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(54) Title: COUGH/COLD MIXTURES COMPRISING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

(57) Abstract

Pharmaceutical compositions and methods of using same comprising a non-steroidal anti-inflammatory drug in combination with at least one other active component selected from an antihistamine, decongestant, cough suppressant (antitussive) or expectorant are provided for the relief of cough, cold and cold-like symptoms.

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COUGH/COLD MIXTURES COMPRISING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Background of the Invention

The present invention relates generally to novel pharmaceutical compositions of matter comprising one or more non-steroidal anti-inflammatory drugs (NSAID) in combination with at least one antihistamine, sympathomimetic drug (nasal decongestant, bronchodilator) cough suppressant and/or expectorant, optionally in combination with suitable pharmaceutically acceptable non-toxic carriers or excipients, and to methods of using said compositions in the treatment, management or mitigation of cough, cold, cold-like and/or flu symptoms and the discomfort, pain, fever and general malaise associated therewith.

Non-narcotic analgesics, most of which are also known as non-steroidal anti-inflammatory drugs (NSAID), are widely administered orally in the treatment of mild to severe pain. Within this class, the compounds vary widely in their chemical structure and in their biological profiles as analgesics, anti-inflammatory agents and antipyretic agents. Among the most commonly used members of the non-narcotic analgesic class of drugs are aspirin, acetaminophen and phenacetin. Aspirin and acetaminophen have heretofore been included as the pain reliever and fever-reducing component in conventional cough/cold multi- symptom alleviating compositions.

However, a number of alternative non-narcotic agents offering a variety of advantages over these conventionally employed non-narcotic analgesic anti-pyretics have now been developed. The principal advantages of these non-steroidal anti-inflammatory

drugs include not only the clinically superior analgesic, anti-inflammatory and antipyretic activity of these agents compared to aspirin, acetaminophen or phenacetin, but also a minimization of the adverse side affects experienced with these conventional agents; more specifically, the gastrointestinal ulcerations experienced with aspirin and the hepatic toxicity prevalent with the chronic use of acetaminophen.

Exemplary prior art cough/cold formulations containing aspirin or acetaminophen include Coricidin®, Coricidin D®, Comtrex®, Dristan®, Daycare®, Cotylenol®, Sinubid® and the like. These formulations generally contain in addition to aspirin or acetaminophen, one or more antihistaminics, decongestants, cough suppressants, antitussives and expectorants.

While aspirin and acetaminophen have been utilized in these previous compositions, it has not been heretofore proposed to use any of the newer non-steroidal anti-inflammatory drugs (i.e., excluding aspirin, acetaminophen and phenacetin) in the preparation of advantageous cough/cold pharmaceutical compositions.

Summary of the Invention

It is, therefore, a primary object of the present invention to provide pharmaceutical compositions of matter comprising an analgesically effective amount of a non-steroidal anti-inflammatory drug (NSAID) in combination with at least one of an antihistamine, decongestant, cough suppressant, expectorant and, optionally, including pharmaceutically acceptable carriers therefor.

It is a further object of the present invention to provide methods for the symptomatic relief

of cough, cold, cold-like and flu symptoms by the administration of preselected dosages of the pharmaceutical compositions of the present invention. Cold-like symptoms as used herein refers to coryza, nasal congestion, upper respiratory infections, allergic rhinitis, otitis, sinusitis, etc.

Another object of the present invention is to provide suitable dosage unit forms of one or more NSAID's in combination with at least one of the aforementioned antihistamines, decongestants, etc. adapted for convenient oral administration.

Brief Description of the Drawing

The Figure of Drawing is a plot of dose of diphenhydramine versus dose of ibuprofen in the phenylquinone writhing assay to indicate the number of mice protected.

Detailed Description of the Invention

More specifically, the applicants herein have found that certain non-steroidal anti-inflammatory agents are ideally suited for use in cough/cold formulations by reason of their enhanced analgesic anti-inflammatory and antipyretic activity and low incidence of untoward side effects, particularly at the optimum dosages provided for in the present invention, compared to aspirin or acetaminophen.

The superiority of various of the non-narcotic analgesics belonging to the non-steroidal anti-inflammatory drug class in comparative studies with aspirin and acetaminophen is well documented in the literature.

