The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers

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- 1 The pharmacokinetics of levodopa and paracetamol after single oral doses have been investigated in eight healthy young volunteers in the fasted state and following isocaloric meals containing either 10.5 g or 30.5 g of protein.
- 2 The initial peak and maximum plasma drug concentrations and the times at which these occurred were not affected by food.
- 3 The mean area under the plasma concentration-time curve (AUC) for paracetamol following an overnight fast did not differ significantly from that observed following the low and high protein meals.
- 4 By contrast, the AUC for levodopa following the low protein meal ($193.9 \pm 15.7 \mu\text{g ml}^{-1} \text{ min}$) was significantly lower compared with administration in the fasted state ($216.5 \pm 26.1 \mu\text{g ml}^{-1} \text{ min}$). However, there were no significant differences in the kinetics of levodopa between the fasting state and following the high protein meal.
- 5 There was no evidence that consumption of a meal containing 30.5 g of protein impaired either the rate or extent of absorption of levodopa. Therefore the reported beneficial effects of a low protein diet in the treatment of patients with Parkinson's disease probably result from reduced competition for levodopa transport across the blood-brain barrier.

Keywords levodopa protein meals food pharmacokinetics absorption

Introduction

High protein meals have been reported to impair the clinical response to levodopa in patients with Parkinson's disease, while low protein diets can enhance the effect of levodopa and may ameliorate fluctuations in clinical response (Carter *et al.*, 1989; Frankel *et al.*, 1989; Gillespie *et al.*, 1973; Juncos *et al.*, 1987; Mena & Cotzias, 1975; Pincus & Barry, 1987; Tsui *et al.*, 1989). Such studies have defined the relationship between dietary manipulation and clinical response and a number have suggested that the deterioration with high protein diets is not associated with a decrease in plasma concentrations of levodopa (Carter *et al.*, 1989; Juncos *et al.*, 1987; Pincus & Barry, 1987; Tsui *et al.*, 1989). This indicates that the main mechanism of interaction may be competition between levodopa and other large neutral amino acids derived from proteins for transport across the blood-brain barrier. However, studies on the plasma concentrations of levodopa measured for up to 6 h after single doses in patients with Parkinson's disease have shown that protein containing meals cause a delay in the

time to peak concentration and a significant reduction in the maximum plasma concentration and the area under the plasma concentration-time curves (Baruzzi *et al.*, 1987; Nutt *et al.*, 1984).

There are a number of ways in which dietary protein could interfere with the absorption of levodopa. The main site of absorption for levodopa is the small intestine which utilises a specific transport system (Wade *et al.*, 1973) similar to that across the blood-brain barrier. Therefore competition between levodopa and other large neutral amino acids (LNAA) derived from dietary protein could occur at this site. In addition, dietary protein has been reported to prolong gastric emptying (Minami & McCallum, 1984) and the stomach, which has limited absorptive capacity, is able to metabolise levodopa (Rivera-Calimlim *et al.*, 1971). Finally gastric emptying, which controls the rate of delivery of levodopa to the small intestine, is inhibited by levodopa and the altered pattern of emptying can result in multiple peaks in the plasma drug concentration-time curve

(Robertson *et al.*, 1990). The influence of a protein containing meal on the altered pattern of gastric emptying produced by levodopa has not been investigated.

The aim of this study was to clarify the extent and contribution of any changes in the peripheral pharmacokinetics of levodopa to the reported interaction between dietary protein and the clinical response to levodopa. We have studied the effect of meals with low or high protein content on the pharmacokinetics of levodopa under controlled conditions.

