REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

FORM P.8
(to be lodged in duplicate)

A&A Ref: **142492**

PUBLICATION PARTICULARS AND ABSTRACT
(Section 32(3)(a) - Regulations 22(1)(g) and 31)

21	01	PATENT APPLICATION NO	22	LODGING DATE	43	ACCEPTANCE DATE
		2000/5758		**17 October 2000**		17.1.2002

51	INTERNATIONAL CLASSIFICATION	NOT FOR PUBLICATION
	A61K	CLASSIFIED BY: **ISA**

71	FULL NAME(S) OF APPLICANT(S)

Aventis Pharma S.A.

72	FULL NAME(S) OF INVENTOR(S)

BLANCHARD-BREGEON, Véronique
IMPERATO, Assunta
MOUSSAOUI, Saliha
OBINU, Marie-Carmen
REIBAUD, Michel

EARLIEST PRIORITY CLAIMED	COUNTRY		NUMBER		DATE	
	33	**FR**	31	**98/05,153**	32	**24 April 1998**

NOTE: The country must be indicated by its International Abbreviation - see schedule 4 of the Regulations

54	TITLE OF INVENTION

Riluzole and levodopa combinations for treating Parkinson's disease

57	ABSTRACT (NOT MORE THAN 150 WORDS)

NUMBER OF SHEETS	45

The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.
~~The figure of the drawing to which the abstract refers is attached.~~

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(57) Abstract

The invention concerns a combination of levodopa and riluzole or a pharmaceutically acceptable salt of said compound and the use of said combination for treating Parkinson disease.

(57) Abrégé

Association de la lévodopa et du riluzole ou d'un sel pharmaceutiquement acceptable de ce composé et utilisation de cette association pour le traitement de la maladie de Parkinson.

COMBINATIONS OF RILUZOLE AND LEVODOPA FOR THE TREATMENT OF PARKINSON'S DISEASE

The present invention relates to a combination of L-DOPA and riluzole or a pharmaceutically acceptable salt of this compound and the use of this combination for the treatment of Parkinson's disease.

Parkinson's disease is connected with destruction of the locus niger (substantia nigra) which results in degeneration of the dopaminergic neurons of the nigrostriatial tract and therefore a massive decrease in the levels of dopamine in the striatum. To compensate the depletion of dopamine which is consequent to the degeneration of dopaminergic neurons of the nigrostriatial tract in parkinsonian patients, L-DOPA, (3-(3,4-dihydroxyphenyl)-L-alanine) or levodopa, which is converted into dopamine by dopa decarboxylase, is used as a symptomatic treatment of Parkinson's disease. After oral administration, the L-DOPA is massively decarboxylated at the peripheral level into dopamine, which does not cross the blood-brain barrier; this is why it is generally administered in combination with a decarboxylase inhibitor such as benserazide or carbidopa. These decarboxylase inhibitors actually allow the dose of L-DOPA to be reduced by approximately 5 (Rondot P. et al.,

Pharmacologie Clinique, bases de la thérapeutique [Clinical Pharmacology, Therapeutic bases], published by J.-P. Giroud, G. Mathé and G. Meyniel, 2nd edition, Expansion Scientifique Française, 1988, page 1127).

In patients suffering from Parkinson's disease, L-DOPA reduces the severity of symptoms such as bradykinesia (poverty of movements), muscular rigidity and trembling. However, chronic treatment with L-DOPA leads, in 30% to 80% of parkinsonian patients, to secondary effects and, in particular, to dyskinesias (J.G. Nutt, Neurology, 40, 340-345, 1990).

These dyskinesias are also reproduced by a chronic treatment with L-DOPA in marmosets rendered parkinsonian following an injection of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a toxin which destroys the dopaminergic neurons of the nigrostriatial path (R.K.B. Pearce et al., Movement Disorders, vol. 10, No. 6, 731-740, 1995; A. Ekesbo et al., Neuroreport, 8, 2567-2570, 1997).

Riluzole (2-amino-6-trifluoromethoxybenzothiazole) is marketed for the treatment of amyotrophic lateral sclerosis. It is also known for its neuroprotective effect in the treatment of Parkinson's disease (WO94/15601).

