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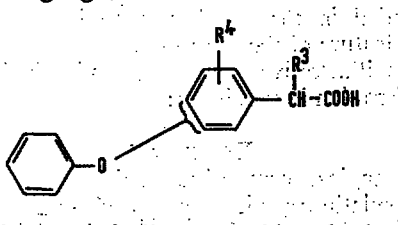
A5B 294 29Y 381 38Y 392 421 423 42Y 431 43Y 480 482 48Y 501 50Y 541 54Y 551 55Y 565 566 56Y 576 57Y 586 58Y 616 61Y 641 642 64Y 650 651 655 65Y

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(54) ANALGESIC COMPOSITIONS

(71) We, ELI LILLY AND COMPANY, a Corporation organised and existing under the laws of the State of Indiana, United States of America, of 307 East McCarty Street, City of Indianapolis, State of Indiana, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to an analgesic composition comprising a narcotic analgesic agent and a 3- or 4-phenoxyphenylalkanoic acid potentiating agent of the formula



or a pharmaceutically acceptable salt thereof, wherein (a) when the phenoxy moiety is in the 3-position R^3 is methyl or ethyl and R^4 is hydrogen and (b) when the phenoxy moiety is in the 4-position R^3 is hydrogen or methyl, and when R^3 is hydrogen, R^4 is hydrogen, fluoro, ethyl, methyl, or methoxy, and when R^3 is methyl R^4 is hydrogen.

The analgesic activity of moderate to potent narcotic analgesics such as codeine, morphine, meperidine, methadon (6 - dimethyl - amino-4,4 - diphenyl - 3 - heptanone), versidyne [1-(*p* - chlorophenylethyl) - 6,7 - dimethoxy - 2-methyl - 1,2,3,4 - tetrahydroisoquinoline], and *m* - (1 - methyl - 3 - propyl - 3 - pyrrolidinyl)phenol is greatly enhanced when administered with the phenoxyphenyl potentiating agent defined above.

Among the preferred pharmaceutically acceptable cationic salts of the above-defined 2 - (4 - phenoxyphenyl)alkanoic acids are the sodium, potassium, calcium, ammonium, and benzylamine salts.

The above phenoxyphenyl compounds are anti-inflammatory agents and have only mild, aspirin-like analgesic activity of their own, quite unlike the powerful analgesia produced by the above potent analgesics. Therefore, the enhancement of the analgesic activity of narcotic analgesic agents obtained by administering the phenoxyphenyl compound therewith is quite surprising and wholly unexpected.

Illustrative phenoxyphenyl compounds employed in the practice of this invention are:

2-(4-Phenoxyphenyl)acetic acid

2-(4-Phenoxyphenyl)acetic acid, ammonium salt

2-(4-Phenoxyphenyl)propionic acid

2-(4-Phenoxyphenyl)propionic acid, potassium salt

2-(4-Phenoxyphenyl)acetic acid, calcium salt

2-(4-Phenoxyphenyl)propionic acid, sodium salt

2-(4-Phenoxyphenyl)butyric acid, benzylamine salt

2-(3-Methyl-4-phenoxyphenyl)acetic acid

2-(2-Ethyl-4-phenoxyphenyl)acetic acid

2-(2-Fluoro-4-phenoxyphenyl)acetic acid

2-(3-Phenoxyphenyl)propionic acid

2-(3-Phenoxyphenyl)butyric acid

2-(3-Phenoxyphenyl)propionic acid, sodium salt

2-(3-Phenoxyphenyl)butyric acid, benzylamine salt

The above compounds are prepared by methods which are well known in the art for the preparation of phenylacetic acids and phenylpropionic acids. Pharmaceutically acceptable cationic salts are prepared by neutralizing the free acids with a suitable aqueous base or basic salt such as ammonium hydroxide, potassium hydroxide, magnesium hydrox-

[Price 25p]

ide and sodium carbonate, and evaporating the resulting solution to dryness.

The present invention also provides a method of enhancing the analgesic activity of a narcotic analgesic agent which comprises administering to a mammalian host, other than man, the narcotic analgesic agent and potentiating agent defined above.

When administered with a potentiating agent in accordance with the present invention, the narcotic analgesic agents can be administered in smaller doses to obtain the same degree of analgesia as is currently obtained with the standard therapeutic dose levels. Thus, the narcotic liability of the potent analgesics is likely to be decreased by employing the methods of this invention.

