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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract

A pharmaceutical composition comprises magnesium oxide, hydroxide or a non-toxic salt of magnesium in a slow-release carrier; this material may be combined with or co-prescribed with a diuretic or cardiac glycoside or adrenergic receptor blocking agent or a calcium antagonist for the treatment of hypertension or angina pectoris.

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"PHARMACEUTICAL COMPOSITIONS"

This invention relates to pharmaceutical compositions comprising magnesium compounds.

In man and in animals, (see Williams RJP, Wacker WEC. Cation balance in biological systems. J.Amer. Med. Ass. 1967; 201/1: 96-100) intracellular concentrations of the four principal cations, sodium, potassium, magnesium and calcium, are in equilibrium such that log concentration ratios of the divalent cations magnesium and calcium are directly related to those for the monovalent cations potassium and sodium: total intracellular concentrations of sodium plus potassium and of magnesium plus calcium are respectively similar to those in extracellular fluid, and thus are similar on both sides of the cell membrane.

In man and in animals (Bloch M. Magnesium depletion: possible significance in ischaemic heart disease. Brit. J. Hosp. Med. 1973; 91-98) magnesium depletion results in negative magnesium and potassium balance, and positive sodium, calcium, and water balance; in intracellular loss of magnesium and potassium, and gain in sodium and calcium; in increase in extracellular fluid space; and in hypomagnesaemia, hypokalaemia, and hypocalcaemia. All these changes are reversible with magnesium.

I have postulated that normal vascular muscle tone, a major determinant of normal blood pressure, is critically dependent on cation balance; that magnesium plays a signficiant role in blood pressure control; and that cation imbalance resulting from magnesium depletion, leading to relative and absolute increase in intracellular and total body calcium and sodium, and to decrease in intracellular and total body magnesium and potassium, would be expected to result in increase in vascular muscle tone and in blood pressure. In support of this hypothesis, it was noted also that magnesium depletion has been observed in association with increase in renal, cardiac, and skeletal-muscle calcification in animals, and that increase in myocardial calcium content has been reported in magnesium-deficient hearts of patients with ischaemic heart disease.

Further support for this hypothesis comes from recent observations in normal subjects and in patients with essential hypertension, linking increase in blood pressure to change in cation balance, these indicating variously

(see Editorial. Essential hypertension: another defect? Lancet 1980; i: 1227-29.

Editorial. Cells, ions, and blood pressure. Lancet 1982; ii: 965-967.

Lever AF, Beretta-Piccoli C, Brown JJ, Davies DL, Fraser R, Robertson JIS. Sodium and

potassium in essential hypertension. Brit. Med. J. 1981; 283: 463-468)

that blood pressure correlates positively with intracellular and total-body sodium content, and negatively with total-body potassium, plasma potassium concentration, and cellular efflux-rate of sodium; and that increase in blood pressure can be produced by increase in dietary sodium, and decrease in blood pressure by increase in dietary potassium

(see Holly JMP, Goodwin FJ, Evans SJW, VandenBurg MJ, Ledingham JM. Re-analysis of data in two Lancet papers on the effect of dietary sodium and potassium on blood pressure. Lancet 1981; ii: 1384-87.

Khaw KT, Thom S.Randomised double-blind cross-over trial of potassium on blood pressure in normal subjects. Lancet 1982; ii: 1127-29.

MacGregor GA, Smith SJ, Markandu ND, Banks RA, Sagnella GA. Moderate potassium supplementation in essential hypertension. Lancet 1982; ii: 567-570.).

In dogs given intravenous solutions producing hypokalaemia, hypomagnesaemia, and hypokalaemia, alone and in combination, mean systolic and diastolic blood pressure increased; local hypermagnesaemia is associated with decrease in resistance in forelimb, kidney, coronary, gastric, mesenteric and hepatic vascular beds in the dog and in the human forearm (see Emerson, TE, Scott JB, Haddy FJ. Effects of acute multiple changes in plasma electrolyte levels on dog blood pressure. Am. J. Physiol. 1970; 218/1: 234-240).

In cats treated intravenously with magnesium, resultant fall in heart rate and in diastolic and systolic blood pressure were dose-dependent and correlated negatively with plasma magnesium concentration (see Ebel H, Classen HG, Marquardt P, Spaeth M. Zur Pharmakologie und Pharmakokinetik von Magnesium. Muench. Med. Wochenschr. 1975; 117/29-30: 1243-48). It is argued in the Editorial in Lancet 1982; ii: 965-967 cited above that increase in vascular muscle tone might result from increase in free intracellular calcium; that abnormality of sodium transport does not have a primary role in genesis of essential hypertension; and that cation changes observed in essential hypertension reflect an unidentified underlying abnormality, the so-called "innocent bystander".

