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(19)

(54) COMPOSITIONS FOR THE RELIEF OF MIGRAINE

(71) I, HENRY WILD, a British Subject, of 8 Winster Place, Mereside, Blackpool, Lancashire, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

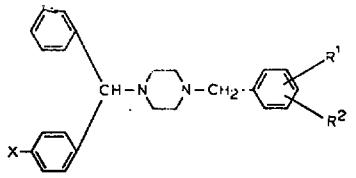
This invention relates to pharmacologically useful compositions.

In British Specification No. 705,979 there are described a number of unsymmetrical 1,4-diarylalkyl piperazines. In particular such piperazines may have as the aralkyl substituent upon one nitrogen atom a *p* - halobenzhydryl group and as the aralkyl substituent upon the second nitrogen atom a benzyl or an alkyl- or dialkyl-benzyl group the alkyl group or groups being present as a substituent or substituents in the benzene ring. Such compounds have been recognised to possess properties characteristic of an antihistamine. Nevertheless such compounds have been found to possess properties unusual in an antihistamine, for example, their prolonged period of activity which, in relation to typical antihistamine properties has been shown to persist for a number of days. Thus in relation to guinea pigs it has been shown that 1 - *p*-chlorobenzhydryl - 4 - *p* - tertiary butyl benzyl piperazine gives protection against histamine in the form of an aerosol for as long as 16 days.

Antihistamines are administered primarily to give protection against various conditions which are recognised to have an allergic origin and, upon the basis that certain patients suffering from migraine do so as the result of an allergic reaction to food which they have consumed. Elsewhere it has been stated that antihistamines are valueless in the treatment of migraine.

It is an object of the invention to provide a pharmaceutical composition of substantially non-toxic character which can be taken by patients who suffer from migraine with at least a reasonable prospect of obtaining relief or, if taken in time, to prevent the occurrence of a migraine attack.

According to the present invention there is provided a pharmaceutical composition for the treatment of migraine which comprises (a) a 1,4 - disubstituted piperazine having the general formula:



wherein X is a hydrogen atom, chlorine or bromine and R^1 and R^2 each represent a hydrogen atom or an alkyl group having not more than six carbon atoms, at least one of R^1 and R^2 being an alkyl group, or a salt of said piperazine and (b) N - acetyl - *p* - amino phenol, p - ethoxyacetanilide, salicylamide and/or acetylsalicyclic acid, the 1,4 - disubstituted piperazine and the compound (b) being respectively present in the weight ratio of 1:20 to 1:200. Preferably the weight ratio is 1:40 to 1:120 and most preferably 1:70 to 1:100.

The 1,4 - disubstituted piperazines used in accordance with the present invention have as a substituent in the 4-position a nuclear substituted benzyl group in which the nuclear substituent or substituents is or are one or two alkyl groups present in the 3-, 4- or 5-positions. The alkyl group or groups each contain one to six carbon atoms. When two alkyl groups are present these may be the same or different groups. When the alkyl group or groups has or have three to six carbon atoms they may be straight or branched chain alkyl groups. Thus the substitutent on the 4-nitro-

gen atom may be para-methylbenzyl, meta-methylbenzyl, para(n - butyl)benzyl, para-(tertiary - butyl)benzyl, meta - (tertiary - butyl)benzyl or a 3,5 - dimethylbenzyl group.

Preferably the substituted piperazine is a 1-*p* - chlorobenzhydryl - 4 - alkylbenzyl - piperazine. Specific examples of 1,4 - disubstituted piperazines which may be used include 1 - *p*-chlorobenzhydryl - 4 - *p* - methylbenzyl-piperazine, 1 - *p* - chlorobenzhydryl - 4 -*m* methylbenzylpiperazine, 1 - *p* - chlorobenzhydryl - 3,5 - dimethylbenzylpiperazine, 1-*p* - chlorobenzhydryl - 4 - *p* - (tertiarybutyl)-benzylpiperazine, 1 - *p* - bromobenzhydryl-4 - *p* - (tertiarybutyl)benzylpiperazine and 1-*p* - chlorobenzhydryl - 4 - *m* - (tertiarybutyl)-benzylpiperazine. These compounds are all di-acid bases and are most conveniently handled in the form of salts thereof with pharmaceutically acceptable acids such as hydrochloric acid, phosphoric acid, lactic acid, maleic acid, fumaric acid or tartaric acid. The above compounds may be prepared by the methods described in British Patent Specification No. 705,979.

