mediated by mast cells) but also the late response and airway hyperresponsiveness, which are more likely to be mediated by macrophage and eosinophil interactions. There is also evidence that long-term treatment with cromones reduces airway hyperresponsiveness,¹³⁴ but there is no convincing evidence that cromones reduce inflammation in asthmatic airways.¹¹

The molecular mechanism of action of cromones is still not understood, but evidence suggests that they may block a particular type of chloride channel that is expressed in sensory nerves, mast cells, and other inflammatory cells.^{135, 136}

Current Use

Cromolyn is a prophylactic treatment and needs to be given regularly. Cromolyn protects against various indirect bronchoconstrictor stimuli, such as exercise and fog.¹³⁷ It is effective only in mild asthma, but it does not appear to be effective in all patients and there seems no sure way of predicting which patients are likely to respond. Cromolyn was often used as the controller drug of first choice in children because it has almost no side effects. However, there is an increasing tendency to use low-dose inhaled corticosteroids instead, because they are safe and far more effective. In adults, inhaled corticosteroids are preferable to cromones; they are effective in all patients, although adults with mild asthma (even when it is nonallergic in type) may respond to cromolyn.¹³⁸ Cromolyn has to be given four times daily to provide good protection, so it is much less useful than inhaled steroids, which may be given twice daily. It may also be taken before exercise in children with exercise-induced asthma that is not blocked by an inhaled β_2 -agonist. In clinical practice, nedocromil has a very similar efficacy to cromolyn and is therefore indicated in patients with mild asthma, but it has the disadvantage of an unpleasant taste.¹³²

There is some evidence that cromones may be effective in some patients with persistent cough, including angio-

tensin-converting enzyme (ACE) inhibitor cough, presumably via an effect on airway C fibers.¹³⁹

Cromones are now used less since inhaled corticosteroids in low doses have been shown to be far more effective, cheaper, more convenient to use, and safe in children. The introduction of anti-leukotrienes has also further eroded the market for cromones, because these drugs are of comparable or greater clinical efficacy and are more conveniently taken by mouth.

Side Effects

Cromolyn is one of the safest drugs available, and side effects are extremely rare. The dry-powder inhaler may cause throat irritation, coughing, and occasionally wheezing, but this is usually prevented by prior administration of a beta₂-agonist by inhalation. Very rarely, a transient rash and urticaria are seen, and a few cases of pulmonary eosinophilia have been reported, all of which are caused by hypersensitivity. Side effects with nedocromil are not usually a problem, although some patients have noticed a sensation of flushing after using the inhaler. Many patients find the bitter taste unpleasant, but a menthol-flavored version is now available that seems to overcome this problem.

MEDIATOR ANTAGONISTS

Many inflammatory mediators have been implicated in asthma, suggesting that inhibition of synthesis of these mediators may be beneficial.¹⁴⁰ However, because these mediators have similar effects, specific inhibitors have usually been disappointing in asthma treatment.

Antihistamines

Histamine mimics many of the features of asthma and is released from mast cells in acute asthmatic responses, suggesting that antihistamines may be useful in asthma therapy. Many trials of antihistamines have been conducted, but there is little evidence of any useful clinical

benefit, as demonstrated by a meta-analysis.¹⁴¹ New antihistamines, including cetirizine and azelastine, have some beneficial effects,^{142, 143} but they may be unrelated to their H₁-receptor antagonism. In addition, antihistamines are effective in controlling rhinitis, and this may help to improve overall asthma control.

Ketotifen

Ketotifen is described as a prophylactic antiasthma compound.¹⁴⁴ Its predominant effect is H₁-receptor antagonism, and it is this antihistaminic effect that accounts for its sedative action. Ketotifen has little effect in clinical asthma after acute challenge, on airway hyperresponsiveness, or on clinical symptoms. A long-term placebo-controlled trial of oral ketotifen in children with mild asthma showed no significant clinical benefit.¹⁴⁵ Ketotifen does not have a steroid-sparing effect in children maintained on inhaled corticosteroids.¹⁴⁶ It is claimed that ketotifen has disease-modifying effects if started early in childhood asthma and may even prevent the development of asthma in atopic children. More carefully controlled studies are needed to assess the validity of these claims.

Anti-Leukotrienes

There is considerable evidence that cysteinyl-leukotrienes are produced in asthma and that they have potent effects on airway function, inducing bronchoconstriction, airway hyperresponsiveness, plasma exudation, and mucus secretion¹⁴⁷ (Fig. 11.11). They may also induce an eosinophilic inflammation.¹⁴⁸ This suggested that anti-leukotrienes may be useful in the treatment of asthma, and several drugs have now been developed for clinical use. Anti-leukotrienes include leukotriene receptor antagonists and 5'-lipoxygenase enzyme inhibitors. Several drugs of each type have now been developed. The initial drugs that were tested clinically were very weak inhibitors and had little effect in challenge studies and clinical trials. More potent drugs were later developed, and several of these drugs are now available throughout the world.¹⁴⁹⁻¹⁵²

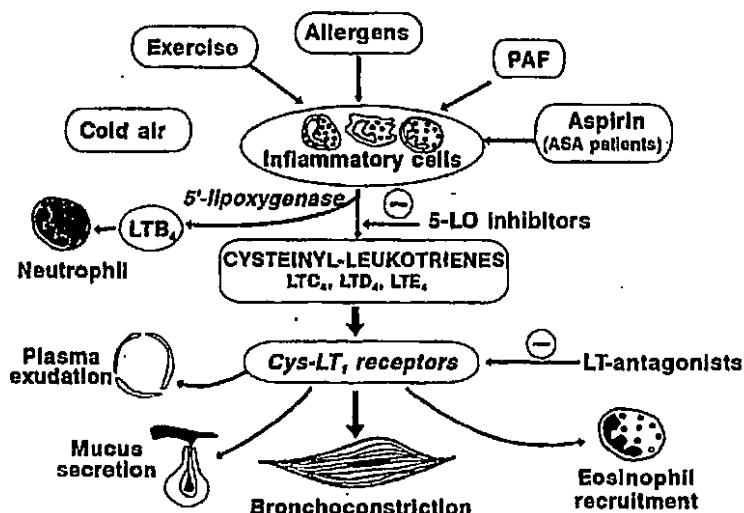


Figure 11.11 Effects of cysteinyl-leukotrienes on the airways and their inhibition by anti-leukotrienes are shown. PAF = platelet-activating factor; ASA = aspirin-sensitive asthmatic; LT = leukotriene; 5-LO = 5'-lipoxygenase.

Clinical Studies

Leukotriene antagonists, such as pranlukast, zafirlukast, and montelukast, inhibit the bronchoconstrictor effect of inhaled leukotriene D₄ (LTD₄) in normal and asthmatic volunteers, as expected. They also inhibit bronchoconstriction induced by a variety of challenges, including allergen, exercise, and cold air, with approximately 50% inhibition. This suggests that leukotrienes account for approximately half of these responses. With aspirin challenge in aspirin-sensitive asthmatic patients, there is complete inhibition of the response, indicating that leukotrienes account entirely for this response.

Very similar results have been obtained with 5'-lipoxygenase inhibitors, such as zileuton. This suggests that there may be no additional advantage in blocking LTB₄ in addition to cysteinyl-leukotrienes, although this may not be the case in other inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease. These drugs are active by oral administration, and this may confer an important advantage in chronic treatment, particularly in relation to compliance.

Several clinical trials of anti-leukotrienes in asthma have now been reported and, as in the challenge studies, leukotriene receptor antagonists and 5'-lipoxygenase inhibitors appear to have similar efficacy.¹⁵³⁻¹⁵⁵ These studies in mild to moderate asthma show a significant improvement in lung function (clinic FEV₁ and home peak expiratory flow measurements) and asthma symptoms, with a reduction in the use of rescue inhaled beta₂-agonists. In addition, there is a reduction in nocturnal symptoms and a reduction in the number of asthma exacerbations.¹⁵⁶ In several studies there was evidence for a bronchodilator effect, with an improvement in baseline lung function, suggesting that leukotrienes are contributing to the baseline bronchoconstriction in asthma.¹⁵⁷⁻¹⁵⁹ This bronchodilator effect varies among patients but is particularly marked in patients with aspirin-sensitive asthma, in which leukotrienes appear to be the major mechanism.

There is less information about patients with more severe asthma, but analysis of the data from existing studies suggests that the greatest benefits may be seen in patients with the most severe asthma who are taking inhaled steroids. This is of particular interest because it suggests that anti-leukotrienes may accomplish something that is not achieved with inhaled steroids. At least two studies have indicated that neither oral nor inhaled steroids, even in high doses, are able to inhibit the increased leukotriene production in asthma.^{160, 161} This suggests that anti-leukotrienes may have a useful additive effect in those patients whose symptoms are not adequately controlled with inhaled steroids.

An important issue is whether this new class of drugs is "anti-inflammatory." There are, of course, different meanings to the term. By definition, anti-leukotrienes (like antihistamines) must be anti-inflammatory, because leukotrienes themselves (like histamine) are inflammatory mediators. But whether anti-leukotrienes suppress the inflammatory response in asthmatic airways (like inhaled steroids) or simply relieve symptoms by bronchodilatation without affecting the underlying inflammatory response

(like beta₂-agonists) remains to be determined. However, in some studies anti-leukotrienes have been associated with reduced numbers of circulating eosinophils and reduced eosinophils in bronchoalveolar lavage fluid.¹⁶²

Side Effects

With any new class of drugs, side effects may be unexpected. For example, no one would have predicted that antihistamines would have sedative effects, and it was only later that the central role of histamine in the brain for alertness was recognized. To date, anti-leukotrienes have been remarkably free of class-specific side effects. Zileuton causes an increased level of liver enzymes, so monitoring of liver enzymes is necessary with this drug, and high doses of zafirlukast may be associated with abnormal liver function. Montelukast is reported to be very well tolerated in adults and children, with no significant adverse effects. The lack of side effects implies that leukotrienes are not important in any physiologic functions, but it is only when these drugs are widely used that unexpected side effects may emerge.

Several cases of Churg-Strauss syndrome have now been associated with the use of zafirlukast in the United States.¹⁶³ Churg-Strauss syndrome is a very rare vasculitis that can affect the heart, peripheral nerves, and kidney and is associated with increased circulating eosinophils and asthma.¹⁶⁴ It is likely that the cases so far reported are caused by a reduction in oral or inhaled corticosteroid dose rather a direct effect of the drug. No cases have so far been reported with montelukast, although this drug has not been used as extensively as zafirlukast.

Future Use

One of the major advantages of anti-leukotrienes is that they are active in tablet form. This may increase the compliance with chronic therapy, and it will make treatment of children easier. Montelukast is effective as a once-daily preparation (10 mg in adults and 5 mg in children) and is therefore easy for patients to use. In addition, oral administration may treat concomitant allergic diseases, such as allergic rhinitis and eczema, which are common in asthmatic patients. There is already some indication that anti-leukotrienes may have a clinically beneficial effect in allergic rhinitis. However, the currently available clinical studies indicate a relatively modest effect on lung function and symptom control, which is less than would be expected with inhaled steroids. This is not surprising; there are many more mediators than leukotrienes involved in the pathophysiology of asthma, and it is unlikely that antagonism of a single mediator could ever be as effective as steroids, which inhibit all aspects of the inflammatory process in asthma. Similarly, if anti-leukotrienes function in asthma as bronchodilators and anticonstrictors, it is unlikely that they will be as effective as a beta₂-agonist, which counteracts bronchoconstriction regardless of the spasmogen.

