

1

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TREATMENT OF PARKINSON DISEASE

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14 Claims

ABSTRACT OF THE DISCLOSURE

Pharmaceutical compositions for treating Parkinson disease which contain as the active anti-Parkinsonism ingredient, L-3-(3,4-dihydroxyphenyl)-alanine (L-dopa) or a pharmaceutically acceptable salt thereof in a mixture with L-tryptophan or a pharmaceutically acceptable salt thereof or L-5-hydroxytryptophan or a pharmaceutically acceptable salt thereof, and as an optional ingredient, a peripheral decarboxylase inhibitor are described. The compositions are useful for the treatment of Parkinson's disease with little or none of the side-effects usually associated with the use of L-dopa itself or in combination with a decarboxylase inhibitor.

BACKGROUND OF THE INVENTION

L-dopa alone or in combination with a peripheral decarboxylase inhibitor is used for the treatment of Parkinson's disease and is particularly effective against idiopathic Parkinson's disease. While L-dopa therapy has been of great benefit to many victims of Parkinson's disease, its use has been associated with undesirable side-effects which are mainly of the following three types:

1. Autonomic: Insomnia, fainting fits, cardiovascular disorders, vertigo, vomiting, loss of appetite and constipation.

2. Motoric: In the course of prolonged administration of high doses of L-dopa dyskinesiae of a choreotic or athetoid character occur. Tonic cramps in the lower extremities also hinder active mobility.

3. Psychic: Psychoses consisting of a transit syndrome with limitation of consciousness, delirious confusion, motoric unrest, acoustic and optic hallucinations, delusions, a mood involving anxiety and disorientation regarding time and place are observed. Complete amnesia of this phase occurs once it is brought under control.

While side effects of autonomic and motoric types allow continuation of the L-dopa therapy, it has been, prior to this invention, necessary to discontinue L-dopa therapy when psychotic side effects appeared causing akinesia to progress again. There is thus a need for a therapeutic agent effective against Parkinson's disease which does not cause the undesirable side effects associated with L-dopa.

SUMMARY OF THE INVENTION

The present invention provides methods for treating Parkinson's disease and pharmaceutical compositions useful in such methods.

The invention is carried out by administering orally or parenterally L-dopa or a pharmaceutically acceptable salt thereof in combination with either L-tryptophan or L-5-hydroxytryptophan or a pharmaceutically acceptable salt of either or the combination together with a peripheral decarboxylase inhibitor.

DETAILED DESCRIPTION OF THE INVENTION

It has been found that on oral or parenteral administration to patients having Parkinson's disease, particularly those with idiopathic Parkinson's disease, of a pharmaceutical preparation containing as the active ingredient L-dopa or a pharmaceutically acceptable salt thereof in combina-

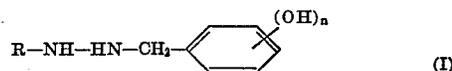
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tion with L-tryptophan or L-5-hydroxytryptophan or a pharmaceutically acceptable salt of either, the typical symptoms of the disease such as rigor, akinesia, and tremor can be significantly improved or abolished without the simultaneous occurrence of undesirable side effects. Furthermore, it has been found that the treatment of the psychotic side effects of L-dopa with L-tryptophan or L-5-hydroxytryptophan or a pharmaceutically acceptable salt of either has considerable practical significance since the L-tryptophan or L-5-hydroxytryptophan or pharmaceutically acceptable salt of either not only causes the psychotic transit phase to disappear, but can be continued in combination with the administration of L-dopa or a pharmaceutically acceptable salt thereof without reappearance of psychotic side effects.

As used herein, the expression "pharmaceutically acceptable salts" means salts with pharmaceutically acceptable acids or bases, e.g., acids such as sulfuric, hydrochloric, nitric, phosphoric acid etc. or bases such as alkali or alkaline earth metal hydroxides, etc. The expression "active ingredient" as used herein means L-dopa or the equivalent amount of a pharmaceutically acceptable salt thereof. The expression "peripheral decarboxylase inhibitor" includes the compounds described herein or the equivalent amount of a pharmaceutically acceptable salt thereof. The expression "tryptophan compound" as used herein means L-tryptophan or L-5-hydroxytryptophan or the equivalent amount of a pharmaceutically acceptable salt of either.

It has been found that the benefits resulting from this invention can be obtained when using a peripheral decarboxylase inhibitor in combination with the active ingredient and the tryptophan compound to treat Parkinsonism. This is advantageous since it permits the utilization of less L-dopa per dosage to achieve the same effect.

Typical suitable peripheral decarboxylase inhibitors which are useful in this invention are those represented by the formula



wherein R is hydrogen, amino-lower alkanoyl or hydroxy-, phenyl- or hydroxyphenylsubstituted amino-lower alkanoyl and n is 2 or 3, and pharmaceutically acceptable salts thereof.

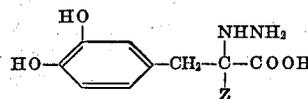
"Lower alkanoyl" as used herein includes branched and straight chain alkanoyl groups, containing from 2 to 7 carbon atoms inclusive.

Compounds within the scope of those represented by Formula I which are preferred for use in this invention are

- N¹-D,L-seryl-N²-(2,3,4-trihydroxybenzyl)-hydrazide;
- N¹-L-seryl-N²-(2,3,4-trihydroxybenzyl)-hydrazide;
- N¹-glycyl-N²-(2,3,4-trihydroxybenzyl)-hydrazide;
- N¹-D,L-tyrosyl-N²-(2,3,4-trihydroxybenzyl)-hydrazide and
- N¹-L-tyrosyl-N²-(2,3,4-trihydroxybenzyl)-hydrazide

and pharmaceutically acceptable salts thereof.

Other typical suitable peripheral decarboxylase inhibitors are, for example, benzylideneacetophenone, L-3-(3,4-dihydroxyphenyl)-2-methylalanine and compounds represented by the formula



wherein Z is hydrogen or lower alkyl.