The second essential component of the composition is N - acetyl - *p* - amino - phenol, salicylamide, acetylsalicyclic acid and/or *p* - ethoxyacetanilide. All these compounds will be recognised as well-known analgesics which can be regarded as phenol derivatives. The present invention is based upon the discovery that these particular analgesics act synergistically in some way with the antihistamines referred to above to antagonise or block the stimulation causing migraine. This synergistic effect is not found with other analgesics which have been tested and is most pronounced in the case of N - acetyl - *p*-amino - phenol (paracetamol) and the most preferred combination is paracetamol and 1-p - chlorobenzhydryl - 4 - *p* - (tertiary butyl) benzyl - piperazine (buclizine). A mixture of the analgesics may be used as component (b) of the composition.

The weight ratio in which the two essential ingredients are present is an important feature of the invention. It has been found that the 1,4 - dibusstituted piperazine is only required in quite a small proportion by weight relative to the selected analgesic. This proportion is 1:20 to 1:200 by weight, more preferably 1:40 to 1:120, and even more preferably 1:70 to 1:100.

In view of the nature of migraine it is highly desirable that the composition of the present invention be available in a form in which it is readily self-administered and accordingly tablets, capsules and suppositories are the preferred forms for the medicament.

For an individual weighing about 10 stone the aim should be to administer sufficient of the composition to provide about 2.5 to 24 milligrams, preferably 8 to 15 milligrams, e.g. 12.5 milligrams, of one of the 1,4 - disubstituted piperazines prior to or at least at the first signs of onset of an attack of migraine. Therefore the composition may be in a dosage unit form containing these quantities of the 1,4 - disubstituted piperazine. However an amount of the order of 12.5 milligrams or more of the 1,4 - disubstituted piperazine is most desirably spread over two or even three tablets or capsules which should be taken one at a time.

The nature of the effect produced by the combined administration of the components of the compositions is not fully understood but it is quite different from that observed when the 1,4 - disubstituted piperazines are administered alone.

It is believed that the analagesic serves to potentiate the 1,4 - disubstituted piperazine. However, since the duration of effect of the analgesic is shorter than that of the fully potentiated 1,4 - disubstituted piperazine, when the relief given by the analgesic wears off the symptoms of the migraine may, in certain instances, reoccur and may even escape further control. Thus in order to maintain the analgesic level it may be necessary if the pain reoccurs to administer additional analgesic alone at intervals after the first dose of the combined administration of the components of the composition. The amount of analgesic employed in the subsequent doses may be the same as that employed in the initial dose. For example, if the total amounts of 1,4 - disubstituted piperazine and analgesic administered in the initial dose are 12.5 mg. and 1000 mg. respectively, a suitable dose of analgesic in each of the subsequent administrations may be 1000 mg.

The subsequent doses may be taken at 3 to 4 hourly intervals after the first dose but only if necessary to maintain relief of pain.

In trials which have been carried out with compositions prepared in accordance with the invention, a success rate of approximately 90% has been reported by patients who took the tabletted compositions while anticipating or actually experiencing a migraine attack. Experience so far has shown that the compositions are most effective if taken before a migraine attack becomes established. Many migraine sufferers have an aura or premonition that they are about to experience a migraine attack and the composition should be taken as soon as this occurs. In other patients, migraine attacks may be associated with particular events such as car journeys and in these cases the compositions should be taken prophylacically prior to such events. An advantageous feature of the compositions of the invention is that their prophylactic effect appears to last for a considerable period, in some patients apparently up to 3 days.

The preferred dose of analgesic depends upon the particular compound selected. Normally a dose in the range 200 to 1500 mg. is

suitable, preferably 300 to 1000. In the case of paracetamol, salicyamide and acetylsalicyclic acid, the preferred dose is 300 to 1000 mg. while for *p* - ethoxyacetanilide (phenacetin) the preferred dose is 300 to 600 mg.