These changes can all be produced by withdrawing dietary magnesium and reversed by magnesium repletion, and are compatible with the view that the reported abnormalities of sodium transport do not have a primary role in genesis of raised blood pressure in essential hypertension.

Since magnesium depletion might be widespread in Westernised communities (see Bloch M. Brit. J.Hosp. Med. 1973; 91-98 cited above), this might constitute a significant factor in the genesis of essential hypertension, and therefore treatment with magnesium might contribute to control of blood pressure in patients with

this condition.

It is known that, when certain pharmaceutical compositions, in particular certain diuretics, are used, they cause loss of magnesium and potassium from the body. Toxicity of other pharmaceutical compositions, in particular of cardiac glycosides, is increased by potassium and magnesium depletion. Diuretics and cardiac glycosides are frequently prescribed for the same patient, and it is a known practice to administer also a potassium salt, e.g. potassium chloride, which might be given in a slow release preparation.

However administration of potassium might give rise to unwanted side effects, e.g. vasoconstriction and gastric ulceration.

In particular, experimentally, these side effects can be prevented by magnesium ions, which have vasodilator activity, provided concentration of magnesium ions (m.eq./1.) exceeds that of potassium ions. Hence it has been proposed in U.K.Patent Specification No.1422193 and in U.S.No.4104370 to provide a pharmaceutical composition comprising magnesium oxide, magnesium hydroxide, or a non-toxic pharmaceutically acceptable salt of magnesium in combination with a non-toxic pharmaceutically acceptable salt of potassium, the

equivalent weight of magnesium being between 1 and 3, and preferably between 1 and 2 times the equivalent weight of the potassium together with a pharmaceutical carrier such that the rate of release of the magnesium and the rate of release of the potassium into the digestive system is controlled. Such a material may be co-prescribed or combined with a diuretic or cardiac glycoside.

Therapeutic usefulness of magnesium is limited by its action on the gut, causing purgation, unless administered in comparatively small doses. This limitation is overcome, in the use of the above-described composition by the employment of a controlled-release preparation so that the magnesium is administered in therapeutically meaningful dosages.

In the present application, it is proposed that, although loss of magnesium from the body might be associated with loss of potassium (arising for example from action of a diuretic), combined administration of magnesium and potassium is mostly not necessary for control of magnesium and potassium loss from the body; administration of magnesium alone serves not only to replace magnesium lost from the body but also to conserve body potassium.

According to the present invention, a pharmaceutical composition comprises magnesium oxide, magnesium hydroxide or a non-toxic pharmaceutically acceptable salt of magnesium together with a pharmaceutically acceptable carrier such that the rate of release of the magnesium into the digestive system is controlled. The controlled release might typically be made to give a duration of action in the range 2 to 24 hours.

In accordance with the present invention, it is proposed that magnesium compounds, e.g. magnesium oxide or hydroxide or salts are used in prophyalxis and treatment of potassium depletion in patients treated long-term with diuretic agents; in other conditions associated with potassium depletion, e.g. cardiac ischaemia, chronic cardiac failure, malabsorption, etc); concommitantly with treatment with cardiac glycosides; and also in treatment of essential hypertension.

More particularly, since cation changes correlating with increase in blood pressure, experimentally and in essential hypertension, namely, increase in intracellular

and total-body sodium and in extracellular fluid space, and decrease in sodium efflux rate, in total-body potassium, and in plasma concentrations of magnesium, potassium, and calcium, can all be produced by withdrawing dietary magnesium and can be reversed with magnesium replenishment, coprescription of magnesium together with diuretic agents and/or adrenergic receptor blocking agents will augment control of blood pressure obtained with these agents; alternatively, magnesium compositions might be used alone in treatment of essential hypertension.

Coprescription of diuretic agents with magnesium, which has a significant role in conserving whole-body and intracellular potassium, will act additionally to prevent or reduce potassium depletion resulting from increased renal loss of potassium and magnesium in patients treated long-term with diuretic agents, and of potassium in patients treated with β adrenergic receptor blocking agents (see Steiness E. Serum potassium and thiazide/beta - blocker combinations, Lancet 1982; i: 971/2).