It has now been found that the combination of riluzole or one of its pharmaceutically acceptable salts and of L-DOPA improves the locomotory activity of

parkinsonian marmosets and, in addition, prevents the dyskinesias induced by L-DOPA.

The activity of the riluzole and L-DOPA combination is determined according to the following protocol: 6 adult marmosets (*Callithrix jacchus*, Harlan UK) aged 25 months and weighing between 300 and 350 g are accommodated in stainless steel cages (50 cm in width × 20 cm in depth × 23 cm in height) with wire netting doors, these cages being connected to smaller cages (28 × 20 × 23 cm) in which the marmosets can sleep. The animals are accommodated in a controlled environment: temperature of 24 ± 2°C, humidity of 55%, with a day-night cycle of 12 hours. The marmosets have free access to water and have available each day 35 g of food rich in carbohydrates, proteins and vitamins mixed with water, milk and sugar and also fresh fruit.

All the animals receive 3 injections of 2 mg/kg of MPTP by the subcutaneous route, on days 1, 7 and 32. On day 32, the animals are divided into 2 groups. Group 1 (control group) receives 2 oral administrations of 10% sucrose and group 2 (treated group) receives 2 oral administrations of riluzole (10 mg/kg) suspended in 0.5% methylcellulose, each day to day 104. On day 47, the two groups of animals receive an oral administration of L-DOPA (Modopar® 125 dispersible Roche (L-DOPA (25 mg) + benserazide (6.25 mg)). On day 48, they receive 2 oral

administrations and from day 49 to day 104 they receive 3 oral administrations of L-DOPA each day.

LOCOMOTORY ACTIVITY

The locomotory activity is determined by placing the animals in test cages (50 cm × 83 cm × 77 cm) which are equipped with 3 perches onto which the animals can jump as well as a Plexiglas door in front of which is placed a camera. This camera is connected to an image analyser system (Vigie Primates, View Point^{R}, which is capable of calculating the quantity of movements of 8 marmosets, simultaneously and independently for the duration of the test. The principle of this system is to quantify the movements of the animals in the cage in a determined time window (5s). The image is digitalized with a 800 × 600 definition with 256 levels of grey and the changes in pixels from one image to another are counted. This allows the locomotory activity to be classified into small, medium or large movements. Each class of movements is analysed every 10 minutes for a period of one hour. The locomotory activity of the animals is measured during the exploration phase, that is to say immediately after they are placed in the test cage.

DYSKINESIC SCORE

The dyskinesic score is determined according to a number of parameters and each with a different degree of intensity:

PARAMETERS	DYSKINESIC SCORE				
	0	1	2	3	4
Perch test	normal	slight	moderate	marked	severe
Climbing test	normal	slight	moderate	marked	severe
Paws (front, rear)	normal amplitude movement	small amplitude movement	large amplitude movement		
Posture (back)	normal	moderate curvature	marked curvature		
Jump	normal	uncoordinated			
Motility	normal	hyperactive			
Chorea	absent	present			
Dystonia	absent	present			
Expression	normal	repetitive			
Stereotyping	absent	present			
Orolingual movements	absent	present			
Vocalization	normal	for watching	for communicating	absent	

This score is measured on days 57, 60, 67 and 104.

The evaluation is made 30 min or 2 h after the first daily injection of L-DOPA (4 h after the riluzole or sucrose solution).

The results are reported in Tables 1 to 5 and Figures 1, 2A, 2B and 3:

Table 1 and Figure 1 show that the acute administration of L-DOPA at a dose of 25 mg/kg, 15 days after the 3rd injection of MPTP, increases the locomotory activity by decreasing the small movements and increasing the large movements. These results therefore demonstrate that the acute administration of L-DOPA improves the locomotory activity.

Tables 2, 3 and 4 and Figures 2A and 2B show that L-DOPA, after a repeated treatment of 10 days and of 20 days, does not have or has little beneficial effect on the locomotory activity of parkinsonian marmosets.

