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(54) THERAPEUTIC ANTI-DEPRESSANT COMPOSITIONS

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, 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:—

The present invention relates to therapeutic anti-depressant compositions and a process for the manufacture thereof.

7 - Chloro - 2,3 - dihydro - 1 - methyl - 5-phenyl - 1H - 1,4 - benzodiazepine (hereinafter referred to as medazepam) and pharmaceutically acceptable acid addition salts thereof are known. This compound and its pharmaceutically acceptable acid addition salts are pharmacologically recognized for their marked sedative activity. Moreover, 5 - (3 - dimethylaminopropylidene) dibenzo[a,d] [1,4]cycloheptadiene (hereinafter referred to as amitriptyline) and its pharmaceutically acceptable acid addition salts are known and have antidepressant activity.

It has now been found in accordance with the present invention that when medazepam or a pharmaceutically acceptable acid addition salt thereof and amitriptyline or a pharmaceutically acceptable acid addition salt thereof are administered together in the form of a therapeutic composition to a patient exhibiting the symptoms of non-psychotic depression, an antidepresant response is achieved which is pharmacologically far more pronounced than the response obtained by administration of either of the two therapeutic agents alone. In addition to the surprisingly increased antidepressant response achieved by administration of the compositions of the present invention, it has been found that the incidence of undesirable side effects which may be attributable to either of the two active ingredients in the course of normal usage is greatly diminished. This reduction in side effects is especially pronounced in terms of the side effects attributable to the administration of amitriptyline alone.

Accordingly, the therapeutic compositions provided by the invention comprise 7 - chloro-2,3 - dihydro - 1 - methyl - 5 - phenyl-1H - 1,4 - benzodiazepine or a pharmaceutically acceptable acid addition salt thereof and 5 - (3 - dimethylaminopropylidene)dibenzo-[a,d] [1,4]cycloheptadiene or a pharmaceutically acceptable acid addition salt thereof, the amounts of the ingredients present being substantially 0.25 to substantially 5.0 parts by weight of said cycloheptadiene ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof for each part by weight of said benzodiazepine ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof.

The therapeutic compositions of this invention can contain, if desired, therapeutically inert pharmaceutically acceptable carrier and/or excipient materials and can be made up into pharmaceutical dosage forms suitable for enteral or parenteral administration.

Amitriptyline can be present in the compositions of this invention as the free base or in the form of an acid addition salt thereof with a pharmaceutically acceptable organic or inorganic acid. Typical suitable inorganic acids, are, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Typical suitable organic acids are, for example, acetic acid, benzoic acid, lactic acid, malic acid, maleic acid and salicyclic acid.

However, the preferred compositions of the invention contain an acid addition salt of the base, and, more particularly, amitriptyline hydrochloride, as the active ingredient. The invenion will be described with particular reference to the use of amitriptyline hydrochloride, but it will, of course, be fully understood that the invention is operable in like manner where the free base or an acid addition salt other than the hydrochloride salt

[*Price 25p*]

Price 33p

is employed. In the case of amitriptyline free base, it is, however, advisable and preferable first to make an adsorbate since the free base is a liquid at room temperature.

Also, while in the preferred compositions of this invention, medazepam free base is present, it is possible to utilize salts of the base with pharmaceutically acceptable inorganic acids such as, for example, hydrochloric acid, sulfuric acid, phosphoric acid and nitric acid as well as salts of the free base with pharmaceutically acceptable organic acids such as benzoic acid, citric acid, malic acid, maleic acid, tartaric acid and salicyclic acid. The invention will be described with particular reference to the use of medazepam free base. It will, however be understood that the invention is operable in like manner when an acid addition salt of the base is utilized.

The therapeutic compositions of the present invention are readily manufactured by simply mixing the two active ingredients in the amounts specified above according to methods well recognized in the pharmaceutical arts. The mixture can then be converted into suitable enteral or parenteral dosage forms. For example, the composition of the present invention can be formulated for oral administration into compressed or coated tablets. Moreover, the composition may be formulated into solutions, syrups, oily suspensions and the like liquid forms for oral administration or suppositories for rectal administration. Additionally, the therapeutic compositions of the present invention can be provided in the form of hard-shell capsules. If desired, the compositions of this invention can be made up into a dosage form suitable for parenteral administration. The methods and techniques by which the various dosage forms are prepared are those conventionally recognized in the art of pharmaceutical compounding.

