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(54) Title: METHOD OF TREATING UNDESIRED UTERINE CONTRACTIONS USING OPTICALLY PURE R- OR RR-ISOMERS OF ADRENERGIC BETA-2 AGONISTS

(57) Abstract

A method of preventing or inhibiting undesired uterine contractions in a female individual by administering a pure eutomer of an adrenergic beta-2 agonist which relaxes uterine smooth muscle, while eliminating side effects caused by the distomer. The method is particularly useful in treating both pregnant and non-pregnant subjects that have demonstrated a propensity for undesired uterine contractions, while reducing side effects in the patients and/or their fetuses, such as bronchial hyperreactivity, tremor, nervousness, shakiness, dizziness, increased appetite and cardiac tachycardia. Importantly, administration of a pure eutomer also eliminates undesired contractions of the uterine smooth muscle while avoiding the uterine hyperreactivity that has now been found to be induced by the S- or SS-isomers of beta-2 agonists.

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METHOD OF TREATING UNDESIRED UTERINE CONTRACTIONS USING OPTICALLY PURE R- OR RR-ISOMERS OF ADRENERGIC BETA-2 AGONISTS

BACKGROUND OF THE INVENTION

Many biologically active molecules exist as enantiomers. Although structurally identical, enantiomers can have different effects in biological systems: one enantiomer may have specific therapeutic activity while the other enantiomer may have no therapeutic activity or may have entirely different forms of biological activity. The form in which adrenergic beta-2 agonists presently are used are as racemic mixtures of two isomers (R- and S-albuterol; R- and S-terbutaline; R- and S-salmeterol; RR- and SS-fenoterol; and RR- and SS-formoterol). An R-isomer of a racemic compound is structurally identical to the S-isomer and structurally the isomers differ only in that one isomer is a mirror image of the other. When a molecule has two chiral centers, there are four isomers, called RR-, SS, RS, and SR. The marketed racemic beta-agonists formoterol and fenoterol each consists of a mixture of an RR-isomer (50%) and an SS-isomer (50%). The term eutomer(s), the isomer that has the desired pharmacological effect, refers to the R-isomers of albuterol, terbutaline or salmeterol and/or the RR-isomers of fenoterol or formoterol, while the term **distomer(s)**, the isomer that has not the desired pharmacological effect, refers to the S-isomer(s) of albuterol, terbutaline or salmeterol and/or the SS-isomer(s) of fenoterol or formoterol. The therapeutic action of beta-2 adrenergic drugs is to activate adrenergic β2-receptors and thereby initiate cellular responses, the most

well-known is the relaxation of bronchial smooth muscles. Beta-2 agonists are most commonly used to treat bronchial spasms associated with asthma. These drugs can also be used to inhibit undesired contractions of the uterus, but there are potentially hazardous side effects of the drug when used for this indication. The potentially hazardous side effects have now been found to include induction of uterine hyperreactivity (stimulation of uterine contractions) and teratogenic and unwanted effects of the drug to the fetus.

SUMMARY OF THE INVENTION

The present invention relates to a method of inhibiting undesired uterine contractions in a female individual, by administering a pure eutomer which relaxes uterine smooth muscle, while eliminating side effects caused by the distomer. The method is particularly useful in treating subjects that have demonstrated a propensity for irregular uterine contractions, induced by known or unknown causes. In cases where there is a risk for undesired uterine contractions, it is important to have an effective spasmolytic medication that does not further facilitate uterine contractions. Also, the medication should not cause harm to the fetus and should not exhibit other adverse side effects. A composition containing the pure eutomer is particularly useful for this application because the eutomers exhibits these desired characteristics. The present method provides a safe, effective method for treating irregular uterine contractions while reducing undesirable side effects, both in non-pregnant females and in