Cooper in 1977 found that ibuprofen 400 mg had a greater peak effect and longer duration of action

than aspirin 650 mg. Cooper, S.A., Needle, A.E., Kruger, G.O. 1977. "An Analgesic Relative Potency Assay Comparing Aspirin, Ibuprofen and Placebo. "J. Oral Surg. 35:898-903. Cooper in another study in 1982 found 400 mg of ibuprofen to be more effective than aspirin 650 mg. Cooper, S.A., Engel, J., Ladov, M., Precheur, H., Rosenheck, A., Rauch, D. 1982. "Analgesic Efficacy of an Ibuprofen-codeine Combination." Pharmacotherapy 2:162-67. Sunshine et al found ibuprofen to be significantly superior to aspirin in the relief of post-episiotomy pain. Sunshine, A. et al, Clinical Pharmacology and Therapeutics, :24:254-250, 1983.

Dionne in 1982 found ibuprofen to be more effective than acetaminophen in delaying the onset and intensity of post-operative dental pain. Dionne, R.A., Campbell, R.A., Cooper, S.A., Hall, D.L., Buckingham, B. "Suppression of Post operative Pain by Preoperative Administration of Ibuprofen in Comparison to Placebo, Acetaminophen and Acetaminophen Plus Codeine." J. Clin. Phamacol. (In press).

Naproxen sodium 550 mg was compared with 650 mg of aspirin and was found to provide earlier and better pain relief than aspirin by Sevelius, H., J. Clin. Pharmacol. 20:480-485, 1980. "Comparative Analgesic Effects of Naproxen Sodium, Aspirin and Placebo."

Flurbiprofen 50 and 100 mg was significantly more effective than aspirin 600 mg. Flurbiprofen 25 mg was slightly less effective than aspirin 600 mg. Sunshine, A., Olson N.Z., Laska, E.M. Zighelboim, I., DeCastro, A., Desarrazin, C., Pharmaco Ther. 3:177-181. " Analgesic Effect of Graded Doses of Flurbiprofen in Postepisiotomy Pain".

Silberman found suprofen 200 mg more effective than aspirin 650 mg for pain relief in the treatment of moderate to severe pain resulting from musculoskeletal pain. Silberman, H.M. "Multiple-Dose Comparison of Suprofen, Aspirin and Placebo in the Treatment of Musculoskeletal Pain." Pharmacology 27:S 1, 65-73 (1983).

While these reported findings with respect to the outstanding analgesic properties of the non-steroidal anti-inflammatory drugs compared to aspirin or acetaminophen have prompted the widespread acceptance and usage of these newer non-narcotic analgesics, as single entities, for the treatment and management of acute and chronic inflammatory states, notably rheumatoid arthritis and osteoarthritis, the utilization of these agents in cough/cold compositions has not heretofore been considered.

The non-steroidal anti-inflammatory drugs (NSAID's) for use in the pharmaceutical compositions and methods of use of the present invention may be selected from any of the following categories:

(1) The propionic acid derivatives;

(2) The acetic acid derivatives;

(3) The fenamic acid derivatives;

(4) The biphenylcarboxylic acid derivatives; and

(5) The oxicams.

Accordingly, the term "NSAID" as used herein is intended to mean any non-narcotic analgesic non-steroidal anti-inflammatory compound, including the pharmaceutically acceptable non-toxic salts thereof, falling within one of the five structural categories above but excluding aspirin, acetaminophen and phenacetin.

The specific compounds falling within the foregoing definition of the non-steroidal anti-inflammatory drugs for use in the present invention are well known to those skilled in the art and reference may be had to various literature reference sources for their chemical structures, pharmacological activities, side effects, normal dosage ranges, etc. See, for example, Physician's Desk Reference, 35th Edition, 1981 and The Merck Index, 9th Edition, Merck and Company, Rahway, New Jersey (1976) and Cutting's Handbook of Pharmacology, 6th Edition, Ed. T. Z. Czacky, M.D., Appleton-Century-Crofts, New York, 1979, Chapter 49:538-550.

Of the propionic acid derivatives for use herein, ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, suprofen, fenbufen, and fluprofen may be mentioned as particularly preferred compounds.

Of the acetic acid derivatives, presently preferred members include tolmetin sodium, zomepirac, sulindac and indomethacin.

Of the fenamic acid derivatives, particularly preferred compounds include mefenamic acid and meclofenamate sodium.

The particularly preferred biphenylcarboxylic acid derivatives for use in the present invention include diflunisal and flufenisal.

The particularly advantageous oxicams include piroxicam, sudoxicam and isoxicam.

