COMBINATION OF THEOBROMINE WITH A DECONGESTANT AND ITS USE FOR THE TREATMENT OF COUGH

Field of the Invention

This invention relates to a drug combination, its composition and its use in therapy, particularly in the therapy of cough.

Background of the Invention

Cough is a protective reflex. Persistent cough can be distressing. Over-the-counter remedies are available but their effectiveness is doubtful.

WO98/42322 discloses the use of theobromine for the treatment of cough, to be given orally.

Usmeni *et al.*, FASEB J. express article 10.1096, discloses that theobromine inhibits sensory nerve action and cough. Data are provided, showing effects following oral dosing in citric-acid induced cough in the guinea pig, and in the capsaicin cough challenge in humans, and following bathing of isolated guinea pig vagus nerve preparations.

The decongestant pseudoephedrine has been to shown to have very limited efficacy in the citric acid induced cough model in guinea-pigs (*Minamizawa et. al., J Pharmacol Sci, 2006*). However, most of the literature fails to demonstrate that pseudoephedrine has an antitussive effect. A number of papers describe effects on "cough and cold" (which has little meaning in the medical field), but none describes or even examines direct antitussive effect.

Summary of the Invention

The invention is based at least in part on data showing a synergistic antitussive effect for theobromine combined with the decongestant pseudoephedrine, in a citric acid-induced cough model. The data show that when theobromine is combined with pseudoephedrine, the effect is surprisingly potent and greater than the sum of the individual drugs, revealing that the combination has a substantially improved effect. This is particularly surprising given that it is doubtful that pseudoephedrine has an antitussive effect at all.

Consequently, a considerably reduced dose of both drugs can be given for an equivalent effect for each individual drug, so reducing side-effects and drug burden.

Therefore, according to a first aspect of the present invention, an agent comprises theobromine and a decongestant, as a combined preparation for simultaneous, sequential or separate use in therapy.

According to a second aspect, a pharmaceutical composition comprises theobromine and a decongestant.

It is believed that this synergistic relationship will be exhibited by all decongestants. Without wishing to be bound by theory, this may be due to the structural similarity of the members of the decongestant class of drugs.

Description of the Drawing

Figure 1 shows the effect of theobromine, and of a combination of theobromine and pseudoephedrine, on citric acid-induced cough in guinea-pig.

Description of the Invention

As used herein, the term "decongestant" is a defined class of drugs, which is well known to the skilled person. Preferably, the decongestant is a α-adrenergic receptor agonist. Any suitable form of the decongestant agent may be chosen. These include salts, prodrugs and active metabolites.

As used herein, the treatment of cough means any therapy that reduces the number and/or the severity of cough. Preferably, it means a reduction in the number of coughs, i.e. a direct antitussive effect that reduces the body's urge to cough. Therefore, according to a preferred embodiment of the invention, an agent comprises theobromine and a decongestant, for use as an antitussive pharmaceutical composition. An agent of the invention is useful as an antitussive in the control of cough. Preferably, it is used in the control of non-productive cough.

The decongestant may be used in an amount that is already known for its use, although combination according to this invention means that a reduced dose may be effective. The dose of the decongestant that is administered with the theobromine will of course depend on the usual factors, including its potency, but is preferably at least 0.1, e.g. at least 5, and may be up to 50 mg/kg/day. Preferably, the decongestant is dosed in a range of 0.1 to 30 mg/kg/day.

Any suitable form of theobromine can be chosen. These include salts, prodrugs and active metabolites. Theobromine may also be in the form of cocoa or chocolate. Suitable dose ranges for theobromine are known in the art and will depend on the usual factors (age etc); although the synergistic effect of the combination means that the effective dose may be reduced.

A combination according to the invention may be provided in a single formulation or in separate formulations, for combined, simultaneous or sequential administration.

This decongestant is preferably chosen from the following drugs: ephedrine, levmetamfetamine, naphazoline, oxymetazoline, phenylephrine, phenylpropanolamine, propylhexedrine, pseudoephedrine, synephrine and tetrahydrozoline. More preferably, the decongestant is pseudoephedrine.

The compounds of the invention may be administered by any available route, such as via the oral, inhaled, intranasal, sublingual, intravenous, rectal and vaginal routes.

The compounds of the invention are preferably as combinations to be administered orally, for example as tables, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. Preferred pharmaceutical compositions of the invention are tablets and capsules. Liquid dispersions for oral administration may be syrups, emulsions and suspensions. More preferably, the pharmaceutical composition of the combination is a pressed tablet or capsule with conventional excipients, examples of which are given below.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the combined active ingredients in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example starch gelatin, acacia, microcrystalline cellulose or polyvinyl pyrrolidone; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action

over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Aqueous suspensions contain the combined active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long-chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, polyoxyethylene hydrogenated castor oil, fatty acids such as oleic acid, or in a mineral oil such as liquid paraffin or in other surfactants or detergents. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the combined active ingredients in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable sweetening, flavouring and colouring agents may also be present.

The combined pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or

mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, flavouring and colouring agents.

Suspensions and emulsions may contain a carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol.

Combined compositions according to the invention may be produced using conventional formulation techniques. In particular, spray-drying may be used to produce microparticles comprising the active agent dispersed or suspended within a material that provides the controlled release properties.

