Levodopa combined with peripheral decarboxylase inhibition in Parkinson's disease

André Barbeau, M.D., F.R.C.P.[C], Harold Mars, M.D., F.R.C.P.[C], Mihai I. Botez, M.D., PH.D. and Marie Joubert, M.D., F.R.C.P.[C], *Montreal*

Summary: The authors report their experience, over a 26-month period, in the management of 60 parkinsonian patients with the combination of levodopa and an inhibitor of peripheral dopa-decarboxylase, Ro 4-4602. This approach to Parkinson's disease is useful, safe, and at least as effective as levodopa alone. To date there have been no recognizable toxic effects attributable to Ro 4-4602. This agent appears to prolong the duration of action of levodopa, smoothing out its therapeutic effects. The percentage of patients obtaining a very good and excellent response is slightly increased. There is a possible diminution in the late-occurring bradykinetic and hypotonic freezing episodes. Nausea and cardiac arrhythmias are lessened, as are the incidence and severity of hypotension. Abnormal involuntary movements remain the limiting adverse side effect.

From the Department of Neurobiology, Clinical Research Institute of Montreal; Hôtel-Dieu Hospital and Department of Medicine, University of Montreal, Quebec.
Supported in part by grants from the Medical Research Council of Canada, the W. Garfield Weston Foundation, and the Huntington's Chorea Foundation.
Reprint requests to: Dr. André Barbeau, Department of Neurobiology, Clinical Research Institute of Montreal, 110 Pine Avenue West, Montreal 130, P.Q.

Numerous authors have now reported adequate series of parkinsonian patients managed with levodopa (L-3,4-dihydroxyphenylalanine), and this form of treatment has gained wide acceptance.[1-5] The general conclusion is that levodopa is the most effective therapy currently available for the treatment of Parkinson's disease. However, its use is somewhat limited by cost, high incidence of various adverse side-effects, and failure to respond satisfactorily in approximately 20% of patients. Analyses of the more than 200 cases treated in the Montreal co-operative study with levodopa alone, have been reported elsewhere.[3, 6] Briefly, 62% of our patients demonstrated a 50 to 79% improvement, and only 12% a better than 80% response. The average daily dose of levodopa used was 4.8 g., with a range of 1.5 to 8.5 g. As in all reported series, we encountered a fairly high incidence of adverse side effects, most notably nausea and/or vomiting (45%), dyskinesia (48%) and hypotension (30%). The hypotension was asymptomatic in 19% of the patients and symptomatic in 11%. These drawbacks have led various clinical investigators to look for other substances which would either potentiate the effect of levodopa or have dopa-like actions, and be associated with fewer side effects.[7]

Because dopamine itself does not cross the blood-brain barrier, the degree of conversion of DOPA to dopamine by systemic decarboxylase is of paramount importance in determining the percentage of orally administered DOPA available for penetration into the brain, and its subsequent action there. Peripheral metabolic degradation of DOPA before it reaches the brain is probably an important factor in some treatment failures.

Since 1967, Bartholini, Pletscher and collaborators in a series of important papers[9-12] demonstrated that a hydrazine derivative, designated Ro 4-4602 by the Hoffmann-La Roche Research Laboratories, markedly enhanced the DOPA-induced increase of catecholamines in the brains of rats, while reducing the correction time of reserpine-induced symptoms, the peripheral side effects and the peripheral degradation of DOPA.

Recently, Lotti and Porter[13] reported that pretreatment of rats with alpha-methyl-dopa-hydrazine (MK-485) (another hydrazine derivative with similar dopa-decarboxylase-inhibiting properties) prior to levodopa, markedly increased the motor activity induced by levodopa, as

well as prolonging the duration of its action. MK-485 did not penetrate the blood-brain barrier to any significant extent, and decreased the vomiting response to levodopa in pigeons and dogs.

Previous clinical trials

Thus, systemic decarboxylase inhibition is associated with marked increases in brain dopamine levels and prolonged pharmacological response to levodopa. These effects offer a rational approach to eliciting the desired response to levodopa at a greatly reduced daily dosage of this compound.

Clinical trials with combined Ro 4-4602 and levodopa therapy in Parkinson's disease were first reported by Birkmayer and Mentasti in 1967 and 1969[14, 15] and subsequently by Tissot *et al.* in Geneva,[16-18] Siegfried *et al.* in Zurich,[19-25] and Barbeau and collaborators in Montreal.[6, 26-29] Alpha-methyl-dopa-hydrazine, racemic form (MK-485) has undergone limited study in the United States by Cotzias, Papavasiliou and Gellene,[2, 30] by Goodwin *et al.*,[31] and by Chase and collaborators.[32, 33] MK-486, the L-form of alpha-methyl-dopa-hydrazine, is presently undergoing clinical studies in a number of laboratories in the United States.