Some patients appear to show better responses than others, suggesting that leukotrienes may play a more important role in some patients. This is seen particularly in aspirin-sensitive asthmatic patients, although such pa-

tients are very rare in this country. Furthermore, the patients who appear to show the best response are those with more severe asthma. The variability in response to anti-leukotrienes may reflect differences in production of leukotrienes among patients, and this in turn may be related to polymorphisms of the 5'-lipoxygenase gene and LTC₄ synthase, which are involved in the synthesis of leukotrienes.^{165, 166}

STEROID-SPARING THERAPIES

Immunosuppressive therapy has been considered in asthma when other treatments are unsuccessful or to reduce the dose of oral steroids required.¹⁶⁷ Therefore, they are only indicated in a very small proportion of asthmatic patients at present. Most immunosuppressive treatments have a greater propensity for side effects than do oral corticosteroids and therefore cannot be routinely recommended.¹⁶⁸

Methotrexate

Low-dose methotrexate (15 mg weekly) has been shown to have a steroid-sparing effect in asthma^{169, 170} and may be indicated when oral steroids are contraindicated because of unacceptable side effects (e.g., in postmenopausal women when osteoporosis is a problem). Some patients show better responses than others, but whether a patient will have a useful steroid-sparing effect is unpredictable. In some studies, no useful beneficial effect is reported.¹⁷¹ A meta-analysis of studies demonstrated a small overall steroid-sparing effect of low-dose methotrexate when given over a 6-month period.¹⁷² Side effects of methotrexate are relatively common and include nausea (reduced if methotrexate is given as a weekly injection), blood dyscrasias, and hepatic damage. Careful monitoring of such patients (i.e., monthly blood counts and liver enzyme analysis) is essential. Methotrexate has been disappointing in most clinical experience.

Gold

Gold has long been used in the treatment of chronic arthritis. There is anecdotal evidence that it may also be useful in asthma, and it has been used in Japan for many years. A controlled trial of an oral gold preparation (Auranofin) demonstrated some steroid-sparing effect in chronic asthmatic patients maintained on oral steroids.¹⁷³ Side effects such as skin rashes and nephropathy are limiting factors.

Cyclosporine

Cyclosporine is active against CD4⁺ T lymphocytes and might therefore be useful in asthma, in which these cells are implicated. A trial of low-dose oral cyclosporine in patients with steroid-dependent asthma indicated that it can improve control of symptoms in patients with severe asthma who are taking oral steroids,^{174, 175} but other trials have been unimpressive.¹⁷⁶ Its use is likely to be limited by side effects such as nephrotoxicity and hypertension,

which are common. In clinical practice, it is very disappointing as a steroid-sparing agent.

Intravenous Immunoglobulin

Intravenous immunoglobulin has been reported to have steroid-sparing effects in steroid-dependent asthma when high doses are used (2 g/kg),¹⁷⁷ although a placebo-controlled double-blind trial in children showed that it is ineffective.¹⁷⁸

Immunotherapy

Theoretically, specific immunotherapy with common allergens should be effective in preventing asthma. Although this treatment is effective in allergic rhinitis, there is little evidence that desensitizing injections to common allergens are very effective in controlling chronic asthma.¹⁷⁹ Double-blind, placebo-controlled studies have demonstrated poor effect in chronic asthma in adults and children.^{180, 181} Because there is a risk of anaphylactic and local reactions, and because the course of treatment is time-consuming, this form of therapy cannot be recommended. In the future, more specific immunotherapies may be developed with cloned allergen epitopes or T cell-reactive peptide fragments of allergens.¹⁸² The use of IL-12 to direct the immune response toward a T helper-1 (Th1) immunity rather than a T helper-2 (Th2) immunity looks particularly promising.¹⁸³

NEW DRUGS FOR ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Several new classes of drug are now in development for asthma and COPD^{1, 184, 185} (Table 11.9). In asthma, there are very effective therapies, but there is a need for more effective treatments to control severe asthma, and there is a search for a cure for asthma.¹⁸⁶ In COPD, there is a need for drugs that prevent progression of the disease, especially because inhaled corticosteroids appear to be ineffective.

Mediator Antagonists

Many mediators are known to be involved in asthmatic inflammation, and many share the same effects on the airways, so it may prove difficult to develop drugs that have a large clinical effect (Table 11.10). Anti-leukotrienes are clearly effective in some asthmatic patients, but antagonists of other mediators have been disappointing. Platelet-activating factor antagonists are clinically ineffective, and thromboxane, bradykinin, and tachykinin antagonists have such weak effects that they are not likely to be useful clinically.

There have been few studies of mediator antagonists in COPD, but because neutrophils are predominant, LTB₄ antagonists or 5'-lipoxygenase inhibitors (which prevent its synthesis) may be effective.

Anti-Cytokines

Cytokines are the mediators of chronic inflammation and play a key role in chronic asthma, so they are natural

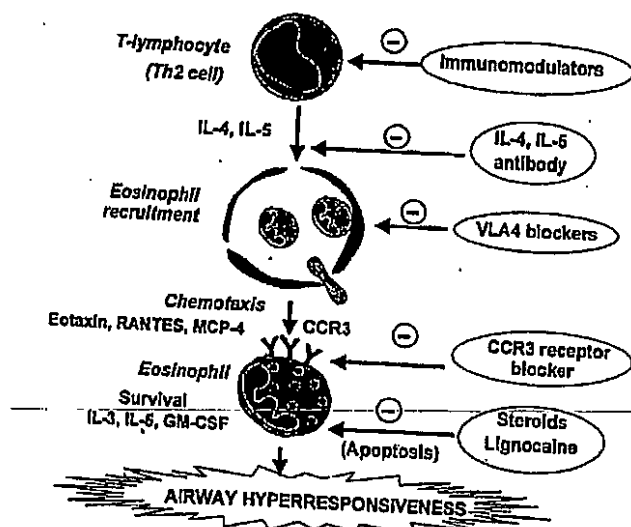


Figure 11.12 Several approaches to blocking eosinophilic inflammation are depicted. IL = interleukin; Th2 = T helper 2; VLA = vascular leukocyte adhesion molecule; CCR = CC chemokine receptor; MCP = macrophage chemotactic protein; GM-CSF = granulocyte-macrophage colony-stimulating factor; RANTES = release of activated normal T cells expressed and secreted.

such as cyclosporine, are nonselective and inhibit Th1 and Th2 cells equally. Selective Th2 inhibitors should be safer in long-term use, and such drugs are now in development.

Some cytokines themselves may have anti-inflammatory and immunomodulatory actions in asthma.¹⁸⁹ IL-10 is a potent suppressor of proinflammatory cytokines, IL-5, and inflammatory enzymes and is currently in exploratory studies. Interferon- γ inhibits Th2 cells and is effective in experimental models of asthma but has been disappointing in clinical studies. IL-12 is a key cytokine for preventing the switching of T lymphocytes into Th2 cells that release IL-4 and IL-5. In animal studies it is able to block the development of allergy, and it may be considered as future preventive therapy.¹⁹⁰ It is the only form of treatment that offers the prospect of a cure. Anti-IL-4 antibodies and soluble IL-4 receptors are also in development for asthma therapy and should suppress synthesis of immunoglobulin E (IgE). IgE antibodies that inhibit IgE-mediated activation of mast cells (and other cells) have also shown some promising results in allergen challenge studies and in longer-term clinical studies.¹⁹¹

Furosemide

The diuretic furosemide has a similar profile of airway effects to cromolyn; it has provided some insight into mechanisms of action of cromones via chloride channels and may form the basis of a new therapeutic approach.¹⁹² However, clinical studies with inhaled furosemide have been disappointing, and it will be necessary to develop more potent and long-lasting drugs.¹⁹³

Neuromodulators

There is some evidence that neurogenic inflammation may be implicated in airway diseases such as asthma and COPD, and there are various strategies to inhibit neurogenic inflammation, which is caused by the release of neuropeptides such as substance P from unmyelinated sensory nerves in the airways. These include inhibition by tachykinin receptor antagonists, such as the nonpeptide antagonist CP 99,994, inhibition of sensory neuropeptide release by agonists such as μ -opioids, or inhibition of sensory nerve activation.¹⁹⁴

Enzyme Inhibitors

Several enzymes are activated in inflammatory diseases of the airways and provide targets for new therapies in asthma and COPD. Mast cell tryptase induces airway hyperresponsiveness in animal models of asthma and also stimulates fibrosis and smooth muscle proliferation. Inhibitors of mast cell tryptase have been developed and have shown some efficacy in animal models of asthma.¹⁹⁵ Other enzyme inhibitors for asthma therefore include 5'-lipoxygenase inhibitors, discussed earlier, and inhibitors of inducible nitric oxide synthase (iNOS), which is up-regulated in asthmatic airways. Several selective iNOS inhibitors are now in development.

In COPD, the progressive airway obstruction is probably caused by unopposed proteolytic activity, due to either excessive release or defective antiproteases. Several treatments are in development, including neutrophil elastase inhibitors, selective matrix metalloprotease inhibitors, and gene therapy with secretory leukoprotease inhibitors.¹⁹⁶

Transcription Factor Blockers

Several transcription factors are activated in inflammatory airway diseases and regulate the expression of multiple inflammatory genes, so the development of transcription factor blockers is an attractive therapeutic option. Corticosteroids exert some of their anti-inflammatory actions via inhibition of NF- κ B and AP-1, making these possible therapeutic targets. Several approaches have been taken to the development of NF- κ B inhibitors, and such drugs may have a use in asthma and COPD.¹⁹⁷ The concern about blocking ubiquitous transcription factors such as NF- κ B is that there may be too profound immunosuppression, with increased risk of infections, so targeting of more specific transcription factors (e.g., signal transduction activated transcription factors) may be a more attractive approach.

Impact of Molecular Genetics

There is much interest in the genetics of asthma as a means of identifying novel and more specific drug targets. Asthma clearly involves many genes, and environmental stimuli are very important in interacting with genetic factors, so it will be impossible to identify a single target. Genetic polymorphisms (variations in gene structure that result in differences in protein and often in function) may account for differences in severity of asthma among

patients and also for differences in response to therapy. In the future, it may be possible to predict which patients are most likely to show response to particular drugs (pharmacogenomics). Gene therapy is a distant prospect in asthma. It may be possible to deliver anti-inflammatory genes (e.g., IL-10 or IL-12) by viral vectors, and these could have prolonged effects in the airways.

