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PLASMA DOPA CONCENTRATIONS AFTER DIFFERENT PREPARATIONS OF LEVODOPA IN NORMAL SUBJECTS

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1 The concurrent administration of levodopa with a decarboxylase inhibitor produced a plasma concentration/time curve comparable with 1/4 to 1/5 of the dose of levodopa given alone.

2 There was no evidence to suggest that the decarboxylase inhibitor slowed the rate of elimination of levodopa from plasma.

3 Metoclopramide (Maxolon) increased the rate of levodopa absorption. Higher plasma concentrations of levodopa during the first 2 h after dosing were followed by lower plasma concentrations during the third and fourth hours. The amount of levodopa absorbed after Larodopa as indicated by the AUC was not altered by adding metoclopramide.

4 None of the current preparations of levodopa produced sustained plasma concentrations.

5 *In vitro* testing confirmed that Brocadopa Temtabs tablets disintegrate and dissolve slowly. *In vivo*, Brocadopa Temtabs behaved as a slow release preparation but it did not produce sustained plasma concentrations of levodopa.

Introduction

There are several ways to give levodopa in the treatment of Parkinsonism. These include tablets (Larodopa), capsules (Brocadopa), a slow release preparation (Brocadopa Temtabs) and tablets (Sinemet) and capsules (Madopar) which contain fixed proportions of levodopa with a decarboxylase inhibitor. Levodopa is also given with anti-emetics (e.g. metoclopramide) and anticholinergic drugs (e.g. benzhexol).

The aim of this study was to examine the plasma concentration/time curve produced by these preparations of levodopa. In particular, we had the following objectives:

1 To compare the plasma concentration/time curve after Larodopa with that produced by two combinations of levodopa with a decarboxylase inhibitor (Sinemet and Madopar) to see if a decarboxylase inhibitor slowed the elimination of levodopa from the plasma.
2 To assess the effect of metoclopramide on the plasma concentration/time curve of levodopa.
3 To ascertain whether Brocadopa Temtabs is a sustained release preparation.

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Methods

In vivo *studies*

Eleven normal subjects (seven males and four females) mean (± s.e. mean) age 28.5 ± 1.9 years, height 172 ± 3.0 cm, weight and 66.03 ± 3.2 kg participated. No subject had any known disease and no other medication was given. The preparations of levodopa were given to the subjects on a weight related basis.

In a pilot study, administration of levodopa (15 mg/kg) to two fasting subjects led to prolonged vomiting. In order to minimize this side effect, each preparation was given 10 min after a standardized breakfast consisting of an unbuttered bun and coffee. A minimum of 7 days elapsed between each study.

Preparations of levodopa

The following preparations were given by mouth:

(a) Larodopa (Roche) tablets in a dose of 15 mg/kg by body weight. For a 70 kg man this is approximately 1 g.
(b) Brocadopa Temtabs (Brocades) tablets 15 mg/kg.
(c) Larodopa (Roche) (15 mg/kg) and metoclopramide (Maxolon) (10 mg) were given simultaneously by mouth.
(d) Sinemet (M.S.D.) One-quarter of the dose of levodopa used in the first three studies (the manufacturers' recommendations) was given. Each tablet of Sinemet contains levodopa (250 mg) and alphamethyldopahydrazine (25 mg, Carbidopa).
(e) Madopar (Roche) One-fifth of the dose of levodopa used in the first three studies (the manufacturers' recommendation) was given. Each capsule of Madopar contains levodopa (200 mg) and benzserazide (50 mg).
(f) Brocadopa Temtabs in a reduced dose (5 mg/kg body weight) was given after the subject had been primed with Carbidopa (25 mg 8 hourly during the 24 h prior to the study). A further 25 mg of Carbidopa was given 2 h before Brocadopa Temtabs.

Analytical methods

Venous blood (5-10 ml) in lithium heparin was taken prior to dosing and at 20 min, 40 min, 60 min, and hourly until 6-8 h after dosing. The samples were centrifuged immediately and sodium metabisulphate added to the plasma within 10 min of venepuncture. The samples were stored at -20°C until analysed by a semi-automated modification of the method of Curzon, Kantamaneni & Trigwell (1972).

