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Peripheral Pharmacokinetic Handling and Metabolism of L-Dopa in the Rat: The Effect of Route of Administration and Carbidopa Pretreatment

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Abstract—The effect of carbidopa (L-α-methyldopa hydrazine; 25 mg kg^{-1} i.p.) pretreatment on the pharmacokinetics and peripheral metabolism of orally and intra-aortically administered L-3,4-dihydroxyphenylalanine (L-dopa; 50 mg kg^{-1}) has been examined in rats. Following intra-aortic (i.a.) administration, plasma levels of the drug declined biexponentially. Pretreatment with carbidopa resulted in higher plasma concentrations after i.a. administration of L-dopa, but had no effect on the half-life ($t_{\frac{1}{2}}$) for its distribution or elimination. Oral L-dopa gave peak plasma concentrations at 1·5 h and then a log-linear decline between 1·5 and 6 h. Pretreatment with carbidopa also produced higher plasma concentrations of L-dopa given orally, and the $t_{\frac{1}{2}}$ for its elimination tended to be increased compared with values achieved after the drug alone. Pretreatment with carbidopa decreased volume of distribution and total plasma clearance and increased area under the curve (0–∞) after L-dopa i.a. and increased $AUC_{0-\infty}$ after L-dopa p.o. The fraction of the oral dose absorbed through the gut was not affected. Carbidopa pretreatment enhanced the accumulation of 3-*O*-methyldopa and decreased dopamine levels in plasma after both i.a. and oral administration of L-dopa. Higher plasma concentrations of 3,4-dihydroxyphenylacetic acid and homovanillic acid (HVA) were detected in the plasma after i.a. rather than oral administration of L-dopa and pretreatment with carbidopa greatly reduced these plasma concentrations. However, following oral L-dopa, only HVA levels were reduced by carbidopa pretreatment. The rat model displays similar peripheral pharmacokinetics and metabolism of L-dopa to those reported in human studies, and may be used for further investigations into the pharmacokinetic handling of the drug.

The rat has been widely used to study the peripheral and central actions of L-dopa owing to its tolerance to high doses of the drug (comparable with those used in man). However, surprisingly there have been few reports on the pharmacokinetic profile of L-dopa in the rat. In the only previous study involving the administration of L-dopa (1, 10, 20 and 100 mg kg^{-1} orally) alone, there was a dose dependent, but non-linear, increase in mean plasma concentrations and area under the curve (AUC) for the drug and its metabolites dopamine and 3-*O*-methyldopa (3-OMD) (Cheng & Fung 1975). Doller et al (1978) described the pharmacokinetics of L-dopa (50 mg kg^{-1} i.v.) administered alone and after pretreatment with the aromatic amino acid decarboxylase (AAAD) inhibitor, benserazide. Those authors reported a triphasic decline in plasma L-dopa following its intravenous administration while pretreatment with benserazide resulted in an increase in the AUC for L-dopa, a decrease in both total plasma clearance (CL_p) and volume of distribution (Vd), with little effect on the slope of the plasma L-dopa decay curve. Similarly, Huebert et al (1983) showed some reversible and irreversible inhibitors of dopa decarboxylase caused an increased half-life ($t_{\frac{1}{2}}$) and AUC, and a decreased CL_p and Vd following administration of L-dopa (20 and 50 mg kg^{-1} p.o.). More recently, Leppert et al (1988) reported that carbidopa (0·5 mg), co-administered with L-dopa (2 mg i.v.), increased the AUC and $t_{\frac{1}{2}}$ of L-dopa after i.v., but not rectal or duodenal, administration. However, pretreatment with carbidopa (0·5 mg) increased the AUC and $t_{\frac{1}{2}}$ of L-dopa (2 mg i.v.) after i.v., rectal and duodenal administration.

Despite the widespread use of the rat to study the actions of L-dopa, there has not previously been a comprehensive investigation of the pharmacokinetic profile of L-dopa, administered alone or after pretreatment with an AAAD inhibitor. With a view to establishing the rat as a model for further investigations into the effect of long-term L-dopa therapy on its pharmacokinetics, we now report the pharmacokinetic and metabolic handling of the drug in the rat following its acute intravascular and oral administration, both alone and after carbidopa (L-α-methyl dopa hydrazine) pretreatment.

