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Experiences With L-Deprenyl in Parkinsonism

E. Csanda, J. Antal, M. Antóny, and **A. Csanaky**

Semmelweis University of Medicine, Department of Neurology, Budapest, Hungary

With 6 Figures

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Summary

In about $^2/_3$ of the cases studied (152 patients), the combination of deprenyl and the substitution-therapy has a favourable effect as it tends to normalize motor activity. Although the administering of deprenyl renders neither L-Dopa nor the decarboxylase inhibitor superfluous, their side effects can be slightly reduced as their dose is reduced. Therefore it is advised to give all patients a trial with this drug.

The progression of Parkinsonism cannot be arrested by even the most carefully arranged medication; the degeneration of nigrostriatal neurons becomes more extensive during the course of the illness. This fact requires the successive raising of the daily L-Dopa dose, and the maintenance of the optimal dopamine level becomes increasingly more difficult.

In advanced Parkinsonism the akinetic phases, the On-Off periods, the occassionally appearing hyperkineses and the psychotic symptoms reflect disturbances of dopamine metabolism.

It is well known that dopamine metabolism can be diminished by L-deprenyl, since this substance is a specific inhibitor of monoamine oxidase type B (*Knoll et al.*, 1968) and this enzyme is responsible for DA-catabolism in the human brain (*Glover et al.*, 1977). This study reports the effects of L-deprenyl supplementary medication in Parkinson's disease.

The substance was clinically tested in three institutes: in the Neurological Institute of the Semmelweis Medical University, Budapest, in the Neurological Departments of the Central State Hospital, Budapest, and of the County Hospital of Tolna.

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The effect of L-deprenyl has been examined by a double blind method in 152 parkinsonian patients. Encephalitis figured in the anamnesis of 28 patients; in the other patients we had no evidence that could be mentioned as an etiological factor. Lesion of the head figured in 5 cases. Parkinsonism was stated as appearing in the family of 6 patients and 14 patients were taking reserpine for shorter or longer periods. We found signs of cardiovascular disorders in many of our older patients.

The age of our 87 male and 65 female patients was 64 years on average, but this included some patients younger than 40 and older than 80 years. We have chosen our patients mainly from those suffering from long-term Parkinsonism. In 114 patients the first symptoms were noted more than 5 years ago, and only 16 patients had showed parkinsonian symptoms for less than 1 year.

Deprenyl was administered at the beginning of treatment in doses of 10—15 mg/day 2—3 tabs Jumex, Chinoin. After about two weeks it was reduced to 2.5—5 mg/day, dose which was maintained for at least one year.

In the present study we report the clinical course of our patients. We have elaborated a test-sheet, and registered the patients' motor performance before the administration of the drug, then after every 2 weeks, later every 2 months, using the following methods.

The stand-up and sit-down test was registered with a simple photo-electric method. The little lamps were attached to the shoulder and to the hip of the patient. Photo has been taken for 5 sec in a semi-dark room. A flash at the beginning of movement visualized the patient's position. On Fig. 1 A the severe parkinsonian patient tried to stand up—unsuccessfully. The same light traces are seen on Fig. 1 B, made by a simple subtraction. Part C shows the successful, if abnormal standing-up motion of the same patient, in his "On" period, after deprenyl medication.

The tremor and hypokinesis of the upper limbs were measured using different methods. First—following Steinbrecher—the patient has to make a mark with his right and left hand in small circles of a figure, and we quantified the disability by counting the number of points made in 1 min and by assessing the accuracy of the marks. Additionally we examined using a piezo-electric accelerometer, the movement of the forefinger of the right and left hand, over 20 sec at rest and with the hand stretched. The number and amplitude of all movements were registered numerically. Finally we recorded with reaction-timer a series of 20 motoric responses given by both hands to light-signals, with a precision of 0.1 msec.