OTHER DRUGS

Several other types of drugs are used in the treatment of airway diseases, and these often have poor efficacy, and this has been shown to be due to the release of membrane-bound elastase, signaled by close adhesive interaction between neutrophils and goblet cells.^{199a}

Mucoregulators

Many pharmacologic agents may influence the secretion of mucus in the airways, but there are few drugs that have useful clinical effects.¹⁹⁸ Mucus hypersecretion occurs in chronic bronchitis and asthma. In chronic bronchitis, mucus hypersecretion is related to chronic irritation by cigarette smoke and may involve neural mechanisms and the activation of neutrophils to release enzymes such as neutrophil elastase, which have powerful effects on mucus secretion.¹⁹⁹ Mast cell-derived chymase is also a potent mucus secretagogue. This suggests that several classes of drug may be developed to control mucus hypersecretion.

Sensory nerves and neuropeptides are important in submucosal gland secretion (which predominates in proximal airways) and goblet cell secretion (in more peripheral airways).^{200, 201} Opioids and K⁺ channel openers inhibit mucus secretion mediated via sensory neuropeptide release,²⁰² and peripherally acting opioids may be developed to control mucus hypersecretion due to irritants in the future.

Several drugs reduce the viscosity of sputum in vitro. These drugs are usually derivatives of cysteine and reduce the disulfide bridges that bind glycoproteins to other proteins, such as albumin and secretory IgA. In addition, these drugs act as antioxidants and may therefore reduce airway inflammation. Orally administered *N*-acetylcysteine, carbocysteine, methyleysteine, and bromhexine are well tolerated, but clinical studies in chronic bronchitis, asthma, and bronchiectasis have been disappointing.^{203, 204} However *N*-acetylcysteine reduces exacerbations in COPD and may improve symptoms²⁰⁵; this is more likely to be a result of its antioxidant effect than of any mucolytic activity.

Expectorants are drugs that enhance the clearance of mucus when administered orally. Although they are commonly prescribed, there is little or no objective evidence for their efficacy. Such drugs are often emetics (guafenesin, ipecac, ammonium chloride) that are given in subemetic doses on the basis that gastric irritation may stimulate an increase in mucus production via a reflex mechanism. However, there is no good evidence for this assumption.²⁰⁶ In patients who find it difficult to clear mucus, adequate hydration and inhalation of steam may be of some benefit.

DNAse (dornase alfa) reduces mucus viscosity in spu-

tum of patients with cystic fibrosis and is indicated if there is significant symptomatic and lung function improvement after a trial of therapy.²⁰⁷ There is no evidence that dornase alfa is effective in COPD or asthma.

Antitussives

Despite the fact that cough is a common symptom of airway disease, its mechanisms are poorly understood and its treatment is unsatisfactory.^{208, 209} Because cough is a defensive reflex, its suppression may be inappropriate in bacterial lung infection. Before treatment with antitussives, it is important to identify underlying causal mechanisms that may require therapy. Treatments such as opioids may act centrally on the "cough center," whereas other treatments may act peripherally.

Opiates have a central mechanism of action on the medullary cough center, but there is some evidence that they may have additional peripheral action on cough receptors in the proximal airways. Codeine and pholcodine are commonly used, but there is little evidence that they are clinically effective.²¹⁰ Morphine and methadone are effective but are indicated only in intractable cough associated with bronchial carcinoma. A peripherally acting opioid agonist, 443C81, does not appear to be effective.²¹¹

Asthma commonly manifests as cough, and the cough usually responds to bronchodilators, to inhaled steroids, and to inhaled cromolyn or nedocromil sodium. A syndrome characterized by cough in association with sputum eosinophilia but with no airway hyperresponsiveness, termed *eosinophilic bronchitis*, responds to steroids and may be regarded as pre-asthma.²¹² Nonasthmatic cough does not respond to inhaled steroids but sometimes responds to cromones or anticholinergic therapy. The cough associated with postnasal drip of sinusitis responds to antibiotics, nasal decongestants, and intranasal steroids. The cough associated with ACE inhibitors responds to withdrawal of the drug and to cromones. In some patients there is underlying gastroesophageal reflux, which leads to cough by a reflex mechanism and occasionally by acid aspiration. This cough responds to effective suppression of gastric acid with an H₂-receptor antagonist or, more effectively, to a proton pump inhibitor, omeprazole.²¹³

Drugs for Breathlessness

Bronchodilators should reduce breathlessness, and chronic oxygen may have some effect, but in a few patients breathlessness may be extreme. Drugs that have been shown to reduce breathlessness may also depress ventilation in parallel.²¹⁴

Ventilatory Stimulants

Several classes of drug stimulate ventilation and are indicated when ventilatory drive is inadequate rather than to stimulate ventilation when the respiratory pump is failing. Nikethamide and ethamivan were originally introduced as respiratory stimulants, but doses stimulating ventilation are close to those causing convulsions, so their use has been abandoned. More selective respiratory stimulants

have now been developed and are indicated if ventilation is impaired as a result of overdose with sedatives, postanesthetic respiratory depression, or idiopathic hypoventilation. Respiratory stimulants are rarely indicated in COPD, because respiratory drive is already maximal and further stimulation of ventilation may be counterproductive because of the increase in energy expenditure caused by the drugs.

Doxapram

At low doses (0.5 mg/kg intravenously) doxapram stimulates carotid chemoreceptors, but at higher doses it stimulates medullary respiratory centers. Its effect is transient, and it must therefore be administered by intravenous infusion (0.3 to 3 mg/kg/min). Unwanted effects include nausea, sweating, anxiety, and hallucinations. At higher doses, increased pulmonary and systemic pressures may occur.²¹⁵ Doxapram is metabolized in the liver and should be used with caution if hepatic function is impaired.

Almitrine

Almitrine bimesylate is a piperazine derivative that appears to selectively stimulate peripheral chemoreceptors and is without central actions.²¹⁶ It is ineffective in patients with surgically removed carotid bodies. Almitrine stimulates ventilation only when there is hypoxia. Long-term use of almitrine is associated with peripheral neuropathy, and it therefore is not available as a therapeutic option in most countries.

Acetazolamide

The carbonic anhydrase inhibitor acetazolamide induces metabolic acidosis and thereby stimulates ventilation, but is not widely used because the metabolic imbalance it produces may be detrimental in the face of respiratory acidosis. The drug has proved useful in prevention of high-altitude sickness.²¹⁷

Naloxone

Naloxone is a competitive opioid antagonist; it is indicated only if ventilatory depression is caused by overdose of opioids.

Flumazenil

Flumazenil is a central nervous system benzodiazepine receptor antagonist that can reverse respiratory depression caused by overdose of benzodiazepines.²¹⁸

Protriptyline

Protriptyline has been used in the treatment of sleep apnea syndromes, but its mode of action is unclear. It appears to stimulate activity of upper airway muscles via some central effect.²¹⁹

DRUGS CONTRAINDICATED IN AIRWAY DISEASE

Several drugs may cause a deterioration in asthma and other airway diseases.²²⁰

Sedatives

Any sedative (opiate, benzodiazepine) may reduce ventilatory drive and should therefore be avoided in patients with COPD or severe asthma.

Beta-Blockers

All beta-blockers should be avoided in patients with asthma. The mechanisms by which beta-blockers impair airway function is not yet certain, but it appears to be mediated by antagonism of beta₂-receptors, although even selective beta₂-blockers are potentially dangerous. Even low doses of beta-blockers (e.g., timolol eye drops) can cause severe worsening of asthma, and fatalities continue to be reported.^{221, 222} The deterioration in lung function may be very severe, even in mild asthmatics. Patients with COPD are less likely to be affected by beta-blockers, but because they may be unrecognized asthmatics, these drugs are best avoided. Alternative treatments for hypertension and ischemic heart disease include calcium channel blockers and alpha-adrenoceptor antagonists, which are safe. Propafenone is a new antiarrhythmic agent that is structurally similar to propranolol and has been reported to increase bronchoconstriction in asthmatic patients.²²³

The mechanism of beta-blocker-induced asthma is not yet certain. The effect of beta-blockers is likely to be mediated via airway cholinergic nerves²²⁴ and may be caused by blockade of beta₂-receptors on airway cholinergic nerves, leading to an increased release of acetylcholine that is not compensated by feedback inhibition because of a defect in M₂ autoreceptors in asthmatic patients.²²⁵ Another possible mechanism may be related to the recently recognized phenomenon of inverse agonism: some mutants of the beta₂-receptor have constitutive activity and activate the coupling protein G_i, even in the absence of occupation by agonist.²²⁶ In this situation, beta-blockers function as inverse agonists and have an inhibitory effect on baseline function. It is possible that in asthmatic patients beta₂-receptors are constitutively active, so beta-blockers result in adverse effects. Beta-blockers have differing potencies as inverse agonists that are unrelated to their beta-blocking potency. For example, propranolol is a potent inverse agonist but pindolol is not, and this may relate to the different tendency of these two agents to induce asthma.

Aspirin and Other Cyclooxygenase Inhibitors

A small proportion of asthmatics (fewer than 1%) develop a worsening of asthma with aspirin.²²⁷ These patients usually have late-onset asthma and also have rhinitis and nasal polyps. Other nonsteroidal anti-inflammatory drugs may have similar effects in these patients, suggesting that

cyclooxygenase inhibition underlies the phenomenon. It is possible that blocking the formation of bronchodilator prostaglandins (e.g., PGE_2) is the critical factor in such patients. Evidence suggests that cyclooxygenase inhibition may result in increased formation of leukotrienes in such patients, and there is increased expression of LTC_4 synthase in airway cells of these patients.²²⁸ Anti-leukotrienes are effective in blocking aspirin-induced bronchoconstriction and give good control of asthma in these patients.²²⁹ If it is necessary for these patients to continue to take aspirin, it is possible to desensitize the response by repeated exposure to low doses of aspirin.

Angiotensin-Converting Enzyme Inhibitors

As many as 20% of hypertensive patients treated with ACE inhibitors develop an irritant cough,²³⁰ but this is unrelated to the presence of underlying airway disease or atopic status. Perhaps it might be related to inhibition of bradykinin metabolism, with bradykinin release and resultant stimulation of unmyelinated C fibers in the larynx. In an animal model of ACE-inhibitor cough, a bradykinin antagonist blocked the cough.²³¹ ACE-inhibitor cough is prevented by cyclooxygenase inhibitors²³² and may be caused by prostaglandin release by endogenous bradykinin, because PGE_2 and $\text{PGF}_{2\alpha}$ increase cough sensitivity,^{233, 234} which is also prevented by sodium cromoglycate.²³⁵

There is some evidence that asthma may be precipitated by ACE inhibitors, and a retrospective cohort study suggested that bronchospasm was twice as common among patients treated with ACE inhibitors, compared with a reference group treated with lipid-lowering drugs.²³⁶ There is no evidence that bronchospasm is more common in patients with cough. In a controlled trial in asthmatic and hypertensive patients (with and without cough), there was no change in lung function after administration of captopril and no increase in reactivity to histamine or bradykinin.²³⁷ Similar findings were obtained in a group of asthmatic patients given ACE inhibitors for 3 weeks, although 1 subject (of 21) developed increased wheezing.²³⁸

Local Anesthetics

Several studies have found that aerosols of the local anesthetics bupivacaine and lidocaine cause bronchoconstriction in some asthmatic patients.²³⁹ The degree of bronchial reactivity to histamine does not predict the development or extent of bronchoconstriction after lidocaine inhalation.²³⁹ The mechanism of local anesthetic-induced bronchoconstriction is unclear, but inhaled local anesthetics may selectively inhibit nonadrenergic noncholinergic bronchodilator nerves and so allow unopposed vagal tone. Some evidence for this hypothesis is provided by the demonstration that lidocaine inhalation blocks nonadrenergic noncholinergic reflex bronchodilatation in human subjects, leading to a reflex bronchoconstrictor response.²⁴⁰

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D11

Integrated Pharmacology

SECOND EDITION

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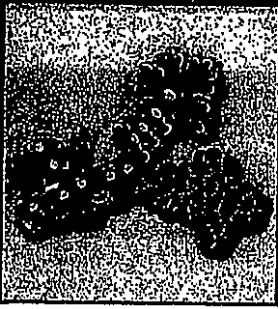
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Note

Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs become necessary. The editors, contributors and the publishers have taken care to ensure that the information given in this text is accurate and up to date. However, readers are strongly advised to confirm that the information, especially with regard to drug usage, complies with the latest legislation and standards of practice.