The compositions of this invention may contain other analgesics in addition to the analgesic selected as component (b). A derivative of the 3-methyl ether of morphine (codeine) in an amount ranging from 7.5 to 22.5 mg./1 gm. of the component (b) or dextropropoxyphene in an amount ranging from 12.5 to 37.5 mg./1 gm. of the component (b) are especially preferred.

The most preferred 1,4 - disubstituted piperazine is 1 - *p* - chlorobenzhydryl - 4- *p* - (tertiary butyl)benzyl piperazine which is also known as buclizine. It is especially preferred in the form of the dihydrochloride.

Increasing the amount of 1,4 - disubstituted piperazine beyond the recommended amount, surprisingly, does not bring about an increase in the relief obtained. In fact, it has been found that if the 1,4 - disubstituted piperazine is administered in amounts significantly in excess of 25 mg. the symptoms of the migraine may become more pronounced and a full migraine may develop which cannot be controlled by the administration of further analgesic.

It has been found that control of migraine is not achieved if the active ingredients of the compositions are administered separately at different times even if the interval between administering the separate ingredients is as short as 30 minutes. However the desired effect is obtained if the active ingredients are formulated separately in the specified relative proportions and the separate formulations administered substantially simultaneously. It is therefore within the scope of the present invention to provide a packaged pharmaceutical which comprises a 1 - *p* - chlorobenzhydryl - 4 - *p* - C - 1,6 - alkylbenzylpiperazine formulated in dosage unit form and packaged together with an analgesic selected from N - acetyl - *p* - aminophenol, p - ethoxyacetanilide, salicyamide, or acetylsalicyclic acid formulated separately in dosage unit form, the dosage unit of the 1,4 - disubstituted piperazine being from 2.5 to 24 mg. and the dosage unit of said analgesic being from 20 to 200 times the dosage unit of said 1,4 - disubstituted piperazine. The 1,4 - disubstituted piperazine and analgesic may be formulated, for example, as tablets or capsules and packaged together in pairs in a "bubble pack", the tablets or capsules possibly being identified by colouring to aid the patient in reliably selecting a tablet or capsule containing one of the active ingredients and another containing the other active ingredient.

In a further embodiment, the two essential active ingredients may be formulated in a single dosage form in which the dosage form is divided into separate portions by an internal division which is easily ruptured or is dissolved by body fluid, the 1,4 - disubstituted piperazine being confined to one compartment while the compound (b) is confined to the other compartment. For example the dosage form may comprise a gelatin capsule having an internal wall dividing the capsule into separate compartments one of which is filled with a formulation containing one ingredient and the other containing the other active ingredient. In use the internal wall would be ruptured or dissolved by fluid in the stomach and both active ingredients release simultaneously.

Normally it will be more convenient to formulate the compositions of the invention into a single dosage unit form which may include tablets, capsules, suspensions, syrups and suppositories. Such dosage forms may be prepared in the following manner.

1. *Tablets*

Buclizine dihydrochloride is triturated with the powdered binding agent. It is then mixed with paracetamol (N - acetyl - *p* - aminophenol) and passed through a 60 mesh BSS sieve. Water, containing any necessary colours dissolved within it, is mixed in with these powders. Sufficient gelatinised starch paste is also added to bind the powders together. The resulting mix is granulated through a 10 mesh BSS screen. The granules formed are dried in an oven at 50° C. and then passed through a 16 mesh screen.

Codeine phosphate is triturated with the necessary glidants, lubricants and disintegrating agents, and if required, any pigments, and the whole is then mixed with the granules. These granules are then compressed on a conventional tabletting machine.

2. *Suspension*

Codeine phosphate and buclizine dihydrochloride are dissolved in distilled water. The paracetamol in finely powdered form is mixed with a further portion of water which contains sufficient of a suitable suspending agent dissolved within it. Any colours, preservatives, buffering agents and flavours are added to a further portion of the water. All portions of water are then mixed together and made to volume.

3. *Syrup*

Paracetamol is dissolved in the required amount of propylene glycol and glycerin. Codeine phosphate and buclizine dihydrochloride are dissolved in the necessary quantity of water. The two portions are mixed together, the ratios of the portions being such that the solids remain dissolved in their respective solvent. Preservatives, flavours, buffering agents and colours are then added in

aqueous solution, the whole then being made to volume.