In this paper the effect of combined Ro 4-4602 and levodopa treatment on a larger series of parkinsonian patients is reported, and an appraisal of therapeutic results is given after more than two years of experience in the continuous treatment of certain patients with this combination. The main purposes of the present study were to evaluate the long-term toxicity of Ro 4-4602 in humans and to find the optimal therapeutic ratio of levodopa and Ro 4-4602 for Parkinson's disease, i.e. the ratio at which a proper balance could be established between clinical efficacy and the least amount of side effects, particularly in the neurological sphere.

Patients and methods

The period of the study covers the two-year span from March 1969 to May 1971. A total of 63 patients have been studied for continuous periods of time, all for more than three months. Sixty had Parkinson's disease. Their overall mean age was 61.8 years, with a range of 37 to 80 years. Average duration of illness was 7.9 years (range two to 28 years). There were 33 males and 27 females. Two patients with the akinetic form of Huntington's chorea and one with Wilson's disease who had not responded to penicillamine were also treated, and have been discussed elsewhere.[34-36]

All patients were admitted to the Hôtel-Dieu Hospital of Montreal for the initial phase of evaluation and treatment, which lasted from four to six weeks. None of these patients had previously received levodopa. They were subsequently followed at the Parkinson Clinic of the Clinical Research Institute of Montreal, at monthly intervals for the first six months and then every eight weeks. Clinical evaluation prior to therapy, and at regular intervals thereafter, consisted of a full neurological examination and a battery of mechanical tests to estimate rigidity, tremor, and bradykinesia. All these tests are fully described in previous publications.[3, 6, 37-39] The general performance was rated according to the scale proposed by McDowell *et al.*[5] The initial evaluation consisted of studies of cerebral, renal, hepatic and blood function. The laboratory studies routinely carried out in the Metabolic Unit included: hemoglobin, hematocrit, complete blood counts, blood glucose, blood urea nitrogen (BUN), blood and urine creatinine, blood uric acid, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), lactic acid dehydrogenase (LDH), calcium, sodium, potassium, cholesterol, total albumin and BSP; electrophoresis and immunoelectrophoresis were also carried out. Most of the above determinations were done on a single sample of serum on the automated SMA 12/60 instrument. Urinary calcium and phosphorus were measured by flame photometry. Each patient also had an electroencephalogram and skull and spine x-rays to evaluate the state of the bone structure and to serve as a control for future studies. Most patients also underwent complete psychological evaluations (Dr. M. I. Botez) and many had a liver scintillogram. Other laboratory studies were carried out as appropriate. In particular, the first 20 patients in this series, in addition to immunoelectrophoresis also had L.E. and Coombs' tests but consistently negative results and cost considerations led to the abandonment of these tests after the first year. In most patients the renin-aldosterone system was also investigated while the patients were on controlled intakes of sodium and in various postural conditions. These studies were done following our original observation of a defect in the renin-aldosterone system in Parkinson's disease.[40-42] Catecholamine metabolism was also studied in each patient, through quantitative determination of urinary dopamine, noradrenaline, adrenaline, homovanillic acid (H.V.A.) and vanylmandelic acid (V.M.A.). Serotonin metabolism was followed by urinary 5-hydroxyindolacetic acid excretion. These studies will be reported elsewhere. Routine laboratory evaluation at each monthly visit consisted of SMA 12/60 (see above) and hematological surveys.

Ro 4-4602 was supplied by Hoffman-La Roche (Montreal)* as capsules containing 50 mg. of the pure substance. Levodopa, first obtained from Nutritional Biochemical Corp. (Cleveland), later from Hoffman-La Roche, was administered in 100 or 250 mg. capsules. The dosages of both drugs were individually adjusted, and were varied as needed from subject to subject since one aim of the study was to establish the optimal dosage combination. As was found with the use of levodopa alone,[1] it was even more important to reach therapeutic levels gradually and slowly. The schedule employed specified drug increments every third day, providing no side effects were encountered. The initial dosage was 50 mg. Ro 4-4602 and 100 mg. levodopa daily. Thereafter, the increments were 50 mg. Ro 4-4602 and 100 mg. levodopa in one to four divided doses during the day, given at 8:00 a.m.,

*Ro 4-4602: N'-(DL-seryl)-n²-(2,3,4-trihydroxybenzyl)-hydrazine, Hoffman-La Roche, S.A. (Basel).

