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Drug combination for the treatment of infectious diseases of the respiratory tract

British Patent Specification No. 1 178 034 describes the compound trans-4-[(2-amino-3,5-dibromobenzyl)-amino]cyclohexanol and physiologically acceptable acid addition salts thereof with inorganic or organic acids, which have expectorant properties. These compounds, and particularly the hydrochloride (generic name: ambroxol), are therefore used for the treatment of acute and chronic diseases of the respiratory tract which are accompanied by pathological changes in secretion. They are used especially in intensive medicine for preventing pulmonary complications.

Antibiotics such as, for example, erythromycin, doxycycline, oxytetracycline, chloramphenicol, cephalexin, ampicillin and amoxicillin, have also proved effective in combating bacterial diseases of the respiratory tract.

Surprisingly, we have now found that the simultaneous administration of an antibiotic or a salt thereof and trans-4-[(2-amino-3,5-dibromobenzyl)-amino]cyclohexanol or a physiologically acceptable acid addition salt thereof increases the bronchopulmonary antibiotic concentrations of the antibiotic used by more than 20%. The levels of antibiotic activity which can be obtained with this new combination thus permit successful treatment even with severe, acute clinical cases. However, a particularly important point is that, even when the acute stage of the disease has passed and the dosage of antibiotics is relatively low, sufficiently high levels of antibiotic activity can be maintained in the bronchopulmonary region, so that relapses are extremely rare.

This invention thus relates to pharmaceutical compositions for combating bacterial infection of the respiratory tract comprising, in combination, an antibiotic having activity in the bronchopulmonary region, or a physiologically acceptable salt thereof and trans-4-[2-amino-3,5-dibromobenzyl)amino] cyclohexanol or a physiologically acceptable acid addition salt thereof, optionally in association with a pharmaceutical carrier or excipient.

The antibiotics in question are, in particular, those which are suitable for combating bacterial diseases of the respiratory tract, e.g. erythromycin, doxycycline, cephalexin, ampicillin and amoxicillin.

By way of example, the effect of trans-4-[(2-amino-3,5-dibromobenzyl)amino] cyclohexanol hydrochloride (ambroxol) on the bronchopulmonary antibiotic concentrations of ampicillin, erythromycin and amoxicillin was investigated as follows:

All the substances were administered, in a single dose, to Wistar rats weighing between 300 and 400 g, by oesophageal tube. The dosage of antibiotics tested was 50 mg/kg in each case, whilst the dosage of ambroxol was 10 mg/kg. The rats were fed with Cargill Dieta R-R pellets and water and the animals were kept under test conditions at a temperature of between 20 and 24°C.

Groups of 20 rats were treated with the antibiotic to be tested and ambroxol, in comparison with a control group (same antibiotic but no ambroxol). The animals were killed 90 minutes after the administration of the test substance and both lungs were removed. The lungs were homogenised and centrifuged at 5000 r.p.m. The concentration of antibiotic was determined microbiologically in the supernatant portion.

The addition of ambroxol caused the antibiotic levels measured to rise as follows:

ampicillin	+ 23%
erythromycin	+ 27%
amoxicillin	+ 27%

It should also be mentioned that the active substances used according to the invention are practically non-toxic; in the mouse, the LD_{50} of the active substances are as follows:

ambroxol	2,720 mg/kg p.o.,
doxycycline	1,650 mg/kg p.o.,
cephalexin	1,600-6,200 mg/kg p.o.,
ampicillin	3,340 mg/kg p.o.,
erythromycin	3,000 mg/kg p.o. and
amoxycillin	1,000 mg/kg p.o.

The compositions according to the invention may be administered, in adults, 1 to 4 times daily, generally as a single dose of from 100 to 750 mg of antibiotic or physiologically acceptable salt thereof + 2 to 100 mg, preferably 7.5 to 75 mg of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino]cyclohexanol or physiologically acceptable acid addition salt thereof. The daily dose is thus generally 0.1 to 3.0 g of antibiotic or physiologically acceptable salt thereof + 7.5 to 150 mg of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino]cyclohexanol or physiologically acceptable acid addition salt thereof. The children's dose is normally one quarter to one half that of the adult dose.