Tables 2, 3 and 4 and Figures 2A and 2B also show that riluzole at a dose of 10 mg/kg, by the oral route, twice per day for 72 days is capable of improving the locomotory activity and this is observed equally well after 10 days as after 20 days of treatment with L-DOPA.

Table 5 and Figure 3 show that the repeated administrations of L-DOPA (25 mg/kg, by the oral route, 3 times per day) produce dyskinesias observed on

days 57, 60, 67 and 104, with a maximum effect on day 104.

Table 5 and Figure 3 also show that riluzole (at a dose of 10 mg/kg, by the oral route, twice per day) reduces the dyskinesias induced by L-DOPA and this is observed from day 57 to day 104.

TABLE 1: Effect of L-DOPA on the locomotory activity of parkinsonian marmosets

		Group 1 (sucrose)								
	Marmoset No.	1	2	3	1	2	3	1	2	3
Class of move-ments	Time interval of measure-ments	*before MPTP*			**before the 1st administration of L-DOPA**			***30 min after the 1st administration of L-DOPA***		
Small move-ments	1 - 10	290	15	10	90	175	50	5	305	20
	11 - 20	25	0	40	135	35	115	25	35	10
	21 - 30	215	20	5	85	95	485	5	20	0
	31 - 40	40	0	0	45	0	455	15	60	55
	41 - 50	60	35	0	45	5	560	45	15	10
	51 - 60	120	5	5	115	50	545	30	35	35
	Average ± S.E.M.	**49 ± 19**			**171 ± 46 ***			**40 ± 16 +**		
Medium move-ments	1 - 10	140	185	60	255	285	375	235	270	250
	11 - 20	165	75	60	260	270	475	190	290	240
	21 - 30	200	245	165	275	175	75	225	205	110
	31 - 40	270	115	15	310	130	130	355	205	255
	41 - 50	270	265	125	280	95	40	260	165	165
	51 - 60	280	150	155	255	110	55	240	200	215
	Average ± S.E.M.	**163 ± 19**			**214 ± 28**			**226 ± 13 ***		
Large move-ments	1 - 10	175	405	535	260	145	180	365	30	335
	11 - 20	410	525	500	205	295	10	385	275	350
	21 - 30	185	335	430	240	330	40	370	375	490
	31 - 40	290	485	585	245	470	15	230	335	290
	41 - 50	270	300	475	275	500	0	295	420	425
	51 - 60	200	445	440	230	440	0	330	365	350
	Average ± S.E.M.	**388 ± 30**			**216 ± 38 ****			**334 ± 23 +**		

Significant difference *versus* the value before MPTP: *P≤0.01 **P≤0.001 (Student's test);

significant difference *versus* the value before L-DOPA:

$^{+}P \leq 0.01$ (Student's test)

TABLE 2: Effect of riluzole on the locomotory activity in dyskinesic marmosets

Before MPTP

Class of movements	Time interval of measurement (min)	**Time passed in moving**					
		Group 1			***Group 2***		
	Marmoset No.	1	2	3	4	5	6
Small movements	1 - 10	290	15	10	35	10	5
	11 - 20	25	0	40	25	0	0
	21 - 30	215	20	5	70	25	40
	31 - 40	40	0	0	45	0	5
	41 - 50	60	35	0	105	0	10
	51 - 60	120	5	5	25	55	5
	Average ± S.E.M.	**37 ± 10**					
Medium movements	1 - 10	140	185	60	50	60	35
	11 - 20	165	75	60	45	85	35
	21 - 30	200	245	165	105	95	150
	31 - 40	270	115	15	80	60	80
	41 - 50	270	265	125	160	60	145
	51 - 60	280	150	155	245	215	95
	Average ± S.E.M.	**132 ± 13**					
Large movements	1 - 10	175	405	535	520	535	565
	11 - 20	410	525	500	530	515	565
	21 - 30	185	335	430	425	480	410
	31 - 40	290	485	585	475	540	515
	41 - 50	270	300	475	335	540	445
	51 - 60	200	445	440	330	330	500
	Average ± S.E.M.	**432 ± 19**					

