Neurology in Europe I: D. Bartko, F. Gerstenbrand & P. Turčáni, eds. © 1990 John Libbey & Co. Ltd. pp 556-563.

Retrospective study of patients suffering from primary Parkinson's disease: cumulative dosage and long-term levodopa induced dyskinesia

R. Formisano, G. Ransmayr*, R. Diercks**, V. Sailer*, W. Poewe, F. Gerstenbrand, A. Agnoli

Department of Neurological Sciences, University 'La Sapienza', Rome, Italy.
**Universitats Klinik für Neurologie, Innsbruck, Austria.*
***Vrije Universiteit of Brussels, Brussels, Belgium.*

Introduction

The factors which influence the incidence of long term levodopa syndrome have been widely discussed by various authors.
In particular levodopa dyskinesia have been correlated with the age of onset of the disease, the duration of the disease, the clinical form, the duration of levodopa treatment, the interval between the onset of the disease and the beginning of levodopa therapy and finally the cumulative dosage of levodopa.
Abnormal involuntary movements and on-off phenomena have been reported as more frequent in patients with onset of the disease before age 60 and in young subjects wich take higher doses of levodopa (cumulative dosage of levodopa) (Granerus 1979, Calne 1983, Pederzoli 1983, Rajput 1984).
The negative prognostic factors in Parkinson's disease seem to be the sex (male), the clinical forms of Parkinson's disease in which tremor is not predominant, the onset of the disease before 60 years of age, the depression and transitory psychotic disorders during the first year of treatment.
Life expectancy is longer in patients in whom the disease starded with isolated tremor and those in whom a good initial therapeutic result is obtained (Guillard 1978).
On the contrary, the development of fluctuations has been related by other authors to duration of levodopa treatment and not to duration or severity of the disease, nor to the nature of the predominant symptom (tremor or akinesia and rigidity) or patients age at the onset of levodopa treatment. De Jong (1987) concluded that treatment should be delayed until the patient reaches Hoehn and Yahr stage III of the disease, the stage at which postural stability is impaired.

The analysis of these factors makes it difficult to answer the question: "To treat early or to treat late?" (Duvoisin 1987).
The authors who support the early treatment have claimed that patients starting levodopa therapy early, live longer and suffer less disability.
On the contrary the authors who sustain that the initiation of treatment should be deferred, enphasized that an earlier levodopa therapy leads to fluctuating responses earlier than if treatment is postponed.
The wide literature on this topic offers good arguments both for the early (Diamond 1976, Markham 1981, Hoehn 1983, Hoehn 1985, Markham 1986) and the late treatment (Lesser 1979, Marsden 1982, Lieberman 1982, Rajput 1984, Melamed 1986).
Early treatment seems to reduce long-term disability and mortality just as less disability and death seems to occur in patients treated immediately after diagnostic than in those in whom treatment with levodopa has been postponed (Diamond 1976, Hoehn 1983).
The aim of our study was to analyze the influence of the different factors and in particular of the cumulative dosage of levodopa on the incidence of levodopa-induced dyskinesia and on the global disability of the patients.

Material and Methods

69 patients out of the 84 who came to our first observation during the entry period January to June '86 to the Outpatients Service for the Extra- pyramidal Diseases (University Neurological Clinic of Innsbruck) were included in the study.
The patients included had been suffering from primary Parkinson's disease for at least one year and were selected because of the possibility to calculate cumulative dosage of levodopa taken from the patients up to our first observation.
The 69 patients (42 male, 39 female) were from 42 to 81 years old (mean age: 65.3 yrs), with a mean duration of the disease of 7.8 yrs (range : 1-25 yrs) and a mean duration of levodopa treatment of 5.7 yrs (range 1-20 yrs). Thirty five (50.7%) of them suffered from the complete or equivalent form (RAT),32 (46.3%) from the rigid-akinetic form and 2 (2.8%) from the tremor or hyperkinetic form.Forty nine (71%) of all the patients complained of symptoms of levodopa long-term syndrome, with a latency from the beginning of the disease of at least 2 years and from the beginning of the levodopa therapy of at least 1 year.
In order to evaluate the incidence of the levodopa long-term syndrome in the patients studied, we considered the presence of the involuntary movements, which is almost constantly associated with the on-off phenomena and the decrease in the efficacy of the therapy, secondary to the chronic treatment with levodopa.

