Long-term persistence of symptomatic effect of selegiline in Parkinson's disease. A two-months placebo-controlled withdrawal study

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Summary. Following a two-months of placebo-controlled withdrawal, the MAO-B inhibitor selegiline was found to maintain a long term significant mild to moderate symptomatic effect on bradykinesia and tremor at rest in nine patients with Parkinson's disease (stage II and III of H&Y), whose functional impairment had also required a dopaminergic therapy with low-dose bromocriptine. Both motor signs found worsened during the wash-out showed a full recovery to pre-withdrawal condition within two months after reinstitution of the drug.

Keywords: Selegiline, Parkinson's disease, withdrawal, symptomatic effect.

Introduction

The irreversible MAO-B inhibitor selegiline is known to exert a definite even though mild to moderate symptomatic effect when given as monotherapy in early Parkinson's disease (PD) (Koller, 1996) or as an adjunct to L-dopa in patients with response fluctuations in more advanced stages of the disease (Myllyla et al., 1996). Although it is commonly reported that the action of the drug wears off on prolonged treatment, i.e. after less than 12 months on average, in both early and advanced stages patients, this notion may be challenged by the concurrent ongoing progression in severity of the degenerative process, thus masking any possible persistence of direct drug effect on motor symptoms (Calzetti et al., 1995). So far the few studies designed to investigate this issue have lead to conflicting results (The Parkinson Study Group, 1993; Palhagen et al., 1998), and, to our knowledge, only one of them has been addressed to evaluate the possible long-term persistence of the symptomatic effect of selegiline given as an adjunct to a dopamine (DA) receptor agonist in patients with PD (Olanow et al., 1995).

We report the results of a two-months period of placebo-controlled withdrawal of selegiline in patients with early PD who were also taking low-dose
bromocriptine in a combined chronic regimen, in order to evaluate indirectly whether or not the MAO-B inhibitor maintains on the long-term its initial effect on motor symptoms of the disease.

Methods

Patients with PD diagnosed according to UK Parkinson's disease Brain Bank criteria attending the out-patient Movement Disorder Clinic at the Institute of Neurology, University of Parma, and who were undergoing a chronic combined regimen with the DA agonist bromocriptine plus selegiline, were asked to give their informed consent about the possible substitution of the MAO-B inhibitor for placebo over a two-months period.

All the nine consenting patients (five male and four female, aged 47 to 77 years, median age 65 years), received under single blind condition (i.e. unaware of whether or not they were still continuing to take active selegiline) identical placebo tablets for a two-months period, followed by the resumption of previous drug regimen. At the time of enrollment, in these patients the duration of the disease (as from the onset of symptoms) ranged from 43 to 60 months (median 52 months) and the duration of selegiline treatment as an add-on to ongoing bromocriptine ranged from 13 to 44 months (median 30 months), whereas prior bromocriptine monotherapy lasted for a median period of 5 months (range 1–9 months). The severity of the disease according to Hoehn & Yahr (H & Y) stage scored II in three patients and III in six patients. The pre-withdrawal daily dosage of selegiline was 10 mg in all patients, whereas the median daily dosage of bromocriptine was 20 mg (range 7.5–20 mg) and remained unvaried during the wash-out period. Likewise unchanged remained the dosage of anticholinergics, which five patients were taking in association. None of the patients had been previously exposed to L-dopa or DAergic drugs other than bromocriptine and selegiline.

In none of the nine patients the neurological status had shown significant change in terms of motor disability for the two months prior to selegiline discontinuation, as reported subjectively and assessed by means of Unified Parkinson's Disease Rating Scale (UPDRS) (section III total scores being on average 38.3 and 38.6 at the pre-baseline and baseline evaluations, respectively).

Clinical evaluations were made by the same investigator (AN) just before (time 0) and 2, 4, 8 weeks following active selegiline discontinuation (wash-out assessment) and 4, 8 weeks following its reinstitution at previous daily dosage (wash-in assessment) by using H & Y stage and sections of the UPDRS, i.e. subcomponents of tremor at rest (item 20), rigidity (item 22) and bradykinesia (items 19, 23, 24, 25, 26 and 31). Patient's self-assessment (S-A) of motor symptoms was carried out by means of an arbitrary rating scale (score 0–10 for each of the 7 items considered) at the same time intervals. Changes in mood were investigated by means of Zung self-rating Depression Scale (SDS index derived).

Statistical analysis was performed by using the Wilcoxon's rank test for paired data and Spearman's rank correlation coefficient.

Results

As compared to pre-withdrawal evaluation (time 0) a significant worsening occurred at the fourth and eighth weeks following selegiline discontinuation in the UPDRS section III total scores and in either bradykinesia or resting tremor scores separately considered (Table 1). All but one patients showed worsening in the UPDRS section III total scores, the overall degree of deterioration, expressed in terms of percentage change of baseline values (time 0), being on average by 8.3% at the fourth and by 10.2% at the eighth week of