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Drugs and the Pulmonary System

PHYSIOLOGY OF THE PULMONARY SYSTEM

☼ *Blood is oxygenated and carbon dioxide removed by the pulmonary system*

The body's metabolic processes use large quantities of oxygen and produce large amounts of carbon dioxide. The oxygen-absorbing surface of the lung (the gas-exchange surface) is therefore large (80 m^2). It can fit into the body because it is folded and shaped into a branching tree-like system of air-conducting tubes (bronchi and bronchioles), which end in millions of tiny sacs called alveoli (Fig. 19.1).

Respiration is controlled by spontaneous rhythmic discharges from the respiratory center in the medulla of the brain,

which is regulated by higher centers in the brain and vagal afferents from the lungs (Fig. 19.2) and influenced by:

- Changes in blood pCO_2 , which activate chemoreceptors in the medulla.
- Changes in blood pO_2 , which activate chemoreceptors in the aortic arch and carotid bodies.

☼ *Airway smooth muscle tone is produced by parasympathetic, sympathetic, and nonadrenergic noncholinergic nerves and circulating epinephrine*

Airway smooth muscle is innervated by:

- The parasympathetic nervous system via the vagus nerve (cranial nerve X), and airway smooth muscle tone is

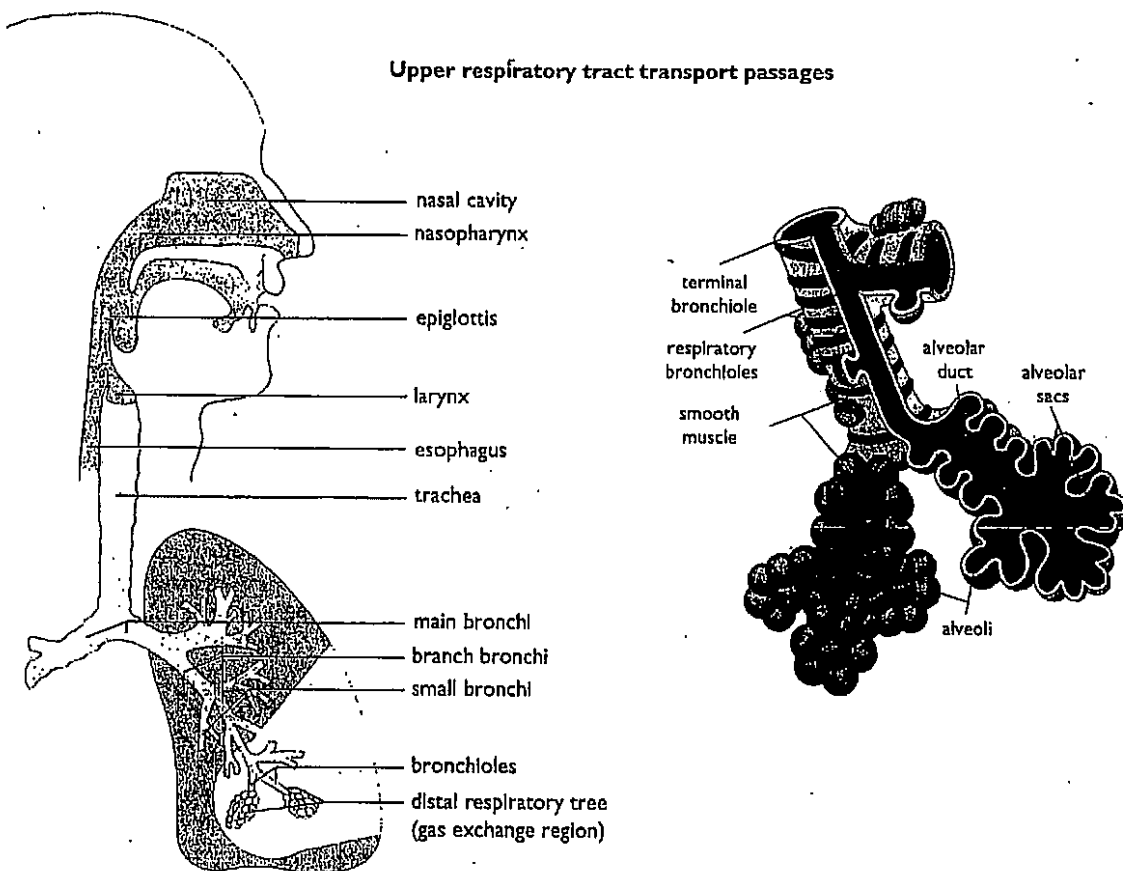


Fig. 19.1 Structure of the respiratory tract.

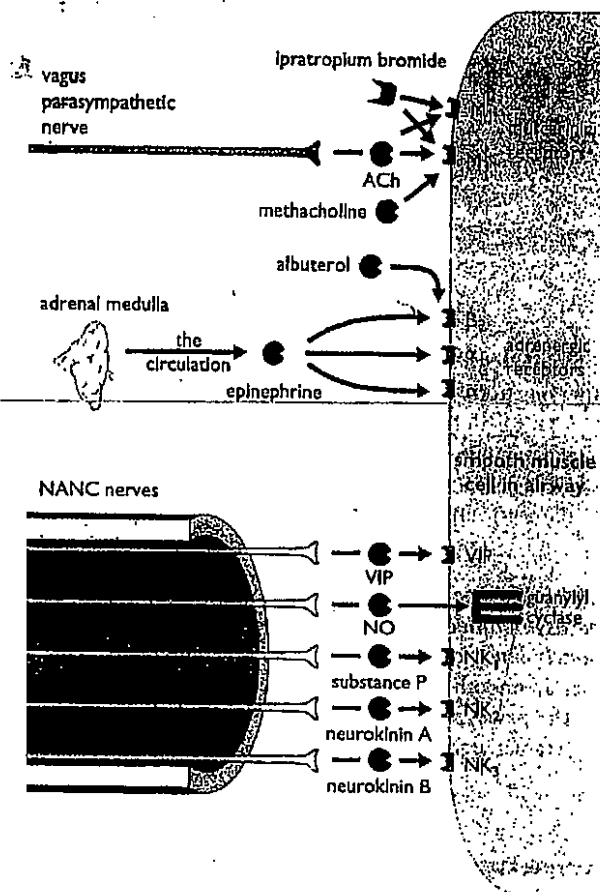


Fig. 19.2 Airway smooth muscle tone and innervation. A constrictor tone is provided by the vagus nerve and release of acetylcholine (ACh). This is blocked by the mixed M_1/M_2 antagonist, ipratropium bromide. Methacholine challenge, to assess for asthma, activates these receptors. Epinephrine relaxes airway smooth muscle by activating β_2 receptors. This is mimicked by the therapeutic drug, albuterol. The other features of the figure, including vasoactive intestinal polypeptide (VIP) activation of VIP receptors, nitric oxide (NO), and activation of various neurokinin (NK) receptors, all part of the nonadrenergic noncholinergic (NANC) system, may represent targets for future drug development.

Drugs that alter respiration

- Narcotic analgesics, barbiturates, certain H_1 receptor antagonists, and ethanol cause respiratory depression
- Doxapram is a respiratory stimulant and is used for patients in ventilatory failure
- Respiratory stimulants are believed to stimulate both carotid chemoreceptors and the respiratory center
- They should be used with caution as they may have unwanted effects on the CNS such as convulsions, and their efficacy is uncertain

generated by acetylcholine acting on muscarinic receptors (Fig. 19.2).

- The so-called 'third nervous pathway,' with the neurotransmitters (nitric oxide and vasoactive intestinal polypeptide

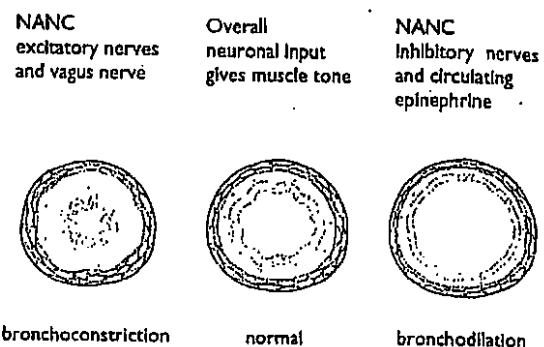


Fig. 19.3 Bronchial smooth muscle tone. Bronchial smooth muscle tone depends upon the balance between the parasympathetic input, circulating epinephrine, nonadrenergic, noncholinergic (NANC) inhibitory nerves, and sympathetic innervation of the parasympathetic ganglia.

Noninfectious diseases of the respiratory tract

- The most common diseases are asthma, allergic rhinitis, chronic bronchitis and cystic fibrosis
- Asthma is an inflammatory disease
- Cystic fibrosis is a genetic disease
- Cough is usually a symptom of an underlying disease

[VIP]) used by the nonadrenergic noncholinergic (NANC) nerves of this system (see Fig. 19.2) producing smooth muscle relaxation and bronchodilation.

Bronchial smooth muscle relaxation (bronchodilation) is also produced by circulating epinephrine (adrenaline) binding to β_2 adrenoceptors on the muscle (see Fig. 19.2). Although the bronchial smooth muscle has little or no direct sympathetic innervation, there is a sympathetic supply to the parasympathetic ganglia:

Airway smooth muscle tone therefore depends on the balance between the:

- Parasympathetic input.
- Inhibitory influence of circulating epinephrine.
- NANC inhibitory nerves.
- Sympathetic innervation of the parasympathetic ganglia (Figs 19.2, 19.3).

PATHOPHYSIOLOGY AND DISEASES OF THE PULMONARY SYSTEM

Pulmonary disease can cause coughing, wheezing, shortness of breath, and abnormal gas exchange. Coughing, wheezing, shortness of breath, and abnormal gas exchange can result from:

- Changes in airway smooth muscle tone (e.g. bronchial asthma).

