The effect of selegiline on the peripheral pharmacokinetics of levodopa in young volunteers

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The plasma pharmacokinetics of levodopa were studied in eight healthy young subjects following an i.v. infusion of 50 mg over 5 min. Subjects were studied on two occasions in random order following treatment with carbidopa; on one occasion they were pretreated with selegiline (four doses of 10 mg over the preceding 3 days) and on the other with a placebo. The mean plasma concentration-time curves on each occasion were essentially superimposable and there were no significant differences in any calculated pharmacokinetic parameter. Selegiline does not significantly alter the distribution or elimination of levodopa from plasma.

Keywords selegiline levodopa pharmacokinetics

Introduction

Levodopa remains the mainstay of drug therapy for Parkinson's disease but is often used in combination with other compounds, particularly in advanced disease. Selegiline is a monoamine oxidase (MAO) B inhibitor which is believed to prolong the duration of action of levodopa by reducing dopamine metabolism in the brain [1]. MAO B is present largely in the central nervous system rather than the intestinal wall, and has dopamine as its principal physiological substrate. Co-administration of levodopa with a dose of selegiline sufficient to produce 80% inhibition of MAO B resulted in two to three-fold higher concentrations of dopamine in rat brain [2]. Selegiline treatment decreased the amounts of the deaminated dopamine metabolite, 3,4-dihydroxyphenylacetic acid, in the cerebrospinal fluid of humans [3].

The concurrent use of levodopa and selegiline in patients with short-duration response to levodopa (the 'wearing off' phenomenon) prolongs the clinical effect when compared with the action of levodopa alone [4]. The combination is also beneficial in patients who respond poorly to levodopa alone [5] including patients in the early stages of the disease [6]. The improved response can often be achieved with a lower dosage requirement for levodopa [7, 8].

The efficacy of levodopa is highly dependent on steady delivery to the brain, particularly in late stages of the disease when neuronal dopamine storage capacity is severely reduced. In this situation the plasma concentration of levodopa becomes an impor-

tant determinant of response [9]. There is little information available on the peripheral pharmacokinetics of levodopa when used in combination with selegiline. Data obtained after oral administration of levodopa to six patients with Parkinson's disease suggested that selegiline had little influence on levodopa absorption or kinetics [10]; however, there are wide inter- and intra-individual variations in levodopa kinetics following an oral dose [11–13] due to variability in gastric emptying and first-pass metabolism [12–14]. There are no published data on the effects of selegiline following the i.v. administration of levodopa which would be more suitable to detect changes in distribution and elimination. We report the results of a study to investigate the effect of selegiline on the pharmacokinetics of a short i.v. infusion of levodopa in young healthy volunteers.

Methods

Eight healthy male volunteers aged 21–22 years with body weights between 69 and 80 kg were studied on two occasions separated by at least 1 week, having fasted for 12 h. Written informed consent was obtained and the study was approved by the local ethics committee. In random order they were given either selegiline (10 mg) or ascorbic acid (50 mg in the absence of a matching placebo) in the morning for 3

days preceding levodopa and on the day of the study 1 h prior to levodopa administration. On each occasion the peripheral dopa decarboxylase inhibitor, carbidopa, was given 1 h before (100 mg) and 5 h after (50 mg) levodopa.

Levodopa (50 mg) was infused i.v. over 5 min in 100 ml of 0.9% saline via a cannula inserted into a forearm vein. Blood samples (10 ml) were obtained immediately prior to levodopa and at the mid-point of the infusion from a cannula inserted into the opposite arm. Subsequent samples were withdrawn at the end of the infusion and 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 180, 240, 300, 360, 420 and 480 min after completion. Plasma was stored at -20°C until analysis as previously described [13].

Pharmacokinetic parameters were calculated according to the methods described by Gibaldi & Perrier [15]; coefficients and exponential terms were derived after fitting a three compartment model with a 5 min zero order input to the plasma concentration-time curve using the SIPHAR programme (SIMED, Creteil, France). Statistical analysis was by Student's *t*-test for paired data and the signed rank test. Data are expressed as the mean $\pm$ s.d. A *P* value of 0.05 or less was taken as statistically significant.

Results

The mean plasma levodopa concentration-time curves (Figure 1) on each occasion were essentially superimposable and there were no statistically significant differences at any time point. The derived pharmacokinetic parameters for levodopa in the presence and absence of selegiline are given in Table 1. There were no significant differences between any of the measures on the two study days. The greater variability in the calculated terminal half-life ($t_{1/2,z}$) and mean residence time (MRT) with selegiline pre-treatment (Table 1) arose from a higher apparent volume of distribution (*V*) for one of the subjects; the difference in clearance in this subject was comparable with that found for the other volunteers.

Discussion

The pharmacokinetics of i.v. levodopa were similar to those previously reported in young volunteers in the presence of carbidopa [13]. The observation of a lack of interaction with levodopa pharmacokinetics in Parkinsonian patients given selegiline with oral levodopa [10] has been supported by this study using

Figure 1 The plasma concentration-time curve for levodopa following an i.v. infusion of levodopa (50 mg) in young healthy subjects also given carbidopa. The points are the mean values ($\pm$ s.d.) for eight subjects following pretreatment with selegiline (solid lines and closed symbols) or placebo (dotted lines and open symbols). None of the points showed a statistically significant treatment related difference.

Table 1 Levodopa pharmacokinetics in the presence and absence of selegiline

	Placebo	Selegiline
CL (ml min ⁻¹)	427 $\pm$ 69 (369–484)	435 $\pm$ 76 (372–499)
<i>V</i> (l)	78.9 $\pm$ 22.0 (60.5–97.3)	140.9 $\pm$ 114.4 (45.1–236.7)
<i>V</i> _{ss} (l)	46.8 $\pm$ 9.5 (38.8–54.7)	67.5 $\pm$ 39.7 (34.2–100.7)
<i>t</i> _{1/2,z} (min)	127 $\pm$ 24 (107–147)	242 $\pm$ 246 (36–449)
MRT (min)	111 $\pm$ 18 (96–126)	169 $\pm$ 130 (60–277)

The results are the mean $\pm$ s.d. for eight young male volunteers pre-treated with either selegiline or placebo (with 95% confidence intervals in parentheses). The data were not significantly different by either paired *t*-test or signed rank test.

an i.v. dose and young volunteers. We have extended the observations by showing a lack of effect of selegiline on the plasma clearance or apparent volume of distribution of levodopa. Previous studies suggested that the administration of selegiline for 3 days prior to levodopa should be sufficient to produce the full pharmacological effect on neuronal MAO B [16] and the dose chosen in the present study was that most commonly employed in clinical practice.

These data provide further support to the evidence

that the major and possibly the sole mechanism of action of selegiline in prolonging the duration of action of levodopa is by its effect on dopamine metabolism in the brain and that there is no significant change in the delivery of levodopa to the site of metabolism. This conclusion contrasts with the data for catechol-O-methyl transferase inhibitors such as entacapone, where much of the clinical benefit probably derives from increased systemic concentrations of levodopa [17, 18].

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