In vitro *studies*

Disintegration times Five tablets (500 mg) of Larodopa and Brocadopa Temtabs were agitated in a B.P. standardized Manesty test unit (model TD 86T133) at pH 2.0 (0.06N Hcl) and at pH 6.8 (5M potassium dihydrogen phosphate; 5N sodium hydroxide buffer) at 37°C. The time taken for all the tablets of each preparation of levodopa to disintegrate and fall through the wire mesh of the basket holding them was measured.

Dissolution times The *in vitro* dissolution rates of Larodopa and Brocadopa Temtabs tablets were measured at pH 1.1, 4 and 8 by the Groves (1973) modification of the beaker method of Levy & Hayes (1960). A tablet of each preparation of levodopa was added to a flask which contained 2 litres of buffer suspended in a water bath at 37°C. The flask was rotated at 100 rev/min. The following buffers were used (0.1 N HCl (pH 1.1); 0.1 M HCl/dihydrogen monopotassium and disodium hydrogen phosphate (pH 4.0) and 0.1M NaOH/dihydrogen monopotassium and disodium hydrogen phosphate (pH 8.0). The pH of these buffers was selected to approximate the pH within the stomach and duodenum. Samples (5 ml) from the flask were withdrawn at intervals. After filtration through a millipore filter, these were analysed spectrophotometrically for levodopa.

Spectrophotometric assay of levodopa

A linear calibration curve for levodopa was constructed by plotting the absorption spectra produced by dilute solutions of levodopa against their concentration (0.02-0.15 μg/ml) using the Unicam SP800 spectrophotometer. The absorption peak for levodopa was sharply defined at 280 nm. Below 250 nm there was non-specific absorption. The concentration of free levodopa in the samples collected during the dissolution time experiment was calculated from this calibration curve.

Statistics

Mean concentrations (± s.e. mean) of the group at each sampling time were calculated for each preparation. Concentrations following each preparation were compared with those following Larodopa by means of Student's paired *t*-test (Bradford Hill, 1971). The only exception to this was the study of Brocadopa Temtabs plus Carbidopa where concentrations were compared with those following Brocadopa Temtabs alone.

It is fortuitous if the measured peak plasma concentration and the actual peak in any individual coincide. We analysed the raw data by a computer programme (Engberg-Pedersen, 1974). This calculated the peak (C_{max}), the time at which it occurred (T_{max}), the time taken for absorption (T_{asc}) and elimination (T_{desc}). The lag time was obtained by subtracting T_{asc} from T_{max}. These computer parameters are graphically represented in Figure 1.

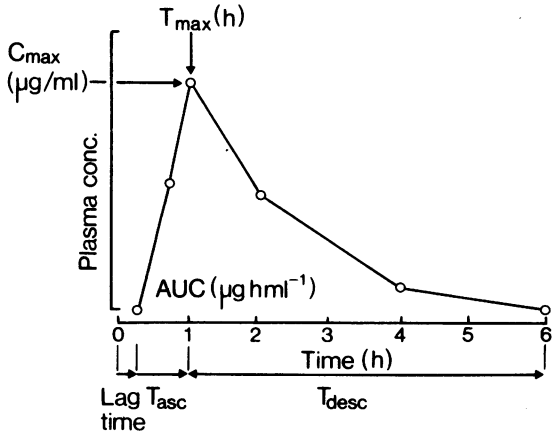

Figure 1 Diagram showing the statistical parameters of the plasma level curves calculated by the computer programme (Engberg-Pedersen, 1974).

Results

In-vivo *studies* The group mean ± s.e. mean plasma levodopa concentrations produced by all six preparations are shown in Table 1. The considerable individual variation in the plasma levodopa concentrations is reflected in the large standard errors.

Table 2 gives the computer calculated values for C_{max}, T_{max}, lag time, T_{asc}, T_{desc} and the area under the plasma concentration/time curve (AUC).

Larodopa The peak plasma levodopa concentration (2.00 ± 0.49 μg/ml) occurred within 60 min of giving Larodopa. By 6 h, the plasma levodopa had fallen to 0.11 ± 0.04 μg/ml.