In the formulation of the compositions in the present invention into the aforementioned dosage forms, one can use, as optional ingredients, any of the various adjuncts or excipients ordinarily employed in the formulation of pharmaceutical products. For example, where the compositions of the present invention are to be provided in the form of tablets, these optional ingredients include, for example, fillers such as, for example, co-precipitated aluminium hydroxide/calcium carbonate, dicalcium phosphate and lactose, disintegrating agents such as, for example, corn starch, and the like, lubricating agents such as, for example, talc and magnesium stearate. On the other hand, where the compositions according to the persent invention are to be provided in liquid form for example solutions, syrups, and suspensions in oil, conventional adjuncts and excipients are utilized. These include, for example, water, sugar syrups, vegetable oils such as, for example, arachis oils, which may contain suitable edible suspending agents, sweetening agents and preservatives of the type normally employed in the pharmaceutical art.

The ratios in which the active ingredients are present vary, and the present composition can contain a ratio of from substantially 0.25 to substantially 5.0 parts by weight of amitriptyline for each part by weight of medazepam. Where the amitriptyline ingredient is used in the form of a pharmaceutically acceptable acid addition salt, as is the case in the preferred embodiment of the present invention, the quantity of such a salt which is used should be sufficient to provide the equivalent from substantially 0.25 to substantially 5.0 parts by weight of amitriptyline free base for each part by weight of medazepam present in the composition. On the other hand, where an acid addition salt of medazepam is used, the quantity of such salt employed should be sufficient to furnish the desired quantity of medazepam free base.

In unit dosage form, the compositions of the present invention contain from substantially 2.5 mg to substantially 30 mg of medazepam or the equivalent of a pharmaceutically acceptable acid addition salt thereof and from substantially 2.5 mg to substantially 75 mg of amitriptyline or of an equivalent amount of a pharmaceutically acceptable acid addition salt thereof, with the proviso, however, that in any such dosage form the weight of amitriptyline or the equivalent amount of the pharmaceutically acceptable acid addition salt thereof is not less than 0.25 or not more than 5.0 times the weight of medazepam present. The compositions which are produced in the preferred embodiment of the invention contain either from substantially 5 to substantially 10 mg of medazepam in the form of the free base and from substantially 10 mg to substantially 30 mg of amitriptyline, preferably as the equivalent amount of the hydrochloride salt. The particularly preferred embodiments of the present invention comprise dosage units containing 5.0 mg of medazepam and 12.5 mg of amitriptyline in the form of the equivalent amount of the hydrochloride salt, or 10.0 mg of medazepam and 25.0 mg of amitriptyline in the form of the equivalent amount of the hydrochloride salt. In producing such dosage forms, however, it is generally desirable and expedient to provide an excess, for example, about 2 or 3%, of the active ingredients.

In general, the frequency with which the compositions of the present invention are administered will vary depending on the amounts of the active ingredients present therein and on the needs and the requirements of the patient as diagnosed by the attending physician. Under usual circumstances, however, up to 2 dosage units (such as tablets or capsules) containing about 10.0 mg of medazepam and the equivalent of about 25.0 mg of amitriptyline can be administered *per os* every 6 hours. On the other hand, up to 2 tablets

or capsules containing about 5.0 mg of medazepam and the equivalent of about 12.5 mg of amitriptyline can be administered every 3 hours. In the case of children aged 6 to 12 years or in the case of debilitated patients, less frequent administration of such tablets or capsules may be more appropriate. On the other hand, more frequent administration of such tablets and capsules can be prescribed by the attending physician, if necessary. It is to be understood, however, that the dosages mentioned herein are exemplary only in that they do not, to any extent, limit the scope or practice of the present invention.

The therapeutic compositions of the present invention have a broad base of utility in the treatment of patients who exhibit the symptoms of varied types of non-psychotic depression such as, for example, simple, acute, psychoneurotic, chronic or involutional depression. The compositions are of particular effectiveness in the treatment of patients who exhibit symptons of apathy, despondency, fatigue, shock, restlessness. Desired therapeutic effects are achieved on administration of the therapeutic compositions of the present invention, unexpectedly in the absence of marked side effects such as, for example, an undesired excitement of the patient.

The acute toxicity of the compositions of the present invention was determined in the mouse and the rat. The determination of the LD_{50} of a mixture comprising 2.5 parts by weight of amitriptyline (as the hydrochloride salt thereof) for each part by weight of medazepam was effected according to the probit procedure, ten animals being employed per dosage. Test results are summarized in the following table:

Animals Species Tested	LD_{50}	Confidence Range
Mouse	179 mg/kg *per os*	163—196
Mouse	76 mg/kg intraperitoneal	69—84
Rat	367 mg/kg *per os*	333—405
Rat	115 mg/kg intraperitoneal	35—140

The results of the above test show the toxicity of the compositions in accordance with the present invention to be extremely slight, since markely low dosages are utilized in therapy.