Table I

Comparative study-results of treatment after three months

Result		Levodopa alone %	Levodopa + Ro 4-4602 %
Very good	(>80%)	14	42
Good	(50-79%)	60	31
Moderate	(20-49%)	13	22
Poor	(0-19%)	13	5
Average daily dose:	Levodopa	4.8 g.	650 mg.
	Ro 4-4602	—	150 mg.
Number of patients		60	60

noon, 4:00 p.m. and 8:00 p.m. The maximum daily quantity of Ro 4-4602 used at first was 200 mg. but within the last three months permission was granted to use up to 400 mg. daily. Once the patients had reached a satisfactory functional plateau, they were discharged from the hospital. Subsequent dosage adjustments of Ro 4-4602 and levodopa were made as dictated by side effects or therapeutic response. We define therapeutic success as an improvement greater than 50% as objectively measured on the battery of tests previously described[37-39] and on the McDowell subjective rating scale[5]:—

$$\%\text{improvement} = \frac{(\text{post-treatment score} - \text{pre-treatment score}) \times 100}{\text{pre-treatment score}}$$

Results

Table I presents in a comparative fashion the overall clinical response of patients treated with levodopa alone, or combined with Ro 4-4602. The results are compared with those for the first 60 patients treated consecutively in our department with levodopa alone and previously reported as part of larger series.[3, 6] For economic reasons the design of the present study did not include the simultaneous evaluation of a series of patients on levodopa alone. Since the same observers had previously carried out the initial levodopa study using the same criteria of evaluation, this procedure of comparison was considered valid, especially since the results observed with our initial series[3, 6] are almost identical with those reported by most other authors.[2, 4, 5, 8] In our hands, on combination therapy the average daily dose of levodopa required for satisfactory clinical response decreased from 4.8 g. to 650 mg.; the average required daily dose of Ro 4-4602 was 150 mg.

The proportion of patients who derived a 50% or better response, measured objectively, remained approximately the same with the use of either levodopa alone or combined with Ro 4-4602. However, the percentage of patients with an excellent clinical response after three months was distinctly higher with the combination, viz. from 14 to 42%. With levodopa alone there was an equal distribution of patients with poor and fair degrees of functional improvement. On combined therapy far fewer patients were classified by our assessment method as poor responders.

Qualitatively, the therapeutic response to the combined regimen is similar to that obtained with levodopa alone. At a fixed daily dosage there may be progressive improvement over a relatively long period of time. All signs and symptoms of Parkinson's disease respond to the combined therapy. Bradykinesia is initially benefited, followed by a reduction in rigidity and, lastly, a lessening of tremor. For example one patient who had failed to respond to 14 g. of levodopa daily manifested marked improvement on the combined therapy at a dosage of 1.5 g. levodopa and 200 mg. Ro 4-4602. We also note that the combination therapy permits a longer duration of the action of levodopa, the increase from a single dose being, in our hands, from 45 to 90 minutes.

Table II

Comparative study: Cumulative percentage of side-effects after three months (60 patients in each series)

	Levodopa alone	Levodopa + Ro 4-4602
Nausea and vomiting	44	23
Hypotension	31	14
Dizziness	20	32
Somnolence	5	5
Mental symptoms (confusion, hallucinations, depression)	27	12
Abnormal involuntary movements	50	43
Cardiac arrhythmias	12	0

The incidence of adverse side effects is minimized when a schedule of gradual dosage increments is adhered to (Table II). In the early phase of levodopa treatment dizziness and nausea were common, as they are also with the combined regimen. These symptoms were usually transient and in no instance forced cessation of the therapeutic trial. Abnormal involuntary movements were a common manifestation of drug toxicity. These included buccolingual dyskinesias, as well as the full spectrum of dystonic and athetotic truncal and limb movements, previously described.[3] Our clinical experience with levodopa alone had indicated that the incidence of dyskinesias increased with the duration of treatment. On combination therapy abnormal movements, when they occur, tend to appear earlier and be more persistent, requiring a much longer time for abatement following dosage reduction than was the case with levodopa alone. Using levodopa alone, abnormal movements tend to appear from two to six months or more after onset of therapy. On combination therapy this interval is from one to three months.

After more than 12 months of continuous therapy with levodopa alone, a syndrome characterized by unsteadiness of gait, hypotonia, "piétinement", and rapid oscillations in performance ("on and off" phenomenon) which we have called "akinesia pardoxica"[43] is observed in 14 to 20% of patients. Its incidence increases with time. Twenty-eight of our patients had received combined therapy for more than 12 months by May 1971. Four have to date shown signs of developing a similar syndrome. As recently noted by Gauthier *et al.*,[18] the movements are more frequent in individuals manifesting moderate or severe hypotonia.

Hypotension developed in 31% of our patients receiving levodopa alone. Two of the first 60 patients developed myocardial infarction, two a cerebrovascular accident, and one a pulmonary embolus. Of the 60 patients treated with levodopa and Ro 4-4602 for more than three months, 14% have manifested hypotension. However, the severity of this adverse side effect with the drug combination was much less. There have been no cardiovascular or cerebrovascular complications with the combined treatment.

