1243474

PATENT SPECIFICATION (11) 1243474

NO DRAWINGS

(21) Application No. 47811/69 (22) Filed 29 Sept. 1969

(31) Convention Application No. 764 325 (32) Filed 1 Oct. 1968

(31) Convention Application No. 835 730 (32) Filed 23 June 1969 in

(33) United States of America (US)

(45) Complete Specification published 18 Aug. 1971

(51) International Classification A 61 k 27/00

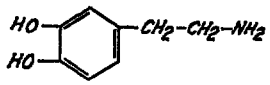
(52) Index at acceptance
A5B 20X 20Y 38Y 39X 401 40Y 421 42Y 431 432 43Y 482 48Y 586 58Y

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(54) COMPOSITIONS COMPRISING *L*-DOPA

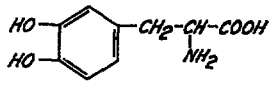
(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with pharmaceutical compositions for increasing the dopamine content in the brain tissue. The increased dopamine content in brain tissue tends to alleviate some of the symptoms caused by Parkinsonism and similar diseases, which are accompanied by dopamine deficiency in certain nuclei of the brain tissue in patients with Parkinsons disease. Dopamine is 3,4-dihydroxyphenylethylamine of the structure:



A dopamine deficiency in the corpus striatum results in increased muscular tension and akinesia which is defined as the absence or disturbance of motion in a muscle. This is characterized by the rigidity of limbs and difficulty in walking, sitting, standing, etc. noted in Parkinson syndrome.

It was first suggested that perhaps dopamine could be administered directly to the animal to compensate for the deficiency. However, a natural blood-brain barrier in the body prevented the absorption in brain tissue. It was then proposed that a metabolic precursor of dopamine be utilized with the body changing the precursor into dopamine after it has traversed the blood-brain barrier. Accordingly, racemic dopa was employed for this purpose as it was a known precursor of dopamine. Dopa is 3,4-dihydroxyphenylalanine of the formula:



and is known to be racemic due to its asymmetric carbon atom. In employing dopa to increase the dopamine content of brain tissue, numerous side effects were encountered such as nausea and vomiting, as well as hypertension in some instances and hypotension in others. Also noted were certain changes in blood chemistry which have not been fully explained. However, the overall results ranged from poor to excellent in alleviating muscular tension and akinesia.

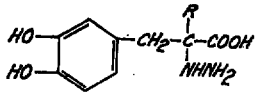
An effort to minimize side effects led to a separation of the dopa, which is racemic, into its *D* and *L* forms with subsequent testing of each. It was found that *L*-dopa was far more effective and resulted in fewer side effects than *D*-dopa. Accordingly, *L*-dopa has now been experimentally accepted as a treatment for the muscular tension and akinesia but it too produces side effects (such as nausea and vomiting) in certain patients due to the fact that it must be administered in quite high dosage levels, i.e. 4—8 grams/day. Obviously, if a combination of drugs could be found which would reduce the amount of *L*-dopa which was required to obtain remission of symptoms thereby lessening or eliminating side effects, it would receive widespread acceptance in the art.

The present invention provides pharmaceutical compositions comprising *L*-dopa or a pharmaceutically acceptable salt thereof together with an α - hydrazino - α - R - 3,4 - dihydroxyphenylpropionic acid or a pharmaceutically acceptable salt thereof, where R re-

presents a hydrogen atom or a lower alkyl radical. Such compositions will normally contain a pharmaceutical diluent, carrier, coating and/or excipient.

The hydrazine compound, like the dopa, contains an asymmetric carbon atom. It exists, and can be used, as the *L*, the *D* or the racemic form.

The compounds used in the present invention have the structural formula:



where R is hydrogen or lower alkyl.

In a preferred embodiment of the present invention, the hydrazine compound, as well as the dopa, is used in the *L* form (unless the hydrazino compound is α - hydrazino - 3,4 - dihydroxyphenylpropionic acid) and the compositions are in orally administrable form, such as a pill or capsule. Other forms include tablets, granules, powders, syrups, elixirs, and sterile injectable liquids. The active ingredients can be made up into the compositions of the present invention in conventional manner as will be apparent to those skilled in pharmacy. The following two formulations are illustrative of compositions of the present invention.

FORMULATION 1

Dry-filled capsule containing 50 mg. of active ingredients

	Per Capsule
L-dopa	33 mg.
α-hydrazino-α-methyl-3,4-dihydroxyphenylpropionic acid	17 mg.
Lactose	273 mg.
Magnesium stearate	2 mg.
	325 mg.