Methods

Eight healthy, non-smoking, male volunteers with a mean age of 23 years (range 21–31) and body weights of 66–81 kg took part in the study. The study was approved by the local Ethics Committee and all subjects gave written informed consent. None had a history of gastrointestinal disorders or was receiving regular medication. Subjects attended, after an overnight fast, on three occasions separated by at least 1 week. On each study day they received 1.5 g of paracetamol as a marker of gastric emptying and 125 mg of levodopa dissolved in 100 ml of water. Blood samples were taken prior to drug administration and at 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, 180, 240, 360, and 480 min after dosing. Plasma concentrations of paracetamol and levodopa were measured by reverse phase h.p.l.c. as described previously (Robertson *et al.*, 1989). Carbidopa (100 mg) was administered 1 h before the levodopa. Subjects remained semi-recumbent for the first 3 h of the study and received a standard meal containing 25 g of protein at 4 h.

The three studies were carried out in random order. On one occasion the subjects remained fasting until 4 h after the dose of levodopa and on the other 2 days they consumed a meal, containing either 10.5 g or 30.5 g of protein, 15 min prior to the dose of levodopa. The diets contained similar amounts of fat and fibre but the carbohydrate content of the high protein diet was lower in order to make the meals of similar calorific value (Table 1).

Data analysis

Multiple peaks occur commonly in the plasma concentration-time curve for levodopa following oral administration. The concentration of the initial plasma peak of paracetamol or levodopa (C_i), the maximum plasma concentration (C_{max}) and the time of C_i (t_i) and C_{max} (t_{max}) are the observed values. The area under the

plasma drug concentration-time curve (AUC) was calculated using the linear trapezoidal rule with extrapolation to infinity, the terminal half-life was calculated by least squares regression analysis and the mean residence time from the AUC and the area under the first moment of the plasma drug concentration-time curve as described by Gibaldi & Perrier (1982). The paracetamol and levodopa assays had coefficients of variation of approximately 5% (Robertson *et al.*, 1989). Results are expressed as mean $\pm$ s.d. and were analysed by the Wilcoxon signed rank test and two-way analysis of variance.

Results

The plasma concentration-time curves for paracetamol and levodopa were similar on each study day (Figures 1 and 2). The concentration at the initial peak (C_i) was the maximum concentration observed, i.e. ($C_i = C_{max}$) on 22 of the 24 study days for paracetamol and on 23 of the 24 study days for levodopa. The values for C_i , t_i , C_{max} and t_{max} for both paracetamol and levodopa were similar on each of the 3 study days and were not significantly affected by food (Table 2). The AUC for paracetamol following an overnight fast did not differ significantly from that observed following either the low or high protein meals (Table 2). In contrast, the AUC for levodopa following the low protein meal was significantly lower compared with administration in both the fasted state and following the high protein meal ($P < 0.05$). Multiple plasma levodopa peaks were observed in 6/8 subjects when fasted, in 5/8 following the low protein meal but did not occur after the high protein meal. In consequence there was much greater inter-individual variability in t_{max} of both levodopa and paracetamol under fasting conditions than following the high protein meal.

Figure 1 The influence of protein containing meals (■ control, + low protein, ○ high protein) on the plasma concentration-time curve of paracetamol. The results are the means for eight volunteers.

Table 1 Composition of the test meals

Nutrient	Low protein	High protein
Protein	10.5 g	30.5 g
Carbohydrate	64.3 g	43.5 g
Fat	14.9 g	17.1 g
Fibre	4.2 g	3.3 g
Energy	417.8 kcal	439.5 kcal

Table 2 The effect of protein meals on the absorption of levodopa and paracetamol