In adults, the single doses for the drug combinations according to the invention are, for example, as follows:

combination of ambroxol/doxycycline:
about 75 mg of ambroxol + about 100 mg of doxycycline once a day (but double the dose on the first day of treatment),

combination of ambroxol/cephalexin:
15 to 30 mg of ambroxol + 250 to 500 mg of cephalexin
2 to 4 times daily,

combination of ambroxol/ampicillin:
15 to 30 mg of ambroxol + 250 to 500 mg of ampicillin
2 to 4 times daily,

combination of ambroxol/erythromycin:
15 to 30 mg of ambroxol + 300 to 600 mg of erythromycin
2 to 4 times daily,

combination of ambroxol/amoxicillin:
15 to 30 mg of ambroxol + 500 to 750 mg of amoxicillin
2 to 4 times daily.

For pharmaceutical use, the compositions according to the invention may be made into the usual galenic preparations such as e.g. plain tablets, film-coated tablets, oblong tablets, coated tablets or capsules and delayed release forms, ampoules, dry ampoules, dry granules or dry syrups, using conventional galenic excipients such as e.g. lactose, mannitol, corn starch, methylcellulose, hydroxyethylcellulose, polyethylene oxide, finely dispersed aluminium oxide, magnesium aluminium silicate, magnesium oxide, magnesium stearate, sodium laurylsulphate, sodium citrate, tartaric acid, sodium pyrosulphite, dioctyl sodium sulphosuccinate, sodium salt of methyl p-hydroxybenzoate, sodium salt of propyl p-hydroxybenzoate, sodium saccharin, flavourings and defoaming agents.

The following non-limiting Examples are intended to illustrate the invention:

Example 1

Film-coated tablets containing 30 mg of ambroxol + 500 mg of cephalexin

Composition:

1 film-coated tablet contains:

ambroxol	30.0 mg
cephalexin	500.0 mg
lactose	100.0 mg
dried corn starch	80.0 mg
polyvinyl pyrrolidone	16.0 mg
magnesium stearate	4.0 mg
	730.0 mg

Preparation:

The first four ingredients are mixed together and moistened with a 10% solution of the polyvinyl pyrrolidone in 70% ethanol. The moist mixture is passed through a screen with a mesh size of 1.5 mm, then dried and passed through the same screen again. The magnesium stearate is then added and tablets are produced from the mixture using a tablet press.

Coating:

A coating consisting of a solution of ethylcellulose in ethanol is applied to the tablets. The weight is increased by 1.5% by this film coating.

Weight of tablets: 730 mg

Punch: 13 mm.

Example 2

Dry granulate for syrup containing 15 mg of ambroxol + 250 mg of cephalexin per 5 ml

Composition:

5 ml contain:

ambroxol	15.0 mg
cephalexin	250.0 mg
sodium citrate	50.0 mg
dioctyl sodium sulphosuccinate	1.0 mg
polyvinyl pyrrolidone	50.0 mg

magnesium aluminium silicate		10.0 mg
sodium saccharin		5.0 mg
sodium salt of methyl p-hydroxy-benzoate		6.0 mg
sodium salt of propyl p-hydroxy-benzoate		1.5 mg
powdered flavouring		10.0 mg
silicone defoaming agent		0.25 mg
mannitol	ad	2.0 g

Method of preparation:

Granulate solution: Dioctyl sodium sulphosuccinate, silicone defoaming agent and some of the polyvinyl pyrrolidone are dissolved or dispersed in sufficient water for the granulation.

Mixture of powders: All the remaining components, with the exception of the flavouring, are homogeneously mixed.

Granulation: The mixture of powders is homogeneously moistened with the granulation liquid. The moist mixture is screened through a mesh with a maximum size of 2 mm, then dried and screened again.

Final mixture: The flavouring is added to the granulate and homogeneously distributed therein.

40 g of granulate + 75 ml of water yield about 100 ml of syrup ready for use.

5 ml (≙ 1 dose) contain 15 mg of ambroxol and 250 mg of cephalexin.

Example 3

Dry granulate for drop suspension containing 15 mg of ambroxol + 250 mg of cephalexin per 1 ml

1 ml contains:

ambroxol	15.0 mg

cephalexin	250.0 mg
sodium citrate	30.0 mg
methyl cellulose	2.0 mg
polyethylene oxide	2.0 mg
sodium salt of methyl p-hydroxy-benzoate	1.2 mg
sodium salt of propyl p-hydroxy-benzoate	0.3 mg
powdered flavouring	3.0 mg
silicone defoaming agent	0.05 mg
powdered sugar ad	0.4 g

Method of preparation:

Granulate solution: Polyethylene oxide, silicone defoaming agent and some of the methylcellulose are dissolved or dispersed in sufficient water for the granulation. The preparation process is continued as in Example 2.

40 g of granulate + 75 ml of water yield about 100 ml of drop suspension ready for use.

1 ml (≙ 1 dose) contains 15 mg of ambroxol and 250 mg of cephalexin.

