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(54) PHARMACEUTICAL CARDIO-ACTIVE COMPOSITIONS CONTAINING PTERIDINE DERIVATIVES

(71) We, ROHM PHARMA G.m.B.H., a German Body Corporate, of Darmstadt, Germany, and KNOLL A.G., a German Body Corporate, of Ludwigshafen, Germany 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 pharmaceutical compositions having a cardio-protective activity.

In the past twenty years increasing importance has been attached in experimental cardiology to those forms of necrosis which are not recognisable from the outset as myocardial disturbances of the circulation. Such myocardial necrosis can be produced experimentally by endogenous release of catecholamine in stress situations or by the injection of high doses of catecholamines, especially of 3,4 - dihydroxy - α - [(isopropylamino)-methyl] - benzylalcohol (isoproterenol, isoprenalin).

The pretreatment of animals with corticosteroids, AT 10, vitamin D or by inducing an alimentary potassium deficiency can considerably intensify these necroses. It has been recognised that a particularly important form of the disease is a heart disease of genetic origin in a strain of the Syrian gold hamster, which is manifested by spontaneously occurring, multifocal coagulation necrosis and calcification of the myocardium cells (cardiomyopathy). This hereditary disease is markedly similar to some degenerative heart diseases in humans. It was of crucial importance for understanding the origin of such myocardial necroses to establish whether they are directly attributable to a critical lack of energy-rich phosphate in the myocardium and whether this deficiency of energy-rich phosphate is caused by overloading of the fibrous interior with calcium.

The mechanistic connection between the necrosis-forming action of catecholamines and the deleterious shortage of energy-rich phosphate in the myocardium became apparent when it was possible to show that adrenalin is capable of suddenly increasing the influx of Ca^{++}ions through the membrane of the myocardium. It is presumed that this is the reason for the therapeutic success which can be achieved in acute (and prophylactic) therapy with calcium - antagonistic inhibitors of electromechanical coupling such as α - isopropyl - α - [(N - methyl - N - homoveratryl) - γ - aminopropyl] - 3,4 - dimethoxyphenyl - acetonitrile hydrochloride (verapamil), α - isopropyl - α - (N - methyl - N - homoveratryl) - γ - aminopropyl] - 3,4,5 - trimethoxyphenyl - acetonitrile hydrochloride (D 600), dimethyl 4 - (2' - nitrophenyl) - 2,6 - dimethyl - 1,4 - dihydro - pyridine - 3,5 - dicarboxylate (nifedipin), N - (3,3 - diphenylpropyl) - N - (α - methylphenethyl)amine lactate (prenylamine), N - (3,3 - diphenylpropyl) - N - α - phenylethyl)amine hydrochloride (fendilin) and also with potassium and magnesium salts as physiological calcium antagonists.

Overloading of the myocardium with Ca^{++}ions can also be prevented by β - receptor blockage. The attack of isoproterenol on the myocardium fibres is thereby directly forestalled. In therapy with β - blockers a cardio-protective activity is probably achieved by this mechanism or possibly by an unspecific membrane effect. As regards the calcium-antagonistic effect, a certain gradation of activity is observed between 1 - isopropylamino - 3 - (1 - naphthyloxy) - propan - 2 - ol - hydrochloride (propranolol), on the one hand, and the "purer" β - receptor blockers with lower antagonistic activity [e.g. 1 - (indol - 4 - yl - oxy) - 3 - isopropylamino-

propan - 2 - ol (visken, 1 - (o - allyloxy-phenoxy) - 3 - isopropylaminopropan - 2 - ol hydrochloride (trasicor)].

Experimental investigations in animals on the etiology of the above-mentioned diseases of the myocardium and the results of the various therapeutic measures have mutually complemented and assisted one another. To keep the myocardium under control, two basically different possibilities are available:

a) elimination of sympathetic impulses by β - receptor blockage,

b) inhibition of electromechanical coupling reactions by calcium antagonists.