In particular, we investigated the influence of the age of onset of the disease and the clinical form (RAT, RA, T) on the incidence of the levodopa induced dyskinesia.
Moreover, we calculated the cumulative dosage of levodopa (without decarboxylase inhibitors), taken by the patients up to our first observation, and we divided the patients in 3 groups according to the different mean daily dosages (1° group: 200-300 mg/die, 2° group: 300-500 mg/die, 3° group 500 mg/die).
Finally the symptom of onset of the disease, the cumulative dosage of levodopa and the clinical form have been correlated with the global disability of the patients.

Results and Discussion

The age of onset of Parkinson's disease was in our patients slightly lower in men (57.5 yrs, range: 36-74 yrs) than in women (58.5 yrs, range: 37-75 yrs), as already reported by some authors (Mendel 1911, Wilson 1955, Fields 1958).
We also confirmed a younger age of onset of the disease in the patients with dyskinesia (55.1 yrs, range: 36-75 yrs) compared to those who did not complain of levodopa induced dyskinesia (60.6 yrs, range: 48-76 yrs, as already found by other authors (Guillard 1978, Granerus 1979).
In subdividing the patients in the 3 groups with different cumulative dosage of levodopa, there was no significant difference in the latency between the beginning of the disease and the onset of the dyskinesia, nor as in the latency between the beginning of levodopa therapy and the onset of the dyskinesia in the 3 groups.
In fact the different cumulative dosage does non seem to be correlated with the 2 latencies (tab.I)

Table 1. CUMULATIVE DOSAGE OF LEVODOPA AND INTERVAL OF ONSET OF DYSKINESIA

Latency onset disease/dyskinesia

	I GROUP	II GROUP	III GROUP
	7.7 yrs	5.4 yrs	7.6 yrs
(range:	2-10 yrs	2-16 yrs	2-20 yrs)

Latency onset levodopa/dyskinesia

	5.0 yrs	3.7 yrs	4.8 yrs
(range:	1-12 yrs	2-8 yrs	1-12 yrs)

In previous retrospective studies tremor was described as the most common initial symptom in more than 70% of the patients with Parkinson's disease (Mjones 1949, Hartmaan 1960).

In particular some authors reported that parkinsonian patients in whom tremor represents the prevalent symptom seem to have a slightly better prognosis than those whose akinesia or rigidity is the main manifestation (Hoehn 1967,Guillard 1978).
More recently some authors have demonstrated that tremor is negatively correlated to motor disability, the stage of the disease and the history of pharmachotoxic psychosis (Marttila 1977).
The tremor type seemed to be favorable, the rigid-akinetic type unfavorable with respect to motor disability and psychosis.
Tremor was the onset symptom in 74.3 % our patients, but it does not seem to represent a factor which could influence the progression of the disease (Tab.II).

Table II. INITIAL SYMPTOM AND PROGRESSION OF THE DISEASE

	N. of patients	Hoehn and Yahr
Tremor	74.3 %	2.5
Other symptoms	24.3 %	2.6

With regard to the influence of the clinical form on the incidence of levodopa induced dyskinesia, we found a marked prevalence of dyskinesia in the patients with the rigid-akinetic (RA) form compared to those with the complete form (RAT) or the hyperkinetic form (T) (Tab.III).

Table III. LEVODOPA INDUCED DYSKINESIA AND CLINICAL FORM

Clinical Form	+	-	H. Y.
RAT	9	26	2.5 (range: I-V)
RA	23	9	2.6 (range: I-IV)
T	1	1	1.3 (range: I-III)
Disease Duration (mean: yrs)	9.1 (range: 2-25)	6.8 (range: 1-16)	
Levodopa treatment (mean dur.:yrs)	7.2 (range: 2-20)	4.2 (range: 1-10)	

Legend
+ with dyskinesia
- without dyskinesia

The influence of the clinical form on the global disability of the patients showed less disability at the Hoenh and Yahr scale

for the hyperkinetic form compared to the other clinical forms.(Tab.III).
In previous studies some authors observed a less global disability in those parkinsonian patients in whom tremor was the prevalent symptom compared to those with the rigid-akinetic clinical form (Guillard 1978, Hoehn 1967, Pollock 1966, Barbeau 1984, Gerstenbrand 1982, Marttila 1977, Poewe 1983, Zatusky 1985, Ribadeau-Dumas 1977).
This datum was not universally confirmed (De Jong 1987).
The major incidence of dyskinesia in the rigid-akinetic form was more evident in the subgroup of patients who took a higher cumulative dosage of levodopa (Tab.IV).

