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Deprenyl (selegiline) in combination treatment of Parkinson's disease

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ABSTRACT — Long-term treatment of parkinsonian patients with levodopa (plus decarboxylase inhibitor) leads to decreasing levodopa efficacy and increasing side-effects. Then main therapeutic problems are on-off phenomena, end-of-dose akinesia and levodopa-induced dyskinesias. Deprenyl, a selective MAO-B inhibitor, has produced good therapeutic effects in combination either with levodopa alone or with levodopa plus decarboxylase inhibitor in the treatment of end-of-dose akinesia and on-off phenomena.

In an open trial with 48 parkinsonian patients deprenyl was added to previous levodopa plus decarboxylase-inhibitor therapy. Good effects were achieved in respect of mild on-off phenomena and end-of-dose akinesia, minor success in the alleviation of dyskinesia and depression. In four further patients with a post-traumatic parkinsonian syndrome, no improvement of rigido-spasticity and vigilance was demonstrable.

Key words: Parkinson's disease; long-term levodopa therapy; levodopa inefficacy; side-effects; monoamineoxidase inhibitor; deprenyl (selegiline).

INTRODUCTION

Gerstenbrand's first attempts to combine levodopa treatment with unspecific monoamine oxidase inhibitors in the treatment of Parkinson's disease began in 1964 and his findings were published in 1965 (1). Like Birkmayer et al. (2) and Bernheimer et al. (3) he failed to achieve any definite therapeutic success. The detection of selective monoamine oxidase (4), the demonstration of multiple forms of this enzyme in the brain (5) and the development of deprenyl by Knoll et al. (6) have all led to new possibilities.

In 1977 Birkmayer et al. (7) experimented with deprenyl, and reported positive results concerning disability. In the same year Lees et al. (8), in a double-blind trial, reported positive results concerning mild on-off phenomena and end-of-dose akinesia. In 1978 Csanda et al. (9) and Rinne et al. (10) described the good effects of deprenyl, as our own group has done during the last year (11).

MATERIAL AND METHODS

At the Innsbruck University Clinic of Neurology 48 patients, 22 male and 26 female, aged 52 to 66, mean 63.4 years, 44 with idiopathic and 4 with a postencephalitic form of Parkinson's disease, were treated with deprenyl in combination with levodopa + DCI (decarboxylase inhibitors benserazide or carbidopa).

42 patients exhibited decreasing benefit from levodopa plus DCI, which became apparent in on-off phenomena, with or without dyskinesias, therapy-resistant diurnal or nocturnal end-of-dose akinesia, dystonic foot cramps and untreatable akinetic crises.

28 of these 42 patients suffered from a rigid-akinetic type and 14 from a rigid-akinetic-tremor (equivalence) type of Parkinson's disease (12). In both groups, the duration of deprenyl treatment ranged from 2 weeks to 18 months. The mean duration of the disease was 6.2 years and of levodopa + DCI therapy 4.8 years, the final mean dosage being 780 mg daily. 34 patients had a medium and 8 a severe progression of the disease.

Six patients with a tremor-dominant type of Parkinson's disease were treated with deprenyl because of severe tremor and the unsatisfactory therapeutic effects of levodopa + DCI, anticholinergics and beta-blocking agents. The duration of deprenyl treatment was 2 to 4 weeks, and the mean duration of the disease 8.1 years. Levodopa + DCI therapy had been given for 4.7 years at a final mean dosage of 470 mg daily. The symptomatology of the disease was mild in three and medium in three patients.

In all three groups 5 mg deprenyl was given 2—3 times daily in addition to the optimum levodopa + DCI dosage. No other anti-parkinsonian medication was added. The levodopa + DCI dosage generally remained unchanged but was slightly reduced in a few cases.

There were also four patients who had a post-traumatic parkinsonian syndrome with severe rigido-spasticity. These patients were treated with deprenyl for 1 to 3 weeks in combination with levodopa.

The follow-up of the 48 parkinsonian patients was assessed by a doctor's rating scale of 9 items (each item being graded from 0 to 6), the North-Western University Disability Scale and the depression scale of Zung. The check-ups were made at intervals of from one to four weeks.

RESULTS

Group I consisted of 28 patients with PD of the rigid-akinetic type. Significant ($p < 0.05$) improvement was achieved in 13 patients. Mild on-off phenomena combined with dyskinesia were temporarily alleviated by a concomitant reduction of levodopa plus benserazide in 4 patients. End-of-dose akinesia, especially severe akinesia at night, was improved in 4 out of 7 patients. Two of these showed improvement in early morning dystonic foot cramps. Deprenyl had no observable effect on severe on-off phenomena or severe akinesia. (Table I).

Group II consisted of 14 patients with PD of the equivalence type. On-off phenomena were reduced in 4 out of 5 patients. Significant ($p < 0.05$) improvement was achieved in 8 out of 14 patients. In 2 out of 4 patients on-off phenomena plus mild dyskinesia were alleviated by the administration of deprenyl and a simultaneous reduction of levodopa plus carbidopa. End-of-dose akinesia was improved in 2 out of 3 patients, one of whom showed marked improvement in nocturnal akinesia. In this group too, deprenyl had no effect on severe akinesia (Table II).