A two week tolerance test on rats was also carried out. In this tolerance test, 75 mg/kg of amitriptyline (as the hydrochloride salt thereof) and 30 mg/kg of medazepam were administered ten times to the test animals. Two further test groups received the single active ingredients in the same dosage and a fourth group of animals received no dosages of active ingredient at all and served as a control group. An examination of the different groups of animals showed that there was no significant haematological, blood chemistry or histological difference. As compared with the control group, the animals receiving medazepam alone showed practically on showing down of the increase in weight. The group receiving amitriptyline hydrochloride alone showed a significant slowing down of the increase in weight and the group receiving both active ingredients showed a certain slowing down of the increase in weight. The combination is thus not more toxic than could be expected from the toxicities of the individual active ingredients; its toxicity is thus dependent on the amount of amitriptyline.

Clinical trials were carried out using the therapeutic compositions of this invention. The results obtained on a total of 141 patients were evaluated, and in 63 cases very good results were observed; the results were good in 44 cases; the results were fair in 22 cases; and in 12 cases no effect was observed. Very good and good results were therefore obtained with about 76% of the cases, whereas the results were fair or non-existant with about 24% of the patients treated. Double blind trials were carried out, using a placebo, on 30 of these patients in order to test the efficacy of the therapeutic compositions of this invention. Particularly impressive results were obtained in the treatment of anxiety neuroses, neurotic depressions, endogenous depressions, reactive depressions and involutional depressions.

The two active ingredients medazepam and amitriptyline were always used in a ratio of 1:2.5, the latter active ingredient administered as the hydrochloride salt thereof. The medium daily dosage was from 15 to 30 mg of medazepam and 37.5 to 75 mg of amitriptyline. In a

few cases, however, considerably higher dosages were administered (up to 110 mg of medazepam and 275 mg of amitriptyline).

Side effects were mainly observed in those patients who had received comparatively high dosages. Eighty-one of the patients treated showed such side effects. Certain of the patients showed several symptoms simultaneously, 88 instances of side effects are therefore reported. The most frequent side effects were dryness of the mouth (36 cases) and drowsiness (30 cases). Other side effects observed were insomnia (5 cases), dizziness (4 cases), agitation (3 cases), trembling (2 cases), ataxia (2 cases), tiredness (2 cases), constipation (2 cases), pyrosis (1 case) and hypertension (1 case). Since the most frequently observed side effects (dryness of the mouth and drowsiness) are of a harmless nature, the therapeutic compositions of this invention can be regarded as safe even when used in the comparatively high dosages mentioned.

The invention is further illustrated by the following examples.

Example 1

A mixture was prepared utilizing the following ingredient quantities hereinafter indicated.

Ingredient	*Per Capsule*
Medazepam	10.0 mg
Amitriptyline Hydrochloride	28.3 mg*
Lactose Powder	221.7 mg
Talc	18.0 mg
Magnesium Stearate	2.0 mg
Total	280.0 mg

* Corresponds to 25.0 mg of the free base

The medazepam, amitriptyline hydrochloride, lactose, talc and magnesium stearate were thoroughly mixed. The resulting mixture was filled into suitable hard shell pharmaceutical grade gelatin capsules.

Example 2

A mixture was prepared utilizing the following ingredient quantities hereinafter indicated.

Ingredient	*Per Capsule*
Medazepam	5.00 mg
Amitriptyline Hydrochloride	14.15 mg*
Lactose Powder	110.85 mg
Talc	9.00 mg
Magnesium Stearate	1.00 mg
	140.00 mg

* Corresponds to 12.5 mg of the free base

The medazepam, amitriptyline, lactose, talc and magnesium stearate were thoroughly mixed.

The resulting mixture was filled into appropriate hard-shell pharmaceutical grade gelatin capsules.

WHAT WE CLAIM IS:—

1. A therapeutic composition comprising 7 - chloro - 2,3 - dihydro - 1 - methyl - 5-phenyl - 1H - 1,4 - benzodiazepine or a pharmaceutically acceptable acid addition salt thereof and 5 - (3 - dimethylaminopropylidene)dibenzo[a,d][1,4]cycloheptadiene or a pharmaceutically acceptable acid addition salt thereof, the amounts of the ingredients present being substantially 0.25 to substantially 5.0 parts by weight of said cycloheptadiene ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof for each part by weight of said benzodiazepine ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof.