The β - blockers have assumed an important position in the treatment of heart diseases. They reduce the effects of adrenergic stimulants on the heart circulation system and lower the oxygen consumption of the myocardium, but they occasionally cause undesirable haemodynamic changes and a reduction of coronary circulation. In diabetics, therapy with propranolol and other β - blockers together with simultaneous treatment with insulin or oral anti-diabetics involves the risk of hypoglycaemia. Generally, β - receptor blockers can be used safely in therapy only if it is established that there is neither heart decompensation nor obstructive diseases of the respiratory tract in the patient.

The therapeutic use of calcium-antagonistic inhibitors of electro-mechanical coupling of which verapamil is a typical example, also entails certain risks. Verapamil causes, among other things, a reduction in peripheral resistance and consequently—owing to the reduction in blood-pressure—relief for the heart. Extension of the refractory period in the AV nodule also contributes to the anti-arrhythmic activity of verapamil.

In hearts which are no longer capable of increasing the heart-time volume to maintain sufficient blood pressure, the reduction in the peripheral resistance can occasionally lead to a critical lowering of blood pressure.

When verapamil is applied intravenously it can cause acute cardio-vascular side effects such as total AV blockage, asystoly and ventricular fibrillation. The standard dosage of verapamil for oral administration is relatively high (80 mg of active material per day). The simultaneous (intravenous) administration of verapamil and β - receptor blockers is therefore ill-advised.

A utilisation of the therapeutic potential, acknowledged to be high, of verapamil and related calcium antagonists, if possible with a reduction in the applied doses, and, as far as possible avoidance of therapeutic risks, is therefore desirable.

A further pharmaceutical preparation which counteracts the calcium influx into the myocardium induced by isoproteronol is triamterene (2,4,7 - triamino - 6 - phenyl - pteridine). This compound already plays an important part in the therapy of oedema and high blood pressure disorders.

This active substance possesses pronounced natriuretic and anti-kaliuretic properties. In the normal organism calciuresis and, at the same time, magnesium retention are observed after the administration of triamterene.

While the administration of verapamil causes by a drop in blood pressure by reflex action a certain increase in the heart-minute volume, triamterene reduces the heart-minute volume. The effects on peripheral resistance also work in the opposite direction: while verapamil reduces peripheral resistance, triamterene increases such resistance.

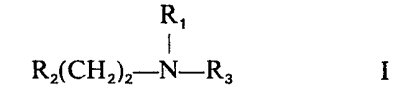
Because of the above-mentioned contradictory activities the two active substances (verapamil and β - blockers) have been considered from the outset as hardly suitable for simultaneous administration.

We have now found that pharmaceutical compositions containing a calcium-antagonistic inhibitor of electromechanical coupling together with triamterene, as active ingredients, surprisingly have a substantially improved therapeutic, especially cardio-protective activity.

According to the present invention, we provide pharmaceutical compositions comprising, as active ingredients, at least one calcium-antagonistic inhibitor of electromechanical coupling, together with triamterene, in association with at least one pharmaceutical carrier or excipient.

The abovementioned calcium-antagonistic inhibitors of electro-mechanical coupling are hereinafter referred to for convenience as "calcium-antagonists".

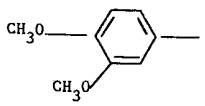
Calcium-antagonists which may be employed together with triamterene in pharmaceutical compositions according to the present invention include compounds represented by general formula I:



I

in which R_1 represents hydrogen or a methyl group,

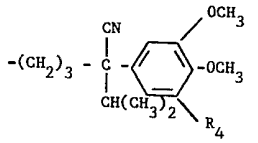
R_2 represents a radical of formula $(C_6H_5)_2CH$— or



R_3 represents a radical of formula

$$-CH(CH_3)-(CH_2)_n-C_6H_5$$

(in which n represents 0 or 1) or



(in which R_4 represents hydrogen or a methoxy group), provided that when R_1 represents a hydrogen atom, R_2 represents a group of formula $(C_6H_5)_2CH-$ and R_3 represents a group of formula

$$-CH(CH_3)-(CH_2)_n-C_6H_5$$

(wherein n represents 0 or 1), and physiologically acceptable acid addition salts thereof.

