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(54) **Title**: THERAPEUTIC COMBINATIONS OF THEOBROMINE AND AN ANTIHISTAMINE

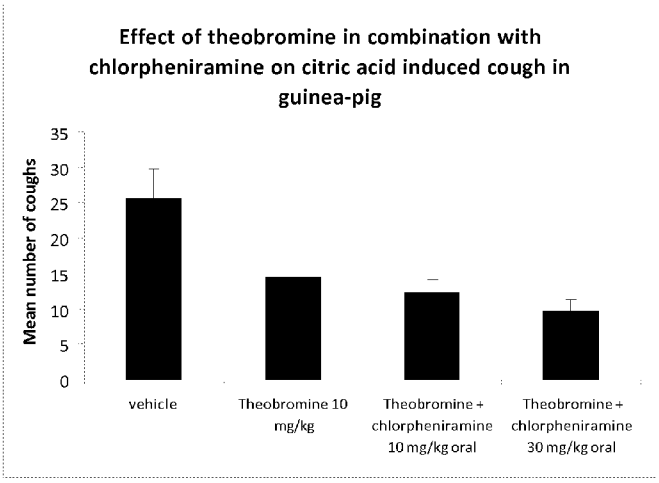

Figure 1

(57) **Abstract**: An agent comprises theobromine and an antihistamine, as a combined preparation for simultaneous, sequential or separate use in therapy, particularly in the therapy of cough.

WO 2011/073647 A1

THERAPEUTIC COMBINATIONS OF THEOBROMINE AND AN ANTIHISTAMINE

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.

Antihistamines namely diphenhydramine have been to shown to have efficacy in the citric acid-induced cough model in healthy human volunteers (Packman et. al., Int J Clin Pharmacol Ther Toxicol, 1991). However, a recent review article, Björnsdóttir *et al*. 2007 Dec, 29(6): 577-83 reports that presumptions about efficacy of diphenhydramine against cough in humans are not univocally substantiated in literature. In other words, there is no strong evidence that antihistamines have any efficacy in cough.

Summary of the Invention

The invention is based at least in part on data showing a synergistic antitussive effect for theobromine combined with the antihistamine chlorpheniramine, in a citric acid-induced cough model. Given the recent literature suggesting that antihistamines have no efficacy in cough, it was therefore surprising to find that a combination of theobromine and chlorpheniramine has an improved antitussive effect, compared to theobromine alone.

Consequently, when theobromine is used in combination with an antihistamine, a considerably reduced dose of theobromine can be given for an equivalent antitussive effect for theobromine alone, so reducing side-effects and drug burden.

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

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

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

Description of the Drawing

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

Description of the Invention

As used herein, the term “antihistamine” means an agent that inhibits the action of histamine via histamine receptors. This term represents a well-defined class of drugs that is well known to the skilled person. In a preferred embodiment, the antihistamine is an H_1-receptor antihistamine. Any suitable form of the antihistamine 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 an antihistamine, 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 antihistamine 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 antihistamine 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, it 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 antihistamine may be chosen from the following drugs: diphenhydramine, loratadine, desloratadine, alimemazine, dimenhydrinate, doxylamine, meclizine, quetiapine, fexofenadine, pheniramine, cetirizine, promethazine, clemastine, chlorpheniramine, dexchlorpheniramine, levocetirizine, hydroxyzine, alimemazine, acrivastine, cyproheptadine, astemizole, fexofenadine, loratadine, cetirizine, levocetirizine, brompheniramine, dextrobrompheniramine, promethazine, mizolastine and triprolidine. Preferably, the antihistamine is chlorpheniramine.

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

Cough was induced in guinea-pigs by the use of citric acid. One group of guinea-pigs was administered 10 mg/kg of theobromine, and two groups were administered theobromine in combination with 10 or 30 mg/kg of chlorpheniramine. As a control, a fourth group received only vehicle. Administration was via the oral route.

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

CLAIMS

1. An agent comprising theobromine and an antihistamine, 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. A pharmaceutical composition comprising theobromine and an antihistamine.