Somnolence and acute mental symptoms (confusion, hallucinations, depression) appear to be less frequent with combination therapy, but it is probable that this is because the first series (levodopa alone) was obtained while we were groping through unknown territories. We, and others, are now more selective in the face of severe cerebral arteriosclerosis and previous history of mental illnesses, go more slowly and are satisfied with lower functional plateau levels both with levodopa and with the combination therapy.

Rare transient elevations of alkaline phosphatase were noted, which could never be correlated with the patient's clinical situation, drug dosage, or therapeutic response. All other routine laboratory parameters measured have

remained normal to date. Liver function, as measured by B.S.P., serum L.D.H., S.G.O.T., S.G.P.T., bilirubin, protein electrophoresis and liver scan, was normal. Immunoelectrophoresis, L.E. and Coombs' tests, when performed, were normal. Calcium and phosphorus metabolism, as measured in blood, urine, and monitored radiologically, has shown no alteration after periods ranging from three to 26 months of treatment.

Discussion

In our hands and after 26 months of observation (as of May 1971) the combined use of levodopa and the peripheral decarboxylase inhibitor Ro 4-4602 is a safe and useful therapeutic measure in the treatment of Parkinson's disease. The primary consideration in the initial evaluation of any new drug, and particularly of drug combinations, is safety. Now after more than 11 years of use in humans,[3, 55] at low or high dosage,[2] the inherent toxicity of levodopa, a natural precursor ("food"), has remained relatively low when compared with that of other active compounds such as corticosteroids, antibiotics, and neuroleptics. The addition of a dopa-decarboxylase inhibitor of the hydrazine family had more serious implications. We were aware, before undertaking the human studies, of the liver changes (fatty deposits) produced in dogs with much higher per weight dosages. We were also aware that with extremely high, sustained doses of Ro 4-4602, skeletal changes had been observed in rats. Hydrazine compounds, through still unknown mechanisms, are thought to alter immune reactions in some individuals.

Because of these reservations we included a large battery of liver function tests and of biochemical and radiological estimates of bone and calcium metabolism. In studies which have been pursued over more than 32 months, we have detected no abnormal reactions except rare, transient elevations of alkaline phosphatase which were also seen with levodopa alone. It can be argued that our studies are still insufficient in length and scope. We can only agree, but feel that the great advantages (as detailed below) far outweigh the eventual, and still hypothetical, dangers of this therapy. The same remarks apply, of course, to the other peripheral decarboxylase inhibitors now being tested which are also hydrazine derivatives. The authors know of no highly active drug which, in some individuals, does not offer risks. As a point of reference in the treatment of such a chronic degenerative and disabling illness as Parkinson's disease, one should consider the acknowledged and acceptable mortality and morbidity of the other effective approach, namely stereotaxic surgery.

On general evaluation the combined therapy appears preferable to levodopa alone. The first advantage is a sharp reduction in a daily dosage of levodopa required to obtain a satisfactory clinical response. This is directly attributable to the action of Ro 4-4602 in inhibiting extracerebral decarboxylase, thus allowing for higher circulating levels of DOPA and greater availability of this amino-acid for blood-brain barrier penetration. Bartholini and Pletscher[11] felt that maximal degradation of orally administered levodopa occurred in the gastrointestinal tract. This view is confirmed by Tissot, Bartholini and Pletscher,[16] who demonstrated in man that following the ingestion of C^{14}-DOPA and Ro 4-4602 there resulted an increase in the intestinal absorption of DOPA. It is therefore possible that a sub-group of patients fails to respond to levodopa because of inadequate absorption and blood levels. These individuals may respond to the combined drug approach. It is also of possible theoretical importance that of the patients who manifested less than 50% overall functional improvement, the number treated with levodopa alone was almost the same as the number treated with both agents. This group may consist of individuals in whom the receptor arcs of the striatal dopaminergic systems are absent or defective, and in whom no significant response to any dose of levodopa is possible. An alternative hypothesis is that in these patients a physicochemical or enzymatic block exists that prevents the proper penetration of DOPA to the active utilization sites in the brain.

The second advantage resides in the ease of handling; with proper galenic preparations it should eventually be possible to have to use only three or four capsules a day. Because the duration of the beneficial effect is appreciably prolonged with the combination, there is need for fewer divided doses during the day. This may also explain the apparent decrease of the oscillations in daily and long term performance, although since the latter are closely associated with the development of hypotonia, other mechanisms may have to be considered.

Another worthwhile advantage of the combination is the fact that it takes much less time to reach a therapeutic plateau. Instead of the minimum four to six weeks required with levodopa alone, patients can be properly stabilized within 10 days on the average, although to avoid the early appearance of neurological side effects we must again stress the need to increase very slowly the dose of levodopa.