TABLE 3: Effect of riluzole on the locomotory activity in dyskinesic marmosets

10 days after L-DOPA

Class of movements	Time interval of measurements (min)	**Time passed in moving** (evaluated 30 min after the 1st daily administration of L-DOPA)					
		Group 1 (sucrose)			***Group 2 riluzole (2 × 10 mg/kg)***		
	Marmoset No.	1	2	3	4	5	6
Small movements	1 - 10	5	510	375	5	5	5
	11 - 20	0	500	295	0	5	45
	21 - 30	0	560	365	0	125	50
	31 - 40	10	485	370	0	145	25
	41 - 50	10	465	230	30	195	40
	51 - 60	205	225	240	35	210	100
	Average ± S.E.M.	**269 ± 47*** **			**57 ± 16^{+++}**		
Medium movements	1 - 10	115	55	190	40	105	80
	11 - 20	70	70	295	35	140	185
	21 - 30	100	40	235	60	120	115
	31 - 40	155	35	175	140	215	190
	41 - 50	155	115	370	155	205	175
	51 - 60	165	305	235	135	125	190
	Average ± S.E.M.	**160 ± 23**			**134 ± 13**		
Large movements	1 - 10	485	40	40	560	495	520
	11 - 20	530	30	10	565	455	370
	21 - 30	500	0	0	540	355	435
	31 - 40	435	80	55	460	240	385
	41 - 50	435	20	0	415	200	385
	51 - 60	230	70	125	430	265	310
	Average ± S.E.M.	**171 ± 48*** **			**410 ± 25^{+++}**		

Significant difference *versus* value before

5 MPTP: ***P≤0.0001 (Student's test)

TABLE 4: Effect of riluzole on the locomotory activity in dyskinesic marmosets

20 days after L-DOPA

Class of movements	Time interval of measurements (min)	**Time passed in moving** (evaluated 30 min after the 1st daily administration of L-DOPA)					
		Group 1 (sucrose)			***Group 2 riluzole (2 × 10 mg/kg)***		
	Marmoset No.	1	2	3	4	5	6
Small movements	1 - 10	105	5	45	5	130	35
	11 - 20	40	0	45	5	395	5
	21 - 30	120	10	105	0	170	20
	31 - 40	125	0	65	5	275	15
	41 - 50	130	15	265	0	135	15
	51 - 60	185	0	230	0	345	15
	Average ± S.E.M.	**83 ± 19**			**87 ± 30**		
Medium movements	1 - 10	360	0	475	155	140	80
	11 - 20	260	20	475	255	160	105
	21 - 30	225	35	400	175	250	100
	31 - 40	325	55	300	180	175	80
	41 - 50	265	95	280	95	220	125
	51 - 60	315	30	315	90	180	105
	Average ± S.E.M.	**235 ± 37****			**148 ± 13^{+}**		
Large movements	1 - 10	140	600	85	445	335	490
	11 - 20	300	580	80	340	45	490
	21 - 30	255	555	95	425	180	480
	31 - 40	150	545	235	415	150	505
	41 - 50	205	490	55	505	245	460
	51 - 60	100	570	55	510	75	480
	Average ± S.E.M.	**283 ± 50****			**365 ± 37**		

Significant difference *versus* value before

5 MPTP: **P≤0.001 (Student's test)

Significant difference *versus* control value:

$^{+++}P \leq 0.0001$ (Student's test).

TABLE 5: Effect of riluzole on dyskinesic marmosets

Day after the 1st injection of MPTP	**Total dyskinesic score** (evaluated 30 min after the 1st daily administration of L-DOPA)							
	Group 1: controls (sucrose)				***Group 2: riluzole (2 × 10 mg/kg p.o.)***			
	Individual values			Average	Individual values			Average
Marmoset No.	1	2	3	± S.E.M.	4	5	6	± S.E.M.
57	4	11	5	6.7 ± 2.1	3	3	1	2.3 ± 0.7
60	4	11	12	9.0 ± 2.5	3	3	1	2.3 ± 0.7^{+}
67	4	14	12	10 ± 3.0	3	3	1	2.3 ± 0.7^{+}
104	4	17	2	11 ± 3.8	1	3	3	2.3 ± 0.7^{+}