4. An agent or composition according to any preceding claim, wherein the antihistamine is selected from diphenhydramine, loratadine, desloratadine, alimemazine, dimenhydrinate, doxylamine, meclizine, quetiapine, fexofenadine, pheniramine, cetirizine, promethazine, clemastine, chlorpheniramine, dexchlorpheniramine, levocetirizine, hydroxyzine, alimemazine, acrivastine, cyproheptadine, astemizole, fexofenadine, loratadine, cetirizine, levocetirizine, brompheniramine, dextrobrompheniramine, promethazine, mizolastine, and triprolidine.

5. An agent or composition according to claim 4, wherein the antihistamine is chlorpheniramine.

6. An agent or composition according to any preceding claim, wherein the antihistamine is to be administered in a dose of 0.1 to 30 mg/kg/day.

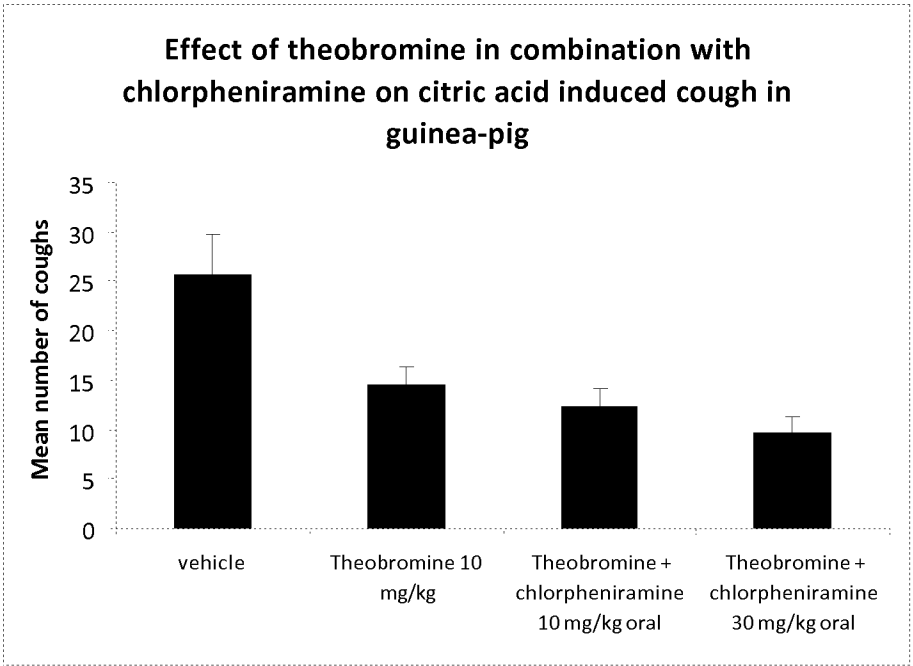
Effect of theobromine in combination with chlorpheniramine on citric acid induced cough in guinea-pig
Mean number of coughs
35
30
25
20
15
10
5
0
vehicle
Theobromine 10 mg/kg
Theobromine + chlorpheniramine 10 mg/kg oral
Theobromine + chlorpheniramine 30 mg/kg oral

Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2010/052086

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4402 A61K31/522 A61K45/06 A61P11/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, PASCAL, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/002514 A2 (LEVINE BRIAN M [US]; BERGER WILLIAM [US]) 3 January 2008 (2008-01-03) the whole document	1-6
X	"Abstracts: Presented at Poster Sessions", ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY, ARLINGTON HEIGHTS, IL, US, vol. 102, no. 1, 1 January 2009 (2009-01-01), pages A23-A128, XP026960247, ISSN: 1081-1206 [retrieved on 2009-01-01] page A113, abstract P331	1-6
X	JP 2003 128549 A (ROHTO PHARMA) 8 May 2003 (2003-05-08) the whole document	1,3-6

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
11 March 2011	18/03/2011

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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2010/052086

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008002514 A2	03-01-2008	US 2008003280 A1	03-01-2008
JP 2003128549 A	08-05-2003	NONE	