In the practice of this invention, the phenoxphenyl compounds of the above formula are administered to mammals in dosages of from 0.25 to 50 mg./kg. of body weight in combination with one-half or less of the known therapeutic dose levels of the narcotics, and can be administered with as little as 10 percent of the known therapeutic dosages of narcotics such as morphine. However, in the treatment of extremely severe pain, which is refractory even to morphine, the full therapeutic dosages are preferred. The phenoxyphenyl compounds of the above formula are active when administered by either the oral or parenteral route. The potentiating agent is preferably administered from one hour before until one hour after the administration of the analgesic agent, and, more preferably, the analgesic agent and the potentiating agent are administered substantially simultaneously.

Reference is made to the *Physicians' Desk Reference to Pharmaceutical Specialties and Biologicals* (22nd Edition, 1967, published by Medical Economics, Inc., a subsidary of Chapman-Rheinhold, Inc., Oradell, N.J.) for the standard dosage levels and routes of administration of a number of the analgesic agents.

When orally active analgesic agents, such as codeine, are to be administered, admixtures of the analgesic agent and a phenoxyphenyl compound of the above formula can be administered in any of the usual therapeutic dosage forms. Solid compositions for oral administration include tablets, pills, powders, filled capsules, and granules. In such solid compositions, the active compounds are admixed with at least one inert diluent such as sucrose, lactose or starch. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Besides inert diluents, such dosage forms may additionally comprise adjuvants, such as wetting, emulsifying, and suspending agents, and sweetening, flavouring and perfuming agents.

Preparations according to this invention for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Such preparations may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. The preparations can be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating sterilizing agents into the composition, by irradiation, or by heating. Parenteral dosage forms can also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Compositions for rectal administration are suppositories which may contain, in addition to the active substance, excipients such as cacoa butter or a suppository wax.

For reasons of convenience in administration and stability, filled capsules are the preferred therapeutic dosage form when codeine or other orally active analgesic agents are to be potentiated. Such filled capsules are readily prepared using conventional excipients and extending agents known in the art. It will be understood by those skilled in the art that other active therapeutic ingredients can be included in the novel compositions provided as a feature of the invention.

An illustrative composition suitable for administration is as follows:

EXAMPLE 1

A typical composition suitable for filling into gelatin capsules is prepared by thoroughly mixing five parts by weight of codeine, one part by weight of 2 - (4 - phenoxyphenyl)-propionic acid, sodium salt, and 1.3 parts by weight of starch. The mixture is filled into No. 1 gelatin capsules (see Remington's Practice of Pharmacy, a Treatise, 7th Ed., (1926), 1678—1679) in an amount such that each finished capsule contains about 32 mg. of codeine and about 6.4 mg. of 2 - (4 - phenoxyphenyl)-propionic acid, sodium salt.

If the analgesic agent to be potentiated is morphine or some other analgesic agent which exhibits only poor oral activity and is, therefore, usually administered parenterally, the phenoxyphenyl potentiating agent is usually administered separately, in any one of the usual oral therapeutic dosage forms, or is administered parenterally as by intramuscular or subcutaneous injection.

Potentiation of the level of analgesic activity is obtained when the phenoxyphenyl potentiating agents are administered substantially simultaneously, either in the same or different dosage

forms, or from 1 hour prior to 1 hour after the administration of the analgesic agent.

The following example further illustrates the present invention.

EXAMPLE 2

Morphine and 2 - (4 - phenoxyphenyl)propionic acid were evaluated separately and jointly in rats, in a test method in which the reaction time of treated and untreated rats to the application of a heat stimulus to the rat tail is the indicator of analgesia. The test method is that described by Robbins (*Journal of the American Pharmaceutical Association, Vol. 44,* page 497 [1955]). The compounds are administered subcutaneously. The reaction to the heat stimulus is determined 30 minutes and 1 hour after injection. Reaction time is recorded as the time between application of the heat stimulus and movement of the tail away from the heat. The average reaction time of untreated control groups is about 4 seconds. The results of the evaluation are set forth in the following table. The reaction time in the table is the mean reaction time of groups of four rats.