	Fasted	Low protein	High protein
<i>Levodopa</i>			
AUC ($\mu\text{g ml}^{-1} \text{ min}$)	216.5 $\pm$ 26.1	193.9 $\pm$ 15.7*	210.9 $\pm$ 16.1
C_i ($\mu\text{g ml}^{-1}$)	2.99 $\pm$ 1.16	2.30 $\pm$ 0.56	2.53 $\pm$ 0.49
t_i (min)	20 $\pm$ 8	16 $\pm$ 5	20 $\pm$ 0
C_{max} ($\mu\text{g ml}^{-1}$)	3.14 $\pm$ 0.96	2.30 $\pm$ 0.56	2.53 $\pm$ 0.49
t_{max} (min)	27 $\pm$ 23	16 $\pm$ 5	20 $\pm$ 0
$t_{1/2}$ (min)	93 $\pm$ 10	89 $\pm$ 10	87 $\pm$ 10
MRT (min)	116 $\pm$ 10	116 $\pm$ 12	113 $\pm$ 11
<i>Paracetamol</i>			
AUC ($\mu\text{g ml}^{-1} \text{ min}$)	4345 $\pm$ 705	4153 $\pm$ 910	4056 $\pm$ 622
C_i ($\mu\text{g ml}^{-1}$)	28 $\pm$ 13	23 $\pm$ 8	22 $\pm$ 6
t_i (min)	18 $\pm$ 7	11 $\pm$ 4	16 $\pm$ 7
C_{max} ($\mu\text{g ml}^{-1}$)	30 $\pm$ 12	23 $\pm$ 8	22 $\pm$ 6
t_{max} (min)	28 $\pm$ 23	16 $\pm$ 14	16 $\pm$ 7
$t_{1/2}$ (min)	143 $\pm$ 15	151 $\pm$ 32	139 $\pm$ 18
MRT (min)	212 $\pm$ 23	228 $\pm$ 49	206 $\pm$ 31

* $P < 0.05$ compared with administration when fasted or following a high protein meal by Wilcoxon's signed rank test and two-way analysis of variance.

C_i = concentration of initial plasma peak; t_i = time of C_i ;

C_{max} = maximum concentration; t_{max} = time of maximum concentration;

AUC = area under the plasma concentration-time curve; $t_{1/2}$ = terminal half-life. MRT = mean residence time.

The results are the means $\pm$ s.d. for eight subjects.

Figure 2 The influence of protein containing meals (■ control, + low protein, ○ high protein) on the plasma concentration-time curve of levodopa. The results are the means for eight volunteers.

Discussion

Studies of the clinical interaction between protein intake and the response to levodopa have used meals with widely different protein contents. In some studies the protein was administered as part of a 'normal' meal, while others used a liquid protein formula. Nevertheless a consistent finding was that the effectiveness of levodopa was reduced by a daily protein intake in excess of 1.6 g kg^{-1} or a single protein load of 0.4 g kg^{-1} , i.e.

approximately 28 g (Carter *et al.*, 1989; Gillespie *et al.*, 1973; Mena & Cotzias, 1975; Tsui *et al.*, 1989). The degree of protein restriction required for clinical benefit was less clear but appeared to be stringent. Most studies reported improvement with a protein restriction to approximately 0.5–0.8 g $\text{kg}^{-1} \text{ day}^{-1}$, i.e. approximately 11–18 g in each of three equal meals per day (Carter *et al.*, 1989; Gillespie *et al.*, 1973; Juncos *et al.*, 1987; Mena & Cotzias, 1975; Tsui *et al.*, 1989). Pincus & Barry (1987) advocated a regimen of less than 7 g of protein during the day with a high protein meal at night to achieve the recommended minimum daily protein intake. In our study, protein contents of 10.5 g and 30.5 g were chosen to represent values for single meals that would be anticipated from the results of earlier studies to have disparate effects on the clinical response to levodopa.

Nutt *et al.* (1984) reported that the administration of a meal prior to the first daily dose of levodopa in nine Parkinsonian patients delayed absorption by an average of 34 min and resulted in a significantly lower C_{max} . The AUC was reduced significantly, but because this was measured for only the first 2 h, the data would not reflect total absorption and cannot be compared with the results in Table 2. The meals consumed by the patients contained an average of 30 g of protein, 54 g of carbohydrate and 35 g of fat. The discrepancy between the effects on C_{max} and t_{max} and the data in this paper may be due to differences in age or clinical condition of the subjects or the fat content of the test meal. Baruzzi *et al.* (1987) reported that the t_i for levodopa in the fasted state was 45 $\pm$ 23 min in a study on 17 Parkinsonian patients. It was shown that consumption of a meal containing 23 g of protein 30 min prior to dosing with levodopa resulted in a three-fold prolongation in t_i , a 47% reduction in the mean C_i and a 22% reduction in the mean 0–6 h AUC for levodopa. Again, comparison with the present study is

complicated because the data were obtained from elderly patients with Parkinson's disease who had received a dose of levodopa 4 h prior to the test dose and who were taking concomitant medication. In addition the test meal was given slightly earlier and had a higher fat content (36 g). In the studies of Nutt *et al.* (1984) and Baruzzi *et al.* (1987) less frequent blood samples were taken which may have led to errors in AUC calculation, especially in the presence of multiple plasma peaks.