The second figure shows the motor performance of a patient who

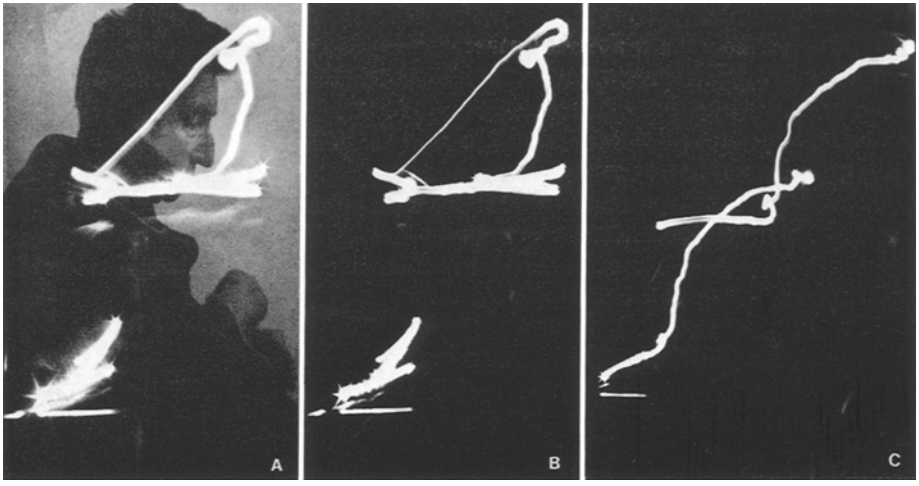

Fig. 1

earlier was started levodopa. The examinations, carried out at the same time of day and under the same conditions, show the improvement in motor performance of the same patient after additionally administered deprenyl. In the last columns the effect of placebo is shown: the values returned to the original level.

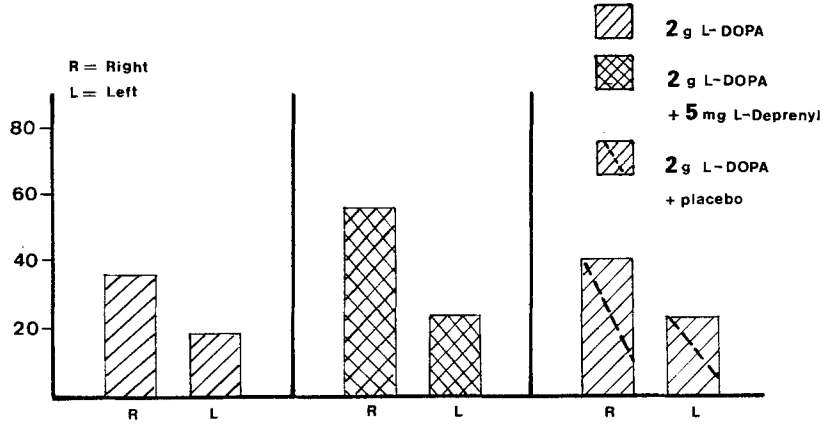

Fig. 2

The objectively registered hypokinesis and tremor are shown in the third figure, comparing these results with the evaluations of the patients themselves after 6 months of deprenyl treatment. This shows that a decrease in tremor is less after deprenyl than is the amelioration

of hypokinesis, as is generally known in this substitution therapy. On the other hand, the subjective opinions of the patients paralleled the general ability of movement, *i.e.* the improvement hypokinesis. A very good result is shown on the figure as ++; a fair improvement with +; the unchanged state with Ø; and a minus sign (—) shows impairment. In the subjective evaluation we have had to create a group marked with ±, because some patients reported an improvement in their movement but complained of side effects at the same time. These mainly referred to gastrointestinal complaints, in consequence of which, 9 of the 15 patients in the "minus" group stopped deprenyl medication, where upon their condition returned to the earlier level. In other patients we changed the therapy from L-Dopa and deprenyl to L-Dopa with benserazide and deprenyl, because the side effects were slighter when this combination was applied.