Compound	Dose mg./kg. (S.C.)	Reaction Time (seconds)
(Control)	—	4.50
Morphine	2	8.08
2-(4-Phenoxyphenyl)-propionic acid	100	3.80
Morphine +	2	8.40
2-(4-Phenoxyphenyl)-propionic acid	10	
Morphine +	2	9.58
2-(4-Phenoxyphenyl)-propionic acid	20	
Morphine +	2	13.30
2-(4-Phenoxyphenyl)-propionic acid	40	

EXAMPLE 3

1 - Methadon and 2 - (4 - phenoxyphenyl)-propionic acid were evaluated following the procedure of Example 2. The results are set forth in the following table.

Compound	Dose mg./kg. (S.C.)	Reaction Time (seconds)
(Control)	—	5.2
2-(4-Phenoxyphenyl)-propionic acid	100	3.8
1-Methadon	0.5	9.6
1-Methadon +	0.5	
2-(4-Phenoxyphenyl)-propionic acid	2.5	10.4
1-Methadon +	0.5	
2-(4-Phenoxyphenyl)-propionic acid	5.0	12.8
1-Methadon +	0.5	
2-(4-Phenoxyphenyl)-propionic acid	10.0	14.1

Similar results can be obtained with combinations such as

2 - (4 - Phenoxyphenyl)butyric acid, calcium salt and codeine;

2 - (4 - Phenoxyphenyl)propionic acid, ammonium salt and merperidine;

2 - (4 - Phenoxyphenyl)acetic acid and versidyne.

EXAMPLE 4

A typical composition suitable for filling into gelatin capsules is prepared by thoroughly mixing 5 parts by weight of codeine, one part by weight of 2 - (3 - phenoxyphenyl) - propionic acid, sodium salt, and 1.3 parts by weight of starch. The mixture is filled into No. 1 gelatin capsules in an amount such that each finished capsule contains about 32 mg. of codeine and about 6.4 mg. of 2 - (3 - phenoxyphenyl)propionic acid, sodium salt.

However, if the analgesic agent to be potentiated is morphine (or other analgesic agents which exhibit only poor oral activity and are therefore usually administered parenterally), the phenoxyphenyl potentiating agent is usually administered separately, in any one of the usual oral therapeutic dosage forms, or can be administered parenterally as intramuscular or subcutaneous injection.

Potentiation of the level of analgesic activity is obtained when the phenoxyphenyl potentiating agents are administered substantially simultaneously, either in the same or different dosage forms, or from 1 hour prior to 1 hour after the administration of the analgesic agent.

The following example further illustrates the present invention.

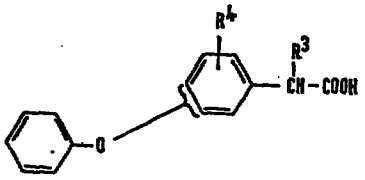
EXAMPLE 5

Morphine and 2 - (3 - phenoxyphenyl)-propionic acid were evaluated separately and jointly in rats, in a test method in which the reaction time of treated and untreated rats to the application of a heat stimulus to the rat tail is the indicator of analgesia. The test method is that described by Robbins (*Journal of the American Pharmaceutical Association, Vol. 44*, page 497 [1955]). The compounds are administered subcutaneously. The reaction to the heat stimulus is determined 30 minutes after injection. Reaction time is recorded as the time between application of the heat stimulus and movement of the tail away from the heat. The average reaction time of untreated control groups is about 4 seconds. The results of the evaluation are set forth in the following table. The reaction time in the table is the mean reaction time of groups of four rats.

Compound	Dose mg./kg. (S.C.)	Reaction Time (seconds)
(Control)	—	4.2
Morphine	2	9.8
2-(3-Phenoxyphenyl)-propionic acid	100	3.8
Morphine +	2	9.6
2-(3-Phenoxyphenyl)-propionic acid	10	
Morphine +	2	10.9
2-(3-Phenoxyphenyl)-propionic acid	20	
Morphine +	2	15.0
2-(3-Phenoxyphenyl)-propionic acid	40	

WHAT WE CLAIM IS:—

1. An analgesic composition comprising a narcotic analgesic agent and a 3- or 4-phenoxyphenylalkanoic acid potentiating agent of the formula



or a pharmaceutically acceptable salt thereof, wherein (a) when the phenoxy moiety is in the 3-position R^3 is methyl or ethyl and R^4 is hydrogen, and (b) when the phenoxy moiety is in the 4-position R^3 is hydrogen or methyl, and when R^3 is hydrogen R^4 is hydrogen, fluoro, ethyl, methyl, or methoxy, and when R^3 is methyl R^4 is hydrogen.