4. *Hard Capsules*

Buclizine dihydrochloride and codeine phosphate are triturated together with paracetamol. A suitable lubricant, for example, magnesium stearate is added and mixed. The whole is then passed through a fine mesh screen and remixed. The resulting powder is then filled into hard gelatin capsules on a conventional capsulating machine.

5. *Soft Gelatin Capsules*

The active ingredients in powder form, together with preservatives, buffering agents, are added to the necessary amount of fixed oil containing sufficient of a mixture of a hydrogenated oil and beeswax to suspend the powders. The whole is passed through a suitable mill and remixed. This mixture is then deaerated and then encapsulated on a conventional encapsulating machine.

6. *Suppositories*

The active ingredients in fine powdered form are added to the correct amount of suppository base which has previously been warmed to a temperature just above its melting point. The powders are dispersed in the melted base by use of a suitable stirrer. It may be necessary to then pass this molten mass through a mill. This will depend on particle size. The suppository mass is then moulded into suitable shaped suppositories.

The following Examples are given to illustrate the invention:—

Example I

Tablets were formulated containing buclizine (as its dihydrochloride) and paracetamol in the quantities specified in the following table.

Formulation Number	Buclizine per tablet (mg.)	Paracetamol per tablet (mg.)
1	6.25	500
2	5	500
3	3.75	500
4	10	500

In preparing the tablets the buclizine dihydrochloride was triturated with powdered startch to form a free-flowing powder. The resulting powder was mixed with the paracetamol in the appropriate proportions and the mixture passed through a 60 mesh B.S.S. sieve. Water was mixed in and then sufficient gelatinised starch paste added to bind the granules together. The resulting mix was granulated through a 10 mesh B.S.S. screen, dried at 50° C. and then passed through a 16 mesh B.S.S. screen. The resulting granules after assaying for concentration of the active ingredients, were compressed on a conventional tabletting machine. The normal dosage of the resulting tablets is 1 to 3 tablets.

Example II

Tablets were prepared containing:

Buclizine hydrochloride	6.25 mg.
Paracetamol	500 mg.
Codeine phosphate	7.5 mg.

The tablets were prepared in the manner described in Example 1 except that the codeine phosphate was triturated with the dried granules containing buclizine and paracetamol and the resulting mixture tabletted.

The following specific experience has been obtained in treating migraine sufferers with the tablets prepared in Example II. In such case the dosage given was 2 tablets per administration.

Case 1 (Female) Age 43

Has suffered attacks for the last 5 years, the migraine being associated always with the menstrual period. Symptoms—intense headache and nausea. The patient is always incapacitated for 1 or 2 days. Prescribed medicines gave unsatisfactory results.

The patient took a "dose" at the first signs of the migraine which prevented it from developing. No incapacitation resulted.

Case 2 (Male) Age 58

Suffered migraine for 20 years. These attacks occur at least once in two weeks and they always occur at weekends. The patient usually waking Saturday mornings suffering from a violent headache; the other symptoms of classical migraine soon follow. The patient has to remain in bed, in a darkened room, for the remainder of the day. The patient found that since taking one "dose" on Friday nights, when retiring, no attacks of migraine have occurred.

Case 3 (Male) Age 53

Patient suffered migraine since the age of

15. Attacks occur now at 4 to 6 week intervals. The prominent predromal symptom is incomplete vision followed, after 15 to 20 minutes by intense intercranial pain, inability to focus, think or speak coherently. These last ½ to ¾ hours leaving the patient with a dull ache at the base of the neck and an almost overwhelming feeling of lethargy.

The patient now takes the "dose" as soon as the predromal symptoms occur; this stops the migraine from developing. A mild feeling of tiredness is apparent for ½ to ¾ hour.

Case 4 (Female) Age 60

Migraine first occurred at 12 years of age; attacks occur once every 1 or 2 weeks. Symptoms are as classical migraine associated with intense nausea and vomitting. Symptoms last up to 12 hours. Patient now takes the "dose" as soon as possible when the attack starts. This prevents the attack developing although a certain amount of mild head pain can remain.

