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Experience with selegiline in the treatment of Parkinson's disease

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Summary

28 patients with Parkinson's disease and long-term levodopa therapy have received additional selegiline (10 mg/d) over the past 3 years and been followed up for a mean period of 18.8 months. Two thirds improved with a reduction of global disability and amelioration of end-of-dose effects, nocturnal and early-morning akinesia. Peak-dose dyskinesias tended to increase with selegiline while biphase and off-period involuntary movements improved in some cases. Patients already on maximally tolerated doses of levodopa and those with severe on-off swings did not gain significant benefit. 8 of 18 responders lost their initial response within 1.5 years.

Introduction

Monoamine oxidase (MAO) inhibitors have been shown to be effective in Parkinson's disease even before levodopa treatment had become generally accepted, but side-effects precluded their further use (Gerstenbrand and Prosenz, 1965). It took another decade before Birkmayer and colleagues introduced the selective MAO-B inhibitor selegiline into the therapy of Parkinson's disease as a means of enhancing the efficacy of levodopa treatment (Birkmayer et al., 1975, 1977). Meanwhile it seems well established that the addition of selegiline can also smooth out some of the response fluctuations which develop in more than 50% of patients on long-term levodopa therapy (Csanda and Tarczy, 1983; Lees, 1987).

This report presents a review of the authors' experience with selegiline in the routine treatment of advanced Parkinson's disease.

Patients and methods

The clinical charts of all patients with advanced Parkinson's disease regularly attending the movement disorder clinic of this hospital who started treatment with selegiline in the past three years were evaluated retrospectively. Twenty of these patients are men and 8 women; mean duration of selegiline therapy at the time of evaluation was 1.5 years. All were on a stable regimen of sustained levodopa substitution and further clinical details are given in Table 1. The reasons for introducing selegiline (5 mg twice

Table 1. Selegiline in Parkinson's disease, patient data (N = 28)

Age at onset	54.8 (39–71) years
Duration of Parkinson's disease	7.3 (1–15) years
Hoehn and Yahr stage	3.3 (2–4) years
Concomitant drugs	
L-dopa	28
bromocriptine	3
lisuride	2
anticholinergics	2
amantadine	2
Duration of selegiline	18.8 (3–37) months

daily) were declining efficacy of levodopa and/or response fluctuations, and some patients were also suffering from pronounced biphasic dyskinesia or off-period dystonia (see Table 2).

Table 2. Selegiline in Parkinson's disease, clinical problems (N = 28)

Declining L-dopa effect	14
Response fluctuations	
end-of-dose	16
random	6
Nocturnal/early morning akinesia	15
Off-period dystonia	
Biphasic dyskinesias	

All patients had been seen at three- to six-monthly intervals and at each visit the following had been recorded: Hoehn and Yahr stage, scores of the Columbia University Rating Scale (CURS) and Northwestern University Disability Scale (NUDS), type of response oscillations and estimate of daily hours "on" or "off", as well as drug-induced dyskinesias (type and severity on a scale from 0 to 3).

Results

18 of the 28 patients gained some benefit after the addition of selegiline to their previous drug regimen. Two thirds improved in their global

disability status as expressed by CURS and NUDS scores, and the majority of those with end-of-dose deterioration also develop a smoother response pattern. Fewer patients had improved nocturnal or early morning akinesia, off-period dystonia or biphasic dyskinesias (see Table 3).

Table 3. Selegiline in Parkinson's disease, clinical improvement (N = 28)

Global disability	12
End-of-dose effects	11
Nocturnal/early morning akinesia	8
Off-period dystonia	2
Biphasic dyskinesia	2
Total responding	18

In 10 patients, selegiline was discontinued prematurely after an average of about 2 months, mainly because of lack of efficacy. Several patients, however, experienced untolerable worsening of their pre-existing abnormal involuntary movements and three developed paranoid-hallucinatory symptoms (see Table 4).

8 of the 18 responders lost their initial benefit after an average of 12 months and their selegiline treatment was subsequently discontinued without further deterioration of their parkinsonian symptoms.

Table 4. Selegiline in Parkinson's disease, treatment failures (N = 28)

Lack of effect	9
Increased dyskinesias	5
Hallucinosis	3
Loss of initial effect	8

Discussion

In this retrospective survey of routine treatment of advanced Parkinson's disease with selegiline, two thirds of the patients derived worthwhile therapeutic benefit from the addition of the MAO-B inhibitor. The most consistent response was seen in those who had experienced a beginning decline in the effectiveness of levodopa and mild end-of-dose deterioration, nocturnal and early-morning akinesia. These results correspond well to what has been reported in early uncontrolled (Birkmayer et al., 1975) as well as controlled trials (Lees et

al., 1977) with this drug. Also, in accordance with observations made by other authors (Lees et al., 1977; Lees, 1987) patients already on maximally tolerated doses of levodopa or those with severe on-off swings showed little or no improved when started on selegiline.

Abnormal involuntary movements induced by levodopa were influenced only in a minority of cases. While biphasic dyskinesias and off-period dystonia improved in two patients each peak-dose chorea increased in five. Enhanced peak-dose dyskinesias with selegiline are a well recognized adverse effect (Lees et al., 1977; Rinne, 1983) and were a reason to stop treatment in some cases of this series. While selegiline is generally well tolerated, induction of hallucinosis is a potentially serious side-effect when the drug is added to levodopa and this was observed in three instances in this survey. Again, patients already on maximally tolerated doses of levodopa and with a history of psychosis or confusional states seem to be at a particular risk of developing this complication.

Mood elevation has been observed with selegiline therapy and some authors have suggested that its effects on Parkinson's disease might be mediated by an unspecific antidepressant action (Eisler et al., 1981). No significant antidepressant effects have been observed in this group of patients, but follow-ups did not include standardized rating scales for depressive symptoms.

Although some have reported on possible dose reductions of levodopa after adding selegiline (Csanda and Tarczy, 1983) this was in early cases and was not possible in the patients of this series.

One third of the initial responders of this survey lost benefit within the first 15 months of treatment and this time course has also been observed by others (Stern et al., 1983). The exact reasons for this relatively shortlived response to selegiline are not clear, but they are probably linked to a progression of the underlying disease.

Overall the results observed in this group of 28 patients confirm the efficacy of additional selegiline in at least temporarily compensating a declining levodopa effect in advanced Parkinson's disease and in smoothing out mild to moderate end-of-dose deterioration.

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