Thus an improved method of treating magnesium/potassium depletion in man might comprise administering orally a pharmaceutical composition, in an effective amount of composition to produce the required activity, (in solid form) for oral administration via a controlled-release carrier, comprising magnesium oxide, magnesium hydroxide or a non-toxic pharmaceutically acceptable salt of magnesium together with a pharmaceutical carrier such that the rate of release of the magnesium into the digestive system is controlled to reduce or minimise the purgative action of the magnesium. The release time may be up to 12 hours but preferably is longer, for example up to 24 hours.

A magnesium compound might be co-prescribed with a diuretic or cardiac glycoside or might include the required dosage of diuretic or cardiac glycoside.

Dosage of magnesium will vary with degree of depletion; proposed unit dosage (per capsule, tablet, etc.) will provide of the order of 5 to 30 mg. equivalents of magnesium.

As previously explained, magnesium release into the gut must be controlled so as to limit purgative action, and to provide for magnesium to be administered in therapeutically meaningful dosages. Release of magnesium might be controlled, if required, so as not

to coincide with that of a diuretic agent or cardiac glycoside with which it is combined or co-prescribed.

Thus according to one aspect of the present invention there is provided a pharmaceutical composition comprising magnesium oxide, magnesium hydroxide, or a non-toxic pharmaceutically acceptable salt of magnesium together with a pharmaceutically acceptable carrier such that the rate of release of the magnesium into the digestive system is controlled, in combination with a diuretic or cardiac glycoside.

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising magnesium oxide, magnesium hydroxide, or a non-toxic pharmaceutically acceptable salt of magnesium together with a pharmaceutically acceptable carrier such that the rate of release of the magnesium into the digestive system is controlled, in combination with an adrenergic receptor blocking agent.

Preferably the magnesium is in the form of magnesium oxide, magnesium hydroxide, magnesium chloride, magnesium sulphate, magnesium gluconate or magnesium phosphate or a combination of these compounds. In some cases however magnesium carbonate may be employed. Because of its high magnesium content, it is found that magnesium oxide is particularly useful. For this purpose any suitable controlled or sustained release formulation may be employed to obtain the required rate of release.

The principal effects of adrenergic receptor blocking agents include peripheral vasodilatation, reduction in cardiac rate and output leading to decrease in oxygen consumption, and a cell membrane stabilising effect. These are complementary to, or supplement, effects produced with magnesium, in particular vasodilatation, and the changes in cation balance referred to above. It is therefore appropriate for the magnesium compound and the adrenergic receptor blocking agent to be prescribed together, for example, in treatment of hypertension; angina pectoris (possibly via coronary artery vasodilatation, reduction in cardiac output and in oxygen consumption); cardiac arrhythmia (possibly via membrane stabilising effect, intracellular potassium conservation), etc.

Examples of adrenergic receptor blocking agents with typical dosages are:

oxprenolol	(20, 40mg)
propranolol	(40, 80mg)
pindolol	(5mg)
sotalol	(40, 80mg)
timolol	(10mg)
nadolol	(40, 80mg)
acebutolol	(100,200mg)

atenolol	(100mg)
metoprolol	(50,100mg)
labetalol	(100,200mg)
prozasin	(0.5, 1, 2 5 mg).

The invention includes within its scope an improved method of treatment by an adrenergic receptor blocking agent comprising administering orally a pharmaceutical composition, in an effective amount of composition to produce the required activity, comprising magnesium oxide, magnesium hydroxide or a non-toxic pharmaceutically acceptable sale of magnesium together with the adrenergic receptor blocking agent. The magnesium compound may be co-prescribed with the adrenergic receptor blocking agent. Preferably the treatment is effected by oral administration, for example by capsule or tablet, of a combination of the adrenergic receptor blocking agent with the magnesium compound.

The magnesium compound, formulated for controlled release, also finds particular application combined with or co-prescribed with a calcium antagonist, such as nifedipine or verapamil, so as to enhance the effects of these latter drugs, via the whole body and intra-cellular effects described above and/or via reduction in peripheral and coronary vascular resistance and/or via a membrane stabilising effect of magnesium, in treatment, for example, of angine pectoris and/or hypertension.

Any suitable controlled or sustained release formulation may be employed for the preparation of the compositions in order to obtain the required controlled rate of release into the digestive system.