Example 4

Oblong tablets containing 15 mg of ambroxol + 500 mg of ampicillin

1 tablet contains:

ambroxol	15.0 mg
ampicillin	500.0 mg
powdered lactose	380.0 mg
dried corn starch	180.0 mg
polyvinyl pyrrolidone	21.0 mg
magnesium stearate	4.0 mg
	1,100.0 mg

Preparation:

The first four ingredients are mixed together and moistened with a 10% solution of the polyvinyl pyrrolidone in 70% ethanol. The moist mixture is further treated as in Example 1.

Weight of tablets: 1,100 mg

Shape: 8 x 17 mm oblong.

Example 5

Ampoules containing 15 mg of ambroxol + 500 mg of ampicillin per 5 ml

1 ampoule of solution contains:

ambroxol		15.0 mg
sodium hydroxide solution		2.5 mg
tartaric acid		5.0 mg
polyethylene oxide		75.0 mg
Water for Injection	ad	5 ml

Dry ampoule:

Sodium ampicillin	500.0 mg

Preparation:

The ambroxol and tartaric acid are dissolved, then the polyethylene oxide is dissolved, with stirring, and adjusted to pH 4.0 with sodium hydroxide solution. The solution is sterilised by filtration through membrane filters, transferred into ampoules and sterilised by filtration at 120°C for 10 minutes.

Example 6

Ampoules containing 75 mg of ambroxol + 100 mg of doxycycline per 5 ml

1 ampoule contains:

doxycycline hydrochloride	100.0 mg
ambroxol	75.0 mg
magnesium oxide	9.1 mg
sodium pyrosulphite	500.0 mg

polyethylene oxide		500.0 mg
Water for Injection	ad	5 ml

Preparation:

The substances are dissolved in the water one after the other and filtered through membrane filters. As the solution is transferred into ampoules, it is treated with a nitrogen current. The solution cannot be sterilised.

Example 7

Capsules containing 75 mg of ambroxol + 100 mg of doxycycline

1 capsule contains:

20% spray pellets, consisting of wax mixture and active substance*	375.0 mg
starch	50.0 mg
lactose	50.0 mg
highly dispersed silicon dioxide	7.0 mg
magnesium stearate	8.0 mg
	490.0 mg

*) the active ingredient is suspended in the melt, heated to 70°C, by means of Ultra-Turrax and is sprayed in a suitable apparatus. Ultra-Turrax is a Registered Trade Mark.

Preparation:

The mixture is transferred into a suitable automatic capsule-making apparatus fitted with a tablet insertion station, and packaged in size 0 long gelatine capsules together with a coated 6 mm core containing 100 mg of doxycycline and conventional tablet excipients.

Weight of capsule: 490 mg.

Example 8

Tablets containing 30 mg of ambroxol + 600 mg of erythromycin

1 tablet contains:

ambroxol	30.0 mg
erythromycin	600.0 mg
powdered lactose	380.0 mg
dried corn starch	265.0 mg
polyvinyl pyrrolidone	21.0 mg
magnesium stearate	4.0 mg
	1,300.0 mg

Preparation:

The first four ingredients are mixed together and moistened with a 10% solution of the polyvinyl pyrrolidone in ethanol. The moist mixture is further treated as in Example 1.

Weight of tablets: 1,300 mg

Shape: 8.5 x 18 mm, oblong.

Example 9

Children's tablets containing 7.5 mg of ambroxol + 150 mg of erythromycin

1 tablet contains:

ambroxol	7.5 mg
erythromycin	150.0 mg
powdered lactose	95.0 mg
dried corn starch	66.25mg
polyvinyl pyrrolidone	5.25mg
magnesium stearate	1.0 mg
	325.0 mg

Preparation:

The first four ingredients are mixed together and moistened with a 10% solution of the polyvinyl pyrrolidone in ethanol. The moist mixture is further treated as in Example 1.

Weight of tablets: 325 mg

Diameter of punch: 10 mm

Example 10

Dry granulate for drop suspensions containing 15 mg of ambroxol + 300 mg of erythromycin per 1 ml

1 ml of drops solution contains:

ambroxol	15.0 mg
erythromycin-base equivalent	300.0 mg
sodium citrate	30.0 mg
sodium lauryl sulphate	1.0 mg
methyl cellulose	2.0 mg
sodium saccharin	1.0 mg
sodium salt of methyl p-hydroxybenzoate	1.2 mg
sodium salt of propyl p-hydroxybenzoate	0.3 mg
polyvinyl pyrrolidone	3.0 mg
powdered flavouring	3.0 mg
silicone defoaming agent	0.05mg
powdered sugar ad	0.4 g

Preparation:

The method of preparation is analogous to that of Example 3.