Of course, it will be appreciated by those skilled in the art, that any of the foregoing compounds may be utilized in the form of their pharmaceutically acceptable salt forms, e.g., $-COO^-Na^+$, $-COO^-K^+$, and the like.

Of the foregoing non-steroidal anti-inflammatory drugs, in the practice of the preferred embodiments of the present invention, ibuprofen and naproxen are most preferred.

With respect to the dosage amount of the non-steroidal anti-inflammatory drugs in the compositions of the invention, although the specific dose will vary depending upon the age and weight of the patient, the severity of the symptoms, the incidence of side effects and the like, for humans, typical effective analgesic amounts of presently preferred NSAID's for use in unit dose compositions of the invention are about 100 - 500 mg diflunisal, about 25 - 100 mg zomepirac sodium, about 50-400 mg ibuprofen, most preferably 100-200 mg, about 125-500 mg naproxen, about 25-100 mg flurbiprofen, about 50-100 mg fenoprofen, about 10-20 mg piroxicam, about 125-250 mg mefenamic acid, about 100-400 mg fenbufen or about 25-50 mg ketoprofen; however, greater or lesser amounts may be employed if desired or necessary. With respect to the compounds set forth hereinabove falling within the propionic acid derivative category, suitable dosage ranges for these compounds will generally fall within the range of 25 mg to 600 mg in each unit dose.

A complete description of the various NSAID's, including acceptable analgesically effective amounts thereof for use in unit dose compositions of the present invention also appears in applicants United States Patent No. 4,486,436.

The cough/cold pharmaceutical compositions of the present invention comprise, in addition to the non-steroidal anti-inflammatory drugs, at least one active ingredient from the following pharmacological classes: antihistamines, sympathomimetics (decon-

gestants), cough suppressants-antitussives and expectorants. Typical therapeutically active components from these categories, along with their usual adult dosage, for use in the pharmaceutical compositions and methods of the invention are set forth in the following Table 1.

TABLE I

DRUG (FORM-SALT)	ACTION[1]	PREPARATIONS	USUAL SINGLE DOSE (ADULT)
chlorpheniramine (maleate)	A	Tablets, Capsules, 4 mg, 8 mg, 12 mg, (substained Action) 12 mg	2-4 mg
brompheniramine (maleate)	A	Tablets, Capsules, 4 mg, 8 mg, 12 mg (Extentabs R)	8-12 mg
dexchlorpheniramine (maleate)	A	Tablets, 2 mg, 4 mg, 6 mg, Syrup, Expectorant (2mg/5cc)	2-6 mg
dexbrompheniramine (maleate)	A	Tablet, 6 mg	6 mg
triproldine (HCl)	A	Tablet, 2.5 mg. Syrup - 1.25 mg/5cc	1.25-2.5 mg
diphenhydramine (HCl)	A	Tablets, Capsules, Elixir, Parenteral, 25 mg, 50 mg 12.5 mg/5cc; 10-50 mg/ml.	12.5-50 mg
doxylamine (succinate)	A	Tablets, Elixir 10 mg, 7.5 mg/10cc.,	7.5 - 10 mg
tripelennamine (HCl)	A	Tablet, Elixir, 25 mg, 50 mg, 37.5 mg/5cc.	25 - 50 mg.
cyproheptadine (HCl)	A	Tablet, Syrup, 4 mg, 1mg/5cc	4 mg.
carbinoxamine (maleate)	A	Syrup 4mg/5cc.,	4 mg.
bromodiphenhydramine (HCl)	A	Syrup 3.75 mg/5cc	3.75 mg.

TABLE I (continued)

DRUG (FORM-SALT)	ACTION	PREPARATIONS	USUAL SINGLE DOSE (ADULT)
phenindamine (tartrate)	A	Tablet, Elixir 10 mg, 5 mg/5cc.	10 mg.
pyrilamine (maleate, tannante)	A	Tablet 12.5 mg.	12.5 mg.
azatadine (maleate)	A	Tablet, 1 mg.	1 - 2 mg.
pseudoephedrine (HCl)	D	Tablet, Capsule 30 mg, 60 mg, 120 mg (sustained action)	60 - 120 mg.
phenylpropanolamine (HCl)	D	Tablet, Capsule, Elixir, 25 mg, 50 mg, 12.5 mg/5cc	25 - 50 mg.
phenylephrine (bitartrate, tannate, HBr, HCl)	D	Tablet, Capsule Elixir, 5 mg, 10 mg, 25 mg, 5 mg/5cc.	5-25 mg.
caramiphen (edisylate)	CS	Capsule, Elixir 20 mg, 5mg/5cc	5-20 mg.
dextromethorphan (HBr)	CS	Tablet, Capsule Elixir 15 mg. 30 mg. 15 mg/5cc.	30 mg.
codeine (phosphate, sulfate)	CS	Tablet, Elixir 10 mg, 10 mg/5cc.	10 mg.
terpin hydrate	E	Tablet 300 mg.	300 mg.
guaifenesin (glyceryl guaiacolate)	E	Tablet, Capsule Elixir, 100 mg, 100 mg/5cc.	100 mg.