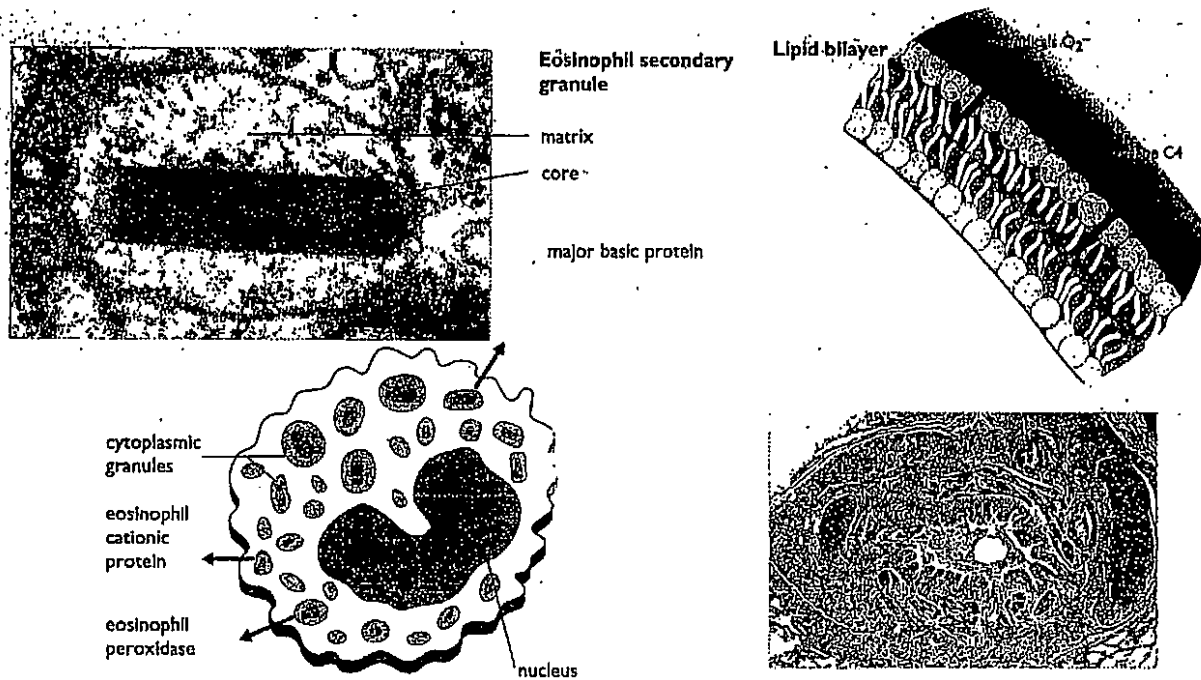


Fig. 19.4 Cytotoxic mediators released by eosinophils lead to epithelial damage. Infiltrating eosinophils release cytotoxic mediators, including major basic protein, eosinophil peroxidase, and eosinophil cationic protein from their granules. Certain inflammatory mediators can be released from the lipid bilayer upon eosinophil activation. Lower right, a section of asthmatic airway showing the pathophysiological changes. (Courtesy of Dr Alan Stevens and Professor James Lowe.)

- Vascular congestion of the upper respiratory tract (e.g. rhinitis).
- Mucous plugging (e.g. chronic bronchitis).

Bronchial asthma

Bronchial asthma is a chronic inflammatory disease of the airways that causes acute bronchospasm and dyspnea. Bronchial asthma is a common disease, affecting up to 20% of the population in some countries. Its associated morbidity and mortality are rising in most countries despite increasing use of anti-asthma drugs.

The characteristic clinical features of bronchial asthma are associated with a chronic inflammatory response in the airways involving local lymphocyte and eosinophil accumulation, which is evident following bronchoalveolar lavage (BAL), on biopsy and at autopsy. It is thought that the granules of infiltrating eosinophils release cytotoxic mediators (Fig. 19.4), which damage the respiratory ciliated epithelium. The tissue damage is associated with increased airway irritability (bronchial hyperresponsiveness), which causes coughing and wheezing in response to stimuli that do not normally provoke such responses (Fig. 19.5).

Bronchial hyperresponsiveness may result from exposure of sensory nerves beneath the damaged epithelium (Fig. 19.6). Activation of these nerves on exertion or the exposure to environmental irritants results in local axon and vagal reflexes, which can produce bronchoconstriction, mucus secretion, and airway vasodilation (Fig. 19.6).

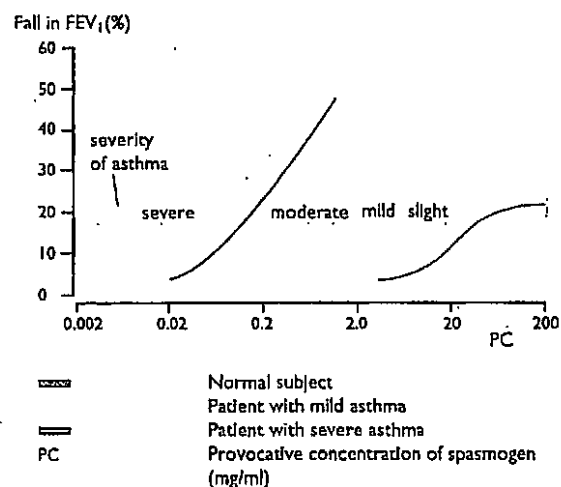


Fig. 19.5 Bronchial hyperresponsiveness. People with bronchial asthma have bronchial hyperresponsiveness, which causes them to cough and wheeze in response to stimuli that would not provoke such responses in normal subjects. Clinically, this hyperresponsiveness can be demonstrated by measuring the change in lung function, which is shown by a reduction in FEV₁ (forced expiratory volume in one second) in response to an inhaled spasmogen such as histamine or methacholine. Increased irritability is observed with increasing disease severity.

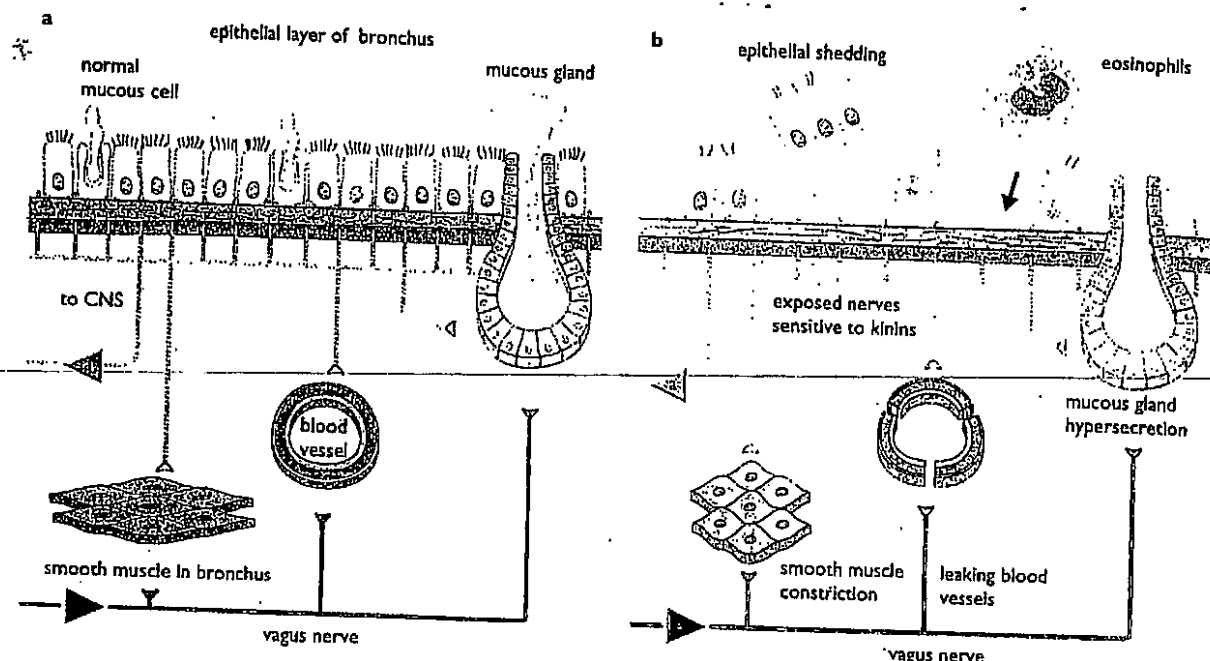


Fig. 19.6 Mechanism of bronchial hyperresponsiveness. This may result from exposure of sensory airway nerves following damage to the ciliated epithelial layer by cytotoxic mediators released by infiltrating eosinophils, which may then become hypersensitive as a result of exposure to inflammatory mediators such as prostaglandins and cytokines. (a) Normal lung; (b) asthmatic lung.

■ **Bronchodilators and anti-inflammatory drugs are used in the treatment of asthma**

Bronchodilators

Acute reversible bronchospasm contributes to the characteristic wheezing of asthma. It is readily treated by three different classes of bronchodilator drugs: β_2 adrenoceptor agonists, anticholinergics, and xanthines.

β_2 ADRENOCEPTOR AGONISTS are the most widely prescribed drugs for the treatment of the bronchoconstriction in asthma and are available by inhalation from a metered-dose inhaler or nebulizer, systemically as well as orally (Fig. 19.7). Short-acting β_2 adrenoceptor agonists for the acute relief of bronchospasm include albuterol, terbutaline, and fenoterol. Epinephrine, isoproterenol, isoetharine and metaproterenol are sometimes

used but are not selective for β_2 receptors, having various degrees of activity at α receptors and β_1 receptors, which are essentially unwanted effects. Most β_2 agonists are available as racemic mixtures, but recently the single R-albuterol has been introduced into clinical practice.

β_2 Adrenoceptor agonists relax airway smooth muscle through the activation of adenylyl cyclase. They are excellent functional (physiologic) antagonists of the bronchoconstriction caused by a wide range of stimuli. One of the drawbacks of albuterol, terbutaline and fenoterol, however, has been their short biologic half-life (2–3 hours), but a variety of long-acting β_2 adrenoceptor agonists have now been introduced that produce bronchodilation for up to 15 hours. Long-acting β_2 adrenoceptor agonists include salmeterol, aformoterol, and bambuterol. The prolonged action of salmeterol is believed to be due to the presence in the molecule of a long lipophilic tail, which binds to an 'exoreceptor' in the vicinity of the β_2 adrenoceptor on airway smooth muscle. These long-acting drugs are intended for long-term prevention of asthma attacks, but are not recommended for acute relief, particularly salmeterol, which has a delayed onset of action. They are particularly useful for treating nocturnal asthma.

The adverse effects of β_2 adrenoceptor agonists include tremor and hypokalemia, and, when given in excessive amounts, tachycardia. The adverse effects of β_2 adrenoceptor agonists are reduced when they are inhaled and this is the preferred route of administration.