Materials and Methods

Experimental details

Male Wistar rats (312 ± 7 g; Bantin and Kingman, Hull, UK) were initially housed in groups of six and exposed to light between 0800 and 2000 h. Food and water were freely available except during experimentation. Two days before experimentation, the animals were cannulated in the descending aorta under sodium pentobarbitone (60 mg kg^{-1} i.p.) anaesthesia, for serial blood sampling and intravascular drug administration. Sixteen hours before drug administration food, but not water, was removed. From preliminary experiments it was found that the pharmacokinetic profiles of L-dopa after i.v. (via the tail vein) and intra-aortic administration were not significantly different (data not shown). However, the reproducibility was greater following

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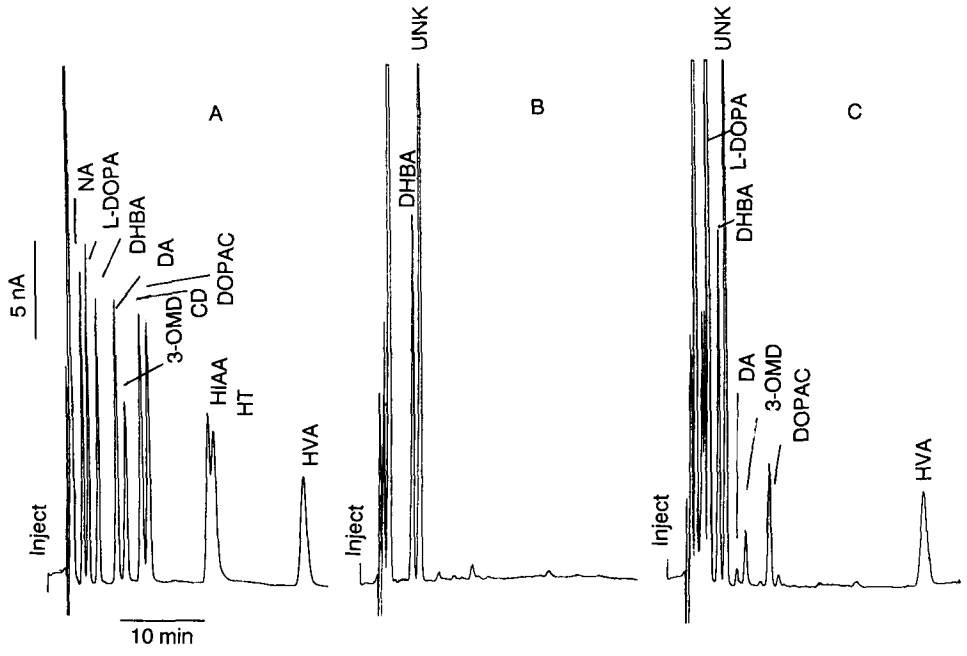

FIG. 1. Sample chromatograms obtained from (A) samples (30 μL) of a standard solution (2 μg mL^{-1}) containing noradrenaline (NA), L-dopa, DHBA, dopamine (DA), 3-OMD, carbidopa (CD), DOPAC, 5-hydroxyindoleacetic acid (HIAA), 5-hydroxytryptamine (HT) and HVA, (B) the supernatant of a prepared plasma sample from a rat treated with vehicle, and (C) the supernatant of a plasma sample from a rat 15 min after the administration of L-dopa (50 mg kg^{-1} i.a.). UNK-unknown peak.

intra-aortic administration. Therefore, intravascular administration of the drug was given via the descending aorta.

On the day of experimentation, carbidopa (25 mg kg^{-1} i.p.) or vehicle was given 1 h before L-dopa (50 mg kg^{-1} orally or intra-aortically). A control blood sample (200 μL) was collected from the aortic cannula into Microvette heparinized blood tubes (300 μL capacity; Sarstedt Ltd, UK) immediately before the L-dopa dose. The volume of blood removed was replaced with an equal volume of heparinized saline (2000 units mL^{-1}). For intra-aortic administration the drug was dissolved in 0·9% NaCl (saline) containing 0·01 M HCl pH 4·5, and followed by an equal volume of heparinized saline. Blood was collected by serial sampling (200 μL amounts) into Microvette heparinized tubes at 5, 10, 15, 30, 60, 90, 120, 180 and 240 min following L-dopa, as described previously. For dosing by gavage the drug was in suspension in 1% (w/v) methyl cellulose containing 1% (w/w) ascorbic acid. Blood samples were collected at 15, 30, 60, 90, 120, 180, 240 and 360 min after L-dopa, as described. The animals were allowed to move freely around the cage at all times, and showed no adverse effects.