TABLE I (continued

DRUG (FORM-SALT)	ACTION	PREPARATIONS	USUAL SINGLE DOSE (ADULT)
potassium (Iodide, citrate)	E	Tablet, Elixir, 100 mg, 100 mg/5cc.	150-300 mg.
potassium guaicolsulfonate	E	Elixir 80 mg/5cc.	80 mg

[1] A = antihistamine
D = decongestant
C = cough suppressant
E = expectorant

Among such Table 1 antihistamines, sympathomimetics, cough suppressants-antitussives and expectorants, in combination with a non-steroidal anti-inflammatory drug, applicants have already demonstrated a synergistically enhanced analgesic and anti-inflammatory response in a mammalian organism, as shown below in Example 1.

Example 1 - Pharmacologic Test for Synergism - Ibuprofen/Diphenhydramine.

The unexpected synergistic analgesic effect of the addition of diphenhydramine to ibuprofen is evidenced by tests conducted on mice. Blue Spruce Farm male mice weighing 18-28 grams at the time of testing are used throughout. All mice are dosed orally by gavage with ibuprofen and/or diphenhydramine. The formulation of each test article is a solution or suspension in 0.25% methylcellulose manufactured by Fisher Scientific Company. A dosing volume of 10 ml/mg is used. All doses are coded and the test is performed under a code not known to the observer. Doses are based upon the weights of the animal taken prior to dosing.

METHOD

A phenylquinone writhing assay in mice was conducted over a four day period to test for synergism of the analgesic activity of ibuprofen and diphenhydramine.

The assay consists of phenyl-p-benzoquinone (PPQ) introduced in mice thirty minutes post dose of the test treatment(s). The PPQ is prepared as a .02%

aqueous solution in 5 ml ethyl alcohol q.s. to 100 ml with distilled water and is administered intraperitoneally at .25 ml/mouse. The mice are injected with the PPQ solution and are placed in individual plastic squares 4"x4"x5" deep and observed for a ten minute period post treatment dose for exhibition of the writhing syndrome. Complete blocking of the writhing syndrome for the ten minute observation period in any one mouse is considered a positive response for that mouse. Conversely, if the mouse definitely writhes at least once, it is considered to be not protected from the PPQ.

Three hundred twenty-eight mice were randomly assigned to 40 groups. Two groups of ten mice per series were assigned to a control group (10 prior to the administration of the test treatments and 10 post administration) to verify the ability of the solutions to produce the writhing response.

The purpose of the assay on the first day is to estimate the ED_{50} (effective dose in 50% of treated mice) of ibuprofen alone and of diphenhydramine alone, and to estimate the relative potency, , of ibuprofen to diphenhydramine, determined as the ratio of the ED_{50} of ibuprofen to the ED_{50} of diphenhydramine. Eight mice per group are dosed orally (via intubation) with 2, 5, 10 and 20 mg/kg of ibuprofen and 5, 10, 20 and 50 mg/kg of diphenhydramine. Table 2 shows the number of mice protected from writhing activity for each dose of ibuprofen and diphenhydramine. The method of Finney ["Statistical Method of Biological Assay", McMillan Pub., 3rd Edition, 1978] is used to estimate the ED_{50}'s of ibuprofen alone and diphenhydramine alone.

On the second day eight combination doses were studied. The doses were chosen based upon the

ED_{50}'s established in the preceding day's experiment, which, under the assumption of additivity, would provide protection for 50% of the mice. These doses were tested in order to observe those ratio(s) of the combination drugs that would yield a synergistic effect. Combinations for which five or more mice exhibit blockage of writhing are candidates for further study. The doses of the constituent drugs in mg/kg for the eight groups were for ibuprofen (I) and diphenhydramine (D) respectively, [abbreviated as (I,D)]: (22,4), (19,8), (16,12), (14,6), (11,20), (9,24), (6,28), (4,32). Table 3 shows for each of these combination doses, the number of mice protected from writhing activity.

