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(54) Title: DRUG COMBINATION WITH THEOBROMINE AND ITS USE IN THERAPY

(57) Abstract: An agent comprises theobromine and an opiate, for simultaneous, sequential or separate use in therapy. Preferably, the therapy is of cough.

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 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.

A number of opiate drugs have been developed for cough therapies. Codeine is an example of one such drug, and it is widely used as an antitussive. However due to the addictive properties of codeine and other opiates, there is a need for replacement cough therapies. Also, as recent evidence suggest, the therapeutic index for certain patient populations is very low.

Summary of the Invention

The invention is based at least in part on data showing a synergistic anti-tussive effect for theobromine combined with the opiate drug, codeine, in a citric acid-induced cough model. The data show that when theobromine is combined with codeine, the effect is surprisingly potent and greater than the sum of the individual drugs, revealing that the combination has a substantially improved effect. One advantage of lowering the minimum effective dose of codeine is that there is less chance of codeine overdose, as described above.

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 codeine, and many other opiate drugs is sedation. It has surprisingly been found that theobromine counteracts the sedative properties of opiates.

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

It is believed that this synergistic relationship will be exhibited by all opiates. Without wishing to be bound by theory, this may be due to the structural similarity of the members of the opiate family.

Description of the Drawing

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

Description of the Invention

As used herein, the term "opiate" describes any of the narcotic opioid alkaloids found as natural products in the opium poppy plant, as well as many chemical derivatives of such alkaloids. The term "opiate" describes a defined class of drugs, and will be understood by the person skilled in the art.

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 opiate 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 opiate 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 30 mg/kg/day.

The opiate is preferably selected from codeine, morphine, diamorphine, thebaine, papaverine, noscapine, oripavine, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, propoxyphene, oxymorphone, oxycodone, hydromorphone, pethidine, dihydrocodeine, buprenorphine, etorphine, ethylmorphine, loperamide and hydrocodone, pentazocine and tramadol, tipepidine and noscapine. Codeine is the most preferred opiate drug, e.g. at a dose of 3 mg/kg/day.

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 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 of the combination 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.

In a preferred embodiment, theobromine in combination with an antitussive drug is to be administered via the oral route. 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. 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, intravenous, sublingual, 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

Cough was induced in guinea-pigs by the use of citric acid. One group of guinea-pigs was administered 7 mg/kg of theobromine, and two groups were administered theobromine in combination with 8 or 16 mg/kg of codeine. A fourth group was given codeine and, as a control, a fifth group receiv ed only vehicle. Administration was via the oral route.

The results are shown in Figure 1. The data show that combinations of theobromine and codeine have a significant, improved efficacy in cough therapy when compared to theobromine monotherapy and codeine monotherapy.

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CLAIMS

1. An agent consisting of theobromine and an opiate as a combined preparation when used in a therapy of cough.

2. The agent according to claim 1, wherein the opiate is codeine, morphine, diamorphine, thebaine, noscapine, oripavine, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, propoxyphene, oxymorphone, oxycodone, hydromorphone, pethidine, dihydrocodeine, buprenorphine, etorphine, ethylmorphine, loperamide, hydrocodone, pentazocine, tramadol, tipepidine or noscapine.

3. The agent according to claim 1 or claim 2, wherein the opiate is codeine.

4. The agent according to claim 1 or claim 2, wherein the opiate is to be administered in a dose of 0.1 mg/kg/day to 30 mg/kg/day.

5. The agent according to claim 2 or claim 3, wherein the codeine is to be administered in a dose of up to 3 mg/kg/day.

6. The agent of any one of claims 1-5 manufactured for oral administration.

7. The agent of any one of claims 1-5 prepared as a tablet, capsule, troche, lozenge, powder, granule, suspension, syrup or emulsion.

8. A pharmaceutical composition consisting of an agent as defined in any one of claims 1-5 and one or more excipients, when used in a therapy of cough, and optionally one or more of sweetening agents, flavoring agents, coloring agents and/or preserving agents.

9. The composition of claim 8, manufactured for oral administration.

10. The composition of any one of claims 8 to 9 prepared as a tablet, capsule, troche, lozenge, powder, granule, suspension, syrup or emulsion.

11. Use of an agent as defined in any one of claims 1-7 or a pharmaceutical composition as defined in any one of claims 8-10 for manufacturing a medicament for treating a cough.

