DRUG COMBINATION WITH THEOBROMINE AND ITS USE IN THERAPY

Field of the Invention

This invention relates to a drug combination, its composition and its use 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 acticle 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.

A number of non-opiate antitussive drugs have been developed for cough therapies. A number of these antitussive drugs are NMDA antagonists. Dextromethorphan is one such drug that has been developed specifically for use as a cough therapy. However, its efficacy and suitability as a treatment for cough has already been brought into question. In J. Ramsey *et al.*, *British Journal of Clinical Pharmacology*, the authors report that the apparent success of dextromethorphan as a clinical treatment for cough is in fact just a placebo effect, and that it has no efficacy in cough.

Summary of the ~~Invention~~Disclosure

The ~~invention~~disclosure is based at least in part on data showing a synergistic anti-tussive effect for theobromine combined with the non-opiate antitussive drug, dextromethorphan, in a citric acid-induced cough model. The data show that when theobromine is combined with dextromethorphan, the effect is surprisingly potent and greater than the sum of the individual drugs, revealing that the combination has a substantially improved effect.

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. One such side-effect of dextromethorphan, and many other non-opiate antitussives is sedation. It has surprisingly been found that theobromine counteracts the sedative properties of such drugs.

Therefore, according to the present ~~invention~~disclosure, an agent comprises theobromine and another non-opiate antitussive, as a combined preparation for simultaneous, sequential or separate use in therapy.

It is believed that this synergistic relationship will be exhibited by all non-opiate antitussives. Without wishing to be bound by theory, this may be because non-opiate antitussives act via a similar mechanism, which may be NMDA antagonism.

In a first aspect, there is provided an agent consisting of theobromine and a non-opiate antitussive as a combined admixture preparation for use in a therapy for cough.

In a second aspect, there is provided a pharmaceutical composition comprising the agent as defined above when used in a therapy of cough.

In a third aspect, there is provided the use of an agent in the manufacture of a medicament when used in a therapy of cough, wherein the agent consists of theobromine and a non-opiate antitussive.

In a fourth aspect, there is provided the use of an agent in a therapy of cough, wherein the agent consists of theobromine and a non-opiate antitussive.

In a fifth aspect, there is provided the use of an agent as defined above in the manufacture of a medicament for treating a cough.

In a sixth aspect, there is provided the use of a pharmaceutical composition as defined above in the manufacture of a medicament for treating a cough.

Description of the Drawing

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

Description of the Invention

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, although the synergistic effect of the combination means that the effective dose may be reduced.

The additional agent (a different non-opiate antitussive drug, i.e. not theobromine) 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. Preferably, the dose of the non-opiate antitussive that is administered with the theobromine is greater than 0.1, e.g. more than 5, and typically up to 30 mg/kg/day.

The non-opiate antitussive drug is preferably selected from dextromethorphan, isoaminile, benzonate, zipeprol, morclofone, prenoxdiazine, dropropizine, piperidione, pentoxyverine, oxolamine, oxeladin, nepinalone, meprotixol, indantadol, dimemorfan, dibunate, cloperastine, clofedanol, butamirate, bibenzonium, benproperine and fedrilate. Dextromethorphan is the most preferred antitussive drug, e.g. at a dose of 0.1 to 6 mg/kg/day.

The non-opiate antitussive drug is preferably an NMDA antagonist.

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 oral route is the preferred route of administration.

The compounds of the invention are preferably as combinations to be administered orally, for example as tables, troches, lozenges, aqueous or oral

CLAIMS

1. An agent comprising theobromine and another non-opiate antitussive, as a combined preparation for simultaneous, sequential or separate use in therapy.

2. An agent according to claim 1, wherein the therapy is of cough.

3. Theobromine for the therapy of cough, wherein the subject to be treated has also been administered another non-opiate antitussive.

4. An agent according to claim 1 or claim 2, or theobromine according to claim 3, wherein the another non-opiate antitussive is selected from dextromethorphan, isoaminile, benzonate, zipeprol, morclofone, prenoxdiazine, dropropizine, piperidione, pentoxyverine, oxolamine, oxeladin, nepinalone, meprotixol, indantadol, dimemorfan, dibunate, cloperastine, clofedanol, butamirate, bibenzonium, benproperine and fedrilate.

5. An agent or theobromine according to any preceding claim, wherein the another non-opiate antitussive is dextromethorphan.