Day after the 1st injection of MPTP	**Total dyskinesic score** (evaluated 2 h after the 1st daily administration of L-DOPA)							
	Group 1: controls (sucrose)				***Group 2: riluzole (2 × 10 mg/kg p.o.)***			
	Individual values			Average	Individual values			Average
Marmoset No.	1	2	3	± S.E.M.	4	5	6	± S.E.M.
57	3	10	5	6.0 ± 2.1	3	3	0	2.0 ± 1.0
60	4	9	12	8.3 ± 2.3	2	3	1	2.0 ± 0.6^{+}
67	4	13	13	10 ± 3.0	3	3	1	2.3 ± 0.7^{+}
104	5	17	12	11 ± 3.0	1	3	3	2.3 ± 0.7^{+}

Significant intergoup difference *versus* value of like control: $^{+}P \leq 0.05$ (Student's test).

In conclusion, these results demonstrate that, on the one hand, L-DOPA after an acute administration increased the locomotory activity by decreasing the small displacements, and by increasing

the large displacements of the parkinsonian marmosets. On the contrary, L-DOPA, after a repeated treatment, not only produced little or no effect on locomotory activity, but in addition produced secondary effects, dyskinesias in parkinsonian marmosets.

On the other hand, these results show that in parkinsonian marmosets, riluzole improves the locomotory activity and prevents the development of dyskinesias induced by chronic treatment with L-DOPA. The combination riluzole and L-DOPA thus has a double beneficial effects in parkinsonian marmosets, by improving the locomotory activity and by decreasing the secondary effects, the dyskinesias, induced by L-DOPA.

Riluzole or one of its pharmaceutically acceptable salts and L-DOPA can be administered in the form of a combination and optionally combined with any other pharmaceutically compatible product, which can be inert or physiologically active.

Riluzole or one of its pharmaceutically acceptable salts and L-DOPA can likewise be administered separately or in a manner which is spread out in time so as to obtain the maximum efficacy.

Thus in the sense of the present invention, the combinations are not uniquely limited to those which are obtained by physical mixing of the constituents but also to those which allow a separate

Significant difference *versus* control value:

$^{+}P \leq 0.01$ (Student's test).

administration which can be simultaneous or spread out in time.

It is likewise possible to add to this combination a decarboxylase inhibitor such as benserazide or carbidopa.

In the combinations according to the invention, 10 to 400 parts by weight of riluzole are generally used per 100 to 6000 parts by weight of L-DOPA and, preferably, 200 to 4000 parts by weight of L-DOPA or the equivalent of this quantity when the L-DOPA is mixed with a decarboxylase inhibitor. Generally, the quantity of L-DOPA when this is mixed with an L-DOPA inhibitor is 50 to 1500 parts by weight.

When the decarboxylase inhibitor is benserazide, a quantity by weight thereof of 2 to 6 times less than the quantity of L-DOPA and more particularly 4 times less than the quantity of L-DOPA is generally used.

When the decarboxylase inhibitor is carbidopa, a quantity by weight thereof of 2 to 15 times less than the quantity of L-DOPA and more particularly 4 to 10 times less than the quantity of L-DOPA is generally used.

The combination can be employed by the oral, parenteral or rectal route.

Pharmaceutically acceptable salts of riluzole which can be especially mentioned are the addition

salts with mineral acids such as the hydrochlorides, sulphates, nitrates, phosphates or organic acids such as the acetates, propionates, succinates, oxalates, benzoates, fumarates, maleates, methanesulphonates, isethionates, theophilline acetates, salicylates, phenolphthaleinates, methylene-bis-ß-oxynaphthoates or of substitution derivatives of these derivatives.

Solid compositions for oral administration which can be used are compressed tablets, pills, powders (gelatin capsules, cachets) or granules. In these compositions, the active principles are mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under a current of argon. These compositions can likewise comprise substances other than the diluents, for example one or more lubricants such as magnesium stearate or talc, a colourant, a coating (coated tablets) or a lacquer.

Liquid compositions for oral administration which can be used are solutions, suspensions, emulsions, syrups and pharmaceutically acceptable elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or paraffin oil. These compositions can comprise substances other than the diluents, for example wetting, sweetening, thickening, aromatizing or stabilizing products.