Clinical features of bronchial asthma

- Acute attacks of dyspnea associated with acute airway obstruction due to contraction of airway smooth muscle
- Mucus hypersecretion, which may lead to mucus plugging
- Airway inflammation
- Bronchial hyperresponsiveness

β_2 Agonists	Route of administration	Dose range	Half-life (hours)
Albuterol	Oral: Extended release	2 mg/12 hours pediatric 4–8 mg/12 hours adult	5–6
Terbutaline	Oral: Tablets	5 mg 3 times daily for adults and children over 12 years 2.5 mg 3 times daily for children 6–12 years	3–4
	Injection: Subcutaneous	0.255 mg (0.25 ml) for adults and children over 12 years 0.006–0.01 mg/kg for children 6–12 years	3–4
	Inhalation: Micronized metered dose	2 inhalations of 0.2 mg separated by a 60-second interval every 4–6 hours for adults and children over 12 years	3–4
Fenoterol	Inhalation: Aerosol	1–2 inhalations (0.1 mg) up to 3 times daily in adults 1 inhalation (0.1 mg) up to 3 times daily for children over 6 years 1–2 inhalations (0.2 mg) up to 3 times daily in adults	6–7
Aformoterol	Inhalation: Breath-activated inhaler	1–2 capsules (12 µg) twice daily 6–12 µg twice daily in adults	
	Breath-activated Dry Powder		
Salmeterol	Inhalation: Aerosol	2 inhalations of 21 µg twice a day for adults and children over 12 years	17
	Powder	1 inhalation of 50 µg twice daily for adults and children over 4 years	17
Isoproterenol	Inhalation: Aerosol	1–2 inhalations of 0.131 mg up to 5 times a day in adults and children 5–15 deep inhalations of a 1:200 dilution of a 0.5% solution administered via a nebulizer in adults and children	
	Solution		
Bambuterol	Oral	10–20 mg daily at night in adults	

Fig. 19.7 β_2 Agonists.

ANTICHOLINERGICS Muscarinic receptor antagonists cause bronchodilation by binding to muscarinic receptors on airway smooth muscle and thereby preventing the action of acetylcholine released from parasympathetic nerves in the vagus nerve. Anticholinergics do not therefore prevent all types of bronchospasm, but are particularly effective against irritant-induced changes in respiratory function. Muscarinic receptor antagonists also decrease mucus secretion.

Currently available muscarinic receptor antagonists do not discriminate between M_1 and M_3 receptors (Fig. 19.8), and it is likely that M_1 autoreceptor antagonism on cholinergic presynaptic terminals may reduce the effectiveness of the antagonism at M_3 receptors on smooth muscle. Selective M_3 receptor antagonists could therefore be an important therapeutic advance.

Muscarinic antagonists include ipratropium bromide, oxitropium bromide, tiotropium bromide, and atropine (Fig. 19.9). The first two drugs are used clinically in many countries by the inhaled route to reduce the systemic adverse effects

otherwise associated with this class of drugs. When inhaled they are poorly absorbed into the circulation from the lung, do not cross the blood–brain barrier, and have few adverse effects. Maximum bronchodilation is usually observed from 30 minutes after administration and they last for up to 5 hours. However, their efficacy in asthma is usually modest compared with their efficacy in chronic obstructive pulmonary disease (COPD) (see below).

XANTHINES have been widely used in the treatment of asthma since the start of the twentieth century following observations that 'strong coffee' relieved the symptoms of asthma. Coffee, tea, and chocolate-containing beverages contain naturally occurring xanthines such as caffeine and theobromine. The main xanthine used clinically is theophylline, which is sometimes used as theophylline ethylenediamine salt (aminophylline). Another xanthine preparation that is occasionally used is elixophylline. Xanthines are usually given orally, but are rapidly metabolized, and have a short biologic half-life. However, this

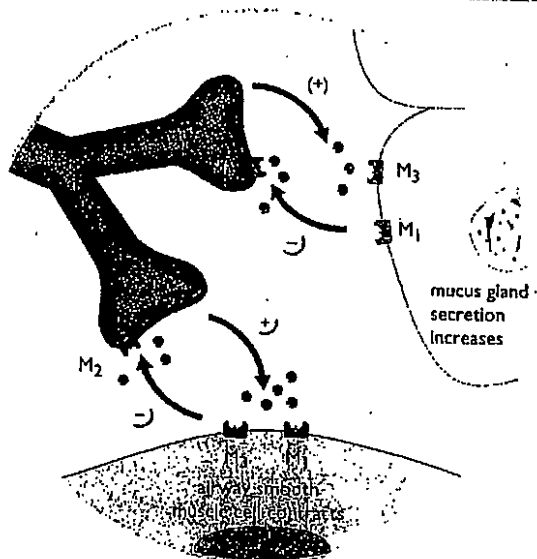
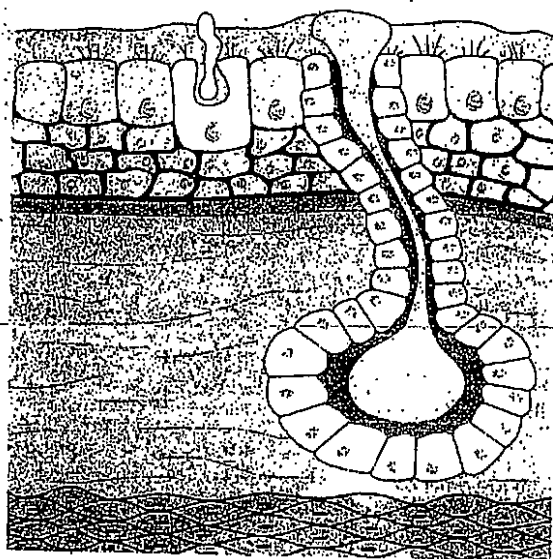


Fig. 19.8 Action of acetylcholine (ACh) on airway smooth muscle. ACh released from parasympathetic neurons acts on M_1 and M_3 muscarinic receptors on airway smooth muscle and submucosal glands to bring about muscle constriction and mucus secretion. In addition, some of the released ACh acts on presynaptic M_2 muscarinic receptors on the nerve terminal to reduce further release of ACh. These M_2 receptors are known as 'autoreceptors.'

limitation is overcome by using 'slow-release' preparations, which will maintain effective plasma concentrations over 16–18 hours.

The major problem with using xanthines as bronchodilators is that they have a very narrow therapeutic window, consequently plasma concentrations over $10 \mu\text{g/ml}$ are required for effective bronchodilation, but plasma concentrations over $20 \mu\text{g/ml}$ are associated with an increased likelihood of adverse effects, including nausea, cardiac arrhythmias, and convulsions.

Plasma xanthine concentrations should therefore be measured routinely. Aminophylline can be given as a slow intravenous infusion with a loading dose for acute severe asthma.

For treatment of acute asthma in patients not receiving theophylline products, a loading dose of 5 mg/kg should be administered and maintained at 4 mg/kg every 6 h in young children (1–9 years), 3 mg/kg every 6 h in children (9–16 years) and smokers, 3 mg/kg every 8 h in nonsmoking adults, and 2 mg/kg in older patients.

Drug interactions are important as the serum theophylline concentration can be increased (barbiturates, benzodiazepines) or decreased (cimetidine, erythromycin, ciprofloxacin, allopurinol) by a variety of drugs. These interactions can cause variations in serum theophylline levels between patients, so the dose of theophylline must be titrated to suit the individual. Initially start at the lowest dose and if tolerated and adequate control of symptoms is not achieved then the dose can be increased in stages up to the maximum dosage recommended. An interval of 3 days must be left between increases in dosage to allow for serum levels to stabilize. In the case of acutely ill patients the serum levels should be monitored every 24 h. In all cases the dose should be adjusted to give a serum concentration of $5\text{--}15 \mu\text{g/ml}$.

Sustained-release preparations are not suitable for the treatment of acute asthma, which should be treated with other medications or an immediate-release preparation.

For the treatment of nocturnal asthma the medication should be given at 8pm and serum theophylline levels should be monitored. It is preferable to titrate the dose with small increments allowing 3 days between increments increasing the dose only if it is tolerated and no adverse effects become apparent.

Xanthines are believed to produce bronchodilation by inhibiting a family of enzymes called phosphodiesterases (Fig. 19.10). These enzymes take part in the metabolism of the second messengers involved in relaxing airway smooth muscle (i.e. cAMP and cGMP). In particular, inhibition of phosphodiesterase 3 and 4 in airway smooth muscle leads to intracellular accumulation of cAMP and therefore smooth muscle relaxation (see Figs 19.10, 19.11).

Anti-inflammatory and prophylactic drugs

Anti-inflammatory drugs may resolve existing bronchial inflammation and/or prevent subsequent inflammation in asthma. Most anti-inflammatory drugs prevent subsequent inflammation and are therefore classed as prophylactic drugs for asthma. Since anti-inflammatory drugs do not cause bronchodilation, they are not recommended for acute asthma attacks.

GLUCOCORTICOSTEROIDS are the best established anti-inflammatory drugs for the treatment of the chronic inflammatory process underlying asthma. They inhibit inflammatory cell infiltration into the airways and reduce edema formation by acting on the vascular endothelium. Their mechanism of action is discussed in detail in Chapter 16.

Muscarinic receptor antagonists	Route of administration	Dose range	Half-life (hours)
Ipratropium bromide	Oral inhalation: Aerosol	20–80 µg 3 or 4 times daily in adults and children over 12 years 20–40 µg 3 times a day in children 6–12 years 20 µg 3 times daily	
	Dry powder Nasal inhalation: Nasal spray	20–80 µg 3 or 4 times daily in adults 42 µg in each nostril 2–3 times daily	
Oxlotropium bromide	Oral inhalation: Aerosol	200 µg 2–3 times daily in adults	2–4
Tiotropium bromide	Oral inhalation: Aerosol		10

Fig. 19.9 Muscarinic receptor antagonists.

Classification of phosphodiesterase isozymes			
Family	Isozyme	Tissue	Inhibitors
1	Ca ²⁺ /calmodulin dependent	Brain, airway smooth muscle	Vinopocetine Theophylline
2	cGMP stimulated	Heart, vascular smooth muscle, platelets, airway smooth muscle	Theophylline
3	cGMP inhibited	Lymphocyte, platelets, heart, vascular smooth muscle, airway smooth muscle	Milrinone Theophylline
4	cAMP selective	Inflammatory cells (neutrophil, macrophage, mast cell, eosinophil, lymphocyte) airway smooth muscle, heart, brain, striated muscle	Rolipram Theophylline Cilomilast Roflumilast
5	cGMP selective	Trachea, platelets, vascular smooth muscle	Zaprinast Theophylline Sildenafil

Fig. 19.10 Classification of phosphodiesterase isozymes.