Brocadopa Temtabs The peak plasma levodopa and C_{max} after Brocadopa Temtabs (1.21 ± 0.21 and 2.44 ± 0.48 μg/ml respectively) were less ($P < 0.05$) than the comparable values after Larodopa (2.00 ± 0.49 and 3.45 ± 0.8 μg/ml respectively). T_{max} after Brocadopa Temtabs (1.41 ± 0.24 h) and Larodopa (1.27 ± 0.19 h) were similar. The mean plasma concentration of levodopa during the 6 h after Brocadopa Temtabs was lower than after the same dose of Larodopa ($P < 0.05$).

Larodopa with metoclopramide The peak plasma levodopa concentration (3.17 ± 1.25 μg/ml) occurred 20 min after administration

Table 1 Mean (± s.e. mean) concentration of levodopa in the plasma (μg/ml) after oral administration of six different preparations of levodopa

Time after dose (h)	Preparation and dose: Larodopa (15 mg/kg) (n = 12)	Larodopa (15 mg/kg) and metoclopramide (10 mg) (n = 10)	Brocadopa Temtabs (15 mg/kg) (n = 12)	Brocadopa Temtabs (5 mg/kg) + Carbidopa (25 mg 8 hourly for 24 h + 25 mg 2 h prior to dosing) (n = 8)	Sinemet (1 tablet contains levodopa (250 mg) with Carbidopa (25 mg)) (n = 11)	Madopar (1 capsule contains levodopa (200 mg) with benserazide (50 mg)) (n = 6)
0.33	0.77 ± 0.40	3.17 ± 1.25*†	0.40 ± 0.10	0.56 ± 0.22	1.25 ± 0.43	1.38 ± 1.00
0.67	1.23 ± 0.35	2.77 ± 0.77	1.17 ± 0.26	0.91 ± 0.27	1.02 ± 0.13	1.77 ± 0.54
1	2.00 ± 0.49	2.11 ± 0.58	1.21 ± 0.21*†	1.30 ± 0.24	1.41 ± 0.16	2.00 ± 0.37
2	1.50 ± 0.22	1.27 ± 0.22	1.16 ± 0.20	1.44 ± 0.26	1.47 ± 0.17	1.35 ± 0.28
3	1.30 ± 0.25	0.64 ± 0.12**†	1.11 ± 0.30	1.16 ± 0.17	1.04 ± 0.13	0.87 ± 0.16
4	0.63 ± 0.13	0.40 ± 0.11	0.63 ± 0.12	0.58 ± 0.08	0.57 ± 0.07	0.63 ± 0.14
5	0.33 ± 0.08	0.22 ± 0.06	0.32 ± 0.08	0.34 ± 0.04	0.40 ± 0.08	0.30 ± 0.05
6	0.11 ± 0.04	0.15 ± 0.06	0.14 ± 0.05	0.20 ± 0.04	0.24 ± 0.04***	0.23 ± 0.04**

† Significance of difference (paired *t*-test) in those individuals who participated in both experiments.
* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$.
The weight related dose of levodopa when giving Sinemet was 5 mg/kg body weight; with Madopar this was 3.75 mg/kg body weight.