Sample preparation

Blood samples were centrifuged in a Sorvall RC-3B refrigerated centrifuge at 1800 *g* for 30 min at 4°C to separate the plasma. A portion of plasma was added to a solution of L-3,4-dihydroxybenzylamine (DHBA; 4 μg mL^{-1}) in 0·4 M perchloric acid containing 1 mM ethylenediaminetetraacetic acid (EDTA)/0·5 mM sodium metabisulphite (1 : 1 v/v). The samples were mixed and allowed to stand on ice for 10 min to complete deproteinization. They were centrifuged for 10 min at 30000 *g* at 4°C. Samples (10–50 μL) of the supernatant were used for HPLC analysis of L-dopa and its metabolites.

HPLC determination of L-dopa and its metabolites

Plasma concentrations of L-dopa, 3-OMD, dopamine, DOPAC and HVA were measured by a modification of the method of Rose et al (1988). Chromatography was on a Spherisorb ODS 2, 5 μm particle size HPLC column (0·46 × 25 cm; Phase Separations Ltd, UK). The mobile phase (0·1 M NaH_2PO_4, 18% (v/v) methanol, 0·4 mM octane sulphonic acid, 1 mM EDTA, pH 3·1, adjusted with 3 M phosphoric acid) was pumped at a flow rate of 1 mL min^{-1} using a Waters 510 pulse free pump. Samples were injected using a 8780XR automated sampler (SpectraPhysics Ltd, UK) fitted with a Rheodyne injection valve and a 100 μL sample loop. The amount of analyte in each injection was measured using a BAS LC3A amperometric detector with a thin layer electrochemical cell fitted with a glassy carbon working electrode and a Ag/AgCl reference electrode set at a potential of +0·70 V. Integration of the signal from the detector was performed using a 4270 computing integrator (SpectraPhysics Ltd, UK). All chromatography was performed at 10°C to prevent sample degradation during storage in the autosampler.

The HPLC-ECD system was calibrated with a single standard solution (containing DHBA, L-dopa, 3-OMD, dopamine, DOPAC and HVA) equal in concentration to the internal standard concentration in the deproteinized plasma (2 μg mL^{-1}). The system was recalibrated every six samples, and the record of the calibration updated. The limit of detection for L-dopa, dopamine, DOPAC and 3-OMD was 10 ng mL^{-1}, and for HVA was 20 ng mL^{-1}. Sample chromatograms of a calibration standard and typical plasma samples are shown in Fig. 1. DHBA hydrobromide, 3-OMD, dopamine hydrochloride, DOPAC and HVA were obtained from Sigma Chemical Co, Poole, UK. L-Dopa was a gift

from Roche Products Ltd, Welwyn Garden City, UK. Carbidopa was a gift from Merck, Sharp and Dohme, Hoddesdon, UK. All other chemicals were supplied by Fisons Scientific Equipment Ltd, Loughborough, UK.

Calculation of results

Pharmacokinetic parameters were calculated for plasma L-dopa levels. The terminal portion of the plasma decay curves (plotted as log plasma concn vs time) were treated by the method of least squares linear regression. The slopes of the regressed lines were used to calculate the apparent first order elimination rate constant ($k_{el} = 2{\cdot}303 \times$ slope) and the half-life ($t_{\frac{1}{2}} = \ln 2/k_{el}$). The $\log_{10}$ plasma L-dopa vs time plot was extrapolated to zero time and the plasma concentration (C_0) was determined at the intersection of the y-axis. The total area under the curve ($AUC_{0-\infty}$) was calculated according to the trapezoid approximation method over the total observation period, and extrapolated beyond the last measured concentration (CP_t/k_{el}). The extrapolated areas constituted no more than 3·9% of the total area. The plasma clearance (CL_p) was calculated from the formula $CL_p = \text{dose}/AUC$ ($AUC = C_0/k_{el}$), and the volume of distribution (Vd) was calculated from the formula $Vd = CL_p/k_{el}$.

