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3,729,563

METHOD OF TREATING MOVEMENT DISORDERS
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3 Claims

ABSTRACT OF THE DISCLOSURE

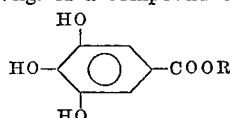
Gallic acid, its salts and its alkyl esters are utilized
in the treatment of involuntary movement disorders. The
compounds can be administered alone or in combination,
as with L-DOPA in the treatment of parkinsonism.

CROSS-REFERENCE

This is a continuation-in-part of Ser. No. 5,940 filed
Jan. 26, 1970.

DETAILED DESCRIPTION

This invention pertains to the treatment of involun-
tary movement disorders such as parkinsonism, Hunting-
ton's chorea, hyperkinesia, spasmodic torticollis and the
like. Treatment of such disorders is effected through the
administration of a daily dose of from about 5 mg./kg.
to about 25 mg./kg. of a compound of the formula:



wherein R is hydrogen or alkyl or from 1 to 9 carbon
atoms, or, when R is hydrogen, a pharmaceutically ac-
ceptable nontoxic alkali metal, alkaline earth metal or
organic amine salt thereof, i.e. a salt of gallic acid.

Certain of these derivatives are known to have ther-
apeutic activity. For example, Sakurai et al., J. Pharm.
Soc. Japan, 69, 434 (1949) describe some anthelmintic
activity for several alkyl gallates. U.S. Pat. No. 3,462,534
describes psychotherapeutic activity, specifically anti-
depressant properties, for alkyl gallates and gallacetol.

In contrast to the latter use which involves exclusively
mental disorders, the present invention is based on the
finding that gallic acid, its salts and esters reduce or
alleviate the physical body movements associated with a
broad group of conditions generally referred to by the
art as involuntary movement disorders. These include the
akinesia, rigidity, tremors associated with parkinsonism,
the dystonic neck movements associated with spasmodic
torticollis, the choreiform movements encountered in
Huntington's chorea and a variety of movement disor-
ders resulting from extrapyramidal dysfunction.

Moreover, in contrast to the use of certain alkyl gal-
lates as anthelmintics, these compounds to date have ex-
hibited no side effects when administered according to
the described method of utilizing the present invention.

The activity of these compounds on involuntary move-

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ment disorders can be conveniently observed in labo-
ratory models utilizing, for example, monkeys with mes-
encephalic lesions. In this method, described by Gold-
stein et al., Proc. Nat. Acad. Science, 63, No. 4, 1113
(1969) unilateral radio frequency lesions are induced in
the animal which then develops hypokinesia almost im-
mediately and a resting tremor within a week, a syn-
drome comparable to the neuropathological profile en-
countered in human parkinsonism. After administration
of a dose of 50 mg./kg. of butyl gallate, the tremor
diminishes or completely disappears for a period of one
to two hours.

Similar responses can be observed in actual clinical
cases. Thus a dose of 250 mg. t.i.d. to a 28 year old
patient suffering from classical Huntington's chorea re-
sulted in a remarkable diminishment of the choreiform
movements. In a second patient, a 43 year old female
with a six year progressive history of chorea and a
family background of Huntington's chorea, choreiform
movements ceased and remained absent upon treatment
with butyl gallate. A third patient with spasmodic torti-
collis, when placed on 250 mg. t.i.d. had almost complete
cessation of dystonic neck movements.

The method of treating involuntary movement dis-
orders with gallic acid, its salts and its esters can also
be practiced in conjunction with other therapy. Most
importantly, it has been found that gallic acid, its salts
and its esters potentiate the action of L-DOPA [L-3-(3,4-
dihydroxyphenyl)alanine] in the treatment of parkin-
sonism. L-DOPA is known to be useful in this regard
but its use is limited by the high doses required and the
resultant side effects, particularly choreiform move-
ments, which develop in patients on long term therapy.

The value of the utilization of these compounds in
conjunction with L-DOPA therapy can be observed in
laboratory models, as well as in man. For example, in a
monkey having mesencephalic lesions, doses of L-DOPA
up to 25 mg./kg. produced no change in the tremor. At
half this dose of L-DOPA however, 12.5 mg./kg., when
administered with either 10 or 15 mg./kg. of butyl gal-
late, the tremor diminished for 40 minutes. When 12.5
mg./kg. of L-DOPA was administered with 20 mg./kg.
of butyl gallate, the tremor ceased for from 40 to 60
minutes. In a second monkey, while 15 mg./kg. of L-
DOPA had no effect, 25 mg./kg. of L-DOPA effected a
cessation of tremor for 30 minutes and a diminished
tremor for 45 minutes. However when 15 mg./kg. of
butyl gallate were administered, substantially the same
effect was obtained with only 15 mg./kg. of L-DOPA as
observed for 25 mg./kg. of L-DOPA alone, namely a
diminished tremor for 40 minutes and a cessation of
tremor for 20 to 30 minutes.