Physiologically acceptable acid addition salts include, for example, the salts of d-tartaric acid, maleic acid, fumaric acid, succinic acid, citric acid, cinnamic acid, salicylic acid, adipic acid, acetic acid, propionic acid, p-aminobenzoic acid, methanesulphonic acid, sulphuric acid, phosphoric acid, and especially the salts of hydrochloric acid and lactic acid.

Particular calcium-antagonists which can be used according to the invention include the compounds α - isopropyl - α - [(N - methyl - N - homoveratryl) - γ - amino-propyl] - 3,4,5 - trimethoxyphenyl - acetonitrile hydrochloride (D 600), dimethyl 4 - (2′ - nitrophenyl) - 2,6 - dimethyl - 1,4 - dihydropyridine - 3,5 - dicarboxylate (nifedipine), N - (3,3 - diphenylpropyl) - N - (α - methyl - phenethyl)amine lactate (prenylamine), N - (3,3 - diphenyl-propyl) - N - (α - phenethyl) - amine hydrochloride (fendilin) and preferably the compound α - isopropyl - α - [(N - methyl - N - homoveratryl) - γ - amino - propyl] - 3,4 - dimethoxy-phenyl - acetonitrile hydrochloride (verapamil). If desired, two or more calcium-antagonists can simultaneously be employed in the compositions according to the invention. By the admixture of the above-identified active ingredients, especially verapamil and triamterene, in the compositions according to the present invention, permeability of calcium through the myocardial membrane may be reduced and intra-cellular calcium fixing blocked. A pronounced cardio-protective effect is achieved at lower dosages of both the calcium antagonist and triamterene than would be necessary in therapy with just one of these ingredients. The effect can be proved, for example, on the hearts of rats *in situ* after isoproterenol-induced lesions or in the above-mentioned cardiomyopathy of the Syrian gold hamster in the pre-necrotic stage.

The possibility of achieving cardio-protective activity using the mixture of said active ingredients in sub-normal doses in compositions according to the invention is particularly interesting since in animal tests with continuous application of triamterene in high doses toxic nephropathy with degenerative changes has been occasionally observed. From experiments which we have carried out, the preparations according to the invention are free of undesirable side effects and are widely compatible.

The pharmaceutical compositions according to the invention preferably contain the calcium antagonist, e.g. verapamil, and triamterene in a weight ratio of 1:5 to 1:0.625, preferably a weight ratio of about 0.8:1. The dosages of the pharmaceutical preparations according to the invention depend on the type and gravity of the disease, the age and disposition of the patient and the individual factors which are normally to be taken into account. However, daily dosages may range for example from about 60 mg of verapamil and 75 mg of triamterene up to 240—320 mg of verapamil and 200—300 mg of triamterene. Generally, it has been found sufficient to employ 75 to 50% of the normal dosages of calcium-antagonists, preferably verapamil, together with triamterene, in order to bring about the desired cardio-protective activity.

The novel pharmaceutical compositions can be administered either parenterally or enterally; they can be produced in conventional manner and may contain the usual carriers and adjuvants or solvents.

Examples of compositions according to the invention include solid preparations suitable for oral administration, such as e.g. tablets, capsules and coated tablets. For oral administration, carrier materials which can be used include pharmaceutically inert solids, such as e.g. mannitol, lactose and organic or inorganic calcium salts.

Binding agents which may be used include polyvinyl pyrrolidone, gelatine or cellulose derivatives. Further additives include tablet disintegrating agents such as e.g. starch or alginic acid, tabletting lubricants, such as e.g. stearic acid or its salts, and inorganic lubricants such as e.g. talc and colloidal silicic acid, as well as flavouring agents.

The active ingredients can be mixed conventionally with the additives and granulated wet or dry. Depending on the type of additives used, a powder which can be made directly into tablets can be obtained optionally by simple mixing. The granules or powder can be filled directly into capsules or compressed conventionally into tablets or tablet cores.

The compositions can also be made up in the form of ampoules or suppositories.

The following Example illustrates the present invention.