Pharmacokinetic parameters were calculated for the initial decline of plasma L-dopa levels after i.a. administration of the drug using the method of residuals and measuring the $t_{\frac{1}{2}}$ as described above.

The (f) fraction of the extravascular dose absorbed) was estimated by dividing mean $AUC_{0-\infty}$ (oral) by mean $AUC_{0-\infty}$ (intravascular).

Statistics

Least squares linear regression was used to determine the linearity of log (plasma L-dopa concentration)—time curves in the estimation of the pharmacokinetics of L-dopa. Only those slopes with a correlation coefficient significant at the 95% level were considered.

The effect of carbidopa pretreatment and route of administration of L-dopa on the pharmacokinetics of L-dopa was analysed using two-way ANOVA. If the resultant F-ratio proved significant ($P < 0{\cdot}05$) then Dunn's multiple comparison test (Howell 1987) was used to compare individual differences. The effect of carbidopa pretreatment on the time course of L-dopa and its metabolite levels in plasma was analysed using two-way ANOVA. If the resultant F-ratio proved significant ($P < 0{\cdot}05$) then the Dunn's multiple comparison test was used to compare individual values with either vehicle-treated control values or values achieved after administration of L-dopa alone.

Results

Plasma L-dopa levels

After i.a. administration of L-dopa alone its plasma levels declined biexponentially (Fig. 2). Pretreatment with carbidopa produced higher plasma L-dopa levels and 5 min after L-dopa they were almost three times greater although the difference did not prove significant ($P > 0{\cdot}05$, Dunn's test). The levels remained elevated for longer (up to 240 min after L-dopa plus carbidopa, compared with 120 min after L-dopa alone).

L-Dopa was quickly absorbed following oral administration, alone and after carbidopa-pretreatment (Fig. 3), with maximum plasma levels being reached after 15 min. Carbidopa pretreatment produced increased plasma levels compared with values after L-dopa alone with peak plasma

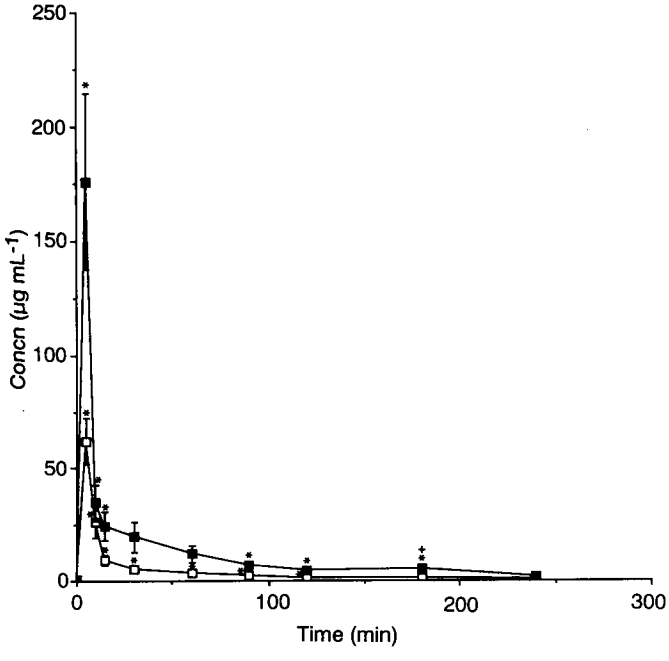

FIG. 2. The effect of carbidopa (25 mg kg^{-1} i.p.) on plasma concentrations of L-dopa following intra-aortic administration (50 mg kg^{-1}). Values are expressed as mean ± s.e.m. of 4–5 determinations. □ L-dopa alone, ■ L-dopa plus carbidopa. *$P < 0{\cdot}05$ compared with pretreatment control (Dunn's test). †$P < 0{\cdot}05$ compared with L-dopa alone (Dunn's test).