One type of such preparation is based on a plurality of small cores which may be themselves of an inactive material such as sugar, synthetic resin or naturally occurring seeds such as rape seeds. Particularly suitable are "nonpareil seeds" as used in the confectionery industry which comprise sugar crystals coated with starch, talc, kaolin and syrup. Alternatively, the cores may themselves be formed of the medicament to be administered.

These cores are then coated with one or more layers of a material which dissolves at a slow but controlled rate in the gastro-intestinal tract of the patient. Examples of such time-delay materials (which are described in greater detail hereinafter) include glyceryl monostearate and beeswax and since the latter is much less dispersible than the former, by carrying the relative amounts of these materials the rate of

dissolution and so the rate of release of the medicament (which may be incorporated within the coating material, form the central core or be applied as a separate layer between the core and the coating material) can be controlled. The rate of release may also be varied by altering the thickness of the coating material applied. A plurality of coated cores are combined in a suitable form such as a capsule, a tablet (a binder may be required in this case) or a suspension in a liquid. By combining coated cores having different time release characteristics a continuing release of medicament over a period of many hours from administration may be achieved. It will be understood that, by including uncoated medicament in the composition, an immediate effect can also be attained. The rate of absorption of the medicament used is a further factor which must be considered, and medicaments which are absorbed slowly generally only require a thin protective coating.

Another type of controlled release formulation which may be used is that which is produced by a process involving microencapsulation techniques.

Other well known methods of preparing sustained release preparations may also be employed. For example, the magnesium compound may be dispersed in a molten wax and then spray congealed.

Fine powders comprising the magnesium compound may be suspended in a tower and coated with time delay material. Those coated powders can then be suspended in a liquid or encapsulated. Sustained release granules may also be prepared and either tabletted or placed in a soft gelatine capsule. Tablets may also be prepared as sustained release layered tablets.

The time delay material is a substantially water insoluble material resistant to disintegration in the gastro-intestinal tract and providing for a gradual release of the medicament in said tract. The time delay material may be, for example, a wax, a fatty acid, alcohol or ester, alone or an admixture thereof.

The wax may be paraffin wax; a petrolatum wax; a mineral wax such as ozokerite, ceresin, utah wax or montan wax; a vegatable wax such as, for example, carnauba wax, Japan wax, bayberry wax, flax wax; an animal wax such as, for example, spermaceti; or an insect wax such as beeswax, Chinese wax or shellac wax. Additionally, the wax material may be an ester of a fatty acid having from 12 to 31 carbon atoms and a fatty alcohol having from 12 to 31 carbon atoms, the ester having a carbon atom content of from 24 to 62, or

a mixture thereof. Exemplary are myricyl palmitate, ceryl palmitate, ceryl cerotate, myricyl mellissate, stearyl palmitate, stearyl myristate, lauryl laurate.

The fatty acid may have from 10 to 22 carbon atoms and may be for example, decenoic, docosanoic stearic, palmitic, lauric or myristic acid.

The fatty alcohols may have from 10 to 36 carbon atoms and may be, for example, lauryl alcohol, cetyl, stearyl, myristyl, myricyl, arachyl, carnaubyl or ceryl alcohol.

The esters may be mono-, di- or triglyceryl esters formed from fatty acids having from 10 to 22 carbon atoms, such as, for example, glyceryl distearate, glyceryl tristearate, glyceryl monostearate, glyceryl dipalmitate, glyceryl tripalmitate, glyceryl monopalmitate, glyceryl dilaurate, glyceryl trilaurate, glyceryl monolaurate, glyceryl didocosanoate, glyceryl tridocosanoate, glyceryl monodocosanoate, glyceryl monocaprate, glyceryl dicaprate, glyceryl tricaprate, glyceryl monomyristate, glyceryl dimyristate, glyceryl trimyristate, glyceryl monodecenoate, glyceryl didecenoate, glyceryl tridenenoate, hydrogenated castor oil, hydrogenated peanut oil and hydrogenated coconut oil.

The preferred sustained release materials are hydrogenated castor oil, glyceryl monostearate, glyceryl distearate, 12-hydroxystearyl alcohol and microcystalline wax.

As previously indicated, a diuretic or cardiac glycoside may be combined or co-prescribed with the magnesium composition.