2. A therapeutic composition as claimed in claim 1, wherein therapeutically inert pharmaceutically acceptable carrier and/or excipient materials is/are also present.

3. A therapeutic composition as claimed in either claim 1 or claim 2, wherein there is present 7 - chloro - 2,3 - dihydro - 1 - methyl-5 - phenyl - 1H - 1,4 - benzodiazepine and 5 - (3 - dimethylaminopropylidene)dibenzo-[a,d][1,4]cycloheptadiene hydrochloride.

4. A therapeutic composition as claimed in claim 2 in dosage unit form for oral administration; there being present per dosage unit from substantially 2.5 mg to substantially 30.0 mg of 7 - chloro - 2,3 - dihydro - 1 - methyl-5 - phenyl - 1H - 1,4 - benzodiazepine or an equivalent amount of a pharmaceutically acceptable acidaddition salt thereof and from substantially 2.5 mg to substantially 75.0 mg of 5 - (3 - dimethylaminopropylidene)dibenzo-[a,d][1,4]cycloheptadiene or an equivalent amount of a pharmaceutically acceptable acid addition salt thereof.

5. A therapeutic composition as claimed in claim 4, wherein there is present 7 - chloro-2,3 - dihydro - 1 - methyl - 5 - phenyl - 1H-1,4 - benzodiazepine and 5 - (3 - dimethylaminopropylidene)dibenzo[a,d][1,4] cycloheptadiene hydrochloride.

6. A therapeutic composition as claimed in claim 5, wherein there is present from substantially 5.0 mg to substantially 10.0 mg of 7 - chloro - 2,3 - dihydro - 1 - methyl - 5-phenyl-1H-1,4-benzodiazepine free base and an amount of 5 - (3 - dimethylaminopropylidene)-dibenzo[a,d][1,4]cycloheptadiene hydrochloride which equivalent to from substantially 10 mg to substantially 30 mg of the free base.

7. A therapeutic composition as claimed in claim 5, wherein there is present about 10 mg of 7 - chloro - 2,3 - dihydro - 1 - methyl-5 - phenyl - 1H - 1,4 - benzodiazepine free base and an amount of 5 - (3 - dimethylaminopropylidene)dibenzo[a,d][1,4]cycloheptadiene hydrochloride which is equivalent to about 25 mg of the free base.

8. A therapeutic composition as claimed in claim 5, wherein there is present about 5 mg of 7 - chloro - 2,3 - dihydro - 1 - methyl-

few cases, however, considerably higher dosages were administered (up to 110 mg of medazepam and 275 mg of amitriptyline).

Side effects were mainly observed in those patients who had received comparatively high dosages. Eighty-one of the patients treated showed such side effects. Certain of the patients showed several symptoms simultaneously, 88 instances of side effects are therefore reported. The most frequent side effects were dryness of the mouth (36 cases) and drowsiness (30 cases). Other side effects observed were insomnia (5 cases), dizziness (4 cases), agitation (3 cases), trembling (2 cases), ataxia (2 cases), tiredness (2 cases), constipation (2 cases), pyrosis (1 case) and hypertension (1 case). Since the most frequently observed side effects (dryness of the mouth and drowsiness) are of a harmless nature, the therapeutic compositions of this invention can be regarded as safe even when used in the comparatively high dosages mentioned.

The invention is further illustrated by the following examples.

Example 1

A mixture was prepared utilizing the following ingredient quantities hereinafter indicated.

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Amitriptyline Hydrochloride	28.3 mg*
Lactose Powder	221.7 mg
Talc	18.0 mg
Magnesium Stearate	2.0 mg
Total	280.0 mg

* Corresponds to 25.0 mg of the free base

The medazepam, amitriptyline hydrochloride, lactose, talc and magnesium stearate were thoroughly mixed. The resulting mixture was filled into suitable hard shell pharmaceutical grade gelatin capsules.

Example 2

A mixture was prepared utilizing the following ingredient quantities hereinafter indicated.

Ingredient	*Per Capsule*
Medazepam	5.00 mg
Amitriptyline Hydrochloride	14.15 mg*
Lactose Powder	110.85 mg
Talc	9.00 mg
Magnesium Stearate	1.00 mg
	140.00 mg

* Corresponds to 12.5 mg of the free base

The medazepam, amitriptyline, lactose, talc and magnesium stearate were thoroughly mixed.