Finally we must emphasize the decreased incidence of most side effects. The occurence of nausea and vomiting is clearly reduced on combined therapy, indicating that the target centres responsible for those symptoms are probably outside the classical blood-brain barrier and, therefore, subject to decarboxylase inhibition.[13, 44] The question of levodopa — induced hypotension has received considerable study, and has been variably related to a defect in the sympathetic nervous system,[45] or in the renin-aldosterone system.[41, 46-49] There was a slight reduction in the incidence of symptomatic and asymptomatic hypotension on combined therapy but, when present, the hypotension was definitely of milder intensity. Numerous investigators[50] have demonstrated a dopamine effect on peripheral vascular resistance. The concomitant administration of Ro 4-4602 with levodopa would decrease the systemic production of dopamine, and in this manner could account for the noted reduction of hypotension in our series. Henning and Rubenson[51, 52] have suggested that a central noradrenaline mechanism is involved in the hypotensive effect of levodopa, and have shown that in the rat this effect is prevented by dopamine-β-hydroxylase inhibition and by doses of Ro 4-4602 large enough to produce central decarboxylase inhibition. Thus the evidence accumulates that the hypotensive action of levodopa involves a peripheral and also a more important central mechanism.

As noted above, combined therapy was not associated with any cerebrovascular or cardiovascular complications. This may merely reflect the relatively small size of our series, and increased experience may alter this conclusion. Although it is recognized that we are dealing with diseases that are age-related, and therefore possibly coincidental, the question must be put as to whether levodopa in any way facilitates the development of these complications.

Watanabe, Parks and Kopin[53] have recently reported that levodopa infusions given to dogs anesthetized with halothane resulted in the development of cardiac arrhythmias. These could be prevented by pre-treatment with decarboxylase inhibitors. During the 26 months of experience with levodopa combined with Ro 4-4602 reported in this paper, and the six months which have elapsed since the end of this comparative study, we have not observed a single new episode of cardiac arrhythmia.

During early experience with large doses of levodopa in the treatment of Parkinson's disease,[3-5, 8] acute psychological and mental manifestations of agitation, hypomania, confusion, vivid dreams, paranoid reactions and even suicidal attempts were recorded.[8] Most of these reactions, except in individuals with pre-treatment morbid changes in the intellectual sphere, were related to rapid and excessive drug increases and could usually be easily controlled by simple dosage reductions. With time, however, more subtle changes in mood, attention span and judgment capacity became noticed after long term treatment with levodopa. First reported by us in early 1971,[43] they have recently been confirmed by other authors, particularly by Lee and co-workers.[54] It is still very difficult to delineate the exact spheres of mental capacity which are most affected, probably because most of the psychological tests heretofore utilized by us and others are inadequate, but the fact remains that careful interviewing of close family members will confirm the presence of these subtle behavioural changes in many patients. The utilization of combined levodopa and Ro 4-4602 treatment appears to accelerate most beneficial and some adverse effects of levodopa therapy. Hence we were not surprised to see evidence of similar behaviour evolution in a few patients after six to eight months of combined therapy. At this stage in our studies it must be strongly emphasized that although we have no doubt about the slow emergence of this new syndrome, we have no evidence which could, directly or indirectly, link these events with levodopa or Ro 4-4602. The alternative hypothesis, that by permitting the patients greater motility and by reducing the psychological isolation inherent to invalidism we are only uncovering the natural history of advancing Parkinson's disease, has not yet been adequately tested. Certainly modern neuropathologists who recognize the primordial role of lesions in the nigro-striatal pathway in this illness, also are willing to accept that other parts of the brain, including the cortex, might eventually be damaged. Such specific and localized cortical symptomatology simply is not looked for by most of us in bedridden patients in the advanced stages of invalidism!

A more difficult question is the incidence of abnormal involuntary movements (A.I.M.) in both series. With levodopa alone we[3, 6] had reported that these movements were related to both total dosage and duration of administration. After three months nearly 50% of patients treated with levodopa had, at one time or another, presented with this complication. This figure increased to more than 80% after two years.[55, 56] In the first series of 20 patients on combined therapy reported by us[26] and in the series of Siegfried *et al.*[19] and Tissot *et al.*,[17] it appeared that the incidence of abnormal movements was decreased. However, a clinical paradox has been observed in the next 40 patients when we attempted to decrease the daily dosage of Ro 4-4602 to below 200 mg. Abnormal movements, but not stereotyped gestures, then became more frequent, appeared earlier and were sometimes difficult to control. Moreover there was a much higher incidence of limb dystonias and choreo-athetosis than previously encountered with levodopa alone, especially in the presence of severe induced hypotonia.