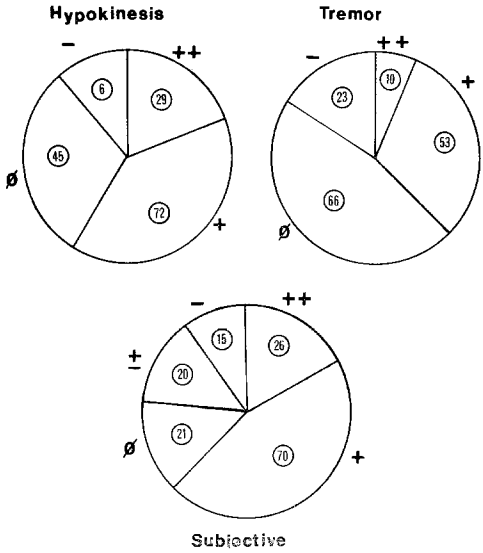

Fig. 3

In respect to the complaints during L-Dopa and deprenyl combination, side effects increased about 50 percent by maintaining the original substitution level, but when the L-Dopa dose was adequately decreased, the side effects decreased again, and at the same time the therapeutic effect proved to be still more favourable than initially. In this way the percentage of the side effects decreased to below the original level, in the periphery as well as centrally independent of, whether L-Dopa was administered with or without decarboxylase inhibitor.

Deprenyl alone, in doses of 5—10 mg, has no disagreable effect and proved to be favourable in 8 of 12 cases of mild parkinsonian patients. This is probably due to the protective effect on dopamine. However most favourable therapeutic effect can be obtained by L-Dopa substitution with simultaneous inhibition of both the dcarboxylase and the MAO B enzymes. Therefore, our clinical results are in good agreement with earlier findings by *Birkmayer et al.* (1975, 1977) and *Lees et al.* (1977).

In patients with long-lasting Parkinsonism the diurnal oscillation of their motoric performance, the "end of dose" askinesis, and On-Off periods could also be registered by our methods.

The effect of deprenyl on these oscillations is to be seen in the fourth figure. The first two columns show the average value of the reaction-time of a healthy young student, and that of a healthy man of 63. The other columns represent the values of a man of similar age, suffering from Parkinson's disease. In the beginning he took his daily dose (3 g L-Dopa) after breakfast, lunch and dinner, afterwards he received a mildly reduced L-Dopa dose/2 g/day and every morning, 5 mg deprenyl. The reaction-time examined in the morning, in relatively drug-free state, is long. This value improves during the forenoon, then, after a transitional impairment, an improvement sets up due to the midday dose. In values obtained with deprenyl the oscillation is much smaller: a rather better average performance can be seen. The S.D.'s of the reaction-times are rather large, even with

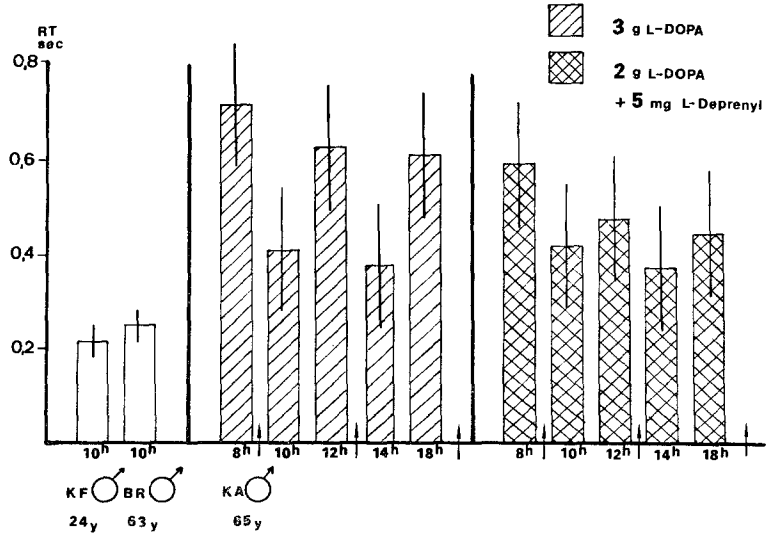

Fig. 4

better performance, which is partly due to the emotional excitement of the patient and partly to the consequences of his tremor.

The tremometric values show the same results (Fig. 5). The amplitude value of tremor at rest examined in the morning is very high. It decreases after taking the morning dose, and is impaired later on. In contrast an interesting effect is apparent in the amplitude values of the postural tremor registered in the stretched-hand position. This tremor appears to be increased after L-Dopa, and, unlike the resting tremor is not improved by deprenyl medication.