TABLE IV. CUMULATIVE DOSAGE OF LEVODOPA

	I GROUP (200-300 mg/die)	II GROUP (300-500 mg/die)	III GROUP (500 mg/die)
N. of Patients	25	23	21
Sex	M 12 F 13	M 14 F 8	M 12 F 8
Mean age (yrs)	64.32 (range: 52-79)	63.4 (range: 43-80)	63.38 (range:58-80)
Levodopa Treatment (mean dur.: yrs)	4.29 (range: 1-12)	5.14 (range: 1-10)	9 (range: 2-20)
Hoehn and Yahr	2.6 (range: I-IV)	2.6 (range: I-IV)	3.1 (range: II-V)
Levodopa induced Dyskinesia	14 (56 %)	15 (65 %)	16 (76 %)

Such a higher incidence did not seem to be caused by the higher cumulative dosage of levodopa, in fact the higher dosage could be secondary to the major severity of the clinical form or to the minor responsivity of this subgroup of patients to levodopa, with consequent need to increase the dosage.
In fact the patients with levodopa induced dyskinesia showed a longer mean duration of the disease and of the treatment, without any significant difference in the cumulative dosage of levodopa between the patients with dyskinesia and those without levodopa induced dyskinesia (Tab.V).
In conclusion:

- a younger mean age at onset of the disease for the patients with levodopa induced dyskinesia is confirmed by our data;
- the incidence of dyskinesia seems to be correlated less to the cumulative dosage of levodopa and more to the mean duration of the disease, but above all to the duration of levodopa treatment (Tab.V) .

Table V. CUMULATIVE DOSAGE OF LEVODOPA AND LEVODOPA INDUCED DYSKINESIA

	I GROUP		II GROUP		III GROUP	
	+	-	+	-	+	-
N.of Patients	14	11	15	8	16	4
Disease duration (mean:yrs)	8	5	7	6.8	11.9	8.7
(range)	(2-17)	(1-6)	(3-17)	(2-16)	(5-25)	(5-12)
L.Dopa Treatment (mean:yrs)	7	3	5.8	4.1	8.8	5
(range)	(2-12)	(1-10)	(3-10)	(2-10)	(3-20)	(4-6)
Cumulative dosage/mg (monthly mean)	7.045	6.993	12.594	12.854	22.507	21.384

Legend
+ with dyskinesia
- without dyskinesia

The rigid akinetic clinical form seems to have a higher incidence of levodopa induced dyskinesia compared to the complete and the hyperkinetic form. The higher susceptibility of the rigid akinetic form to the dyskinesia and in general to the long term levodopa syndrome suggests, if confirmed, different biochemical and pathophysiological basis for the different clinical forms of Parkinson's disease.

REFERENCES

Barbeau A., Roy M.(1984): Familiar subjects in idiophatic Parkinson's disease. Can.J.Neurol.Sci. 11,144-150.
Calne D.B.(1983): Current views on Parkinson's disease. Can. J.Neurol.Sci. 10,11-5.
de Jong G.J., Meerwaldt J.D., Schmitz P.I.M.(1987): Factors that