Thus, as Tissot had previously reported to us, and since published,[18] a nearly complete peripheral inhibition of dopa-decarboxylase is preferable to only partial peripheral inhibition. To test this hypothesis in a more recent series of 20 parkinsonian patients, we have experimented with a fixed 600 mg. per day dosage of levodopa and a variable amount of Ro 4-4602. A clinical paradox of importance was observed: with a daily dosage averaging 150 mg. the incidence of A.I.M. was the same as with levodopa alone after a similar time interval (54%). If the dosage of Ro 4-4602 is reduced to an average of 100 mg. per day, the incidence of A.I.M. increased to 71%; on the other hand if we use 250 mg. to 300 mg. per day, the A.I.M. are seen in only 28% of cases. At present the safest clinical results (i.e. satisfactory improvement with minimal neurological side effects) are obtained with a levodopa/Ro 4-4602 ratio between 3:1 and 3:2 with a maximum of 400 mg. per day of the decarboxylase inhibitor. Optimal clinical effects on neurological signs, and particularly rigidity and bradykinesia, necessitate a ratio equal to or above the 4:1 ratio which we previously recommended[28] and which almost always also causes severe hypotonia. However, this improvement is obtained at the risk of fairly severe A.I.Ms. The biochemical and physiological implications of this latest observation are still being studied and will not be discussed in this paper. We are presently evaluating for safety and clinical efficacy a series of patients treated with a fixed dosage ratio (3:2) of 600 mg. levodopa and 400 mg. Ro 4-4602. The ease of handling of such a fixed combination, if proved safe and equally useful, could facilitate the wider utilization outside specialized clinics of what we feel is presently, despite some drawbacks and limitations, the best overall available form of therapy for Parkinson's disease.

The authors are indebted to Dr. J. Gareau for supplies of levodopa and Ro 4-4602; to Miss Gabrielle Fullum, R.N., Miss Lise Demers, R.N., Miss Lyne Millette, R.N. and the staff of the Metabolic Unit, Hôtel-Dieu Hospital, for excellent patient care; to Mrs. Nicole Guay-Poirier for the careful monitoring of all records and for secretarial assistance. The authors would also like to express their appreciation for the help and understanding given throughout this study by the Department of Health and Welfare, Ottawa, and the Food and Drug Directorate of Canada.

Résumé

Les auteurs font part de leurs résultats dans le traitement de la maladie de Parkinson (60 patients), pendant une période de 26 mois, de mars 1969 à mai 1971, avec la combinaison médicamenteuse levodopa et Ro 4-4602, un inhibiteur périphérique de la dopa-décarboxylase. Cette approche s'avère utile, sans danger et aussi efficace que celle avec la levodopa seule. A date et aux doses employées, aucun effet secondaire spécifique n'est attribuable à l'emploi du Ro 4-4602. Les avantages de la combinaison sont: dose diminuée de levodopa, nombre inférieur de comprimés à prendre, augmentation de la durée d'action d'une dose de levodopa, diminution des oscillations diurnes de performance. Le pourcentage de patients bénéficiant d'une réponse bonne ou excellente est légèrement supérieur. Il y a moins d'épisodes de nausées et d'arrythmies et l'hypotension orthostatique, quoique

encore présente, est moins sévère. Les mouvements anormaux constituent toujours l'obstacle majeur. Lorsqu'ils sont présents, ils sont plus précoces et semblent plus difficiles à maîtriser, sauf lorsque le rapport DOPA/Ro 4-4602 varie entre 3:1 et 3:2.

Les auteurs concluent que l'emploi combiné de la levodopa avec un inhibiteur de la dopa-décarboxylase périphérique est à préférer à celui de la levodopa seule.

