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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 91/09596
A61K 31/135	A1	(43) International Publication Date:	11 July 1991 (11.07.91)

(21) International Application Number: PCT/US91/00088

(22) International Filing Date: 4 January 1991 (04.01.91)

(30) Priority data:
461,262 5 January 1990 (05.01.90) US

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(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: OPTICALLY PURE R(-) ALBUTEROL FOR TREATING ASTHMA

(57) Abstract

The optically pure R(-) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(-) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

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Optically pure R(-) albuterol for treating asthma.

Description

Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on $beta_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a

specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

Summary of the Invention

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is

administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

Detailed Description of the Invention

The present invention relies on the bronchodilation activity of the R(-) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily

obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is administered to an individual who has asthma. For example, R(-) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of

administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(-) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in

tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(-) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(-) isomer may reduce the teratogenic potential associated with albuterol.

CLAIMS

1. Use of R(-) isomer of albuterol, which is substantially free of the S(+) isomer of albuterol, for the manufacture of a medicament for the treatment of asthma and, at the same, for reducing or eliminating undesirable side effects associated with racemic albuterol, wherein the treatment results in bronchodilation.

2. The use of Claim 1 wherein the amount of the R(-) isomer of albuterol is greater than about 90% by weight.

3. The use of Claim 2 wherein the amount of the R(-) isomer of albuterol is greater than about 99% by weight.

4. The use of Claim 1 for the manufacture of a medicament in unit dosage form for inhalation administration having between about 30 and 90 mcg of the R(-) isomer of albuterol.

5. The use of Claim 1 for the manufacture of a medicament in unit dosage form for oral administration having between about 1 and 8 mg of the R(-) isomer of albuterol.

6. Use of the R(-) isomer of albuterol and at least one additional drug for the manufacture of a medicament for the treatment of asthma and, at the same time, for reducing or eliminating undesirable side effects associated with racemic albuterol, wherein the treatment results in bronchodilation.

7. The use of Claim 6 wherein the additional drug is selected from the group consisting of bronchodilators, antihistamines and analgesics.

8. The use of Claim 7 wherein the analgesic is selected from the group consisting of aspirin, acetaminophen and ibuprofen.

9. The R(-) isomer of albuterol, substantially free of the S(+) isomer of albuterol, and at least one additional drug for use as a medicament for the treatment of asthma.

10. The composition of Claim 9 wherein the R(-) isomer of albuterol is at least 90% by weight of the albuterol portion.

11. The composition of Claim 10 wherein the R(-) isomer of albuterol is at least 99% by weight of the albuterol portion.

12. The composition of Claim 9 wherein the additional drug is selected from the group consisting of bronchodilators, antihistamines and analgesics.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/00088

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 31/135

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	Br. J. Pharmacol., vol. 48, no. 1, 1973, R.T. Brittain et al.: "Some observations on the beta-adrenoceptor agonist properties of the isomers of salbutamol", pages 144-147 see page 145, lines 28-34; page 146, lines 13-16 --	1-8
X	The Journal of Pharmacology and Experimental Therapeutics, vol. 189, no. 3, 1974, The Williams & Wilkins Co., (US), C.K. Buckner et al.: "Studies on the effects of enantiomers of soterenol, trimetoquinol and salbutamol on beta adrenergic receptors of isolated guinea-pig atria and trachea", pages 616-625 see page 620, table 1, salbutamol; page 621, left-hand column, lines 2-4, 15-17; figure 3; page 623, left-hand column, lines 31-35 --	1-8

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
9th April 1991	31. 05. 91
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	Clinical Chemistry, vol. 33, no. 6, 1987, Y.K. Tan et al.: "Stereoselective disposition of salbutamol enantiomers in man: investigation using chiral HPLC", see page 1026 abstract 712 --	1-8
X	EP, A, 0248150 (BRISTOL MYERS) 9 December 1987 see page 10, table IV: Aspirin + albuterol --	1,9-12
X	EP, A, 0320550 (BRISTOL MYERS) 21 June 1989 see page 8, table IV: Aspirin + albuterol --	1,9-12
X	Trends Pharmacol. Sci., vol. 7/5, 1986, Elseviers Science Publishers B.V., (Amsterdam, NL), E.J. Ariëns: "Chirality in bioactive agents and its pitfalls", pages 200-205 see page 201, table 1: salbutamol --	1-8
A	The Merck Index, 11th edition, 1989, Merck & Co., Inc., (Rahway, N.J., US), see page 37, no. 209, "Albuterol" ----------	1-12

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND incompletely SEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ....., because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claim numbers 1-8, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The subject matter of claims 1-8 is not supported by pharmacological evidence. As a result, this subject matter is speculative (PCT Art. 6, Rule 39.1 (i)). In the absence of pharmacological data, the evaluation the technical nature of the subject matter and the comparison with the prior art are equivocal and subjective. As a consequence, it may well be that relevant prior art is not comprised in the search report.

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9100088 SA 43954

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 07/05/91
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0248150	09-12-87	US-A- 4965065	23-10-90
		AU-B- 594125	01-03-90
		AU-A- 6969987	10-09-87
EP-A- 0320550	21-06-89	None	