Exemplary of diuretics in the compositions of this invention are carbonic anhydrase inhibitors, for example acetazolamide; benzothiadiazides, for example bendroflumethiazide, benzthiazide, hydrochlorothiazide, chlorothiazide, cyclopenthiazide and altrizide; benzensulfonamides for example, furosemide, mefruside, bumetanide; chlorthalidone, metolazone, xipamide, clopamide; and ethacryic acid. Exemplary of cardiac glycosides in the composition of this invention are digoxin, digitoxin and lanatoside C. The diuretic agents and cardiac glycosides are present in amounts effective to produce the diuretic and cardiotonic activity. The effective amounts of the abovementioned diuretics and cardiac glycosides are known to the art. The appropriate daily dose of diuretic agent and cardiac glycoside may be given in divided doses and may

be administered in conjunction with tablets or capsules containing only a magnesium composition, and all made available in one presentation pack. The diuretic agent and cardiac glycoside may be present in the pharmaceutical formulation with or without means for controlling their release into the digestive system.

As previously explained, the magnesium compound may be co-prescribed with a diuretic or a cardiac glycoside and presented as a tablet, capsule, suspension, etc. Thus the invention furthermore includes within its scope a pharmaceutical composition for co-prescribing with a diuretic or cardiac glycoside for treating magnesium/potassium depletion in a human comprising magnesium oxide, magnesium hydroxide or a non-toxic pharmaceutically acceptable salt of magnesium together with a pharmaceutically acceptable carrier, for oral administration, the carrier being such that rate of release of magnesium into the digestive system is controlled so that duration of action of said composition is up to 24 hours. Use of

such a co-prescribed compound thus gives freedom for adjusting the amount of magnesium taken relative to other medicaments.

The invention is illustrated but in no way limited by the following specific examples.

EXAMPLE 1

A mixture of magnesium oxide, a flowing agent such as fumed silicon dioxide, a disintegrant such as an alginate and starch or another pharmaceutical excipient to aid in disintegration and dispersion is milled and added to a tacky suspension of nonpareil seeds in an adhesive mixture comprising polyvinylpyrrolidone and a wetting agent dissolved in methylated spirits. When no more of the milled powder will adhere to the seeds, the coated pellets are dried by a stream of air and a further layer or coating applied by the same method. Finally a protective coating of glycerol monostearate/beeswax is applied to the pellets which now have a diameter of approximately 1 mm.

The pellets are filled into capsules such that each capsule contains 100 mg (5 milli-equivalents) of magnesium oxide.

EXAMPLE 2

(a) A mixture of furosemide and a disintegrant such as starch is milled and added to a tacky suspension of nonpareil seeds in an adhesive mixture comprising gelatine in aqueous ethanol. When no more of the milled powder will adhere to the seeds, the coated pellets are dried by a stream of air and a further layer of coating applied by the same method. Finally a very thin coating of glycerol monostearate/beeswax is applied to the pellets.

(b) These pellets containing furosemide are mixed with pellets containing magnesium oxide described in Example 1 and filled into capsules or tablets in such proportions that each capsule or tablet contains for example 20 mg furosemide and 5 m.eq. magnesium oxide, or alternative quantities of these compounds.

EXAMPLE 3

Pellets containing

(a) hydroflumethiazide

(b) mefruside

(c) chlorthalidone

(d) clopamide

(e) hydrochlorothiazide

(f) methylclothiazide

(g) bendrofluazide

(h) bumetanide

(i) cyclopenthiazide

(j) ethacrynic acid

(k) metolazone

(l) acetazolamide

are prepared by substituting the above compounds for furosemide in the procedure of Example 2a and these pellets are mixed with pellets containing magnesium oxide described in Example 1 and filled into capsules in such proportions that the capsules contain for example 5 m.eq. magnesium oxide, and

(a) 25 mg hydroflumethiazide

(b) 25 mg mefruside

(c) 25 mg chlorthalidone

(d) 20 mg clopamide

(e) 12.5 mg hydrochlorothiazide

(f) 5 mg methylclothiazide

(g) 2.5 mg bendrofluazide

(h) 1 mg bumetanide

(i) 0.25 mg cyclopenthiazide.

(j) 50 mg ethacrynic acid

(k) 5 mg metolazone

(l) 250 mg acetazolamide

EXAMPLE 4

Nonpareil seeds are coated with a mixture of digoxin and polyvinylpyrolidone in ethanol, and the coated pellets are dried by a stream of air.

These pellets are mixed with pellets containing magnesium oxide as described in Example 1 and filled into capsules in such proportions that each capsule contains 0.25 mg digoxin and 5 m.eq. magnesium oxide.