Glucocorticosteroids can be given prophylactically by inhalation to achieve a local anti-inflammatory effect without causing systemic adverse effects. Inhaled glucocorticosteroids used for bronchial asthma include triamcinolone, beclomethasone,

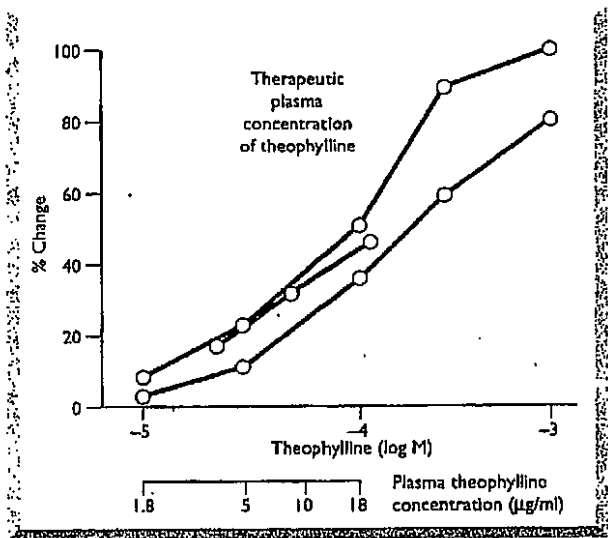


Fig. 19.11 Effects of theophylline at therapeutic concentrations. Percentage change in FEV₁ (red), percentage inhibition of airway smooth muscle relaxation (green), or percentage inhibition of phosphodiesterase activity in airway smooth muscle (purple) in relation to plasma concentrations of theophylline (µg/ml) or theophylline concentration (logM in an isolated tissue experiment). (Adapted with permission from Rabe et al. *Eur Resp J* 1995; 289: 600–603.)

budesonide, and fluticasone. Oral glucocorticosteroids may be required for severe asthma unresponsive to inhaled glucocorticosteroids, and usually prednisone, methylprednisolone, or prednisolone is prescribed (see Fig. 19.12).

Both oral and intravenous glucocorticosteroids are useful in the treatment of acute severe asthma. However, oral glucocorticosteroids have systemic adverse effects involving suppression of the hypothalamus–pituitary axis (see Chapter 15 and Fig. 19.12). Chronic use can lead to a variety of serious adverse effects, including stunting of growth in children (see Chapter 15 and Fig. 19.12).

Chapter 19 Drugs and the Pulmonary System

Glucocorticosteroids	Route of administration	Dose range	Drug Interactions
Beclomethasone	Nasal Inhalation aerosol	1 Inhalation (42 µg/inhalation) in each nostril 2–4 times a day in adults and children over 12 years 1 inhalation (42 µg/inhalation) in each nostril 3 times a day in children 6–12 years	
	Suspension	1–2 Inhalations (42 µg/inhalation) in each nostril twice a day in adults and children over 12 years 1 inhalation (42 µg/inhalation) in each nostril twice a day in children 6–12 years	
	Oral Inhalation Aerosol	2 Inhalations (42 µg/inhalation) given 3 or 4 times a day in adults and children over 12 years 1–2 inhalations (42 µg/inhalation) 3 or 4 times a day in children 6–12 years	
	Aerosol	2 Inhalations (84 µg/inhalation) twice daily in adults and children over 12 years	
	Dry powder	2 Inhalations (84 µg/inhalation) twice daily in children 6–12 years 200 µg twice daily or 100 µg 4 times daily in adults and children over 12 years 50–100 µg 2–4 times daily in children	
Budesonide	Nasal inhalation Nasal inhaler	256 µg daily either 2 sprays per nostril twice daily or 4 sprays per nostril once daily in adults and children over 6 years	Cytochrome P-450 3A inhibitors
	Nasal spray	64 µg per day (one spray of 32 µg per nostril once daily) in adults and children over 6 years	Cytochrome P-450 3A inhibitors
	Oral inhalation Dry powder	200–400 µg twice daily in adults and 200 µg twice daily in children previously maintained with bronchodilators alone 200–400 µg twice daily in adults and 200 µg twice daily in children previously maintained with inhaled corticosteroids 400–800 µg twice daily in adults and 400 µg twice daily in children previously maintained with oral corticosteroids	Cytochrome P-450 3A inhibitors Ketoconazole
	Aerosol	200 µg twice daily in adults and children	Cytochrome P-450 3A inhibitors
Fluticasone	Oral Inhalation Dry powder	100 µg twice daily in adults and children over 12 years and 50 µg twice daily in children 4–7 years previously maintained with bronchodilators alone 100–250 µg twice daily in adults and children over 12 years and 50 µg twice daily in children 4–7 years previously maintained with inhaled corticosteroids 1000 µg twice daily in adults and children over 12 years previously maintained with oral corticosteroids	Cytochrome P-450 3A inhibitors
	Aerosol	88 µg twice daily in adults previously maintained with bronchodilators alone 88–220 µg twice daily in adults previously maintained with inhaled corticosteroids 880 µg twice daily in adults previously maintained with oral corticosteroids	Cytochrome P-450 3A inhibitors
	Intranasal Nasal spray	220 µg/day given once or twice a day in adults 100–200 µg/day given once a day in children 4 years and older	Cytochrome P-450 3A inhibitors
Mometasone	Intranasal Nasal spray	200 µg/day given once a day in adults and children over 12 years 100 µg/day given once a day in children 6–12 years	

Glucocorticosteroids	Route of administration	Dose range	Drug Interactions
Triamcinolone	Oral Inhalation		
	Aerosol	200 µg 3–4 times a day in adults and children over 12 years 100–200 µg 3–4 times a day in children 6–12 years	
	Nasal Inhalation		
	Nasal spray	220 µg once a day in adults and children over 6 years	
	Systemic		
	Oral tablets	8–16 mg/day	Phenytoin Phenobarbitone Primidone Rifampin Carbamazepine Aminoglutethimide Ephedrine Diuretics Antihypertensives Estrogens Anticholinesterases Cardiac glycosides Hypoglycemics Oral anticoagulants NSAIDs Salicylates Live vaccines Amphotericin Acetazolamide Carbenoxolone Methotrexate Cyclosporine Erythromycin Azole antifungals As above
	Intramuscular injection	2.5–60 mg/day	
Dexamethasone	Systemic		
	Oral	0.75–9 mg/day	See triamcinolone
Prednisone	Systemic		
	Oral	5–60 mg/day	See triamcinolone
Methylprednisolone	Systemic		
	Oral	4–48 mg/day	See triamcinolone
	Intramuscular injection	4–48 mg/day	As above
	Intravenous infusion	30 mg/kg over 30 minutes every 4–6 hours for 48 hours	As above
Cortisone	Systemic		
	Oral	25–300 mg/day	See triamcinolone
	Intramuscular injection	25–300 mg/day	As above

Fig. 19.12 Glucocorticosteroids for asthma.

- All β adrenoceptor agonists promote bronchodilation
- The principal action of glucocorticosteroids is suppression of the inflammatory response
- Xanthines combine bronchodilator and anti-inflammatory properties
- Muscarinic receptor antagonist-induced bronchodilation is occasionally useful

XANTHINES not only produce bronchodilation, as described above, but also inhibit inflammatory cell activation and infiltration in the airways of asthmatics. Furthermore, xanthine withdrawal from some asthmatics after chronic treatment leads to a worsening of asthma, even in patients taking glucocorticosteroids. The anti-inflammatory effects are associated with plasma concentrations lower than those required to produce bronchodilation (5–10 mg/ml). Such findings have led to a reappraisal of the place of xanthines in the treatment of asthma (Fig. 19.11), particularly because:

- Xanthines are administered orally, which greatly enhances patient adherence compared with that for inhaled drugs.
- Low plasma concentrations of theophylline have fewer adverse effects.

The anti-inflammatory action of xanthines may be mediated through inhibition of phosphodiesterase 4, the isozyme found predominately in inflammatory cells (see Fig. 19.10). Recent evidence suggests that theophylline, which is an established agent for the treatment of acute bronchospasm in asthmatics, may be effective when used at low doses for long-term maintenance treatment in asthmatics as a result of this anti-inflammatory action.

CROMOLYN SODIUM, KETOTIFEN, AND NEDOCROMIL SODIUM are anti-allergic drugs used prophylactically in the treatment of bronchial asthma. Cromolyn and nedocromil sodium are active by inhalation. Ketotifen is orally active and is used worldwide except in the US. The mechanisms of action of these prophylactic drugs are not clearly understood, but cromolyn sodium was originally thought to be a 'mast cell stabilizer,' so preventing the release of histamine and other inflammatory mediators (see Chapter 16). It is now clear that this action is not the only effect of these prophylactic drugs. They are capable of affecting many inflammatory cell types including alveolar macrophages, thereby preventing inflammatory cell recruitment into the airway wall. In addition, cromolyn sodium and nedocromil sodium can depress the exaggerated neuronal reflexes triggered by irritant receptors in the airways, probably by suppressing the response of exposed irritant nerves (see Fig. 19.6). This action has led to their use in the treatment of 'asthmatic cough.'

Drugs affecting leukotriene synthesis and actions

ZAFIRLUKAST AND MONTELUKAST are orally active cysteinyl-leukotriene receptor antagonists that antagonize the actions

Drugs that modify serum theophylline concentrations

- *Drugs that increase serum theophylline concentrations include:*
Oral contraceptives
Erythromycin
 Ca^{2+} antagonists
Cimetidine (but not ranitidine)
- *Drugs that decrease serum theophylline concentrations include:*
Rifampin
Phenobarbital
Phenytoin
Carbamazepine

of LTC_4 and LTD_4 on airway smooth muscle and vascular endothelium. They are particularly effective in patients with aspirin-induced asthma. They are also very effective in treating exercise-induced asthma and are available as once-a-day formulations which may improve adherence which is a major clinical problem in the treatment of asthma. Zileuton is an orally active inhibitor of the synthesis of cysteinyl-leukotrienes and other 5-lipoxygenase metabolites derived from arachidonic acid metabolism (see Fig. 16.10) which has also been shown to have a modest clinical effect in the treatment of asthma.

Cyclosporine analogs

Cyclosporine has been successfully used in the treatment of immune disorders involving lymphocytes (see Chapter 16) and has recently been shown to have some clinical benefit in asthmatics resistant to therapy with glucocorticosteroids. However, it has considerable adverse effects and so there is a growing interest in finding safer analogs of this drug to use in the treatment of asthma and other diseases.

Anti-inflammatory treatment is used much earlier in asthma now than in the past

As asthma is a chronic inflammatory disease of the airways, and not just a disease associated with bronchoconstriction, a number of organizations and societies around the world including the National Institutes of Health in the United States, the World Health Organization, the Canadian Thoracic Society, the British Thoracic Society, and the Australasian Thoracic Society have issued guidelines on the optimal treatment of bronchial asthma. These are based on a stepwise approach, but stress the need for anti-inflammatory treatment much earlier in the disease than has been used in the past.