On the third and fourth days the four specific fixed ratios that achieved 5 or more protected mice were studied in more detail, i.e., the first combination treatment used a ratio of ibuprofen to diphenhydramine of 19:8 and the doses of the constituent drugs in mg/kg that were studied were (8,3), (12,5), (16,7) and (28,12). The second combination treatment used a ratio of doses of ibuprofen to diphenhydramine of 6:28 and the doses of the constituent drugs in mg/kg that were studied were (3,14), (4.5,21) and (9,42). The third combination treatment used a ratio of doses of ibuprofen to diphenhydramine of 9:24 and the doses of the constituent drugs in mg/kg that were studied were (3,8), (6,16), (12,32) and (15,40). The fourth combination treatment used a ratio of doses of ibuprofen to diphenhydramine of 4:32 and the doses of the constituent drugs in mg/kg that were studied were (3,24), (3.5,28) (4.5,36) and (5,40).

Under the assumption of additivity each dose of each combination is equivalent to a dose of

ibuprofen, based on the relative potency (ρ) of diphenhydramine to ibuprofen obtained from the experiment on the first day. Thus, for example, in the dose ratio 19:8 the combination of 28 mg/kg of ibuprofen and 12 mg/kg of diphenhydramine is, under the assumption of additivity, equivalent to (28+12ρ) mg/kg of ibuprofen. Table 4 shows for each dose of each of the combination doses tested the number of mice observed to be protected and the ibuprofen equivalent dose. For each of the four combination ratios, ED_{50}'s were estimated based on the observed number of mice protected at each ibuprofen equivalent dose using the method of Finney. Table 5 displays the estimated ED_{50}'s for each ratio.

RESULTS

The surprising synergistic effects of combining ibuprofen with diphenhydramine can be seen from the results of Tables 4 and 5 and the Figure of Drawing. The Figure of Drawing summarizes all of the findings by depicting the ED_{50}'s obtained for each treatment alone, the ED_{50} line if the treatments were additive, the number of mice/protected from writhing for each treatment studied and the estimated ED_{50}'s for each combination ratio.

The ED_{50} of ibuprofen alone is estimated to be 24 mg/kg and for diphenhydramine to be 38 mg/kg. The relative potency of diphenhydramine to ibuprofen is 24/38. Among the 8 ratios tested on the second day, synergism appears to be present for four ratios, and these ratios were further investigated on days 3 and 4. The ED_{50}'s were found to be for the dosage ratio of 19:8, 23 mg/kg of ibuprofen, for the dosage ratio 6:28, 19 mg/kg of ibuprofen, for the dosage ratio 9:24, 18

mg/kg of ibuprofen, and for the dosage ratio 4:32, 23 mg/kg of ibuprofen. Two of these ED_{50}'s are substantially less than 24 mg/kg of ibuprofen which is the ED_{50} that would be expected if the effects were additive. This represents a 25% reduction of the amount of ibuprofen that is required to obtain the effect in 50% of the animals. The Figure of Drawing indicates that many other dose ratios as well would produce an unexpected synergistic effect.

TABLE 2

NUMBER OF MICE PROTECTED AT TESTED DOSE LEVELS
OF IBUPROFEN AND DIPHENHYDRAMINE

Dose of Ibuprofen mg/kg	Dose of Diphenhydramine mg/kg	Number of Mice Protected	Number of Mice Not Protected
2	-	0	8
5	-	0	8
10	-	1	7
20	-	3	5
-	5	1	7
-	10	2	6
-	20	3	5
-	40	4	4

TABLE 3

NUMBER OF MICE PROTECTED AT TESTED DOSES* OF THE COMBINATION OF IBUPROFEN AND DIPHENHYDRAMINE

Dose of Ibuprofen mg/kg	Dose of Diphenhydramine mg/kg	Number of Mice Protected	Number of Mice Not Protected
22	4	4	4
19	8	5	3
16	12	3	5
14	16	4	4
11	20	4	4
9	24	5	3
6	28	5	3
4	32	5	3

* Doses were chosen based upon ED_{50}'s of ibuprofen and diphenhydramine which under the assumption of additivity would provide protection for 50% of the mice.