The tablets or capsules of Examples 2, 3, and 4 contain a diuretic or a cardiac glycoside together with a magnesium compound. The capsules of Example 1 containing a magnesium compound are co-prescribed with a diuretic or a cardiac glycoside.

EXAMPLE 5

Magnesium oxide (5mEq) is combined with labetalol (100mg) or propranolol (80mg) or acebutolol (200mg). The combined material is made up into pellets each having a core of a nonpareil seed using a suitable adhesive mixture comprising polyvinyl pyrrolidone and a wetting agent dissolved in methylated spirits. The pellets are provided with a protective wax coating and filled into capsules containing the required dosage.

In some cases, it may be desirable, in the treatment of a patient, to co-prescribe or combine the magnesium compound not only with an adrenergic receptor blocking agent but also with a diuretic. Typical diuretics which may be employed are as follows:

(a) hydroflumethiazide
(b) mefruside
(c) chlorthalidone
(d) clopamide
(e) hydrochlorothiazide
(f) methylclothiazide
(g) bendrofluazide
(h) bumetanide
(i) cyclopenthiazide
(j) ethacrynic acid
(k) metolazone
(l) acetazolamide

Such diuretics, when used, may cause loss of magnesium and potassium from the body. Although it is a known practice to administer also a potassium salt such as potassium chloride, which may be given in a slow release preparation, such administration of potassium is mostly inadequately effective in restoring normal body potassium content and may give rise to unwanted side effects such as vasoconstriction and gastric ulceration. Administration of magnesium may be employed not only to replace magnesium loss from the body but also to conserve body potassium.

It is well-known to co-prescribe adrenergic receptor blocking agents with diuretics. The present invention provides an improved method of treatment and pharmaceutical composition for such treatment in which magnesium oxide is administered with the adrenergic receptor blocking agent and diuretic thereby enhancing blood pressure control, and conserving body potassium.

An example of such a composition is as follows:

EXAMPLE 6

Magnesium oxide (5mEg) is combined with propranolol (80mg) plus hydrochlorothiazide (12.5, 25mg) or hydroflumethiazide (25mg) or bumetanide (1mg) or bendrofluazide (2.5, 5mg) or mefruside (25mg). The combined material is formed into pellets and made up into capsules in a similar manner to the material of the previously described Examples.

EXAMPLE 7

As previously mentioned, the magnesium, formulated for controlled release, may be combined or co-prescribed together with a calcium antagonist such as nifedipine or verapamil so as to enhance the effects of these latter drugs.

As an example, magnesium oxide (5mEq) is combined with nifedipine (5 or 10mg) or with verapamil (40 or 80 or 120 mg); the combined material being made up into capsules giving controlled release as in the previously described Examples.

These further combinations may be coprescribed or combined together with diuretic agents, as above, and /or together with adrenergic receptor blocking agents, as above, but adjusting dosages so as to provide for any additive or summation effects of these further combinations.

CLAIMS:

1. A pharmaceutical composition comprising magnesium oxide, magnesium hydroxide or a non-toxic pharmaceutically acceptable salt of magnesium together with a pharmaceutically acceptable carrier such that the rate of release of the magnesium into the digestive system is controlled.

2. A pharmaceutical composition comprising magnesium oxide, magnesium hydroxide, or a non-toxic pharmaceutically acceptable salt of magnesium together with a pharmaceutically acceptable carrier such that the rate of release of the magnesium into the digestive system is controlled, in combination with a diuretic or cardiac glycoside.

3. A pharmaceutical composition comprising magnesium oxide, magnesium hydroxide, or a non-toxic pharmaceutically acceptable sale of magnesium together with a pharmaceutically acceptable carrier such that the rate of release of the magnesium into the digestive system is controlled, in combination with an adrenergic receptor blocking agent.

4. A composition as claimed in any of the

preceding claims wherein the magnesium is in the form of magnesium oxide, magnesium hydroxide, magnesium chloride, magnesium sulphate, magnesium gluconate, magnesium carbonate or magnesium phosphate or a combination of these compounds.

5. A composition as claimed in any of the preceding claims in which all of the magnesium is coated with a coating such that its rate of release into the digestive system may be controlled.

6. A composition as claimed in any of the preceding claims wherein unit dosage will provide of the order of 5 to 30 milligram equivalents of magnesium, presented as a tablet, capsule, suspension, etc.