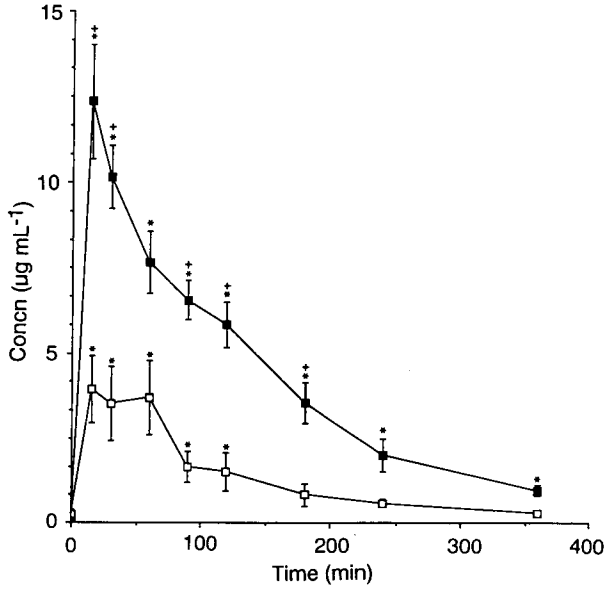

FIG. 3. The effect of carbidopa (25 mg kg^{-1} i.p.) on plasma concentrations of L-dopa following oral administration (50 mg kg^{-1}). Values are expressed as mean ± s.e.m. of 4–5 determinations. □ L-dopa alone, ■, L-dopa plus carbidopa. *$P < 0{\cdot}05$ compared with pretreatment control (Dunn's test). †$P < 0{\cdot}05$ compared with L-dopa alone (Dunn's test).

Table 1. The effect of carbidopa (25 mg kg^{-1} i.p.) pretreatment on the $t_{\frac{1}{2}}$, Vd, CL_p and $AUC_{0-\infty}$ following intra-aortic and oral administration of L-dopa (50 mg kg^{-1}). Values are expressed as mean ± s.e.m. of 4–5 determinations.

Route of administration		Pharmacokinetic parameter	Treatment L-dopa alone	Treatment L-dopa + carbidopa
Intra-aortic (n = 5)	Distribution	$t_{\frac{1}{2}}$ (h)	0·05 ± 0·01	0·04 ± 0·01
	Elimination	$t_{\frac{1}{2}}$ (h)	1·08 ± 0·27	1·13 ± 0·13
		Vd (L kg^{-1})	9·80 ± 2·16	3·40 ± 1·12†
		CL_p (L kg^{-1} h^{-1})	6·53 ± 1·06	2·33 ± 0·96†
		AUC (mg h L^{-1})	24·90 ± 2·60	87·66 ± 22·72†
Oral (n = 4)	Elimination	$t_{\frac{1}{2}}$ (h)	0·62 ± 0·16	1·15 ± 0·18
		Vd (L kg^{-1})	2·94 ± 1·09*	2·05 ± 0·99
		CL_p (L kg^{-1} h^{-1})	3·20 ± 1·06*	1·44 ± 0·32
		AUC (mg h L^{-1})	8·75 ± 1·37*	28·40 ± 1·10*†
		F-ratio	0·35	0·32

* $P < 0.05$ compared with i.a. administration of L-dopa (Dunn's test). † $P < 0.05$ compared with administration of L-dopa alone (Dunn's test).

Table 2. The effect of carbidopa (25 mg kg^{-1} i.p.) pretreatment on plasma concentrations of dopamine following intra-aortic and oral administration of L-dopa (50 mg kg^{-1}). Values are expressed as mean ± s.e.m. of 4–5 determinations (μg mL^{-1}). n.d. = not detectable.

Time after L-dopa (min)	Treatment L-dopa (intra-aortic) alone	L-dopa (intra-aortic) + carbidopa	L-dopa (oral) alone	L-dopa (oral) + carbidopa
0	0·06 ± 0·02	n.d.	n.d.	n.d.
5	0·40 ± 0·06*	n.d.†		
10	0·30 ± 0·13	n.d.		
15	0·17 ± 0·09	n.d.	0·04 ± 0·01*	n.d.†
30	0·04 ± 0·02	n.d.	0·03 ± 0·01*	n.d.†
60	n.d.	n.d.	0·03 ± 0·00*	n.d.†
90	n.d.	n.d.	0·01 ± 0·01	n.d.
120	n.d.	n.d.	0·01 ± 0·00	n.d.
180	n.d.	n.d.	0·01 ± 0·01	n.d.
240	n.d.	n.d.	n.d.	n.d.
360			n.d.	n.d.

* $P < 0.05$ compared with pretreatment control (Dunn's test). † $P < 0.05$ compared with L-dopa alone (Dunn's test).

concentrations being more than three times greater than those achieved after L-dopa alone; the levels also remained raised for longer (360 min compared with 120 min for L-dopa alone).