In actual clinical tests, these compounds have been
shown to be effective in combatting the dose-related toxic
effects of L-DOPA therapy. In nine patients, for example,
treated with a daily dose of 750 mg. of butyl gallate, not
only was there a significant reduction in the dose of L-
DOPA required, but also a remarkable decrease in un-
wanted side-effects, as shown in Table I.

TABLE I

Patient.....	L-DOPA										L-DOPA and butyl gallate									
	A	B	C	D	E	F	G	H	I	J	A	B	C	D	E	F	G	H	I	J
Dose L-DOPA (grams).....	1.5	2.5	5	5	6	7	5	6	4	6	1.0	2.0	2.0	2.0	5	6	3	4	4	5
Abnormal.....	1	0	1	3	1	0	3	2	2	1	0	0	0	0	0	0	1	0	0	0
Nausea and vomiting.....	1	4	1	1	0	1	2	1	0	1	0	0	0	0	0	0	0	0	0	0
Rigidity.....	1	3	1	3	3	2	3	3	2	3	0	0	0	1	0	1	1	1	1	1
Tremor.....	0	3	0	2	3	1	2	2	2	1	0	0	0	1	1	0	1	0	1	0
Bradykinesia.....	1	3	0	1	2	2	1	3	2	2	1	1	0	1	1	1	0	1	1	1
Nervousness.....	2	0	0	3	0	0	1	0	1	1	0	0	0	1	0	0	1	0	1	1
Postural hypertension.....	1	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0
Dystonia.....	1	2	0	2	1	2	1	2	2	1	0	1	0	1	0	1	1	1	1	0

NOTE.—0=no observable abnormality; 1=minimal abnormality; 2=minimal to moderate abnormality; 3=moderate to severe abnormality; 4= maximal abnormality.

Gallic acid, a salt thereof or an ester thereof is preferably administered orally as a treatment for involuntary movement disorders. This can be accomplished through the use of any of the usual pharmaceutical forms, including solid and liquid unit oral dosage forms such as tablets, capsules, powders, suspensions, solutions, syrups and the like, including sustained release preparations. The term unit dosage form as used in this specification and the claims refer to physically discrete units to be administered in single or multiple dosage to humans, each unit containing a predetermined quantity of active materials in association with the required diluent, carrier or vehicle. The quantity of active material is that calculated to produce the desired therapeutic effect upon administration of one or more of such units in a single or multiple dose regimen.

Powders are prepared by comminuting gallic acid, a salt thereof or an ester thereof to a suitably fine size and mixing with a similarly comminuted diluent pharmaceutical carrier such as an edible carbohydrate material as for example, starch. Sweetening, flavoring, preservative, dispersing and coloring agents can also be present.

Capsules are made by preparing a powder mixture as described above and filling formed gelatin sheaths. A lubricant such as talc, magnesium stearate and calcium stearate can be added to the powder mixture as an adjuvant before the filling operation; a glidant such as colloidal silica may be added to improve flow properties; a disintegrating or solubilizing agent may be added to improve the availability of the medicament when the capsule is ingested.

Tablets are made by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base such as starch, sucrose, kaolin, dicalcium phosphate and the like. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acacia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the resulting imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets, the medicaments can also be combined with free flowing inert carriers and compressed into tablets directly without going through the granulating or slugging steps. A protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as syrups and elixirs can be prepared in unit dosage form so that a given quantity, e.g., a teaspoonful, contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous sucrose solution while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the medicament in a non-toxic vehicle in which it is insoluble.

When utilized alone, gallic acid, a salt thereof or an ester thereof is generally administered in a single or multiple dose regimen so that the patient receives a daily dose of from about 5 mg./kg. to about 25 mg./kg. This range is however merely a guideline for in all cases the actual dose must be adjusted to the age, weight and condition of the patient and most importantly, titrated to the response observed. Thus, for example, for a human of average weight of 70 kg., if an initial daily dose of about 500 mg. does not produce a satisfactory response, the dose is carefully increased to a point in which such a response is observed.