40 g of granulate + 75 ml of water yield about 100 ml of drop suspension ready for use.

1 ml (≙ 1 dose) contains 15 mg of ambroxol and 300 mg of erythromycin-base equivalent.

Example 11

Dry granulate for syrup containing 30 mg of ambroxol + 600 mg of erythromycin per 5 ml

5 ml contain:

ambroxol	30.0 mg
erythromycin-base equivalent	600.0 mg
sodium citrate	100.0 mg
hydroxyethyl cellulose	15.0 mg
magnesium aluminium silicate	15.0 mg
aluminium oxide	15.0 mg
sodium saccharin	4.0 mg

sodium salt of methyl p-hydroxybenzoate		6.0 mg
sodium salt of propyl p-hydroxybenzoate		1.5 mg
powdered flavouring		10.0 mg
silicone defoaming agent		0.15mg
powdered sugar	ad	2.0 g

Preparation:

Unlike in Example 2, some of the hydroxyethyl cellulose, instead of polyvinyl pyrrolidone, is dissolved in water together with the silicone defoaming agent. Otherwise, the method of preparation is analogous to Example 2.

40 g of granulate + 75 ml of water yield about 100 ml of syrup ready for use.

5 ml (= 1 dose) contain 30 mg of Ambroxol and 600 mg of erythromycin-base equivalent.

Example 12

Tablets containing 15 mg of ambroxol + 750 mg of amoxicillin

1 tablet contains:

ambroxol	15.0 mg
amoxicillin	750.0 mg
lactose	400.0 mg
dried corn starch	305.0 mg
polyvinyl pyrrolidone	25.0 mg
magnesium stearate	5.0 mg
	1,500.0 mg

Preparation:

The first four ingredients are mixed together and moistened with a 10% solution of the polyvinyl pyrrolidone in ethanol. The moist mixture is further treated analogously to Example 1.

Weight of tablets: 1,500 mg

Shape: 8 x 17 mm, oblong.

CLAIMS

1. Pharmaceutical compositions for combating bacterial infections of the respiratory tract comprising, in combination, an antibiotic having activity in the bronchopulmonary region or a physiologically acceptable salt thereof and trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol or a physiologically acceptable acid addition salt thereof, optionally in association with a pharmaceutical carrier or excipient.

2. Compositions as claimed in claim 1 containing erythromycin, doxycycline, cephalexin, ampicillin or amoxicillin as the antibiotic.

3. Compositions as claimed in any preceding claim in the form of dosage units.

4. Compositions as claimed in claim 3 wherein each dosage unit contains from 100 to 750 mg of the antiboitic or physiologically acceptable salt thereof.

5. Compositions as claimed in claim 3 or claim 4 wherein each dosage unit contains from 2 to 100 mg of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol or a physiologically acceptable acid addition salt thereof.

6. Compositions as claimed in claim 5 wherein each dosage unit contains from 7.5 to 75 mg of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol or a physiologically acceptable acid addition salt thereof.

7. Compositions as claimed in claim 6 wherein each dosage unit contains about 75 mg of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol hydrochloride and about 100 mg of doxycycline.

8. Compositions as claimed in claim 6 wherein each dosage unit contains 15 to 30 mg of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol hydrochloride and 250 to 500 mg of cephalexin.

9. Compositions as claimed in claim 6 wherein each dosage unit contains 15 to 30 mg of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol hydrochloride and 250 to 500 mg of ampicillin.

10. Compositions as claimed in claim 6 wherein each dosage unit contains 15 to 30 mg of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol hydrochloride and 300 to 600 mg of erythromycin.

11. Compositions as claimed in claim 6 wherein each dosage unit contains 15 to 30 mg of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol hydrochloride and 500 to 750 mg of amoxicillin.

12. Compositions as claimed in claim 5 wherein each dosage unit contains from 1/4 to 1/2 the amount of trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol hydrochloride and of antibiotic specified in claim 8.

13. Pharmaceutical compositions as claimed in claim 1 substantially as herein described.

14. Pharmaceutical compositions substantially as herein described in any one of Examples 1 to 12.

15. A synergistic combination of an antibiotic having activity in the bronchopulmonary region or a physiologically acceptable salt thereof and trans-4-[(2-amino-3,5-dibromo-benzyl)-amino] cyclohexanol or a physiologically acceptable acid addition salt thereof for use in the treatment of infections of the respiratory tract.

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