Pharmacokinetic parameters of L-dopa

The pharmacokinetic parameters were calculated for the linear portions of the plasma decay curve for the individual animals (Table 1). Carbidopa had no effect on the plasma $t_{\frac{1}{2}}$ of L-dopa during the distribution or elimination phase of the plasma decay curve following i.a administration of the drug. The $t_{\frac{1}{2}}$ for elimination tended to be shorter after oral compared with intra-aortic administration. This difference was not observed following carbidopa since, after oral L-dopa, the $t_{\frac{1}{2}}$ for elimination tended to be greater compared with rats treated with L-dopa alone. Pretreatment with carbidopa decreased the Vd and CL_p in the elimination phase after intra-aortic L-dopa. However, there was no apparent effect of carbidopa on Vd or CL_p following oral L-dopa. Both Vd and CL_p were greater after intra-aortic L-dopa compared with the oral route. After carbidopa pretreatment, the $AUC_{0-\infty}$ for L-dopa was increased following both its intra-aortic and oral administration and was greater after intra-aortic than after oral administration of L-dopa alone or after carbidopa. The fraction of oral dose of L-dopa absorbed (F-ratio), denoted as the ratio of (AUC after oral administration)/(AUC after intra-aortic administration), showed that about 65% of the dose was lost by first pass metabolism. The F-ratio was not affected by carbidopa pretreatment.

Plasma 3-OMD levels

Levels of 3-OMD gradually increased in plasma after both intra-aortic and oral L-dopa (Fig. 4). Plasma levels of 3-OMD were greater than control values at 5 min and between 30 and 240 min (maximum 240 min) following intra-aortic L-dopa, and between 60 and 240 min (maximum 180–240 min) following oral L-dopa. Carbidopa pretreatment produced greater plasma 3-OMD levels between 90 and 240 min after intra-aortic and 15 to 360 min after oral L-dopa compared with levels after the drug alone.

Plasma dopamine levels

A small amount of dopamine was detected in the plasma 5 min after intra-aortic and between 15 and 60 min following oral L-dopa alone (Table 2). Pretreatment with carbidopa decreased the dopamine plasma to below detection after both intra-aortic and oral doses of the drug.

Plasma DOPAC levels

Plasma levels of DOPAC were raised between 5 and 60 min (peak 10 min) after intra-aortic L-dopa, although the variability of the results prevented the differences reaching statistical significance at all times (Fig. 5). Following oral L-dopa, plasma DOPAC levels were raised between 30 and 120 min (peak 30 min) later. Pretreatment with carbidopa resulted in plasma DOPAC levels remaining at pretreatment control values following intra-aortic L-dopa and being raised between 15 and 60 min (peak 30 min) after oral L-dopa. Plasma DOPAC levels attained up to 30 min after intra-aortic L-dopa were reduced following pretreatment with carbidopa compared with values after the drug alone, but following oral drug dosing they were not different from values after the drug alone.