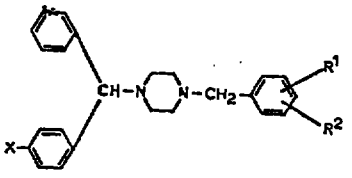
Case 5 (Female) Age 61

Attacks first occurred in the early 20's. They always, as now, are precipitated by a particular event e.g. a journey or social occasion. The migraine starts as general headache, intensifying to right, hemicranial severe pain. Nausea is prominent but vomitting does not occur.

Patient now takes a "dose" prior to travelling or social gathering and is not troubled by migraine, although on several occasions, a mild headache has occurred.

WHAT I CLAIM IS:—

1. A pharmaceutical composition for the treatment of migraine which comprises (a) a 1,4 - disubstituted piperazine having the general formula:



wherein X is a hydrogen atom, chlorine or bromine and R^1 and R^2 each represent a hydrogen atom or an alkyl group having not more than six carbon atoms, at least one of R^1 and R^2 being an alkyl group, or a salt of said piperazine and (b) N - acetyl - *p* - aminophenol, *p* - ethoxyacetanilide, salicylamide and/or acetylsalicyclic acid, the 1,4 - disubstituted piperazine and the compound (b) being respectively present in the weight ratio of 1:20 to 1:200.

2. A composition according to claim 1 in which the 1,4 disubstituted piperazine is a 1 - *p* - chlorobenzhydryl - 4 - alkylbenzyl piperazine.

3. A composition according to claim 2 in which the substituted piperazine is 1 - *p*-chlorobenzhydryl - 4 - *p* - (tertiary butyl)-benzyl piperazine.

4. A composition according to any one of the preceding claims in which the 1,4 - disubstituted piperazine and the compound (b) are present in relative proportions by weight within the range of 1:40 to 1:120 respectively.

5. A composition according to claim 4 in which said range is from 1:70 to 1:100.

6. A composition according to any one of the preceding claims which is in dosage unit form and in which the 1,4 - disubstituted piperazine is present in an amount from 2.5 to 24 mg.

7. A composition according to claim 6 in which the 1,4 - disubstituted piperazine is present in an amount of from 8 to 15 mg.

8. A composition according to claim 6 or claim 7 in which the compound (b) is present in an amount of from 200 to 1500 mg.

9. A composition according to claim 8 in which the compound (b) is present in an amount of from 300 to 1000 mg.

10. A composition according to any one of the preceding claims which additionally contains codeine in an amount of from 7.5 to 22.5 mg. per gram of compound (b) or dextropropoxyphene in an amount of from 12.5 to 37.5 mg. per gram of compound (b).

11. A pharmaceutical composition in dosage unit form which comprises from 2.5 to 24 mg. of 1 - p - chlorobenzhydryl - 4 *p*-(tertiary butyl) - benzyl - piperazine and N-acetyl - *p* - aminophenol in an amount of from 20 to 200 times the amount of the substituted piperazine.

12. A packaged pharmaceutical composition which comprises a 1 - *p* - chlorobenzhydryl-4 - *p* - C1 - 6 alkylbenzyl - piperazine formulated in dosage unit form and packaged together with an analgesic selected from N-acetyl - *p* - aminophenol, p - ethoxyacetanilide, salicylamide or acetylsalicyclic acid formulated separately in dosage unit form, the dosage unit of the 1,4 - disubstituted piperazine being from 2.5 to 24 mg. and the dosage unit of said analgesic being from 20 to 200 times the dosage unit of said 1,4 - disubstituted piperazine.

13. A pharmaceutical composition in dosage unit form as claimed in any one of claims 1 to 10 in which the dosage form is divided into separate portions by an internal division which is easily ruptured or is dissolved by body fluid, the 1,4 - disubstituted piperazine being confined to one compartment while the compound (b) is confined to the other compartment.

15. Attacks occur now at 4 to 6 week intervals. The prominent predromal symptom is incomplete vision followed, after 15 to 20 minutes by intense intercranial pain, inability to focus, think or speak coherently. These last ½ to ¾ hours leaving the patient with a dull ache at the base of the neck and an almost overwhelming feeling of lethargy.

The patient now takes the "dose" as soon as the predromal symptoms occur; this stops the migraine from developing. A mild feeling of tiredness is apparent for ½ to ¾ hour.