2. The composition of claim 1 wherein the narcotic analgesic agent is selected from codeine, morphine, methadon, meperidine, versidyne, and *m* - (1 - methyl - 3 - propyl - 3-pyrrolidinyl)phenol.

3. The composition of claim 1 or 2 wherein said phenoxyphenyl compound is 2 - (3-phenoxyphenyl)propionic acid, 2 - (3 - methyl-4 - phenoxyphenyl)acetic acid, 2 - (3 - phenoxyphenyl)butyric acid, 2 - (4 - phenoxyphenyl)propionic acid, or pharmaceutically acceptable salts thereof.

4. A method of enhancing the analgesic activity of a narcotic analgesic agent which comprises administering to a mammalian host, other than man, the narcotic analgesic agent and potentiating agent defined in any one of claims 1 to 3.

5. The method of claim 4 wherein from 0.25 to 50 mg./kg. of the potentiating agent is administered to the mammalian host.

6. The method of claim 4 or 5 wherein the potentiating agent is administered from one hour before to one hour after the administration of the analgesic agent.

7. The method of claim 6 wherein the analgesic agent and the potentiating agent are administered substantially simultaneously.

8. The composition of claim 1 substantially as herein described.

9. The method of claim 4 substantially as herein described.

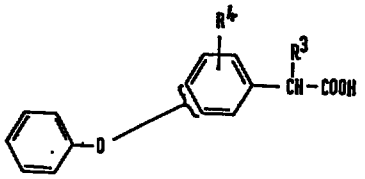
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Compound	Dose mg./kg. (S.C.)	Reaction Time (seconds)
(Control)	—	4.2
Morphine	2	9.8
2-(3-Phenoxyphenyl)-propionic acid	100	3.8
Morphine + 2-(3-Phenoxyphenyl)-propionic acid	2 10	9.6
Morphine + 2-(3-Phenoxyphenyl)-propionic acid	2 20	10.9
Morphine + 2-(3-Phenoxyphenyl)-propionic acid	2 40	15.0

WHAT WE CLAIM IS:—

1. An analgesic composition comprising a narcotic analgesic agent and a 3- or 4-phenoxyphenylalkanoic acid potentiating agent of the formula



or a pharmaceutically acceptable salt thereof, wherein (a) when the phenoxy moiety is in the 3-position R^3 is methyl or ethyl and R^4 is hydrogen, and (b) when the phenoxy moiety is in the 4-position R^3 is hydrogen or methyl, and when R^3 is hydrogen R^4 is hydrogen, fluoro, ethyl, methyl, or methoxy, and when R^3 is methyl R^4 is hydrogen.

2. The composition of claim 1 wherein the narcotic analgesic agent is selected from codeine, morphine, methadon, meperidine, versidyne, and *m* - (1 - methyl - 3 - propyl - 3-pyrrolidinyl)phenol.

3. The composition of claim 1 or 2 wherein said phenoxyphenyl compound is 2 - (3-phenoxyphenyl)propionic acid, 2 - (3 - methyl-4 - phenoxyphenyl)acetic acid, 2 - (3 - phenoxyphenyl)butyric acid, 2 - (4 - phenoxyphenyl)propionic acid, or pharmaceutically acceptable salts thereof.

4. A method of enhancing the analgesic activity of a narcotic analgesic agent which comprises administering to a mammalian host, other than man, the narcotic analgesic agent and potentiating agent defined in any one of claims 1 to 3.

5. The method of claim 4 wherein from 0.25 to 50 mg./kg. of the potentiating agent is administered to the mammalian host.

6. The method of claim 4 or 5 wherein the potentiating agent is administered from one hour before to one hour after the administration of the analgesic agent.

7. The method of claim 6 wherein the analgesic agent and the potentiating agent are administered substantially simultaneously.

8. The composition of claim 1 substantially as herein described.

9. The method of claim 4 substantially as herein described.

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