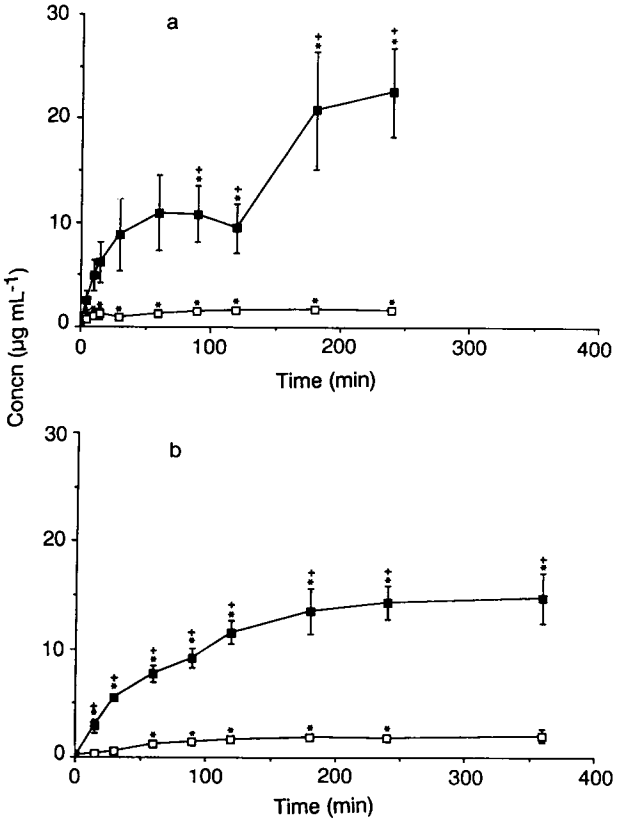

FIG. 4. The effect of carbidopa (25 mg kg^{-1} i.p.) on plasma concentrations of 3-OMD following (a) intra-aortic and (b) oral administration of L-dopa (50 mg kg^{-1}). Values are expressed as mean ± s.e.m. of 4–5 determinations. □ L-dopa alone, ■ L-dopa plus carbidopa. *$P < 0.05$ compared with pretreatment control (Dunn's test). †$P < 0.05$ compared with L-dopa alone (Dunn's test).

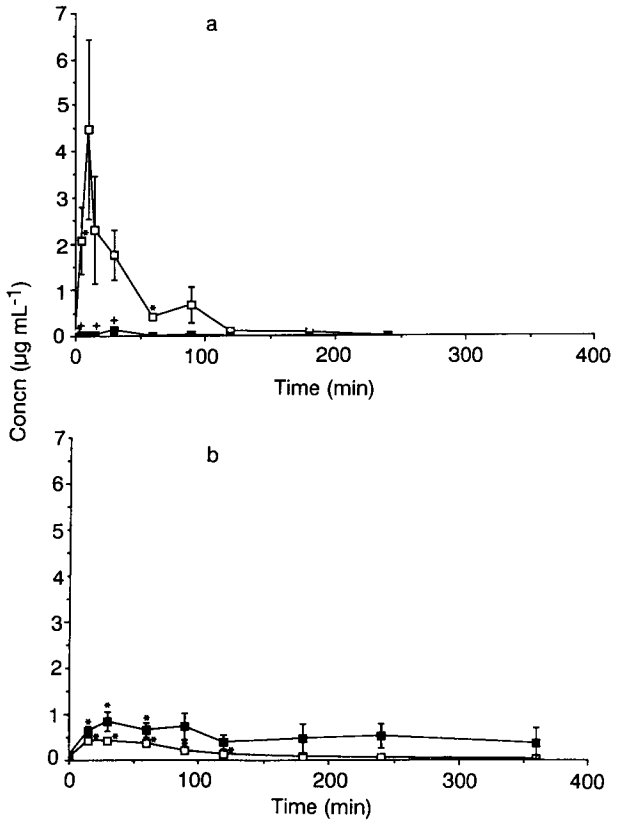

FIG. 5. The effect of carbidopa (25 mg kg^{-1} i.p.) on plasma concentrations of DOPAC following (a) intra-aortic and (b) oral administration of L-dopa (50 mg kg^{-1}). Values are expressed as mean ± s.e.m. of 4–5 determinations. □ L-dopa alone, ■ L-dopa plus carbidopa. *$P < 0.05$ compared with pretreatment control (Dunn's test). †$P < 0.05$ compared with L-dopa alone (Dunn's test).

Plasma HVA values

Plasma levels of HVA were raised between 5 and 180 min (peak 10 min) following intra-aortic L-dopa, and between 15 and 180 min (peak 60 min) after the oral dose (Fig. 6). Pretreatment with carbidopa produced raised HVA values 5 min following intra-aortic and between 15 and 240 min after oral L-dopa. Although plasma HVA values were not altered by pretreatment with carbidopa following intra-aortic L-dopa, after the oral dose the HVA values fell below those achieved after L-dopa alone between 15 and 90 min after drug administration.

Discussion

These data demonstrate that in the rat, there was a biexponential decline in plasma L-dopa concentrations following its intra-aortic administration, both alone and after carbidopa. This biexponential decay following its intravascular administration has also been demonstrated in the dog and man (Sasahara et al 1980a, b).

The initial rapid decline in plasma L-dopa values mainly represents its distribution from plasma to other tissues, especially muscle (Romero et al 1973; Ordonez et al 1972; Rose et al 1988), liver and kidney (Lyles 1978). This distribution phase demonstrated a short $t_{\frac{1}{2}}$ of around 2·4 min in the rat and is similar to the $t_{\frac{1}{2}}$ of L-dopa reported by Doller et al (1978) in rats and by Sasahara et al (1980a, b) in dogs and man.