Chronic obstructive pulmonary disease

Chronic bronchitis and emphysema often occur together in heavy smokers, a condition referred to as chronic obstructive pulmonary disease (COPD). Chronic obstructive pulmonary disease is an airways disease associated with chronic bronchitis, and in the later stages, emphysema. COPD mainly occurs in smokers. Chronic bronchitis is defined in functional terms as a disorder associated with the excessive production of sputum

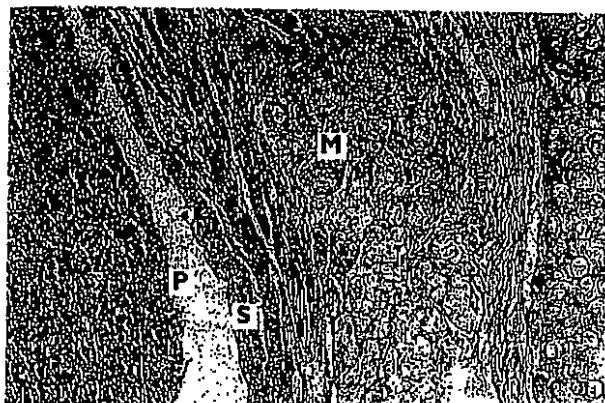


Fig. 19.13 Chronic bronchitis. The main abnormality is hypersecretion of mucus, which plugs the airway (P). Hypersecretion is associated with hypertrophy and hyperplasia of bronchial mucus-secreting glands (M). The Reid Index, which is the ratio of gland:wall thickness in the bronchus, is increased in chronic bronchitis. Inflammation is typically absent, although excessive mucus production is frequently associated with the development of coincidental respiratory tract infections, leading to secondary inflammation. Squamous metaplasia (S) is common in patients who have persistent or recurrent superimposed infections. (Courtesy of Dr Alan Stevens and Professor James Lowe.)

Adverse effects of anti-asthma drugs

- β_2 Adrenoceptor agonists may cause tremor and their long-term use may worsen the underlying disease
- Xanthines cause tremor, tachycardia, and gastrointestinal irritation
- Oral glucocorticosteroids should be reserved for patients who do not adequately respond to other therapy, because they have a wide spectrum of adverse effects
- Aerosol glucocorticosteroids cause fewer adverse effects than oral glucocorticosteroids, and mainly overgrowth of *Candida* in the mouth and hoarseness

and cough, daily or on most days. Airway obstruction is the result of luminal narrowing and mucus plugs, and may lead to secondary respiratory infection (Fig. 19.13). Typically, chronic bronchitis causes alveolar hypoventilation, hypercapnia, and hypoxia, although some patients hyperventilate in order to avoid severe hypoxia. Secondary pulmonary hypertension may develop and lead to right heart failure (cor pulmonale). Patients typically have a productive cough, sputum production, breathlessness on exertion, and airway obstruction. Respiratory infection is common and can worsen the progress of the disease.

■ *Bronchodilators, mucokinetic drugs, and antibiotics are used to treat chronic bronchitis*

Bronchodilators

β_2 ADRENOCEPTOR AGONISTS (short- and long-acting) are used to treat breathlessness on exertion in chronic bronchitis,

but with this condition they are generally less effective than in the treatment of bronchial asthma because less of the airways obstruction is due to abnormal airway smooth muscle contraction.

XANTHINES are used in the treatment of chronic bronchitis, particularly for their effects on airway smooth muscle. They also have central nervous system (CNS) effects, leading to increased alertness, which may be important in chronic bronchitis, and can increase diaphragm contractility.

Mucokinetic drugs

N-ACETYLCYSTEINE breaks the disulfide bonds that hold mucus glycoproteins together and thereby reduce the viscosity of mucus. N-Acetylcysteine and a related drug ambroxol have been shown to have some clinical benefit in the treatment of COPD. Other mucokinetic agents include guaifenesin, potassium iodide and even saline.

MUSCARINIC RECEPTOR ANTAGONISTS are the mainstay of therapy for chronic bronchitis because they can reduce much of the bronchospasm associated with smoking and the subsequent inhalation of irritants. Their ability to reduce mucus secretion in the airway by antagonizing acetylcholine acting on muscarinic receptors in mucus glands is also very beneficial (see Fig. 19.8).

Antibiotics

Patients with chronic bronchitis commonly get secondary bacterial infections colonizing the sputum. Antibiotics are therefore often prescribed for these patients and are discussed in more detail in Chapter 9 and below.

PDE4 inhibitors

Selective phosphodiesterase inhibitors inhibit the PDE4 isoenzyme present in most inflammatory cells. Recent clinical studies have suggested that the orally active PDE4 selective inhibitors, roflumilast and cilomilast, show clinical benefit in the treatment of COPD and to a lesser extent in asthma.

Adult respiratory distress syndrome

Adult respiratory distress syndrome (ARDS) is an acute life-threatening condition. It results from increased leakiness of the pulmonary capillary network leading to hypoxia, reduced lung compliance, alveolar infiltrates, and noncardiogenic pulmonary edema. It is common in patients with sepsis, who account for 50% of ARDS cases. The mortality rate of ARDS is approximately 60–70%.

Current therapy for ARDS is inadequate

No drug specifically prevents the onset of ARDS or lessens its lethality. However, there are promising studies in animals and case reports of emerging therapies for the future including monoclonal antibodies directed against cytokines, PAF, TNF, and IL-1 receptor antagonists.

circulation that can lead to significant alteration in both pulmonary and cardiac function, and even death. Venous thromboembolism is relatively common with an estimated 140,000 deaths per year in the US. There are also individuals with chronic cor pulmonale resulting from chronic unresolved emboli.

The goal of treatment of venous thromboembolism is the prevention of recurrent, fatal pulmonary embolism. Heparin is initially used with doses adjusted to maintain the APTT within therapeutic levels (see Chapter 13). Heparin treatment is normally maintained for 5–10 days and is usually simultaneous with warfarin administered orally. Newer, low molecular weight heparin fractions are increasingly used in the treatment of venous thromboembolism in place of unfractionated heparin as they have the advantage of fixed-dose subcutaneous administrations without monitoring or dose adjustment and with a comparable or lower risk of hemorrhage. Meta-analysis of various trials also suggests that prophylactic treatment with antiplatelet drugs (see Chapter 13) reduces the incidence of deep vein thrombosis and pulmonary embolism.

Pulmonary hypertension

Primary pulmonary hypertension is rare, but secondary pulmonary hypertension is more common and results from a variety of causes such as connective tissue destruction, pulmonary embolism, COPD, fibrosing lung disease, and from the increased use of anorectic drugs such as aminorex fumarate and more recently dexfenfluramine hydrochloride.

Vasodilator drugs

Pulmonary hypertension is primarily treated with vasodilators, although there is still no consensus as to which vasodilator is best. In primary pulmonary hypertension, treatment is with calcium channel blockers, the most commonly used drugs being nifedipine and diltiazem (see Chapter 18). They are active acutely and are useful in identifying patients who will respond to long-term vasodilator treatment. Their relatively long half-lives mean that it takes up to 12 h to complete an acute vasodilator assessment, and as these drugs are able to affect all vascular beds, systemic vasodilation and hypotension are common side effects. If there is no acute response to calcium channel blockers, continuous i.v. infusion of prostacyclin (PGI_2) should be started. PGI_2 has a 3-minute half-life which makes it ideal for assessment of pulmonary hypertension. However, this also means PGI_2 must be infused continuously for chronic treatment making it expensive. PGI_2 also has many adverse effects including systemic hypotension, nausea, headache, flushing and abdominal pain, all of which resolve with a reduction in the infusion rate. Such side effects may be reduced by aerosolizing PGI_2 . Infusion of PGI_2 should be 1 ng/kg/min and increased by 1–2 ng/kg/min until there is a positive response or appearance of adverse effects, with a maximum dose in adults of 12 ng/kg/min. Stable orally active PGI_2 analogs such as iloprost and beraprost have also shown positive clinical benefit.

Recently, inhaled nitric oxide has been shown to be effective in the treatment of pulmonary hypertension via pulmonary

vasorelaxation. It has a great advantage over other vasodilator drugs in being selective regarding pulmonary hypertension as it has minimal effects on systemic blood vessels when inhaled. It is cheap, has a rapid onset of action (albeit very short-lived in the presence of O_2) and minimal adverse effects acutely. However, it requires the availability of a metered gas delivery system and careful environmental monitoring since some NO metabolites, such as NO_2 , are toxic.

Adenosine is another potent vasodilator, which increases cAMP in vascular smooth muscle, and it can be useful for the assessment of vasodilator treatment of primary pulmonary hypertension. Adenosine has a very short half-life (10 sec) and is cheaper than PGI_2 . It does, however, cause significant coronary vasodilation and reduced systemic vessel resistance.

O_2 is a selective pulmonary vasodilator and should be considered in all patients with pulmonary hypertension who are hypoxic at rest or who desaturate with exercise. This is particularly important in patients with raised pulmonary artery pressure resulting from COPD. 15–17 hours per day O_2 treatment in all patients has been shown to provide a marked improvement in disease progression and morbidity in patients with COPD. This selective effect of O_2 is by virtue of its effect on hypoxic pulmonary vasoconstriction.

Other drugs used for the treatment of pulmonary hypertension

The cardiac glycosides such as digoxin have been widely used to treat pulmonary hypertension although there is no consensus as to the benefit they bring. Symptomatic benefit has also been shown with sublingual isoproterenol, and both dopamine and dobutamine have been suggested to be useful in the event of acute deterioration of right ventricular function. Diuretics are also useful in right heart failure to reduce excessive right ventricular preload and to counteract the edema associated with pulmonary hypertension, although there is no evidence that these drugs alter survival.

Drugs with adverse effects in patients with respiratory disease

β Adrenoceptor antagonists

β_1 Adrenoceptor antagonists such as propranolol, with its potent capacity to block β_1 adrenoceptors, are strictly contraindicated in patients who have bronchial asthma because they precipitate severe bronchoconstriction, which may be lethal. This adverse effect results from the dependence of asthmatics on circulating epinephrine and/or the innervations of parasympathetic ganglia by sympathetic nerves as inhibitory mechanisms to offset vagal tone, which tends to reduce airway diameter. β Adrenoceptor antagonist eyedrops can also induce life-threatening asthma attacks in asthmatic subjects.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors such as captopril and enalapril are used increasingly in the treatment of hypertension and congestive heart failure. However, ACE inhibitors such as captopril can induce coughing in some patients with concomitant allergic airway diseases. The mech-

Adverse effects of drugs used for respiratory diseases other than asthma and infection

- Mucokinetic drugs have relatively few adverse effects
- The opioids are the only cough suppressants with a major adverse effect (i.e. the potential for drug abuse and social withdrawal)

Adverse effects of antibiotics

- The principal adverse effect of penicillin and cephalosporins is allergy
- The principal adverse effect of aminoglycosides is renal toxicity
- The principal adverse effects of sulfonamides are allergy and skin photosensitivity
- The principal adverse effects of antitubercular drugs vary with the drug

anism is believed to be local generation of bradykinin because ACE inhibitors inhibit peptidyl peptidase enzymes involved in the metabolism of bradykinin in addition to inhibiting the conversion of angiotensin I to angiotensin II. The concentration of bradykinin in the lung can then become elevated and stimulate the afferent receptors, initiating cough. ACE-induced coughing is effectively treated with cromolyn sodium.

Nonsteroidal anti-inflammatory drugs

Approximately 20% of people with asthma can develop severe bronchoconstriction following ingestion of nonsteroidal anti-

inflammatory drugs (NSAIDs). The mechanism is not fully understood, but may relate to the generation of lipoxigenase metabolites of arachidonic acid because it can be inhibited by 5-lipoxygenase inhibitors. NSAIDs, including aspirin, must therefore be used with caution in patients with asthma.

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