TABLE 4

NUMBER OF MICE PROTECTED AT TESTED DOSE LEVELS OF FOUR DIFFERENT RATIOS OF DOSES OF IBUPROFEN TO DIPHENHYDRAMINE

Combination Dose Ratio	Dose of Ibuprofen mg/kg	Dose of Diphenhydramine mg/kg	Ibuprofen Equivalent Dose Under Assumption of Additivity mg/kg	Number of Mice Protected	Number of Mice Not Protected
19:8	8	3	9.9	1	7
	12	5	15.2	3	5
	16	7	20.4	2	6
	28	12	35.6	6	2
9:24	3	8	8.0	2	6
	6	16	16.1	2	6
	12	32	32.2	6	2
	15	40	40.2	8	0
6:28	3	14	11.8	2	6
	4.5	21	17.7	3	5
	9	42	35.5	7	1
4:32	3	24	18.1	2	6
	3.5	28	21.1	3	5
	4.5	36	27.2	6	2
	5	40	30.2	6	2

TABLE 5

ED_{50}'s OF COMBINATION TREATMENTS
IN IBUPROFEN EQUIVALENT DOSES

Tested Combination Dose Ratios of Ibuprofen to Diphenhydramine		Ibuprofen Equivalent ED_{50} mg/kg
I	D	I
100	0	24
19	8	23
9	24	18*
6	28	19*
4	32	23
0	100	24

* ED_{50}'s substantially less than 24 mg/kg, the dose that would be expected were the effects additive.

In the pharmaceutical compositions and methods of the present invention, the foregoing active ingredients will be combined with the non-steroidal anti-inflammatory drug(s) and will typically be administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, i.e., oral tablets, capsules, elixirs, syrups, etc. and consistent with conventional pharmaceutical practices. For instance, for oral administration in the form of tablets or capsules, the active drug components may be combined with any oral non-toxic pharmaceutically acceptable inert carrier such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, etc. Disintegrators include, without limitation, starch, methylcellulose, agar, bentonite, guar gum, etc. Sweetening and flavoring agents and preservatives can also be included where appropriate.

Of course, additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components to optimize the

therapeutic effects, i.e., analgesia, antihistaminic, etc. while minimizing undesirable side effects. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

As representative suitable formulations consistent with the objects, features and advantages of the present invention, the following non-limiting examples are provided.

Example 2

Ibuprofen - 200 mg
Chlorpheniramine maleate - 8 mg
Phenylpropanolamine hydrochloride - 8 mg
Dextromethorphan hydrobromide - 30 mg
Guaifenesin - 100 mg

Triturate active ingredients and q.s. with lactose to selected capsule size

Example 3

In each fluid ounce:

Naproxen (sodium) 250 mg, dextromethorphan HB 30 mg, phenylpropanolamine hydrochloride 25 mg, orange flavoring and alcohol 10% v/v.

From the foregoing, other typical acceptable pharmaceutical formulations will be apparent to those skilled in the art of pharmaceutical formulations.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit of the invention. For example, effective dosages other than the preferred ranges set forth hereinabove with respect to the active ingredients may be applicable as a consequence of variations of the responsiveness of the mammal treated, severity of symptoms, dosage related adverse effects, if any, observed and similar considerations. Accordingly, such expected variations or differences in the practice of the present invention and the results obtained are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore that the invention be limited only by the scope of the claims which follow.

CLAIMS:

1. In a pharmaceutical composition comprising an analgesic in combination with at least one of an antihistamine, decongestant, cough suppressant or expectorant, the improvement comprising an analgesically effective amount of a non-steroidal anti-inflammatory drug or pharmaceutically acceptable salt thereof as the analgesic component.

2. A composition according to Claim 1, wherein said non-steroidal anti-inflammatory drug is selected from a propionic acid derivative, an acetic acid derivative, a fenamic acid derivative, a biphenylcarboxylic acid derivative, an oxicam or the pharmaceutically acceptable salts thereof.

3. A composition according to Claim 2, wherein said non-steroidal anti-inflammatory drug comprises a propionic acid derivative selected from ibuprofen, naproxen, benoxaprofen, flurbiprofen, fenoprofen, fenbufen, ketoprofen, indoprofen, pirprofen, carprofen, oxaprozin, pranoprofen, miroprofen, trioxaprofen, suprofen, alminoprofen, tiaprofenic acid, fluprofen, or bucloxic acid.

4. A composition according to Claim 3, wherein said drug is ibuprofen or naproxen.

5. A composition according to Claim 3, wherein said analgesically effective amount of said drug comprises between about 50 mg to 600 mg in each unit dose thereof.