The sterile compositions for parenteral administration can preferably be aqueous or non-aqueous

solutions, suspensions or emulsions. As a solvent or vehicle, it is possible to employ water, propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, injectable organic esters, for example ethyl oleate or other suitable organic solvents. These compositions can likewise contain adjuvants, in particular wetting, isotonicizing, emulsifying, dispersing and stabilizing agents. Sterilization can take place in several ways, for example by sterile filtration, by incorporating sterilizing agents in the composition, by irradiation or by heating. They can likewise be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories or rectal capsules which contain, apart from the active product, excipients such as cocoa butter, semisynthetic glycerides or polyethylene glycols.

The present invention likewise relates to the method of treatment of parkinsonian patients which consists in administering to the patient a L-DOPA and riluzole combination or one of its pharmaceutically acceptable salts and optionally a decarboxylase inhibitor either simultaneously or separately or in a manner which is spread out in time.

The doses depend on the effect sought, on the duration of treatment and on the route of administration used; they are generally from 10 to 400 mg per day by the oral route for an adult with unit doses ranging from 10 to 200 mg of riluzole and from 100 to 6000 mg and preferably 200 to 4000 mg per day by the oral route for an adult with unit doses of 100 to 250 mg of L-DOPA or the equivalent of this dose when the L-DOPA is administered with a decarboxylase inhibitor. Thus when the L-DOPA is administered with a decarboxylase inhibitor the dose of L-DOPA is generally from 50 to 1500 mg per day by the oral route.

When the decarboxylase inhibitor is benserazide, it is preferable to administer per day, by the oral route, for an adult, 10 to 400 mg of riluzole, 50 to 1500 mg of L-DOPA and a quantity of benserazide by weight which is 2 to 6 times less and particularly 4 times less than the quantity by weight of L-DOPA.

When the decarboxylase inhibitor is carbidopa, it is preferable to administer per day, by the oral route, for an adult, 10 and 400 mg of riluzole, 50 to 1500 mg of L-DOPA and a quantity of carbidopa by weight which is 2 to 15 times less and particularly 4 to 10 times less than the quantity by weight of L-DOPA.

Generally speaking, the physician will determine the appropriate dosage as a function of the

age, the weight and all of the other factors peculiar to the subject to be treated.

AMENDED CLAIMS

[received by the international office on 9 August 1999 (09.08.1999); Claim 11 added; other claims unchanged (1 page)]

1. Combinations of levodopa and riluzole or a pharmaceutically acceptable salt of the latter.

2. Combinations according to Claim 1 also comprising a decarboxylase inhibitor.

3. Combinations according to Claim 3 in which the decarboxylase inhibitor is benserazide or carbidopa.

4. Combinations according to Claim 1 in which 10 to 400 parts by weight of riluzole are used per 100 to 6000 parts by weight of levodopa.

5. Combinations according to Claim 1 in which 10 to 400 parts by weight of riluzole are used per 200 to 4000 parts by weight of levodopa.

6. Combinations according to Claim 2 in which 10 to 400 parts by weight of riluzole and 50 to 1500 parts by weight of levodopa are used as a mixture with a decarboxylase inhibitor.

7. Combinations according to Claim 6 in which benserazide is used as a decarboxylase inhibitor.

8. Combinations according to Claim 6 in which carbidopa is used as a decarboxylase inhibitor.

9. Combinations according to one of Claims 1 to 8 as a combined preparation for simultaneous use, separate use or use which is spread out in time.

10. Combinations according to one of Claims 1 to 9 for the treatment of Parkinson's disease.

11. Use of riluzole for the preparation of a medicament useful in the prevention and treatment of dyskinesias induced by levodopa.

12. A substance or composition for use in a method for the prevention and treatment of dyskinesias induced by levodopa, said substance or composition comprising riluzole, and said method comprising administering said substance or composition.