When utilized in conjunction with L-DOPA therapy, it is of course possible to administer the two therapeutics mixed as in a single dosage unit form. It is generally desirable however to first stabilize the dose of L-DOPA and then begin the administration of the gallic acid, salt or ester. In this fashion, the required dose of L-DOPA, which will vary from patient to patient, can be significantly reduced with, as described above, a significant reduction of elimination of side effects.

In the practice of this method, one can employ gallic acid, a salt thereof or an alkyl ester thereof. The salts are those derived from alkali metals, alkaline earth metals or organic amines, such as the sodium, potassium, calcium and those of ammonia, ethylamine, triethylamine, ethanolamine, diethylaminoethanol, ethylenediamine, piperidine, morpholine, 2-(piperidino)-ethanol, benzylamine, procaine and the like. Esters are those derived from gallic acid and straight or branched chain alcohols having from 1 to 9 carbon atoms, such as methyl gallate, ethyl gallate, n-propyl gallate, isopropyl gallate, n-butyl gallate, pentyl gallate, hexyl gallate, octyl gallate, nonyl gallate and the like. The preferred form of gallic acid for the practice of the present invention is the n-propyl and n-butyl esters.

The following examples will serve to further typify the nature of the present invention but should not be construed as a limitation thereof.

EXAMPLE 1

Ingredient:	Quantity/capsule, mg.
Butyl gallate	250
Lactose	146
Corn starch	91.5
Cab-O-Sil M5	3.66
Stearic acid	2.44

The lactose, corn starch and Cab-O-Sil are blended and granulated with an alcoholic solution of the stearic acid. This granulate is blended with the butyl gallate and the resulting blend is encapsulated in #0 capsules.

EXAMPLE 2

Ingredient:	Quantity/capsule, mg.
Butyl gallate	80
Corn starch	80

The two ingredients are thoroughly blended and encapsulated in #4 capsules.

EXAMPLE 3

Ingredient:	Quantity/capsule, mg.
L-DOPA	100
Butyl gallate	200
Corn starch	500

The foregoing ingredients are mixed and introduced into a two-piece #1 hard gelatin capsule.

EXAMPLE 4

Ingredient:	Quantity/capsule, mg.
L-DOPA	100
Butyl gallate	300
Corn starch	150
Lactose	200
Cab-O-Sil M5	4
Gelatin	5
Magnesium stearate	1

The L-DOPA, butyl gallate, corn starch and lactose are thoroughly blended and granulated with a 10% aqueous solution of gelatin. The wet granulate is dried, screened and combined with the Cab-O-Sil and magnesium stearate. This mixture is pressed into tablets suitable for oral administration of 100 mg. of L-DOPA and 300 mg. of butyl gallate. The tablets may be scored to permit the administration of fractional doses.

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EXAMPLE 5

Ingredient:	Quantity/capsule, mg.
L-DOPA	500
Propyl gallate	300
Corn starch	200
Lactose	200
Cab-O-Sil M5	400
Gelatin	5
Magnesium stearate	1

The foregoing ingredients are combined in accordance with the procedure described in Example 4 and pressed into tablets suitable for oral administration of 50 mg. of L-DOPA and 300 mg. of propyl gallate.

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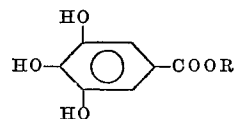
EXAMPLE 6

Ingredient:	Quantity/tablet, mg.
L-DOPA	100
Pentyl gallate	250
Lactose	100
Corn starch	100
Soluble starch	15
Magnesium stearate	5

The first four ingredients are thoroughly mixed and granulated with a 10% aqueous solution of soluble starch. This granulate is dried, mixed with magnesium stearate and pressed into tablet cores which are coated with sugar.

What is claimed is:

1. The method of treating involuntary movement disorders which comprises orally administering to a human suffering from such disorder in a single or multiple dosage regimen, a daily dose of from about 5 mg./kg. to about 25 mg./kg. of a compound of the formula:



wherein R is hydrogen or alkyl of from 1 to 9 carbon atoms, or when R is hydrogen, a pharmaceutically acceptable non-toxic alkali metal, alkaline earth metal or organic amine salt thereof.

2. The method of claim 1 wherein R is propyl.

3. The method of claim 1 wherein R is butyl.

References Cited

UNITED STATES PATENTS

3,462,534 8/1969 Greengard et al. 424—308

STANLEY J. FRIEDMAN, Primary Examiner

U.S. Cl. X.R.

424—267, 308, 316, 317, 319