12. Use of an agent as defined in any one of claims 1-7 or a pharmaceutical composition as defined in any one of claims 8-10 for the treatment of cough.

13. A method for treating a cough, the method comprising the step of administering an agent as defined in any one of claims 1-7 or a pharmaceutical composition as defined in any one of claims 8-10.

14. Use of an agent in the manufacture of a medicament for a therapy of cough, wherein the agent consists of theobromine and an opiate as a combined preparation.

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15. The use according to claim 14, wherein the opiate is codeine, morphine, diamorphine, thebaine, noscapine, oripavine, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, propoxyphene, oxymorphone, oxycodone, hydromorphone, pethidine, dihydrocodeine, buprenorphine, etorphine, ethylmorphine, loperamide, hydrocodone, pentazocine, tramadol, tipepidine or noscapine.

16. The use according to claim 14, wherein the opiate is codeine.

17. The use according to claim 14 or claim 15, wherein the opiate is in a dose of 0.1 mg/kg/day to 30 mg/kg/day.

18. The use according to claim 15 or claim 16, wherein the codeine is in a dose of up to 3 mg/kg/day.

19. The use according to any one of claims 14-18, wherein the medicament is manufactured for oral administration.

20. The use according to any one of claims 14-18, wherein the medicament is prepared as a tablet, capsule, troche, lozenge, powder, granule, suspension, syrup or emulsion.

21. Use of an agent for a therapy of cough, wherein the agent consists of theobromine and an opiate as a combined preparation.

22. The use according to claim 21, wherein the opiate is codeine, morphine, diamorphine, thebaine, noscapine, oripavine, fentanyl, alphamethylfentanyl, alfentanil, sufentanil, remifentanil, carfentanyl, propoxyphene, oxymorphone, oxycodone, hydromorphone, pethidine, dihydrocodeine, buprenorphine, etorphine, ethylmorphine, loperamide, hydrocodone, pentazocine, tramadol, tipepidine or noscapine.

23. The use according to claim 21, wherein the opiate is codeine.

24. The use according to claim 21 or claim 22, wherein the opiate is in a dose of 0.1 mg/kg/day to 30 mg/kg/day.

25. The use according to claim 22 or claim 23, wherein the codeine is in a dose of up to 3 mg/kg/day.

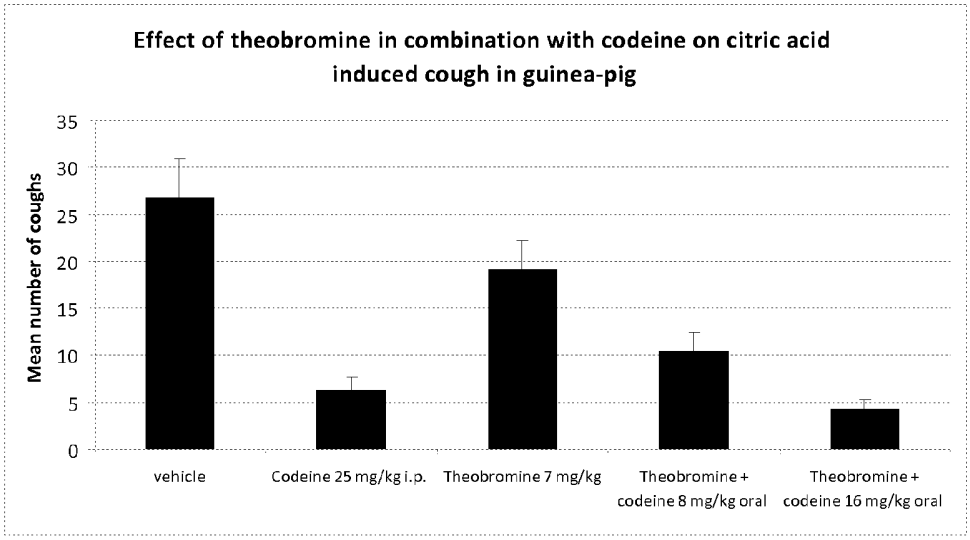
Effect of theobromine in combination with codeine on citric acid induced cough in guinea-pig
Mean number of coughs
35
30
25
20
15
10
5
0
vehicle
Codeine 25 mg/kg i.p.
Theobromine 7 mg/kg
Theobromine + codeine 8 mg/kg oral
Theobromine + codeine 16 mg/kg oral

FIGURE 1