influence the occurence of response variations in Parkinson's disease. Ann.Neurol. 22,4-7.
Diamond S.G., Markham C.H., Treciokas L.J.(1976): Long term experience with L.dopa: efficacy, progression and mortality. In Birkmayer W., Hornnykievicz O. (eds.) : Advances in Parkinsonism. Fifth International Symposium on Parkinson's disease, Vienna,1975. Basel, Editiones Roche, 444-445.
Duvoisin R.C.(1987): To treat early or late? Ann.Neurol. 22,2-3
Fields W.S.(1958): Pathogenesis and treatment of Parkinson's disease. Springfield: Charles C.Thomas.
Gerstenbrand F., Poewe W., Ransmayr(1982): The clinical spectrum of Parkinson's disease. In: Cecchini A., Nappi G., Arrigo A. (eds.): Cerebral pathology in old age. Neuroradiological and Neurophysiological correlations. Emiras, Pavia,pp. 31-33.
Granerus A.K., Carlsson A., Svanborg A.(1979): The aging neuron: influence on symptomatology and therapeutic response in Parkinson's syndrome.In : Poirier L.J., Sourkes T.L., Bedard P.eds. Advances in Neurology.New York,Raven Press. 24,327-334
Guillard A, Chastang C. (1978): Maladie de Parkinson. Rev. Neurol. 134, 5, 341-354.
Hartmaan-Von Monakori K. (1960): Das Parkinson-Syndrome. Basel: S.Karger. Hoen M.M.,Yarh M.D.(1967): Neurology 17,5, 427-442.
Hoen M.M. (1983) : Parkinsonism treated with levodopa: progression and mortality. J.Neurol.Trasmission.Suppl. 19,253-264.
Hoen M.M. (1985): The result of chronic levodopa therapy and its modification by bromocriptine in Parkinson's disease. Acta Neurol. Scand. 71, 97-106.
Lesser R.P., Fahn S., Snider S.R. (1979): : Analysis of clinical problems in parkinsonism and the complications of long term levodopa therapy. Neurology 29, 1253-1260.
Lieberman A.N., Goldestein M. (1982): Treatment of advanced Parkinson's disease with dopamine agonists. In Marsden CD, Fahn S. (eds.): Movement disorders. London, Butterworth Scientific, pp. 146-165.
Markham C.H., Diamond S.G. (1981): Evidence to support early levodopa theraphy in Parkinson's disease.Neurology 31,125-131
Markham C.H., Diamond S.G.(1986): Modification of Parkinson's disease by long term levodopa treatment. Arch. Neurol. 43, 405-407.
Marsden C.D., Fahn S. (1982): Problems in Parkinson's disease. In Marsden C.D., Fahn S. (eds.): Movement disorders. London, Benterworth Scientific, 1-7.
Marttila R.J.,Rinne U.K. (1977): Disability and progression in Parkinson's disease. Acta Neurol.Scand. 56, 159-169.
Melamed E.(1986): Initiation of levodopa therapy in parkinson patients should be delayed until the advanced stages of the disease. Arch.Neurol. 43, 402-405.
Mendel K.(1911): Die Paralysis Agitans. Berlin: Verlag von S. Karger.

Mjines H.(1949): Paralysis Agitans. Copenhagen: Epinar Munksgaard.
Pederzoli M., Girotti F., Scigliano G.(1983): L-dopa long term treatment in Parkinson's disease: age-related side effects. Neurology 33, 1518-1522
Pollock M., Hornabroock R.W.(1966): The prevalence, natural history and dementia of Parkinson's disease.Brain 89, 429-448
Poewe W., Gerstenbrand F., Ransmayr G. (1983): Klinische Manifestationstypen des Parkinson-Syndroms. Neuropsychiatria Clin. 2, 223-227.
Rajput A.H., Stern W., Laverty W.H.(1984): Chronic low dose levodopa theraphy in Parkinson's disease: an argument for delaying levodopa therapy. Neurology 34, 991-996.
Ransmayr G., Poewe W., Plorer S., Gerstenbrand F.(1983): Prognostic implications of the motor symptoms of side effects. Neurology 33, 1518-1522.
Ribadeau-Dumas, Rondot P., Cardon P.(1977): Development des etudes sur le traitment des syndromes parkinsoniens par la levodopa. II Effects a long term de la L-dopa seule ou en association avec un inhibiteur de la decarboxylase. Therapie 32, 61-172.
Wilson S.A.K.(1955): Neurology. Baltimore: Williams and Wilkins Co, 922. Zatusky W.J., Jankovic J., Pirozzolo F.(1985): The heterogeneity of Parkinson's disease: Clinical and prognostic implications. Neurology 35, 522-526.

British Library in Cataloguing in Publication Data
European Congress of Neurology (*1st: 1988*)
Neurology in Europe 1.
1. Medicine. Neurology
I. Title II. Bartko, Daniel III. Gerstenbrand, F. IV. Turčáni, P. (Peter)
616.8

ISBN 0 86196 202 8
ISSN 0957 9257

Published by
John Libbey & Company Ltd.,
13 Smiths Yard, Summerley St, London SW18 4HR, UK. +44 (0)81 947 2777
John Libbey Eurotext Ltd.
6 rue Blanche, 92120 Montrouge, France. +33 (1) 47 35 85 52
John Libbey-CIC s.r.l.,
via L. Spallanzani 11, 00161 Rome, Italy. +39 (06) 873054/869810

Printed in Great Britain by Whitstable Litho Ltd., Whitstable, Kent.

NEUROLOGY IN EUROPE I

Proceedings of the 1st European Congress of Neurology
April 1988, Prague, Czechoslovakia

Edited by

Daniel Bartko, Franz Gerstenbrand
and Peter Turčáni

John Libbey
LONDON · PARIS · ROME