6. A composition according to Claim 2, wherein said non-steroidal anti-inflammatory drug comprises an acetic acid derivative selected from indomethacin, sulindac, tolmetin, zomepirac, diclofenac, tiopinac, zidometacin, acemetacin, fentiazac, clidanac or oxpinac.

7. A composition according to Claim 6 wherein said analgesically effective amount of said drug ranges between about 25 to 400 mg in each unit dose thereof.

8. A composition according to Claim 2 wherein said fenamic acid derivative is selected from mefenamic acid, meclofenamic acid, flufenamic acid, niflumic acid or tolfenamic acid.

9. A composition according to Claim 8, wherein said analgesically effective amount of said drug ranges between about 250 to 500 mg in each unit dose thereof.

10. A composition according to Claim 2 wherein said non-steroidal anti-inflammatory drug comprises a biphenylcarboxylic acid derivative selected from diflunisal or flufenisal.

11. A composition according to Claim 10, wherein said analgesically effective amount of said drug ranges between about 250 to 500 mg in each unit dose thereof.

12. A composition according to Claim 2, wherein said non-steroidal anti-inflammatory drug com-

prises an oxicam selected from piroxicam, sudoxicam, or isoxicam.

13. A composition according to Claim 12 wherein said analgesically effective amount of said drug ranges between about 10 to 20 mg in each unit dose thereof.

14. A composition of matter according to Claim 1, wherein said antihistamine is selected from chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, diphenhydramine, doxylamine, tripelennamine, cyproheptadine, carbinoxamine, bromodiphenydramine, phenyltoloxamine, phenindamine, pyrilamine or azatadine.

15. A composition according to Claim 1 wherein said decongestant is selected from pseudoephedrine, phenylpropanolamine, or phenylephrine.

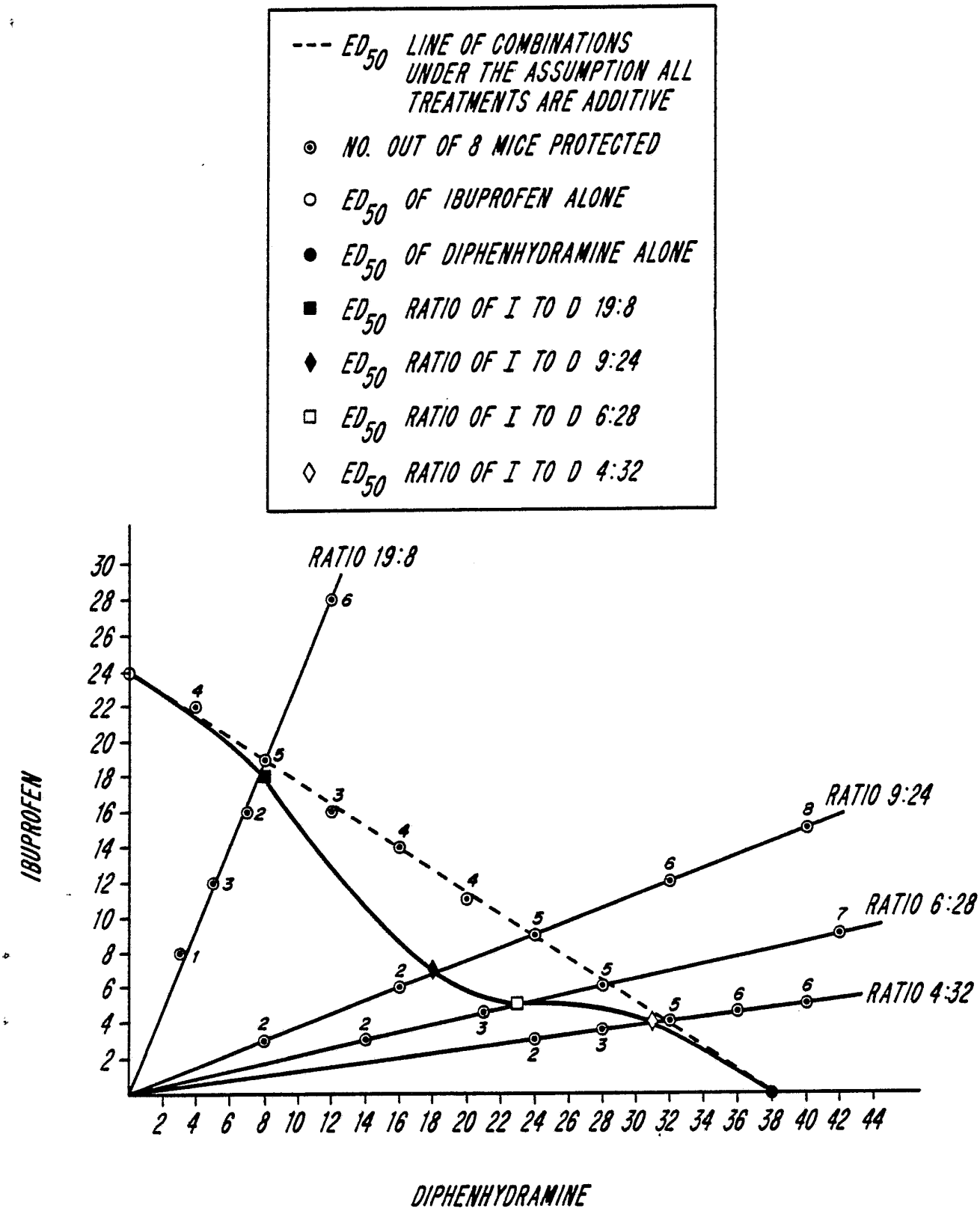
16. A composition according to Claim 1 wherein said cough suppressant is selected from caramiphen, dextromethorphan or codeine.