pregnant females and their fetuses, for example bronchial hyperreactivity, tremor, nervousness, shakiness, dizziness, increased appetite, cardiac tachycardia, and particularly uterine hyperreactivity, associated with adrenergic beta-2 agonists. In addition to the above, racemic mixtures of beta-2-agonists may also cause teratogenic effects, which are believed to be associated with the distomer(s). Administration of a pure eutomer eliminates any side effect that is associated with the distomer. Importantly, administration of a pure eutomer also eliminates irregular contractions of the uterine smooth muscle while avoiding the uterine hyperreactivity that has now been found to be induced by the S- or SS-isomers of beta-2 agonists.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the utero-spasmolytic activity of the R-isomer (resp. the RR-isomer) of a beta-agonist to provide relief from undesired uterine contractions, both in the non-pregnant female ("dysmenorrhea") and in the pregnant female ("tocolysis"), while simultaneously eliminating uterine hyperreactivity and other side effects, that have now been found to be caused by the distomer. (The term "undesired uterine contractions" is intended herein to include irregular contractions of the non-pregnant uterus in female individuals as well as premature uterine contractions of the pregnant uterus in female individuals.) Simultaneously other side effects that are caused by the S-isomer (resp the SS-isomer) - ex. bronchial hyperreactivity induced by the

distomer in asthmatic subjects - are eliminated by using the pure R-isomer (resp the RR-isomer). Also side effects that reside in both isomers will be reduced by using the pure R- or RR-isomer. In the present method, the optically pure R- or RR-isomer of a beta-agonist, substantially free of the S-isomer (resp the SS-isomer), is administered alone, or in combination with one or more other drugs in adjunctive treatment, to an individual in whom relief from uterine contractions is desired.

The R-isomer of albuterol as used herein refers to the optically pure isomer of α' [(tert-butylamino) methyl]-4-hydroxy-m-xylene-α,α'-diol, and to any biologically acceptable salt or ester thereof. The RR-isomer of fenoterol as used herein refers to the optically pure RR-isomer of 1-(3,5-dihydroxy phenyl)-1-hydroxy-2-[(4-hydroxyphenyl) isopropylamino]ethane, and to any biologically acceptable salt or ester thereof. The RR-isomer of formoterol as used herein refers to the optically pure isomer of 2'-hydroxy-5'-[(RS)-1-hydroxy-2-[[(RS)-p-methoxy-α-methylphenethyl] amino] ethyl]formanilide, and to any biologically acceptable salt or ester thereof. The R-isomer of terbutaline as used herein refers to the optically pure isomer of 1-(3,5-dihydroxyphenyl)-2- (tert-butylamino)ethanol, and to any biologically acceptable salt or ester thereof. The R-isomer of salmeterol as used herein refers to the optically pure isomer of 4-hydroxy-α'-[[[6-(4-phenylbutoxy)-hexyl]amino]methyl]- m-xylene α,α'-diol, and to any biologically acceptable salt or ester thereof. The term

"optically pure" or "substantially free of the S- or SS-enantiomer" as used herein means that the composition contains at least 85% by weight of the R- or RR-isomer of a beta-agonist and 15% by weight or less of the S- or SS-isomer. Optically pure adrenergic betaagonists are readily obtainable by methods known to those skilled in the art, for example, by synthesis from an optically pure intermediate or resolution of the racemic compound into its isomers.

In the present method, the eutomer of a beta-agonist is administered to an individual, who suffers from undesired uterine contractions of uterine smooth muscle. For example, R-albuterol or RR-formoterol is administered to an individual after the onset of undesired uterine smooth muscle contractions to reduce or eliminate said contractions. In another embodiment, an optically pure eutomer of a beta-agonist is administered prophylactically to an individual predisposed to undesired uterine contractions, that is, administration of the drug before the uterine contractions begin, to prevent their occurrence or to reduce the extent to which they occur.

In the present method, the optically active R- or RR-isomer of a beta-agonist can be administered by inhalation, parenterally, subcutaneously, intravenously, intramuscularly or other injection or infusion, orally, sublingually, topically, transdermally, vaginally, 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 etc.) 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 on the pharmacological potency of the drug, the route of administration, and at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the results sought. In general, quantities of optically pure R- or RR-isomer sufficient to eliminate undesired uterine contractions will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the pharmacokinetic property of the drug and the mode of drug administrations, for example, by inhaler, nebulizer or oral administration. For example about 10 to 3000 mcg of the optically pure R(-)-isomer of albuterol may be given by various forms of inhalation devices (metered dose inhalers, dry powder inhalers, nebulizers etc.), 1 to 50 mg may be given by the oral route (tablets, caplets, controlled release formulations including enteric coated oral preparations, etc.) or the sublingual routes once or more times per day may be adequate in most individuals to produce the desired effect. For oral administration of R-albuterol, e.g. tablet or syrup, a dose of about 1 mg to about 15 mg one to four times daily is administered to produce the desired effect. Controlled - release, sustained-released or delayed-released formulations of R-albuterol, containing 1 mg to 50 mg may be used to obtain controlled, sustained, or delayed therapeutic effects. Controlled or delayed release formulations (e.g. enteric coated formulations or other formulations that avoid exposing

the drug substance to the acid environment of the stomach, other types of slow-release formulations or of sustained release formulations) may avoid or minimize any racemization that may occur in the environment of the stomach. If a more potent compound or a compound with longer duration of therapeutic activity than R-albuterol is chosen, the dose and the dosing frequency will be decreased. Thus the dose of RR-formoterol may be half or less than half the dose of R--albuterol and the dosing may also be less frequent.