References

1. COTZIAS GC, VAN WOERT MH, SCHIFFER LM: Aromatic amino acids and modification of parkinsonism. *N Engl J Med* 276: 374-379, 1967
2. COTZIAS GC, PAPAVASILIOU PS, GELLENE R: Modification of parkinsonism—Chronic treatment with L-DOPA. *N Engl J Med* 280: 337-345, 1969
3. BARBEAU A: L-DOPA therapy in Parkinson's disease—A critical review of nine years' experience. *Can Med Assoc J* 101: 791-800, 1969
4. YAHR MD, DUVOISIN RC, SHEAR MJ, et al: Treatment of parkinsonism with levodopa. *Arch Neurol* 21: 343-354, 1969
5. MCDOWELL F, LEE JE, SWIFT RD, et al: Treatment of Parkinson's syndrome with L-dihydroxyphenylalanine (Levodopa). *Ann Intern Med* 72: 29-35, 1970
6. BARBEAU A: Parkinson's disease—Recent advances in treatment. *NY State J Med* 70: 2437-2443, 1970
7. DONALDSON J, MINNICH JL, BARBEAU A: Search for L-DOPA potentiators. Int. Soc. for Neurochemistry—Third Intern. Meeting, Volume of Abstracts; Budapest, Akadémiai Kiado 1971, p 9
8. BARBEAU A, MCDOWELL FH (eds): *L-DOPA and Parkinsonism.* Philadelphia, F. A. Davis, Co., 1970, p 1-433
9. BARTHOLINI G, BURKARD WR, PLETSCHER A, et al: Increase of cerebral catecholamines caused by 3,4-dihydroxyphenylalanine after inhibition of peripheral decarboxylase. *Nature* 215: 852-753, 1967
10. BARTHOLINI G, DA PRADA M, PLETSCHER A: Decrease of cerebral 5-hydroxytryptamine by 3,4-dihydroxyphenylalanine after inhibition of extracerebral decarboxylase. *J Pharm Pharmacol* 20: 228-229, 1968
11. BARTHOLINI G, PLETSCHER A: Cerebral accumulation and metabolism of C^{14}-DOPA after selective inhibition of peripheral decarboxylase. *J Pharmacol Exp Ther* 161: 14-20, 1968
12. BARTHOLINI G, BLUM JE, PLETSCHER A: DOPA-induced locomotor stimulation after inhibition of extracellular decarboxylase. *J Pharm Pharmacol* 21: 297-301, 1969
13. LOTTI VJ, PORTER CC: Potentiation and inhibition of some central actions of L(-)-DOPA by decarboxylase inhibitors. *J Pharmacol Exp Ther* 172: 406-415, 1970
14. BIRKMAYER W, MENTASTI, M: Weitere experimentelle Untersuchungen über den catecholaminstoffwechsel bei extrapyramidalen Erkrankungen (Parkinson und Chorea Syndrom). *Arch Psychiatr Nervenkr* 210: 29-35, 1967
15. BIRKMAYER W: Experimentelle Erzebnisse über die Kombinationsbehandlung des Parkinson-syndroms mit L-DOPA und einen Decarboxylasehemmer (Ro 4-4602). *Wien Klin Wochenschr* 81: 677-679, 1969
16. TISSOT R, BARTHOLINI G, PLETSCHER A: Drug-induced changes of extracerebral dopa metabolism in man. *Arch Neurol* 20: 187-190, 1969
17. TISSOT R, GAILLARD JM, GUGGISBERG M, et al: Thérapeutique du syndrome de Parkinson par la L-DOPA "per os" associée à un inhibiteur de la décarboxylase (Ro 4-4602). *Presse Méd.* 77: 619-622, 1969
18. GAUTHIER G, DE AJURIAGUERRA J, SIMONA BL, et al: Thérapeutique du syndrome parkinsonien par la L-DOPA associée à des inhibiteurs de la décarboxylase (II). *Revue Neurol* 123: 297-319, 1970
19. SIEGFRIED J, ZIEGLER WH, REGLI F, et al: Treatment of Parkinsonism with L-DOPA in association with a decarboxylase inhibitor. First objective results. *Pharmacol Clin* 2: 23-26, 1969
20. SIEGFRIED J: Traitement de parkinsonisme avec la L-DOPA associée à un inhibiteur de la décarboxylase. *Méd Hygiène* 27: 543-545, 1969
21. SIEGFRIED J, KLAIBER R, PERRET E, et al: Behandlung des morbus Parkinson mit L-DOPA in Kombination mit einen Decarboxylasehemmer. *Dtsch Med Wochenschr* 94: 2678-2681, 1969
22. SIEGFRIED J, ZIEGLER WH, PERRET E, et al: Behandlung der Akinesh beim morbus Parkinson mit L-DOPA und einen Decarboxylasehemmer. *Schweiz Arch Neurol* 104: 316-317, 1969
23. SIEGFRIED J: Deux ans d'expérience avec la L-DOPA associée à un inhibiteur de la décarboxylase. *Rev Neurol* 122: 243-248, 1970
24. KRAYENBUHL H, SIEGFRIED J: Treatment of Parkinson's disease: stereotaxic operation or L-DOPA. *Neuro-Chirurgie* 16: 71-76, 1970
25. KLAIBER R, SIEGFRIED J, ZIEGLER WH, et al: Psychomotor effects of L-DOPA combined with decarboxylase inhibitor on Parkinsonian patients. *Eur J Clin Pharmacol* 3: 172-175, 1971