Table 2 Computer analysis of absorption of various preparations of levodopa

	Larodopa (15 mg/kg)	*Larodopa (15 mg/kg) and metoclopramide (10 mg)*	*Brocadopa Temtabs (15 mg/kg)*	*Brocadopa Temtabs (5 mg/kg) + Carbidopa (25 mg 8 hourly for 24 h + 25 mg 2 h prior to dosing)*	*Sinemet (1 tablet contains levodopa (250 mg) with Carbidopa (25 mg))*	*Madopar (1 capsule contains levodopa (200 mg) with benserazide (50 mg))*
C_{max} (μg/ml)	3.45 ± 0.80	5.69 ± 2.17	2.44 ± 0.48	1.79 ± 0.22	2.16 ± 0.30	5.37 ± 1.96
P		NS	NS	NS	NS	NS
T_{max}(h)	1.27 ± 0.19	0.67 ± 0.16	1.41 ± 0.24	1.44 ± 0.25	1.44 ± 0.14	1.19 ± 0.24
P		<0.005	NS	NS	NS	NS
Lag time (h)	0.58 ± 0.11	0.30 ± 0.13	0.65 ± 0.13	0.78 ± 0.13	0.60 ± 0.11	0.49 ± 0.13
P		<0.025	NS	NS	NS	NS
T_{asc} (h)	0.68 ± 0.11	0.38 ± 0.04	0.77 ± 0.18	0.66 ± 0.14	0.75 ± 0.06	0.70 ± 0.17
P		<0.01	NS	NS	NS	NS
T_{desc} (h)	2.86 ± 0.24	1.95 ± 0.43	3.11 ± 0.28	3.49 ± 0.36	3.31 ± 0.28	2.46 ± 0.43
P		<0.025	NS	NS	NS	NS
Area under the curve ($\mu g h ml^{-1}$)	8.69 ± 1.29	7.13 ± 1.54	6.33 ± 0.87	5.48 ± 0.52	5.89 ± 0.48	5.48 ± 0.52
P		NS	NS	NS	NS	NS
Mean difference between each preparation and Larodopa		0.38 ± 0.21	0.20 ± 0.10	0.01 ± 0.11	0.01 ± 0.11	0.10 ± 0.18
P		<0.05	<0.05	NS	NS	NS

The weight related dose of levodopa when giving Sinemet was 5 mg/kg body weight; with Madopar this was 3.75 mg/kg body weight.

and was higher ($P < 0.05$) than the peak after Larodopa alone (2.00 ± 0.49 μg/ml). This trend was confirmed by comparing C_{max} (5.69 ± 2.17 μg/ml Larodopa with metoclopramide; 3.45 ± 0.80 μg/ml Larodopa alone). The addition of metoclopramide reduced T_{max} from 1.27 ± 0.19 h to 0.67 ± 0.16 h ($P < 0.005$). This was due to significantly ($P < 0.01$) faster absorption (T_{asc}). Three hours after the combination, the plasma levodopa concentration had fallen from 3.17 ± 1.25 to 0.64 ± 0.12 μg/ml. This was less ($P < 0.025$) than the 3 h value after Larodopa alone (1.30 ± 0.25 μg/ml). T_{desc} after metoclopramide and Larodopa was reduced from 2.86 ± 0.24 h (Larodopa alone) to 1.95 ± 0.43 hours. There was no significant difference in the AUC after Larodopa with metoclopramide and Larodopa alone.

Sinemet The AUC after Sinemet was less ($P < 0.05$) than after Larodopa. The concentration at 6 h was higher than with Larodopa but in quantitative terms, the difference was very small.

Madopar There was no difference between Larodopa and Madopar.

Brocadopa Temtabs and Carbidopa There was no difference in any parameter between Brocadopa Temtabs (15 mg/kg) and at a reduced dose (5 mg/kg) with Carbidopa.

In vitro *studies*

Disintegration times (Table 3). The mean disintegration time of Brocadopa Temtabs was twelve times that of Larodopa (5 min approximately). It took 15 min longer for the disintegration of Brocadopa Temtabs at pH 2.0 than at pH 6.8.

Dissolution times (Figure 2). Larodopa reached equilibrium concentrations between 20 and 40 min at all three pH values. By contrast, Brocadopa Temtabs took between 180 and 200 min to completely release all the levodopa.

Table 3 Disintegration times of Larodopa and Brocadopa Temtabs in 0.06N HCl and phosphate buffer (5M KH_2PO_4, 5N NaOH).

Preparation	*Buffer pH*	*0.06N HCl 2.0*	*Phosphate buffer 6.8*
		Disintegration times	
Larodopa		5 min 25 s	5 min 20 s
Brocadopa Temtabs		1 h 18 min 15 s	1 h 3 min

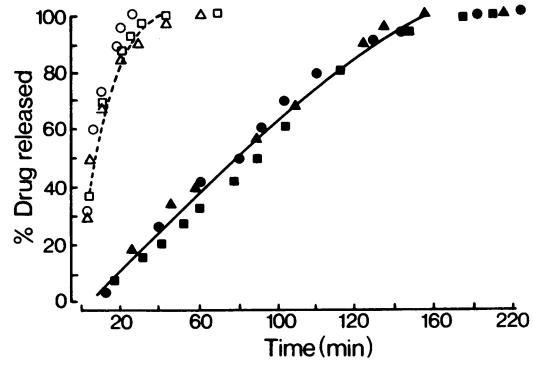

Figure 2 Dissolution times of Larodopa (open symbols) and Brocadopa Temtabs (closed symbols) at pH 1.1 (○, ●), pH 4.0 (△, ▲) and pH 8.0 (□, ■).

