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Ipratropium bromide enantiomer with prolonged duration of effect

The invention relates to the use, by inhalation, of (endo, syn) - (-) - 3 - (3-hydroxy-1-oxo-2-phenylpropoxy) - 8 - methyl-8 - (1-methylethyl) - 8-azoniabicyclo[3,2,1]octane salts as bronchospasmolytics with a powerful and particularly long-lasting effect and the use of the salts in the manufacture of asthma preparations.

The racemate of the above-mentioned compound (in the form of the bromide) is on sale under the name Ipratropium bromide as an active substance in anticholinergic drugs.

It has now been found, surprisingly, that the conditions of activity of the racemate, laevorotatory and dextrorotatory enantiomers are significantly different and have major peculiarities which differ substantially from the norm. The eutomer (i.e. the enantiomer having the desired or sought activity) is the L-(-)-enantiomer. Receptor binding studies on CHO-HM receptors have shown that the L-(-)-enantiomer has approximately twice as high an affinity as the racemate. This ratio corresponds to observations which have frequently been made when comparing the effects of enantiomers and racemates.

However, what is surprising in the present case is that administration by inhalation to the (anaesthetised) dog in a comparison of the eutomer with the racemate in the weight ratio 1:2 exhibits not only a higher potency but also a considerably longer duration of activity.

The diagram shown in Figure 1 gives the percentage inhibition of bronchospasm as a function of time. The

dotted line (curve B) represents the pattern for the (endo, syn)-(-)-3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3,2,1]octane and the continuous line (curve A) gives the pattern for the corresponding racemate, the hydrobromides having been used. 5 μ g of the pure L-(-)-enantiomer and, accordingly, 10 μ g of the racemate were administered. The experiment was carried out on five test animals using the pure L-enantiomer (BIIH 150 BR) whilst the racemate was administered to seven test animals.

Figure 1 shows that the inhibition of acetylcholine-induced bronchospasm in the dog by the administration of the Ipratropium bromide aerosol (curve A) has reached a peak of about 55% after about 10 minutes and has fallen back to its initial level after 60 minutes. The same quantity of eutomer (curve B), as contained in the racemate, achieves a 60% inhibition after about 10 minutes and does not fall back to its starting level for 180 minutes.

The half-lives measured show that the eutomer BIIH 150 BR has a duration of activity which is approximately four times longer.

The eutomer is obtained in substantially pure form from the racemate by combined application of high pressure liquid chromatography and recrystallisation. The term "eutomer" for the purposes of the present invention also includes strongly concentrated products (over about 90%), preferably containing more than 95, and particularly more than 97% of the L-(-)-enantiomer. The anion corresponds to the one in the starting compound. If desired, an exchange may be carried out.

The Example which follows is intended to illustrate the preparation of the L-(-)- and D-(+)-enantiomer:

18 grams of Ipratropium bromide are separated by high-pressure liquid chromatography over a Chiralcel OD column (250x20 mm) with a mobile phase composed of 600 hexane, 250 methanol, 150 ethanol and 1 saturated alcoholic NaBr solution (V:V:V:V, throughflow rate 6 ml/min., wavelength 254 nm; sensitivity 0.5 A.U.F.S, solution containing 1 g Ipratropium bromide/5 ml ethanol + 5 ml mobile phase + 2.5 ml conc. acetic acid).

By repeated chromatography and recrystallisation from ethanol, the L-(-)-enantiomer, white crystals, m.p. 239-40°C (decomp.), specific rotation $[\alpha]_D^{20} = -24.06^\circ$ (c = 1.014; H₂O), enantiomeric purity 97.4% (HPLC) and the D-(+)-enantiomer, white crystals, m.p. 238-39°C (decomp.), specific rotation $[\alpha]_D^{20} = +24.26^\circ$ (c = 1.018; H₂O), enantiomeric purity 98.9% (HPLC), are obtained. Elemental analyses and spectra indicate that these compounds are present.

The L-(-)-eutomer in the form of the various salts is suitable, by virtue of being an anticholinergic, for treating chronic obstructive bronchitis and asthma by inhalation, whilst side effects are largely excluded.

For use, the active substance is processed with known excipients and/or carriers to form conventional galenic preparations, e.g. solutions for inhalation, suspensions in liquefied propellant gases, preparations containing liposomes or proliposomes, powders for inhalation (optionally in capsules) for use in conventional inhalers.