26. BARBEAU A, GILLO-JOFFROY L: *Treatment of Parkinson's disease with L-DOPA and Ro 4-4602.* Proc. 4th Can Congress Neurological Sciences, June 21, 1969, p 15
27. Idem: Treatment of Parkinson's disease with L-DOPA and Ro 4-4602. Excerpta Med., Int. Congress Series no 193: 171, 1969
28. BARBEAU A, GILLO-JOFFROY L, MARS H: Treatment of Parkinson's disease with Levodopa and Ro 4-4602. *Clin Pharmacol Ther* 12: 353-359, 1971
29. BARBEAU A, BOTEZ MI, MARS H, et al: Treatment of Parkinson's disease with Levodopa alone or with Ro 4-4602 — A comparative study. *Neurology* 21: 409, 1971
30. COTZIAS GC: Metabolic modification of some neurologic disorders. *JAMA* 210: 1255-1262, 1969
31. GOODWIN FK, BRODIE HKH, MURPHY DL, et al: Administration of a peripheral decarboxylase inhibitor with L-DOPA to depressed patients. *Lancet* i: 908-911, 1970
32. WATANABE AM, CHASE TN, CARDON PV: Effect of L-DOPA alone and in combination with an extracerebral decarboxylase inhibitor on blood pressure and some cardiovascular reflexes. *Clin Pharmacol Ther* 11: 740-746, 1970
33. CHASE TN: Cerebrospinal fluid monoamine metabolites and peripheral decarboxylase inhibitors in Parkinsonism. *Neurology,* 20, no 12 (Part 2): 36-40, 1970
34. BARBEAU A, FRIESEN H: Treatment of Wilson's disease with L-DOPA after failure with penicillamine. *Lancet* i: 1180-1181, 1970
35. BARBEAU A: L-DOPA and juvenile Huntington's disease. *Lancet* ii: 1066, 1969
36. KLAWANS HC, PAULSON GW, BARBEAU A: Predictive test for chorea. *Lancet* ii: 1185-1186, 1970
37. DERY JP, DE GROOT JA, LAURIN C, et al: Nouvelle méthode d'évaluation objective de la rigidité et du tremblement dans la maladie de Parkinson. *Union Méd Can* 91: 842-847, 1962
38. JOUBERT M, BARBEAU A: Méthode de mesure de l'akinésie. *Union Méd Can* 95: 531-535, 1966
39. DE GROOT JA, BARBEAU A: The problem of measurement of akinesia. *J Neurosurg* 24: 331-334, 1966
40. BARBEAU A: Dopamine and blood pressure regulation. *Clin Res* 17: 634, 1969
41. BARBEAU A, GILLO-JOFFROY L, BOUCHER R, et al: Renin-aldosterone system in Parkinson's disease. *Science* 165: 291-292, 1969
42. GANTEN D, MINNICH JL, GRANGER P, et al: Angiotensin-forming enzyme in brain tissue. *Science* 173: 64-65, 1971
43. BARBEAU A: Long term side-effects of Levodopa. *Lancet* i: 395, 1971
44. CLARK C, LOTTI VJ: Attenuation of the vomiting response to L-DOPA after decarboxylase inhibition. *Fed Proc* 29: 512, 1970
45. BURN JH: Hypotension caused by L-DOPA. *Br Med J* 1: 629, 1970
46. MICHELAKIS AM, ROBERTSON D: Plasma renin activity and Levodopa in Parkinsonism. *JAMA* 213: 83-85, 1970
47. FOTINO S, BLAUFOX MD: Renin activity and catecholamine excretion in Parkinsonism. *Clin Res* 18: 499, 1970
48. BARBEAU A, GILLO-JOFFROY L, BROSSARD Y: Renin, dopamine and Parkinson's disease. *in:* L-DOPA and Parkinsonism. (A. Barbeau and F. H. McDowell, eds), Philadelphia, F. A. Davis Co., 1970, p 286-293
49. KUCHEL O, CUCHE JL, BARBEAU A, et al: The role of dopamine, norepinephrine and epinephrine in the orthostatic regulation of renin in normotensive and hypertensive subjects. *in: L-DOPA and Parkinsonism.* edited by A. Barbeau and F. H. McDowell, Philadelphia, F. A. Davis Co., 1970, pp 293-305
50. MCNAY, JL, MCDONALD RH, GOLDBERG LI: Direct renal vasodilation produced by dopamine in the dog. *Circ Res* 15: 510-517, 1965
51. HENNING M, RUBENSON A: Evidence for a centrally mediated hypotensive effect of L-DOPA in the rat. *J Pharm Pharmacol* 22: 241-243, 1970
52. Idem: Central hypotensive effect of L-3,4-dihydroxyphenylalanine in the rat. *Ibid* pp 553-560
53. WATANABE AM, PARKS LC, KOPIN LJ: Modification of the cardiovascular effects of L-DOPA by decarboxylase inhibitors. *J Clin Invest* 50: 1322-1328, 1971
54. LEE JE, SWEET RD, MCDOWELL FH: Treatment of Parkinsonism with Levodopa. *Ann Intern Med* 75: 703-708, 1971
55. BARBEAU A: Dopamine and disease. *Can Med Assoc J* 103: 824-832, 1970
56. Idem: L-DOPA therapy: past, present and future. *Ariz Med* 27: 1-4, 1970