Discussion

Design of the study

Interpretation of results is complicated by the fact that even under standardized conditions there is considerable variation between individuals in the way they absorb levodopa (Morris, 1973; Wade, Mearrick, Birkett & Morris, 1974).

When comparing different preparations of levodopa it is therefore preferable to perform 'within-subject' studies, i.e. to give the same group of subjects all the preparations. As most Parkinsonian patients are frail and elderly, they are not ideal subjects for tests involving multiple venepunctures. Furthermore, interpretation of results of studies of levodopa absorption in Parkinsonian patients is complicated by the following factors:

(1) Most patients are already receiving levodopa (Bergman, Curzon, Friedel, Godwin-Austen, Marsden & Parkes, 1974).
(2) Many are on anticholinergic drugs which can alter the rate of gastric emptying (James & Hume, 1968; Howarth, Cockel, Roper & Hawkins, 1969).
(3) There is altered autonomic activity in some Parkinsonian patients (Shy & Drager, 1960).

Another important difference between Parkinsonian patients and our group of young subjects is that drug metabolism (O'Malley, Crooks &

Stevenson, 1971; Irvine, Grove, Toseland & Trounce, 1974; Castleden, Kaye & Parsons, 1975), and hepatic function in the Parkinsonian age group (Thompson & Williams, 1965) are impaired.

For these reasons, we conducted the study in healthy young adults on a 'within-subject' basis.

Effect of the decarboxylase inhibitor on bioavailability of levodopa

The main clinical advantages of combined preparations of levodopa with a decarboxylase inhibitor are a reduced incidence of nausea and vomiting (Cotzias, Papavasiliou & Gellene, 1969; Calne, Reid, Vakil, Rao, Petrie, Pallis & Gawler, 1971; Marsden, Barry, Parkes & Zilkha, 1973) and a reduction in the time taken to reach maximum improvement after commencing treatment (Marsden *et al.*, 1973).

Our results confirm those of other workers (Bianchine, Messiha & Hsu, 1972; Kuruma, Bartholini, Tissot & Pletscher, 1972) who found comparable plasma levodopa concentrations followed one-quarter to one-fifth of the oral dose of levodopa, when it was given with a decarboxylase inhibitor.

Orally administered levodopa is 95% metabolized outside the brain (Bianchine *et al.*, 1972). The major metabolic pathway is by decarboxylation. The enzyme responsible for this, L-aromatic amino acid decarboxylase, is present in most body tissues including the gut, liver and brain (Sourkes, 1966). It might be expected therefore that the administration of a decarboxylase inhibitor would slow the rate of elimination of levodopa from the plasma. The only evidence for this in our studies was a slightly higher concentration of levodopa in the plasma at 6 h after both Sinemet and Madopar. In quantitative terms, this difference is unlikely to be sufficient to enable patients to take levodopa less frequently when it is given with a decarboxylase inhibitor.

These results may be explained in two ways. Firstly, decarboxylase inhibitors may exert their main effect on decarboxylase within the gut. This would increase the proportion of levodopa which is absorbed unchanged, without altering its rate of removal from the plasma.

Secondly, after oral administration, several factors contribute to the plasma concentration of levodopa at any one sampling time. These include distribution, metabolism, excretion and continued intestinal absorption. One factor affecting the plasma levodopa concentration is decarboxylation, but it is unlikely that this is inhibited completely. Moreover, decarboxylation is not the only route of levodopa metabolism. Other minor pathways may be important when decarboxylase is inhibited—in particular transamination (Sandler, Carter, Johnson & Ruthven, 1972). Thus, inhibition of dopa decarboxylase alters only one factor affecting the plasma concentration/time curve of levodopa. Although there was a statistically significant difference between the mean 6 h plasma levodopa concentration after Larodopa and both Sinemet and Madopar, the quantitative difference was small (0.12 μg/ml).