Tablets

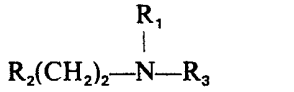
Tablets containing verapamil and triamterene as active ingredients were prepared by mixing the ingredients in a tumble mixer and pressing the resulting mixture into tablets having the following composition:—

100.0 mg triamterene,
80.0 mg verapamil,
100.0 mg lactose,
10.0 mg talc,
5.0 mg Aerosil (registered Trade Mark),
10.0 mg magnesium stearate,
10.0 mg maize starch,
20.0 mg micro crystalline cellulose (100 μm particle size).

WHAT WE CLAIM IS:—

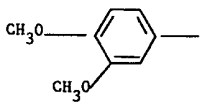
1. Pharmaceutical compositions comprising, as active ingredients, at least one calcium-antagonistic inhibitor of electromechanical coupling, together with 2,4,7 - triamino - 6 - phenyl - pteridine, in association with at least one pharmaceutical carrier or excipient.

2. Compositions as claimed in claim 1 wherein the said calcium-antagonistic inhibitor comprises a compound of general formula



(I)

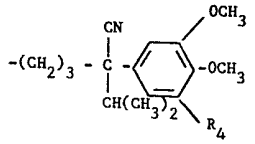
in which R_1 represents hydrogen or a methyl group; R_2 represents a radical of formula $(C_6H_5)_2CH$— or



R_3 represents a radical of formula

$$—CH(CH_3)—(CH_2)_nC_6H_5$$

(in which n is 0 or 1) or



(in which R_4 represents hydrogen or a methoxy group), provided that when R_1 represents hydrogen, R_2 represents a radical of formula $(C_6H_5)_2CH$— and
R_3 represents a radical of formula

$$—CH(CH_3)—(CH_2)_n—C_6H_5$$

(in which n is 0 or 1), and physiologically acceptable acid addition salts thereof.

3. Compositions as claimed in claim 2 wherein the said compound of formula I is in the form of a salt with d-tartaric acid, maleic acid, fumaric acid, succinic acid, citric acid, cinnamic acid, salicylic acid, adipic acid, acetic acid, propionic acid, p-aminobenzoic acid, methanesulphonic acid, sulphuric acid, phosphoric acid, hydrochloric acid or lactic acid.

4. Compositions as claimed in claim 1 wherein the said calcium-antagonistic inhibitor comprises α - isopropyl - α - [(N - methyl - N - homoveratryl) - γ - aminopropyl] - 3,4 - dimethoxyphenyl - acetonitrile hydrochloride.

5. Compositions as claimed in claim 1 wherein the said calcium-antagonistic inhibitor comprises α - isopropyl - α - [(N - methyl - N homoveratryl) - γ - aminopropyl] - 3,4,5 - trimethoxy - phenyl - acetonitrile hydrochloride; dimethyl 4 - (2' - nitrophenyl) - 2,6 - dimethyl - 1,4 - dihydropyridine - 3,5 - dicarboxylate; N - (3,3 - diphenylpropyl) - N - (α - methyl - phenethyl) - amine lactate; or N - (3,3 - diphenylpropyl) - n - (α - phenethyl) - amine hydrochloride.

6. Compositions as claimed in claim 4 wherein the said calcium-antagonistic inhibitor and 2,4,7 - triamino - 6 - phenyl-pteridine are present in a weight ratio of 1:5 to 1:0.625.

7. Compositions as claimed in claim 5 wherein the said calcium-antagonistic inhibitor and 2,4,7 - triamino - 6 - phenyl-pteridine are present in a weight ratio of about 0.8:1.

8. Compositions as claimed in any of the preceding claims in the form of tablets, capsules or coated tablets.

9. Compositions as claimed in any of claims 1 to 7 in the form of ampoules or suppositories.

10. Pharmaceutical compositions as

claimed in claim 1 substantially as herein described.

11. Pharmaceutical compositions substantially as herein described in the Example.

For the Applicants,
FRANK B. DEHN & CO.,
Imperial House,
15—19 Kingsway,
London WC2B 6UZ.

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