The resulting mixture was filled into appropriate hard-shell pharmaceutical grade gelatin capsules.

WHAT WE CLAIM IS:—

1. A therapeutic composition comprising 7 - chloro - 2,3 - dihydro - 1 - methyl - 5-phenyl - 1H - 1,4 - benzodiazepine or a pharmaceutically acceptable acid addition salt thereof and 5 - (3 - dimethylaminopropylidene)dibenzo[a,d][1,4]cycloheptadiene or a pharmaceutically acceptable acid addition salt thereof, the amounts of the ingredients present being substantially 0.25 to substantially 5.0 parts by weight of said cycloheptadiene ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof for each part by weight of said benzodiazepine ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof.

2. A therapeutic composition as claimed in claim 1, wherein therapeutically inert pharmaceutically acceptable carrier and/or excipient materials is/are also present.

3. A therapeutic composition as claimed in either claim 1 or claim 2, wherein there is present 7 - chloro - 2,3 - dihydro - 1 - methyl-5 - phenyl - 1H - 1,4 - benzodiazepine and 5 - (3 - dimethylaminopropylidene)dibenzo-[a,d][1,4]cycloheptadiene hydrochloride.

4. A therapeutic composition as claimed in claim 2 in dosage unit form for oral administration; there being present per dosage unit from substantially 2.5 mg to substantially 30.0 mg of 7 - chloro - 2,3 - dihydro - 1 - methyl-5 - phenyl - 1H - 1,4 - benzodiazepine or an equivalent amount of a pharmaceutically acceptable acidaddition salt thereof and from substantially 2.5 mg to substantially 75.0 mg of 5 - (3 - dimethylaminopropylidene)dibenzo-[a,d][1,4]cycloheptadiene or an equivalent amount of a pharmaceutically acceptable acid addition salt thereof.

5. A therapeutic composition as claimed in claim 4, wherein there is present 7 - chloro-2,3 - dihydro - 1 - methyl - 5 - phenyl - 1H-1,4 - benzodiazepine and 5 - (3 - dimethylaminopropylidene)dibenzo[a,d][1,4] cycloheptadiene hydrochloride.

6. A therapeutic composition as claimed in claim 5, wherein there is present from substantially 5.0 mg to substantially 10.0 mg of 7 - chloro - 2,3 - dihydro - 1 - methyl - 5-phenyl-1H-1,4-benzodiazepine free base and an amount of 5 - (3 - dimethylaminopropylidene)-dibenzo[a,d][1,4]cycloheptadiene hydrochloride which equivalent to from substantially 10 mg to substantially 30 mg of the free base.

7. A therapeutic composition as claimed in claim 5, wherein there is present about 10 mg of 7 - chloro - 2,3 - dihydro - 1 - methyl-5 - phenyl - 1H - 1,4 - benzodiazepine free base and an amount of 5 - (3 - dimethylamino-propylidene)dibenzo[a,d][1,4]cycloheptadiene hydrochloride which is equivalent to about 25 mg of the free base.

8. A therapeutic composition as claimed in claim 5, wherein there is present about 5 mg of 7 - chloro - 2,3 - dihydro - 1 - methyl-

5 - phenyl - 1H - 1,4 - benzodiazepine free base and an amount of 5 - (3 - dimethylaminopropylidene)dibenzo[a,d] [1,4]cycloheptadiene chloride which is equivalent to about 12.5 mg of the free base.

9. A process for the manufacture of the therapeutic compositions claimed in any one of claims 1 to 8 inclusive which process comprises mixing 7 - chloro - 2,3 - dihydro- 1-methyl - 5 - phenyl - 1H - 1,4 - benzodiazepine or a pharmaceutically acceptable acid addition salt thereof with 5 - (3 - dimethylaminopropylidene)dibenzo[a,d] [1,4] cycloheptadiene of a pharmaceutically acceptable acid addition salt thereof in an amount such that substantially 0.25 to substantially 5.0 parts by weight of said cycloheptadiene ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof for each part by weight of said benzodiazepine ingredient or the equivalent amount of a pharmaceutically acceptable salt thereof is used, and, if required, adding therapeutically inert pharmaceutically acceptable carrier and/or excipient materials.

10. A process for the manufacture of the therapeutic compositions claimed in any one of claims 1 to 8 inclusive, substantially as described with reference to the foregoing Examples.

11. Therapeutic compositions as claimed in any one of claims 1 to 8 inclusive, when manufactured by the process claimed in claim 9 or claim 10.

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