Effect of metoclopramide

Metoclopramide led to a higher and earlier peak plasma concentration of levodopa. Faster absorption was achieved at the cost of lower concentrations at the third and fourth hours after administration. Metoclopramide increased the rate of absorption as shown by the earlier T_{max} and shorter T_{asc}. The amount of levodopa absorbed as indicated by the AUC after adding metoclopramide was unchanged. This has also been found by others (Mearrick, Wade, Birkett & Morris, 1974).

Metoclopramide hastens gastric emptying (James & Hume, 1968; Howarth *et al.*, 1969). Changes in the rate of absorption of paracetamol (Nimmo, Heading, Tothill & Prescott, 1973), digoxin (Manninen, Melin, Apajalhati & Karesoja, 1973), ampicillin and tetracycline (Gothoni, Pentikainen, Vapaatalo, Hackman & Af Bjorkstein, 1972) and riboflavin (Levy, Gibaldi & Procknal, 1972) have also followed concurrent oral administration of metoclopramide.

Levodopa, like other amino acids, is probably mainly absorbed in the small intestine (Matthews & Lastor, 1965; Adibi & Gray, 1967).

By delivering levodopa more rapidly from the stomach to its optimum site of absorption, metoclopramide may reduce the exposure of levodopa to decarboxylase in the gut (Rivera-Calimlim, Dujovne, Morgan, Lasagna & Bianchine, 1970). Thus a higher earlier peak results from using levodopa with metoclopramide than is the case with levodopa alone.

Two theoretical considerations deserve mention: firstly, since the plasma concentration fell more quickly after giving levodopa with metoclopramide, more frequent dosing might be necessary when this drug is used. Secondly, dyskinetic movements might be provoked by the higher peaks achieved. These may also follow metoclopramide (De Silva, Muller & Pearce, 1973; Casteels-van Daele, Jaecken, Van der Schueren, Zimmerman & Van Den Bon, 1970).

Brocadopa Temtabs

The *in vitro* studies showed that Brocadopa Temtabs tablets dissolve slowly in a simulated gut environment. Although *in vivo* Brocadopa Temtabs tablets were absorbed slowly, the plasma concentration of levodopa was not sustained. Thus Brocadopa Temtabs is a slow release preparation but not a sustained release preparation (Brocades advertisement pamphlet, 1972). In the light of these results, it is unlikely that the frequency of dose for levodopa could be reduced by using this preparation.

There are two possible explanations for this failure of Brocadopa Temtabs to produce sustained plasma concentrations of levodopa.

(1) If levodopa is mainly absorbed by the proximal small intestine (Matthews & Lastor, 1965) it is possible that Brocadopa Temtabs tablets do not completely disintegrate and dissolve until they have passed their optimum site for absorption. In these circumstances the proportion of levodopa absorbed from an oral dose would be reduced.

(2) There is now *in vitro* and *in vivo* evidence that levodopa is metabolized when exposed to gastric and small intestinal mucosa (Rivera-Calimlim, Dujovne, Morgan, Lasagna & Bianchine, 1971; Rivera-Calimlim, Morgan, Dujovne, Lasagna & Bianchine, 1971). Thus, the longer levodopa remains in contact with the intestinal mucosa, the more is metabolized prior to absorption.

In an experiment designed to assess the relative importance of these hypotheses, a reduced dose of Brocadopa Temtabs (5 mg/kg body weight) was given to the subjects after they had received Carbidopa for 24 hours. If the failure of Brocadopa Temtabs to behave as a sustained release preparation was largely due to increased breakdown of levodopa in the gut, then the combination of a decarboxylase inhibitor with Brocadopa Temtabs should produce sustained plasma concentrations of levodopa. A comparison of Brocadopa Temtabs alone with Brocadopa Temtabs with Carbidopa, shows that this did not occur (Table 1). The addition of Carbidopa to Brocadopa Temtabs resulted in similar concentrations of levodopa being achieved with a third of the dose. Thus, inhibition of decarboxylase reduced peripheral metabolism but did *not* produce sustained plasma concentrations of levodopa.

In conclusion, the limiting factor to the production of an effective sustained release preparation seems to be that the absorption of levodopa is probably confined to the proximal small intestine.

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