7. A composition as claimed in any of claims 1 to 5 wherein the composition is in the form of a tablet or capsule containing 5 to 10 milligram equivalents of magnesium.

8. A pharmaceutical composition for co-prescribing with a diuretic or cardiac glycoside or an adrenergic receptor blocking agent for treating magnesium/potassium depletion in a human comprising magnesium oxide, magnesium hydroxide or a non-toxic

pharmaceutically acceptable carrier, for oral administration the carrier being such that rate of release of the magnesium into the digestive system is controlled so that duration of action of said composition is from 2 to 24 hours.

9. A pharmaceutical composition comprising magnesium oxide, magnesium hydroxide, or a non-toxic pharmaceutically acceptable sale of magnesium together with a pharmaceutically acceptable carrier such that the rate of release of the magnesium into the digestive system is controlled, in combination with a calcium antagonist.

10. A composition as claimed in any of claims 2 to 8 and further including a calcium antagonist.

11. A composition as claimed in either claim 9 or claim 10 wherein the calcium antagonist is nifedipine or verapamil.

12. A composition substantially as hereinbefore described with reference to Example 1 or Example 2 or Example 3 or Example 4 or Example 5 or Example 6 or Example 7.

13. A method of treatment for hypertension, angina pectoris or cardiac arrhythmia by an adrenergic receptor blocking agent which comprises administering orally a pharmaceutical composition, in an effective amount of composition to produce the required activity, comprising magnesium oxide, magnesium hydroxide or a non-toxic pharmaceutically acceptable sale of magnesium together with the adrenergic receptor blocking agent.

14. A method as claimed in claim 13 wherein said composition is in solid form in a capsule or tablet containing a combination of the adrenergic receptor blocking agent with the magnesium compound.

15. A method as claimed in claim 14 wherein the combined material includes a pharmaceutically acceptable carrier giving a required controlled release of the magnesium into the digestive system.

16. A method as claimed in any of claims 13 to 15 wherein said pharmaceutical composition further includes a diuretic.

17. A method of treatment for hypertension which comprises administering orally a pharmaceutical composition, in an effective amount to produce the

required activity, comprising magnesium oxide, magnesium hydroxide, or a non-toxic pharmaceutically acceptable sale of magnesium either alone or in combination with a diuretic or in combination with an adrenergic receptor blocking agent or in combination with both a diuretic and an adrenergic receptor blocking agent.

18. A method or treatment for angina pectoris and/or hypertension which comprises administering orally a pharmaceutical composition, in an effective amount to produce the required activity, comprising magnesium oxide, magnesium hydroxide, or a non-toxic pharmaceutically acceptable sale of magnesium in combination with a calcium antagonist.

19. A method as claimed in claim 18 wherein the calcium antagonist is nifedipine or verapamil.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 84/00099

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

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

IPC[3]: A 61 K 9/22; A 61 K 33/08; A 61 K 33/06

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC[3]	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	GB, A, 1422193 (SMITH KLINE & FRENCH LABORATORIES LTD.) 21 January 1976 see page 1, lines 39-83; page 2, lines 5-63 (cited in the application)	1-12
X	US, A, 4104370 (MAURICE BLOCH) 1 August 1978 see column 2, line 4 - column 4, line 20 (cited in the application)	1-12
X	FR, M, 4265M (WALTON JOHN SMITH) 8 August 1966 see page 3, abstract 3°-4°	1-12
X	US, A, 4150111 (ALLISTER WARREN) 17 April 1979 see column 3, line 16 - column 4, line 24	1-12

* Special categories of cited documents: [15]

"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 [2]	Date of Mailing of this International Search Report [2]
11th July 1984	06 AOUT 1984
International Searching Authority [1]	**Signature of Authorized Officer [20]**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (October 1981)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

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 13-19, because they relate to subject matter [12] not required to be searched by this Authority, namely:

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 [13], specifically:

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

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/GB 84/00099 (SA 6921)

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 01/08/84

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
GB-A- 1422193	21/01/76	None		
US-A- 4104370	01/08/78	None		
FR-M- 4265		None		
US-A- 4150111	17/04/79	NL-A-	7506269	02/12/75
		FR-A,B	2272639	26/12/75
		DE-A-	2523394	11/12/75
		BE-A-	829975	01/10/75
		GB-A-	1464192	09/02/77
		CA-A-	1033300	20/06/78