Mix the ingredients listed and reduce the mixture to a No. 60 mesh powder. Encapsulate, filling 325 mg. into each No. 2 capsule.

FORMULATION 2

Tablet	Per Tablet
L-dopa	33 mg.
α-hydrazino-α-methyl-3,4-dihydroxypropionic acid	17 mg.
Corn Starch	100 mg.
Magnesium stearate	2 mg.
Hydroxypropylmethyl cellulose	4 mg.
Titanium dioxide	4 mg.
Propylene glycol	1 mg.

The starch is made into a thick paste with water and the paste is intimately mixed with the active ingredients. If necessary, a small additional amount of water is added for thorough mixing of these ingredients and thereafter the water is removed by drying in an oven. After thorough drying, the material is ground, the magnesium stearate and talc are added and intimately mixed with the ground material and the mixture then is passed through a No. 10 screen and compressed into tablets. The hydroxypropylmethylcellulose and titanium dioxide are suspended in the propylene glycol and then mixed with a mixture of alcohol and chloroform (50:50) which is used as the film coating material. This mixture then is poured or sprayed into a coating pan in which the tablets are rotating thereby film coating the tablets.

Other formulations comprising more or less of active ingredient can be prepared by conventional methods for oral or parenteral administration.

The combination is usually given in amounts of from about 5 to about 200 mg/kg of body weight a day with the ratio of *L*-dopa to the hydrazine compound being from about 0.2 to about 8, preferably about 0.5 to about 6 with about 2 being the optimum ratio (weight basis).

In a preferred embodiment of the present invention, the hydrazine compound is α - hydrazino - α - methyl - 3,4 - dihydroxyphenylpropionic acid or α - hydrazino - 3,4 - dihydroxyphenylpropionic acid and the former compound is used in its *L*-form.

The pharmaceutically acceptable salts of the drugs which may be used include the alkali metal and ammonium salts of the carboxy function and the hydrochloride, hydrobromide, sulfate and the like salts of the amino function. The term "lower alkyl" means an alkyl group containing from 1 to 4 carbon atoms. In one of the preferred embodiments of the present invention, the free base compounds are used and not the salts.

The invention will now be described by reference to the following examples in which all parts are expressed in parts by weight unless otherwise indicated. Examples 1—4 are comparative tests.

Examples 1 to 18

Female albino mice weighing between 18 and 22 g. each are used. *L*-dopa, the α - hydrazino - α - substituted - 3,4 - dihydroxyphenylpropionic acid and combinations of the two are administered orally, in solution or suspension in water, and the animals are decapitated 90 minutes later. Brains are removed and pooled in groups of three, three separate pools per drug treatment.

The brains are homogenized with *n*-butanol, 5 ml. per 0.75 g. tissue. The butanol extract is back extracted with 0.1 *N* hydrochloric acid, an aliquot of which is subjected to iodine oxidation for the fluorimetric determination of dopa plus dopamine (Porter, C.C., Totaro, J.A. and Barcin, A., J. Pharmac, Exp. Therap. *150* 17 (1965)).

Control groups of mice are included, and results are expressed as the ratio of total dopa plus dopamine in the brains of drug-treated mice to the total dopa plus dopamine in the brains of untreated controls. The average value for the three trials at each dosage level is given in Table I. In the table, Example 9 is a repeat run as a control for Example 8.

Table I

Ex.	*L*-Dopa Dosage in mg/kg	α-methyl Hydrazine Compound Dosage in mg/kg	Ratio $\frac{\text{Dopa + Dopamine}}{\text{Normal Dopa + Dopamine}}$
1	None	None	1.00
2	240	None	1.77
3	480	None	5.50
4	960	None	7.32
5	20	10 racemate	1.79
6	40	20 racemate	5.73
7	80	40 racemate	13.50
8	40	20 L-form only	6.7
9	40	20 racemate	5.0

As shown by the table, 30 mg. of the combination drug (Example 5) is as effective as 240 mg. of L-dopa by itself (Example 2). Similarly, 60 mg. of the combination drug (Example 6) is as effective as 480 mg. of L-dopa by itself (Example 3). Also as shown by the table, 120 mg. of the combination drug (Example 7) is much more effective than 960 mg. of L-dopa by itself (Example 4). The table also shows the L-form of the hydrazine compound (Example 8) to be more active than the racemate (Example 9).