The process of milling, for example jet milling, may also be used to formulate the therapeutic composition. This applies particularly to particles intended for administration by inhalation. The manufacture of fine particles by milling can be achieved using conventional techniques. The term "milling" is used herein to refer to any mechanical process which applies sufficient force to the particles of active material to break or grind the particles down into fine particles. Various milling devices and conditions are suitable for use in the production of the compositions of the invention.

The selection of appropriate milling conditions, for example, intensity of milling and duration, to provide the required degree of force, will be within the ability of the skilled person. Ball milling is a preferred method. Alternatively, a high pressure homogeniser may be used, in which a fluid containing the particles is forced through a valve at high pressure, producing conditions of high shear and turbulence. Shear forces on the particles, impacts between the particles and machine surfaces or other particles, and cavitation due to acceleration of the fluid, may all contribute to the fracture of the particles.

Suitable homogenisers include the EmulsiFlex high pressure homogeniser, the Niro Soavi high pressure homogeniser and the Microfluidics Microfluidiser. The milling process can be used to provide the microparticles with mass median aerodynamic diameters as specified above. If hygroscopic, the active agent may be milled with a hydrophobic material, as stated above.

If it is required, the microparticles produced by the milling step can then be formulated with an additional excipient. This may be achieved by a spray-drying process, e.g. co-spray-drying. In this embodiment, the particles are suspended in a solvent and co-spray-dried with a solution or suspension of the additional excipient. Preferred additional excipients include polysaccharides. Additional pharmaceutically effective excipients may also be used.

Compositions of the combination intended for inhaled, topical, intranasal, sublingual, intravenous, rectal and vaginal use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions.

Therapy according to the invention may be conducted in generally known manner, depending on various factors, such as the sex, age or condition of the patient, and the existence or otherwise of one or more concomitant therapies. The patient population may be important.

The present invention is based at least in part on the following study.

Study

A study was designed to investigate the antitussive activity of theobromine in combination with two different doses of pseudoephedrine, on citric acid-induced cough in conscious guinea pigs.

Test Doses

1 - vehicle control

2 - theobromine (10 mg/kg. p.o.)

3 - theobromine (10 mg/kg, p.o.) + pseudoephedrine (10 mg/kg. p.o.)

4 - theobromine (10 mg/kg, p.o.) + pseudoephedrine (30 mg/kg. p.o.)

Method

Male Dunkin Hartley guinea pigs (400-500 g, supplied by Harlan UK Ltd) were used throughout the study.

Thirty guinea pigs were randomly allocated to one of the four treatment groups according to the blinding code. The blinding code was not revealed to the investigator until coughs from all of the animals had been tallied.

Guinea pigs were dosed via oral gavage (dose volume 2 mL/kg) with theobromine dosed 2 hours prior to citric acid exposure. Pseudoephedrine was dosed 30 min prior to citric acid exposure and vehicle control animals were dosed both at 2 hours and 30 minutes prior to citric acid exposure.

Individual guinea pigs were placed in an exposure chamber with airflow of 2 L/min at t -10 min prior to citric acid exposure to acclimatise. At t = 0 min, cough responses were induced by exposure to citric acid aerosol (1 M) generated by an ultrasonic nebuliser at a nebulisation rate of 0.6 mL/min for 10 min.

Coughs were counted throughout the 10 min citric acid exposure and for a further 5 min post exposure.

Results

The results show that pre-treatment with theobromine (10 mg/kg, p.o.) caused a significant reduction to the number of citric acid induced coughs (13 ± 3) (see Figure 1), as well as to the onset to the first cough (156 ± 15s) (data not shown). In combination with pseudoephedrine (10 mg/kg and 30 mg/kg), the inhibitory response of theobromine on the citric acid-induced tussive activity, was potentiated with the highest dose, both in respect of total number of coughs (9 ± 2 c.f. 13 ± 3) (Figure 1) and onset time to the first cough (170 ± 15s c.f. 156 ± 15s) (data not shown).

'CLAIMS

1. An agent consisting of theobromine and a decongestant as a combined preparation.

2. An agent consisting of theobromine and a decongestant as a combined preparation for therapy of cough.

3. The agent according to claim 1 or claim 2, wherein the decongestant is ephedrine, levmetamfetamine, naphazoline, oxymetazoline, phenylephrine, phenylpropanolamine, propylhexedrine, pseudoephedrine, synephrine or tetrahydrozoline.

4. The agent according to claim 1 or claim 2, wherein the decongestant is pseudoephedrine.

5. The agent according to any one of claims 1 to 4, wherein the decongestant is in a dose of 0.1 to 30 mg/kg/day.

6. The agent according to claim 4, wherein the pseudoephedrine is in a dose of 0.1 mg/kg/day to 30 mg/kg/day.

7. The agent according to any one of claims 1 to 6 manufactured for oral administration.

8. The agent according to any one of claims 1 to 7 prepared as a tablet, capsule, troche, lozenge, powder, granule, suspension, syrup or emulsion.

9. A pharmaceutical composition consisting of an agent as defined in any one of claims 1-6, one or more excipients, and optionally one or more of sweetening agents, flavoring agents, coloring agents and/or preserving agents.

10. The composition according to claim 9, wherein the composition is manufactured for oral administration.

11. The composition according to claim 9 or claim 10, wherein the composition is prepared as a tablet, capsule, troche, lozenge, powder, granule, suspension, syrup or emulsion.

12. Use of an agent as defined in any one of claims 1-8 or a pharmaceutical composition as defined in any one of claims 9-11 for the manufacture of a medicament for treating cough.