13. A combination according to claim 1, substantially as herein described and illustrated.

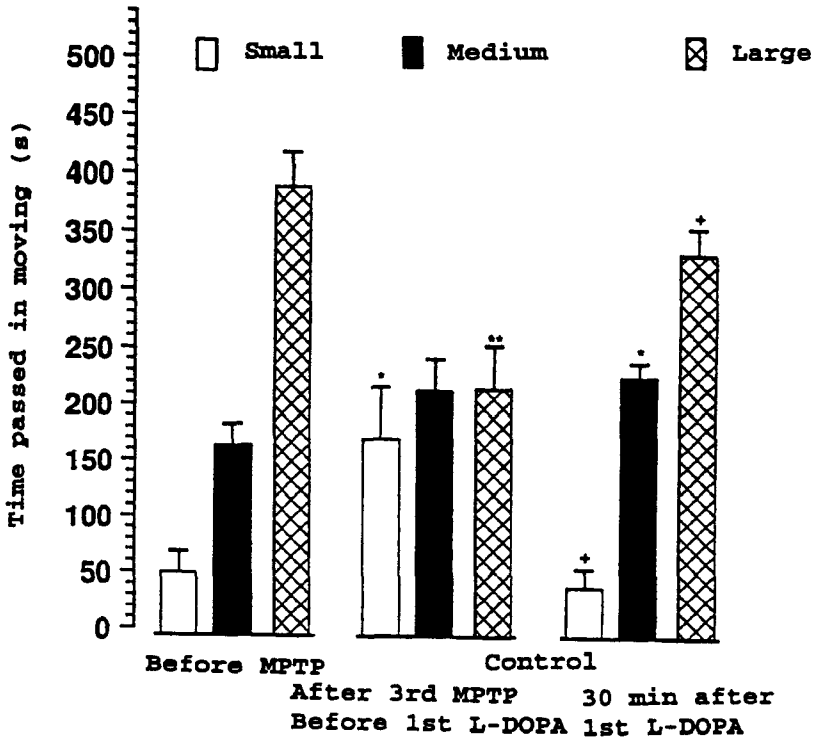
14. Use according to claim 11, substantially as herein described and illustrated.

15. A substance or composition for use in a method of treatment according to claim 12, substantially as herein described and illustrated.

16. A new combination of levodopa and riluzole, new use of riluzole, or a substance or composition for a new use in a method of treatment, substantially as herein described.

Figure 1

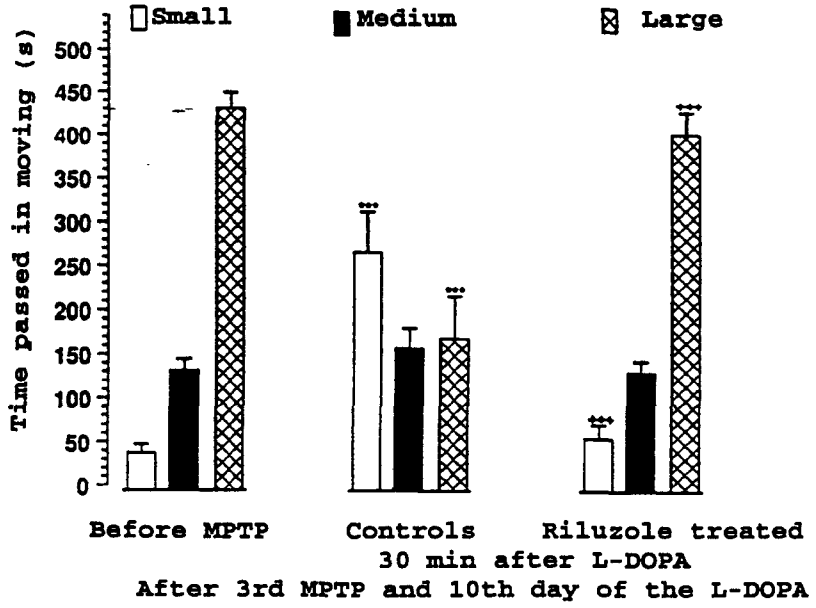
Effect of L-DOPA on locomotory activity in Parkinsonian marmosets