Examples of formulations (amounts given in percent by weight):

1. Metering aerosols

Active substance according to the invention	0.005
Sorbitan trioleate	0.1
Monofluorotrichloromethane and difluorodichloromethane 2:3	ad 100

The suspension is transferred into a conventional aerosol container with metering valve. 50 μ l of suspension, for example, are released on each actuation. If desired, the active substance may also be present in higher doses (e.g. 0.02 wt.-%).

Instead of the chlorinated propellant gases, alternative propellant gases such as TG 134a (1,1,1,2-tetrafluoroethane) and/or TG 227 (1,1,1,2,3,3,3-heptafluoropropane) may also be used.

2. Powder for inhalation

Micronised powdered active substance (particle size 0.5 to 7 μ m) is mixed with micronised lactose and packed into hard gelatine capsules, optionally with other additives. For example, 0.01 mg of active substance and 5 mg of lactose are packed into each capsule. The powder may be inhaled using conventional inhalers, e.g. as in DE-A 3345772.

3. Solutions for inhalation

Aqueous solutions of the active substance may also be used, the aerosol being produced, for example, by a device according to WO91/14468. 0.005 mg of active substance may be administered per spray dose, for example.

The active substance which may be used according to the

invention may advantageously also be used in conjunction with other active substances for respiratory tract therapy. β_2 -mimetics may be mentioned in particular; these are used in combinations with 50 - 100% of the dose for individual use.

The following may be mentioned:

Bambuterol

Bitolterol

Carbuterol

Clenbuterol

Fenoterol

Formoterol

Hexoprenaline

Ibuterol

Pirbuterol

Procaterol

Reproterol

Salbutamol

Salmeterol

Sulfonterol

Terbutaline

Tulobuterol

1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol

erythro-5'-hydroxy-8'-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one

1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol

1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol.

Inhalable steroids such as Budesonide, Beclomethasone (or the 17,21-dipropionate), dexamethasone-21-isonicotinate, Flunisolide and antiallergics such as disodium cromoglycate, Nedocromil, Epinastine may also be used as ingredients in the combination. These combination ingredients may also be administered in the same or smaller doses than when they are used on their

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own.

Patent Claims

1. (endo, syn) - (-) - 3 - (3-Hydroxy-1-oxo-2-phenylpropoxy) - 8-methyl-8- (1-methylethyl) - 8-azoniabicyclo[3,2,1]octane salts with an enantiomeric purity of 90 to 100, preferably 95 to 100%.
2. Salts according to claim 1 containing $\text{Br}^\ominus$, $\text{Cl}^\ominus$ or $\text{CH}_3\text{CO}_3^\ominus$ as anion.
3. Pharmaceutical preparations for inhalation, characterised in that they contain a compound according to claim 1 or 2, optionally together with conventional excipients and/or carriers and/or other active substances.
4. Pharmaceutical preparations for inhalation according to claim 3, characterised in that they contain, in addition to a compound according to claim 1 or 2, an effective dose of a β_2 -mimetic, an inhalable steroid or an inhalable antiallergic agent.
5. Inhalable pharmaceutical preparations according to claim 4, characterised in that the β_2 -mimetic used is
Bambuterol
Bitolterol
Carbuterol
Clenbuterol
Fenoterol
Formoterol
Hexoprenaline
Ibuterol
Pirbuterol
Procaterol
Reproterol
Salbutamol
Salmeterol
Sulfonterol



Terbutaline

Tulobuterol

1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol

erythro-5'-hydroxy-8'-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one

1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol

1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol,

the steroid used is Budesonide, Beclomethasone (or the 17,21-dipropionate), dexamethasone-21-isonicotinate, Flunisolide and the antiallergic agent used is Disodium cromoglycate, Nedocromil, Epinastine.

6. Use of compounds according to claim 1 or 2, optionally combined with other active substances, for respiratory tract therapy by inhalation, in the preparation of drugs for treating respiratory tract diseases.

7. Use according to claim 6, in which β_2 -mimetics, steroids or antiallergics are used as the combination partners.

8. Administration by inhalation of effective doses of active substances according to claim 1 or 2 or combinations of these active substances with other active substances used for respiratory tract therapy, for the treatment of respiratory tract diseases.