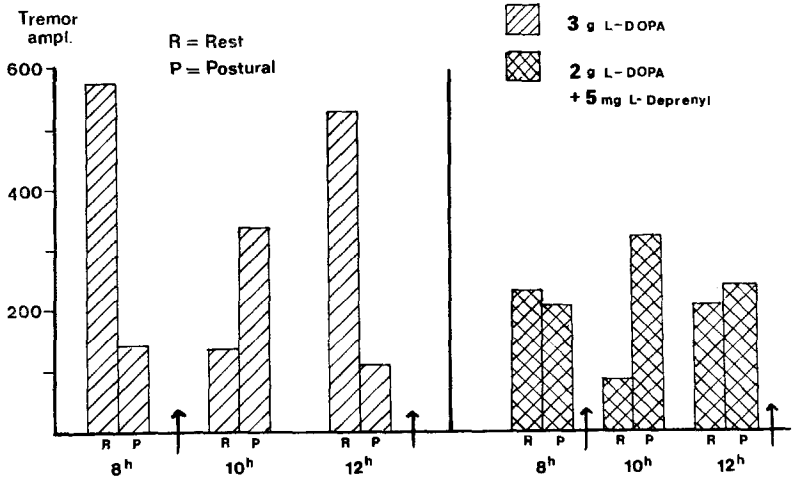

Fig. 5

In Fig. 6 we have illustrated our hypothesis of the effects of deprenyl. The continuous line marks the approximately optimal dopamine level characteristic to healthy persons. In mild Parkinsonism, with L-Dopa treatment by 3 medications per day a therapeutic level may be obtained, which oasses only slightly over and under the normal level.

In grave and advanced Parkinsonism the dopamine level decreases almost to Zero, but can be increased by a large dose of L-Dopa. This level may increase too much producing side effects. The level sinks again suddenly, and this alteration is repeated after each dose.

In such patients, L-deprenyl combined with the adequately decreased L-Dopa slows the metabolism of dopamine, and re-establishes the earlier dopamine level, characteristic of slight Parkinsonism.

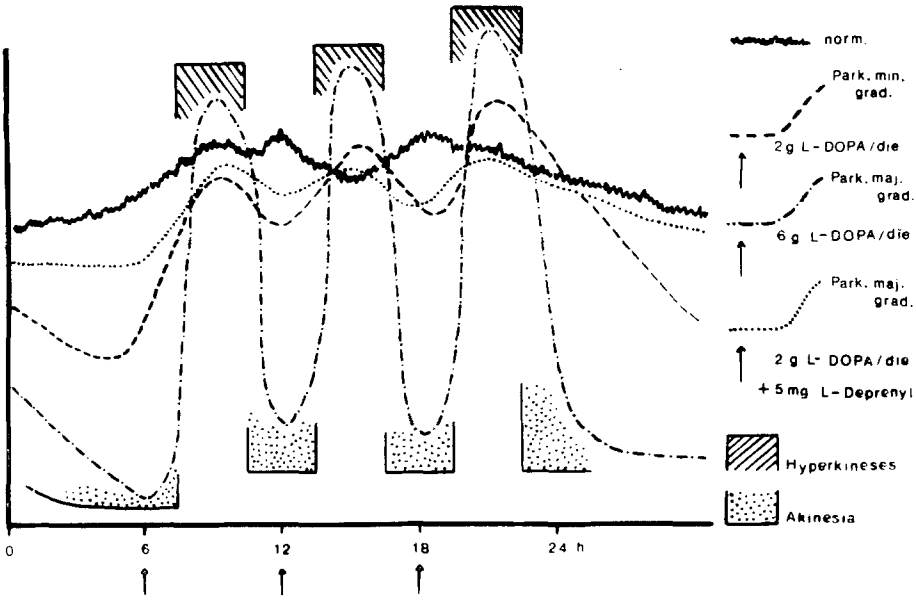

Fig. 6

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Author's address: Dr. *E. Csanda*, Department of Neurology, Semmelweis University of Medicine, Budapest, Hungary.