In the method of the present invention, the optically pure R- or RR-isomer of a beta-agonist can be administered together with one or more other compound(s). For example, various utero-spasmolytic drugs such as anticholinergic drugs, leucotriene antagonists, lipoxygenase inhibitors, cyclooxygenase inhibitors, thromboxane antagonists, thromboxane synthetase inhibitors, PAF-antagonists, antihistaminergic drugs, antiserotonergic drugs or other adrenergic beta-2 stimulators can be given with or between the doses of the selected R-or RR-isomer. Compounds that improve or prolong the therapeutic effect of the selected R- or RR-isomer, e.g. compounds that inhibit the chemical (e.g. antacids) or metabolic (e.g., acetaminophen) degradation of the selected R- or RR-isomer, may also be co-administered to patients given the selected isomer. The two (or more) drugs (the optically pure isomer and another drug) can be administered in one composition or as separate entities. For example they can be administered in a single formulation, such as a capsule, tablet, powder, or liquid, mist, aerosol, injec-

tion, etc. or as separate formulations. The components included in a particular formulation, in addition to an optically pure beta-agonist 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 inhalant form can include, in addition to the drug(s), a liquid carrier and/or propellant. A composition to be administered in tablet form for oral or sublingual use can include in addition to the drug a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arable, 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. A composition to be administered vaginally or rectally may include the combination of drugs consisting of the selected R- or RR-isomer and for example at least one additional drug selected from the group consisting of smooth muscle relaxants, antihistamines, antiserotonergics, anticholinergics, antiprostaglandins, and metabolic sulfation inhibitors.

In general, according to the method of the present invention, the optically pure R- or RR-isomer of albuterol, terbutaline, fenoterol, salmeterol or formoterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce undesired uterine contractions.

The present composition and method provide effective

treatment to inhibit or reduce uterine contractions while minimizing the undesired effects associated with the use of the racemic drug. These side effect include central nervous system effects, tremor, shakiness, dizziness and increased appetite, and cardiac effects and uterine contractions, induced by the S- or SS-isomer of the selected drug. In addition, teratogenic effects associated with racemic beta-2 agonists are believed to reside in the S- or SS-enantiomer. Thus, by the administration of the pure R- or RR-isomer of a beta-2 agonist, the teratogenic effects and the unwanted uterine contractile or contraction-promoting effects of the corresponding S- or SS-isomer will be avoided. Administration of the pure eutomer instead of the racemate may also result in a prolonged duration of therapeutic activity, for example by the distomer counteracting the therapeutic effects (e.g. causing smooth muscle hyperreactivity) of the eutomer.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein, including the use of therapeutically active metabolites or break-down products of the eutomers. Such equivalents are intended to be encompassed in the scope of the following claims.

What is claimed is:

1. A method of preventing or treating undesired uterine contractions in a non-pregnant individual with an optically pure R- or RR-isomer of an adrenergic beta-2 agonist, while reducing side effects associated with administration of the corresponding racemic drug or the corresponding S- or SS-isomer, comprising acutely or chronically administering to said individual a quantity of the optically pure R- or RR-isomer, sufficient to result in a reduction or the elimination of said undesired uterine contractions while simultaneously eliminating or reducing undesirable side effects residing in the corresponding S- or SS-isomer, said R- or RR- isomer being substantially free of its corresponding S- or SS-isomer.

2. A method of preventing or treating undesired uterine contractions in a pregnant individual with the optically pure R-isomer of albuterol, while reducing side effects associated with administration of the corresponding racemic drug or with the corresponding S-isomer, comprising acutely or chronically administering to said pregnant individual a quantity of the optically pure R-isomer, sufficient to result in a reduction or the elimination of said undesired uterine contractions while simultaneously eliminating or reducing undesirable side effects residing in the corresponding S-isomer, said R-isomer of albuterol being substantially free of its corresponding S-isomer.