Unlike levodopa, paracetamol is absorbed passively in the small intestine and therefore can be used as a marker of gastric emptying (Robertson *et al.*, 1990). In this study paracetamol was given to distinguish between effects due to competition for active transport from those due to changes in gastric emptying. Other factors that could influence the absorption of levodopa include the tablet dissolution rate and the extent of first pass metabolism of levodopa (Robertson *et al.*, 1989). To minimise these possible variables levodopa and paracetamol were administered in solution and the peripheral decarboxylase inhibitor carbidopa was given 1 h prior to levodopa. The C_i and t_i data for paracetamol and levodopa showed no evidence of significant prolongation of gastric emptying by the test meals. Levodopa itself delays gastric emptying (Robertson *et al.*, 1990) which may explain the lack of any detectable effect of food. Furthermore, t_i reflects the initial phase of liquid emptying which might not be affected by protein.

The absorption of paracetamol, as measured by the AUC (Table 2) was similar in fasting and fed states. By contrast, the AUC for levodopa following the low protein meal was 10% lower compared with administration in the fasting state. A reduction in the AUC for levodopa but not for paracetamol is compatible with competition for absorption between levodopa and LNAA. However, there was no evidence that increasing the concentration of dietary protein to 30.5 g resulted in any further impairment of levodopa absorption. The paradoxical finding of higher plasma concentrations of levodopa in patients receiving high, compared with low protein diets has been noted previously (Pincus & Barry, 1987; Tsui *et al.*, 1989). This could occur if any decrease in absorption with high protein diets was accompanied by altered systemic kinetics. In our data the absence of a change in terminal half-life or MRT indicates that any decrease in systemic clearance would have to be accom-

panied by a similar decrease in the apparent volume of distribution. Data following intravenous dosing with levodopa would be necessary to define the influence of protein on systemic pharmacokinetics.

Parkinsonian patients frequently develop fluctuations in their response to levodopa as the condition progresses (Marsden & Parkes, 1976). The most widely accepted explanation for this is a neuronal degeneration resulting in reduced central storage capacity for dopamine. Consequently the clinical response becomes sensitive to short term variations in plasma levodopa concentrations (Fabbrini *et al.*, 1988). Multiple plasma peaks of levodopa due to periodic delays in gastric emptying (Robertson *et al.*, 1990), are common following administration of a single dose to fasted subjects and, therefore, could contribute to fluctuations in clinical response. But the improved response to levodopa with low protein meals cannot be explained by an effect on multiple plasma peaks since they were as frequent with the low protein meal as in the fasted state while they were abolished following the high protein meal.

In conclusion, there was no evidence that consumption of a meal containing 30.5 g of protein altered the pharmacokinetics of levodopa in healthy volunteers. A recent study in four patients with Parkinson's disease demonstrated that dietary protein reduced the effectiveness of an intraduodenal infusion of levodopa without significantly altering the plasma drug concentration (Frankel *et al.*, 1989). The data from the present study also suggest that neither competition for active transport from the gut lumen nor changes in gastric emptying contribute to the observed interaction between protein intake and clinical response to levodopa. Leenders *et al.* (1986), using positron emission tomography, have provided direct evidence that an intravenous dose of amino acids reduces the uptake of the dopa analogue, L-[^{18}F]fluorodopa, into the human brain. Therefore, it is probable that the clinical benefits of low protein diets in patients treated with levodopa arise from a reduced competition for transport across the blood-brain barrier.

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