17. A composition according to Claim 1 wherein said expectorant is selected from terpin hydrate, guaifenesin, potassium iodide, potassium citrate or potassium guaiacolsulfonate.

18. A composition according to Claim 1 further comprising a pharmaceutically acceptable nontoxic carrier.

19. A composition according to Claim 18 adapted for oral administration in tablet, capsule or liquid form.

20. A method of alleviating cough, cold and cold-like symptoms in a mammal in need thereof, comprising administering thereto a symptom alleviating amount of a composition according to Claim 1.


--- ED_{50} LINE OF COMBINATIONS UNDER THE ASSUMPTION ALL TREATMENTS ARE ADDITIVE
NO. OUT OF 8 MICE PROTECTED
ED_{50} OF IBUPROFEN ALONE
ED_{50} OF DIPHENHYDRAMINE ALONE
ED_{50} RATIO OF I TO D 19:8
ED_{50} RATIO OF I TO D 9:24
ED_{50} RATIO OF I TO D 6:28
ED_{50} RATIO OF I TO D 4:32
RATIO 19:8
RATIO 9:24
RATIO 6:28
RATIO 4:32
IBUPROFEN
DIPHENHYDRAMINE
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/00596

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 45/06; A 61 K 31/19; A 61 K 31/44; A 61 K 31/485; //(A 61 K 31/19, 31/135)(A 61 K 31/44,31/19)(A 61 K 31/485, ./.

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	UNLISTED DRUGS, volume 20, nr. 11, November 1968, (Chatham, New Jersey, US) page 169n "SINUBID" (cited in the application)	1
X	UNLISTED DRUGS, volume 23, nr. 3, March 1971, (Chatham, New Jersey, US) page 36, "CO-TYLENOL" (cited in the application)	1
P,X	Chemical Abstracts, volume 101, nr. 23, 3 December 1984, (Columbus, Ohio, US) TRABER, Daniel L.:"Ibuprofen and diphenhydramine reduce the lung lesion of endotoxemia in sheep" page 39, column 1, abstract nr. 204101x & J. Trauma,1984, 24(9), 835-40 see abstract	1-19
X	US, A, 4322427 (JOSEPH P. BUYNISKI) 30 March 1982, see column 7, lines 45-51; claim 1	1-19
A	EP, A, 0097953 (E.I. DU PONT DE NEMOURS AND	

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
2nd July 1985	26 JUIL. 1985
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (January 1985)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 85/00596

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 31/19)

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	:

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
	COMPANY) 11. January 1984, see page 1 of claims, lines 1-19 (claim 1)	1-19

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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2nd July 1985	
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 20....., because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv);

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/US 85/00596 (SA 9298)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 17/07/85

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A- 4322427	30/03/82	GB-A-	2096894	27/10/82
		FR-A-	2504007	22/10/82
		DE-A-	3213788	04/11/82
		BE-A-	892884	18/10/82
		SE-A-	8202380	17/10/82
		JP-A-	57179117	04/11/82
		NL-A-	8201544	16/11/82
		AU-A-	8258282	21/10/82
		LU-A-	84089	13/04/83
		CA-A-	1173362	28/08/84
EP-A- 0097953	11/01/84	US-A-	4404210	13/09/83
		AU-A-	1594283	05/01/84
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