*P<0.01, **P<0.001 vs before MPTP +P<0.01 vs before L-DOPA

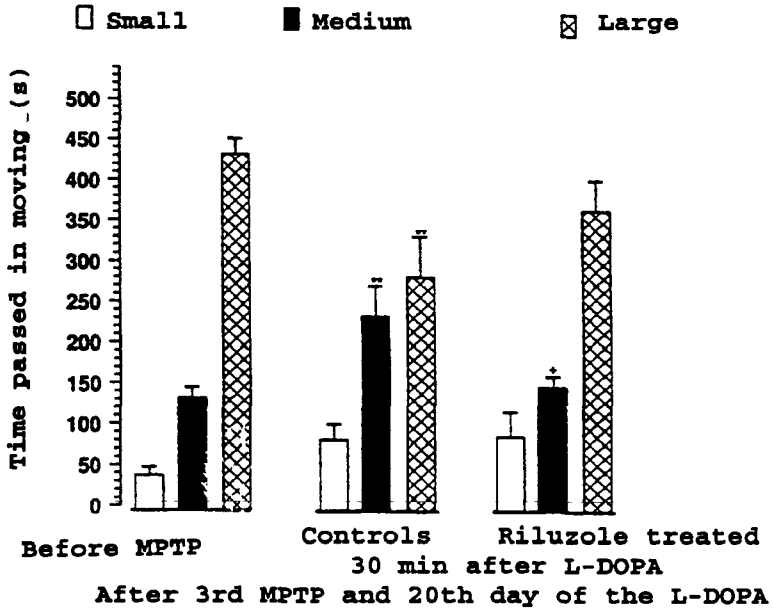
FIGURE 1

Effect of riluzole on locomotory activity in dyskinesic marmosets



***P<0.001 vs before MPTP +++P<0.001 vs controls

FIGURE 2A



**P<0.001 vs before MPTP +P<0.01 vs controls

FIGURE 2B

Effect of riluzole on dyskinesias induced by L-DOPA in Parkinsonian marmosets

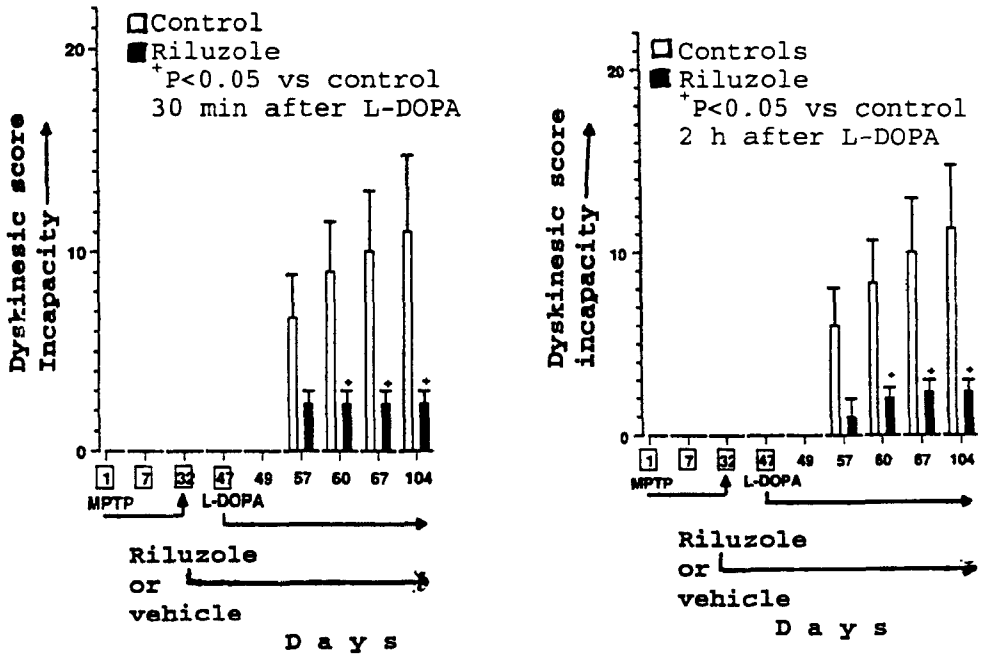


FIGURE 3