In order to determine the optimum ratio of L-dopa to the hydrazine compound to be utilized in the compositions, the testing procedure given above is carried out using a constant dosage of 60 mg/kg of body weight. Only the ratio of the two drugs is changed. The results are given in Table II.

The α-methyl hydrazine compound is used in the examples.

TABLE II

Ex.	Ratio L-Dopa / Hydrazine Compound	Ratio Dopa+Dopamine / Normal Dopa+Dopamine
10	8 racemate	2.54
11	6 racemate	2.99
12	4 racemate	3.53
13	2 racemate	4.29
14	1 racemate	3.61
15	0.5 racemate	2.90
16	0.25 racemate	2.28
17	0.17 racemate	1.86
18	0.13 racemate	1.51

As shown by the table, the most effective dosage is obtained when the ratio of the L-dopa to the racemic hydrazine compound is from about 0.2 to about 8 with a preferred ratio being from about 0.5 to about 6. In actuality the optimum ratio of about 2 would be used.

EXAMPLES 19 AND 20

The procedures of Examples 13 and 15 above are repeated using α - hydrazino - 3,4 - dihydroxyphenylpropionic acid in place of the α-methyl hydrazino compound. The results show the desmethyl compound to be from 2 to 3½ times as active as the α-methyl compound.

EXAMPLE 21

In order to again test the effectiveness of *L*-dopa in combination with the α-methyl hydrazine compound (as compared to *L*-dopa alone) the method of Anden and co-workers is used (Anden, N., Dalhstrom, A., Fuxe, K., and Larsson, K. "Acta pharmacol. et Toxicol", vol. 24, p. 263—274 (1966)). *L*-dopa (500 mg/kg) administered intraperitoneally to rats with appropriate unilateral brain lesions causes the rats to circle in the direction of the lesion showing effectiveness of the drug. This effect is believed to result from the *L*-dopa being converted by the body into dopamine which acts upon the corpus strittum of the intact side of the rat. The beneficial effect of *L*-dopa in Parkinsonian patients is also believed to result from the action of dopamine upon the corpus striatum. Lower doses of *L*-dopa (150 mg/kg, intraperitoneally) are ineffective. However, after one hour pretreatment with racemic α - hydrazino - α - methyl - 3,4 - dihydroxyphenylpropionic acid (50 mg/kg, intraperitoneally), a dose of 150 mg/kg of *L*-dopa is now sufficient to again cause circling movements in lesioned rats.

While in the above examples only the combination of the two compounds is shown, it should be noted that the compounds would generally be utilized with other drugs such as tranquillizers, anti-cholinergic agents, muscle relaxants and anti-histamines to alleviate other symptoms of Parkinsonism and like diseases.

WHAT WE CLAIM IS:—

Pharmaceutical compositions comprising *L*-dopa or a pharmaceutically acceptable salt thereof together with an α - hydrazino - α - R - 3,4 - dihydroxyphenylpropionic acid or a pharmaceutically acceptable salt thereof, where R represents a hydrogen atom or a C_{1-4} alkyl radical.

2. A composition as claimed in claim 1 and also containing a pharmaceutical diluent, carrier, coating and/or excipient.

3. A composition as claimed in claim 2 in the form of a pill, tablet or capsule.

4. A composition as claimed in any one of claims 1 to 3 in which the seocnd ingredient is *L* - α - hydrazino - α - methyl - 3,4 - dihydroxy - phenylpropionic acid.

5. A composition as claimed in any one of claims 1 to 3 in which the second ingredient is racemic α - hydrazino - α - methyl - 3,4 - dihydroxyphenylpropionic acid.

6. A composition as claimed in any one of claims 1 to 3 in which the second ingredient is α - hydrazino - 3,4 - dihydroxyphenylpropionic acid.

7. A composition as claimed in any one of claims 1 to 3 in which the second ingredient is racemic α - hydrazino - 3,4 - dihydroxyphenylpropionic acid.

8. A composition as claimed in any one of claims 1 to 7 in which the weight of the *L*-dopa or its salt is from 0.2 to 8 times that of the second mentioned ingredient.

9. A composition as claimed in claim 8 in which the weight of the *L*-dopa or its salt is from 0.5 to 6 times that of the second mentioned ingredient.

10. A composition as claimed in claim 9 in which the weight of the *L*-dopa or its salt is about twice that of the second mentioned ingredient.

11. A composition as claimed in claim 1, substantially as hereinbefore described in the foregoing formulations.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1971.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

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