6. An agent or theobromine according to any preceding claim, wherein the another non-opiate antitussive is to be administered in a dose of 0.1 to 30 mg/kg/day.

7. An agent or theobromine according to claim 5, wherein the dextromethorphan is to be administered in a dose of 0.1 to 6 mg/kg/day.

CLAIMS:

1. A agent consisting of theobromine and a non-opiate antitussive as a combined admixture preparation for use in a therapy for cough.

2. The agent according to claim 1, wherein the non-opiate antitussive is a N-methyl-D-aspartate receptor antagonist.

3. The agent according to claim 1, wherein the non-opiate antitussive is dextromethorphan, isoaminile, benzonatate, zipeprol, morclofone, prenoxdiazine, dropropizine, piperidione, pentoxyverine, oxolamine, oxeladin, nepinalone, meprotixol, indantadol, dimemorfan, dibunate, cloperastine, clofedanol, butamirate, bibenzonium, benproperine or fedrilate.

4. The agent according to any one of claims 1-3, wherein the non-opiate antitussive is dextromethorphan.

5. The agent according to any one of claims 1-3, wherein the non-opiate antitussive is to be administered in a dose of 0.1 to 30 mg/kg/day.

6. The agent according to claim 3 or claim 4, wherein the dextromethorphan is to be administered in a dose of 0.1 to 6 mg/kg/day.

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

8. The agent according to any one of claims 1-6 prepared as a tablet, capsule, troche, lozenge, powder, granule, suspension, syrup or emulsion.

9. A pharmaceutical composition comprising the agent of claims 1-6 when used in a therapy of cough.

10. The pharmaceutical composition according to claim 9, further comprising one or more excipients, and optionally one or more of sweetening agents, flavoring agents, coloring agents and/or preserving agents.

11. The pharmaceutical composition according to claim 9 or claim 10 manufactured for oral administration.

12. The pharmaceutical composition according to any one of claims 9-11 prepared as a tablet, capsule, troche, lozenge, powder, granule, suspension, syrup or emulsion.

13. Use of an agent in the manufacture of a medicament when used in a therapy of cough, wherein the agent consists of theobromine and a non-opiate antitussive.

14. The use according to claim 13, wherein the non-opiate antitussive is a N-methyl-D-aspartate receptor antagonist.

15 The use according to claim 13, wherein the non-opiate antitussive is dextromethorphan, isoaminile, benzonatate, zipeprol, morclofone, prenoxdiazine, dropropizine, piperidione, pentoxyverine, oxolamine, oxeladin, nepinalone, meprotixol, indantadol, dimemorfan, dibunate, cloperastine, clofedanol, butamirate, bibenzonium, benproperine or fedrilate.

16. The use according to any one of claims 13-15, wherein the non-opiate antitussive is dextromethorphan.

17. The use according to any one of claims 13-16, wherein the medicament is manufactured for oral administration.

18. The use according to any one of claims 13-16, wherein the medicament is prepared as a tablet, capsule, troche, lozenge, powder, granule, suspension, syrup or emulsion.

19. Use of an agent in a therapy of cough, wherein the agent consists of theobromine and a non-opiate antitussive.

20. The use according to claim 19, wherein the non-opiate antitussive is a N-methyl-D-aspartate receptor antagonist.

21. The use according to claim 19, wherein the non-opiate antitussive is dextromethorphan, isoaminile, benzonatate, zipeprol, morclofone, prenoxdiazine, dropropizine, piperidione,

pentoxyverine, oxolamine, oxeladin, nepinalone, meprotixol, indantadol, dimemorfan, dibunate, cloperastine, clofedanol, butamirate, bibenzonium, benproperine or fedrilate.

22. The use according to any one of claims 19-21, wherein the non-opiate antitussive is dextromethorphan.

23. The use according to any one of claims 19-21 wherein the non-opiate antitussive is to be administered in a dose of 0.1 to 30 mg/kg/day.

24. The use according to claim 21 or claim 22, wherein the dextromethorphan is to be administered in a dose of 0.1 to 6 mg/kg/day.

25. The use of an agent as defined in claims 1-8 in the manufacture of a medicament for treating a cough.

26. The use of a pharmaceutical composition as defined in claims 9-12 in the manufacture of a medicament for treating a cough.