3. The method of claim 1, wherein said beta-2- agonist is optically pure R-albuterol, substantially free of its

corresponding S-isomer.

4. The method of claim 1, wherein said beta-2 agonist is optically pure R-terbutaline, substantially free of its corresponding S-isomer.

5. The method of claim 1, w herein said beta-2 agonist is optically pure R-salmeterol, substantially free of its corresponding S-isomer.

6. The method of claim 1, wherein said beta-2 agonist is optically pure RR-fenoterol, substantially free of its corresponding SS-isomer.

7. The method of claim 1, wherein said beta-2 agonist is optically pure RR-formoterol, substantially free of its corresponding SS-isomer.

8. The method of claim 1 wherein the optical purity of the R- or RR-isomer of said beta agonist is greater than 85% by weight of total drug substance.

9. The method of claim 1 wherein the optical purity of the R- or RR-isomer of said beta agonist is greater than 98% by weight of total drug substance.

10. The method of claim 2 wherein the optical purity of the R-albuterol is greater than 85% by weight of total drug substance.

11. The method of claim 2 wherein the optical purity of the R-albuterol is greater than 98% by weight of total drug substance.

12. The method of claim 1 comprising administration to said individual with undesired uterine contractions by inhalation from approximately 10 mcg to approximately 2000 mcg

of the R-isomer or the RR-isomer of said adrenergic beta-2 agonist per dose, one to four times daily.

13. The method of claim 1 comprising administering to said individual with undesired uterine contractions by oral route from approximately 1 mg to approximately 50 mg of the R-isomer or the RR-isomer of said adrenergic beta-2 agonist, one to four times daily.

14. The method of claim 1 comprising administering to said individual with undesired uterine contractions, by sublingual route from approximately 1 mg to approximately 50 mg of the R-isomer or the RR-isomer of said adrenergic beta-2 agonist, one to four times daily.

15. The method of claim 1 comprising administering to said individual with undesired uterine contractions by transdermal route from approximately 1 mg to approximately 100 mg of the R-isomer or the RR-isomer of said adrenergic beta-2 agonist, one to two times daily.

16. The method of claim 1 comprising administering to said individual with undesired uterine contractions by intravaginal route from approximately 1 mg to approximately 100 mg of the R-isomer or the RR-isomer of said adrenergic beta-2 agonist, one to two times daily.

17. The method of claim 2 comprising administration to said individual with undesired uterine contractions by inhalation from approximately 10 mcg to approximately 2000 mcg of said R-isomer of albuterol, one to four times daily.

18. The method of claim 2 comprising administering to said individual with undesired uterine contractions by oral

route from approximately 1 mg to approximately 50 mg of the R-isomer of albuterol, one to four times daily.

19. The method of claim 2 comprising administering to said individual with undesired uterine contractions by sublingual route from approximately 1 mg to approximately 50 mg of the R-isomer of albuterol, one to four times daily.

20. The method of claim 2 comprising administering to said individual with undesired uterine contractions by transdermal route from approximately 1 mg to approximately 100 mg of the R-isomer of albuterol, one to two times daily.

21. The method of claim 2 comprising administering to said individual with undesired uterine contractions, by intravaginal route from approximately 1 mg to approximately 100 mg of the R-isomer of albuterol, one to two times daily.

22. The method of treating or preventing undesired uterine contractions in an individual with an adrenergic beta-2 agonist, while reducing side effects associated with the racemic drug, comprising administering to the individual a quantity of an optically pure eutomer of the adrenergic beta-2 agonist sufficient to result in uterine relaxation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of smooth muscle relaxants, antihistamines, antiserotonergics, anticholinergics, antiprostaglandins, antacids, and metabolic sulfation inhibitors.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01342

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/195
US CL :514/653, 649, 935

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/653, 649, 935

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS- beta-2 agonist compounds herein for premature labor or uterine contractions

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,290,561 (FARHADIEH et al.) 01 March 1994, see entire document.	1-3 and 8-22
Y	US 5,164,189 (FARHADIEH et al.) 17 November 1992, see entire document.	1-3 and 8-22
Y	US 5,362,755 (BARBERICH et al.) 08 November 1994, see entire document.	1-22
Y	US 5,370,135 (DULLIEN) 06 December 1994, see entire document.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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