Case 4 (Female) Age 60

Migraine first occurred at 12 years of age; attacks occur once every 1 or 2 weeks. Symptoms are as classical migraine associated with intense nausea and vomitting. Symptoms last up to 12 hours. Patient now takes the "dose" as soon as possible when the attack starts. This prevents the attack developing although a certain amount of mild head pain can remain.

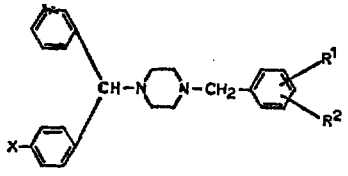
Case 5 (Female) Age 61

Attacks first occurred in the early 20's. They always, as now, are precipitated by a particular event e.g. a journey or social occasion. The migraine starts as general headache, intensifying to right, hemicranial severe pain. Nausea is prominent but vomitting does not occur.

Patient now takes a "dose" prior to travelling or social gathering and is not troubled by migraine, although on several occasions, a mild headache has occurred.

WHAT I CLAIM IS:—

1. A pharmaceutical composition for the treatment of migraine which comprises (a) a 1,4 - disubstituted piperazine having the general formula:



wherein X is a hydrogen atom, chlorine or bromine and R^1 and R^2 each represent a hydrogen atom or an alkyl group having not more than six carbon atoms, at least one of R^1 and R^2 being an alkyl group, or a salt of said piperazine and (b) N - acetyl - *p* - aminophenol, *p* - ethoxyacetanilide, salicylamide and/or acetylsalicyclic acid, the 1,4 - disubstituted piperazine and the compound (b) being respectively present in the weight ratio of 1:20 to 1:200.

2. A composition according to claim 1 in which the 1,4 disubstituted piperazine is a 1 - *p* - chlorobenzhydryl - 4 - alkylbenzyl piperazine.

3. A composition according to claim 2 in which the substituted piperazine is 1 - *p*-chlorobenzhydryl - 4 - *p* - (tertiary butyl)-benzyl piperazine.

4. A composition according to any one of the preceding claims in which the 1,4 - disubstituted piperazine and the compound (b) are present in relative proportions by weight within the range of 1:40 to 1:120 respectively.

5. A composition according to claim 4 in which said range is from 1:70 to 1:100.

6. A composition according to any one of the preceding claims which is in dosage unit form and in which the 1,4 - disubstituted piperazine is present in an amount from 2.5 to 24 mg.

7. A composition according to claim 6 in which the 1,4 - disubstituted piperazine is present in an amount of from 8 to 15 mg.

8. A composition according to claim 6 or claim 7 in which the compound (b) is present in an amount of from 200 to 1500 mg.

9. A composition according to claim 8 in which the compound (b) is present in an amount of from 300 to 1000 mg.

10. A composition according to any one of the preceding claims which additionally contains codeine in an amount of from 7.5 to 22.5 mg. per gram of compound (b) or dextropropoxyphene in an amount of from 12.5 to 37.5 mg. per gram of compound (b).

11. A pharmaceutical composition in dosage unit form which comprises from 2.5 to 24 mg. of 1 - p - chlorobenzhydryl - 4 *p*-(tertiary butyl) - benzyl - piperazine and N-acetyl - *p* - aminophenol in an amount of from 20 to 200 times the amount of the substituted piperazine.

12. A packaged pharmaceutical composition which comprises a 1 - *p* - chlorobenzhydryl-4 - *p* - C1 - 6 alkylbenzyl - piperazine formulated in dosage unit form and packaged together with an analgesic selected from N-acetyl - *p* - aminophenol, p - ethoxyacetanilide, salicylamide or acetylsalicyclic acid formulated separately in dosage unit form, the dosage unit of the 1,4 - disubstituted piperazine being from 2.5 to 24 mg. and the dosage unit of said analgesic being from 20 to 200 times the dosage unit of said 1,4 - disubstituted piperazine.

13. A pharmaceutical composition in dosage unit form as claimed in any one of claims 1 to 10 in which the dosage form is divided into separate portions by an internal division which is easily ruptured or is dissolved by body fluid, the 1,4 - disubstituted piperazine being confined to one compartment while the compound (b) is confined to the other compartment.

* C L M S *

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