Group III: the addition of deprenyl to anticholinergics or beta-blocking agents and levodopa plus DCI did not have any effect on tremor (Table III).

In 4 patients with post-traumatic parkinsonian symptomatology, rigidity as well as vigilance were improved by deprenyl. Not all of these patients suffered from side-effects.

In 8 of the 19 parkinsonian patients with concomitant depressive symptomatology an improvement was demonstrable on the Zung scale (not significant).

Side-effects of deprenyl, partly dosage-dependent, were apparent in 19 of the 48 pa-

Table I. Efficacy of deprenyl in combination with levodopa + decarboxylase inhibitor in the treatment of Parkinson's disease (U-test of Mann and Whitney)

Treatment of 28 patients with PD of the RIGID-AKINETIC TYPE (Group I)
mean duration of disease 5.9 yrs.
mean duration of levodopa therapy 4.9 yrs.
mean dosage of levodopa + DCI: 795 mg daily

Deprenyl significantly effective ($p < 0.05$) in:

Clin.Rating Scale	North-West.U. Disab.Scale	Total	
4	3	5	out of 7 patients with mild on-off phenomena
3	2	4	out of 8 patients with mild on-off phenomena + dyskinesia
0	0	0	out of 4 patients with severe on-off phenomena
1	2	2	out of 4 patients with end-of-dose akinesia
2	1	2	out of 3 patients with end-of-dose akinesia + dystonic foot cramps
0	0	0	out of 2 patients with severe therapy-resistant akinesia
10	8	13	28

Table II. Efficacy of deprenyl in combination with levodopa + decarboxylase inhibitor in the treatment of Parkinson's disease (U-test of Mann and Whitney)

Treatment of 14 patients with PD of the RIGID-AKINETIC-TREMOR TYPE (EQUIVALENCE TYPE) (Group II)
mean duration of illness 6.6 yrs.
mean duration of levodopa therapy 4.6 yrs.
mean dosage of levodopa + DCI: 750 mg daily

Deprenyl significantly effective ($p < 0.05$) in:

Clin.Rating Scale	North-West.U. Disab.Scale	Total	
2	3	4	out of 5 patients with mild on-off phenomena
2	2	2	out of 4 patients with mild on-off phenomena + dyskinesia
1	1	2	out of 3 patients with end-of-dose akinesia
0	0	0	out of 2 patients with severe therapy-resistant akinesia
5	6	8	14

Table III. Efficacy of deprenyl in combination with levodopa + decarboxylase inhibitor in the treatment of Parkinson's disease (U-test of Mann and Whitney)

Treatment of 6 patients with PD of the TREMOR-DOMINANCE TYPE (Group III)
mean duration of illness 8.1 yrs.
mean duration of levodopa therapy 4.7 yrs.
mean dosage of levodopa + DCI: 470 mg daily

No improvement of tremor achieved.

tients. Only in two cases was an interruption of deprenyl therapy necessary, because of severe nausea. Both these patients had severe, therapy-resistant akinesia. Side-effects closely resembled those of levodopa and could in some cases be reduced by lowering the dose of levodopa (Table IV).

Table IV. Side-effects of deprenyl

Side-effect	Number of patients
Nausea	11
Dizziness	3
Hypotension	4
Hallucination + Confusion	5
Dyskinesia	4
	Total 19 patients

SUMMARY AND DISCUSSION

Deprenyl in combination with levodopa + DCI was effective in altogether 15 of 24 patients with mild on-off phenomena, in two subgroups (the rigid-akinetic and rigid-akinetic-tremor type of Parkinson's disease). In six cases dyskinesia was improved by reducing the dose of levodopa. In 6 of 10 patients deprenyl in combination with levodopa + DCI brought about pronounced improvement in end-of-dose akinesia which also appeared as nocturnal and early morning akinesia. Dystonic foot cramps were diminished in 2 out of 3 patients. According to the Zung scale depression was mildly alleviated in 8 out of 19 patients. There was no effect on severe on-off phenomena, severe, therapy-resistant akinesia or severe tremor. None of the four patients with the post-traumatic parkinsonian syndrome showed any improvement in rigidospasticity and vigilance. The side-effects resembled those of levodopa and could in most cases be managed by dose-reduction of deprenyl or levodopa. In two patients deprenyl had to be discontinued.

It should be pointed out that deprenyl was given only to parkinsonian patients with advanced symptomatology who received optimum levodopa treatment. It will be necessary to test the efficacy of deprenyl in mild Parkinson's disease, both in combination with levodopa + DCI and without concomitant parkinsonian medication. Our results compare well with those of Lees (8) Birkmayer (7), Csanda (9) and Rinne (10). Our findings reported in 1982 (11) have since been confirmed in a further 18 patients. On the alleviation of depression, reference should be made to Eisler et al. (13), who described the behavioural benefits of deprenyl. Deprenyl completes the spectrum of medicaments for the above-mentioned indications and is an effective drug in combination treatment of Parkinson's disease.

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