The distribution of L-dopa from plasma to other tissues was probably more important in the contribution to the short $t_{\frac{1}{2}}$ than any other factor during this initial rapid decline in its plasma level. The concentrations of its metabolites in plasma during this distribution phase were not enough to account for the massive and rapid drop in its plasma values.

The initial distribution phase was not apparent in the plasma following oral administration because the processes of absorption, distribution and excretion occurred simultaneously. Hence the initial high plasma values achieved after intra-aortic L-dopa were not seen after its oral administration. Nevertheless, after a small dose of L-dopa (1 mg kg^{-1}) was given orally to rats, Cheng & Fung (1976) demonstrated a decline in its plasma concentration more akin to that observed after intra-aortic administration. Indeed, Nutt et al (1984) observed an initial rapid fall in plasma L-dopa following oral administration to fasting patients. Since the proportion of protein in the diet, and hence fasting, affects the drug's absorption (Nutt et al 1984, 1987), it is clear that its rate of absorption, as well as the size of the oral dose, determines the plasma profile.

The second or "elimination" phase of the plasma L-dopa decay curve was observed after both its intra-aortic and oral administration alone and after carbidopa. The $t_{\frac{1}{2}}$ of elimination of L-dopa after both oral and intra-aortic dosing was not significantly altered by carbidopa. Nevertheless, the pretreatment increased the $AUC_{0-\infty}$ after oral L-dopa suggesting

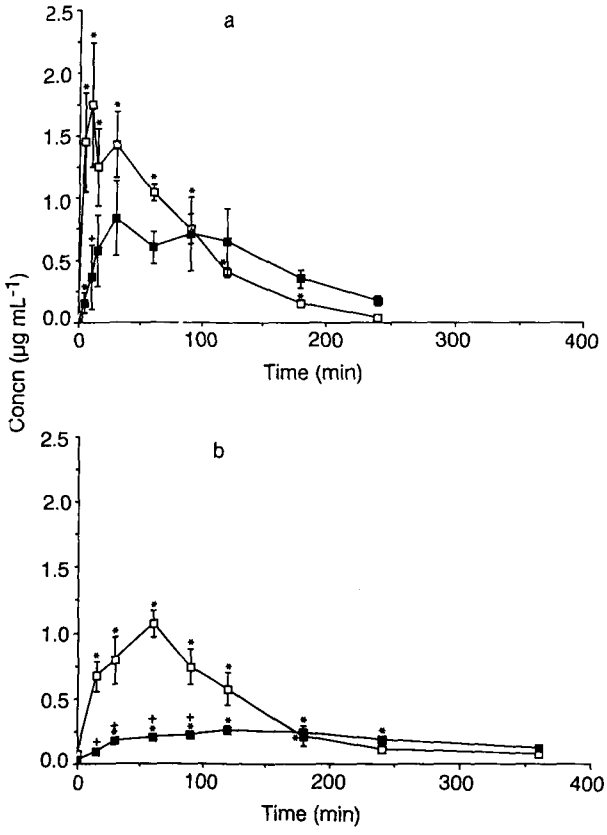

FIG. 6. The effect of carbidopa (25 mg kg^{-1} i.p.) on plasma concentrations of HVA following (a) intra-aortic and (b) oral administration of L-dopa (50 mg kg^{-1}). Values are expressed as mean ± s.e.m. of 4–5 determinations. □ L-dopa alone, ■, L-dopa plus carbidopa. *$P < 0.05$ compared with pretreatment control (Dunn's test). †$P < 0.05$ compared with L-dopa alone (Dunn's test).

an increase in its bioavailability. This was further ratified by the effect of cabidopa on Vd and CL_p, both appearing smaller after oral compared with intra-aortic L-dopa. However, if Vd and CL_p are corrected for reduced bioavailability orally (32–35% of intra-aortic L-dopa) they then fall within the same range after L-dopa alone by either route. The differential effect of carbidopa pretreatment then becomes apparent. Since the corrected values for Vd and CL_p were greater after oral L-dopa. This suggests that, after oral L-dopa, carbidopa acts at a site not involved in the decarboxylation of intra-aortic L-dopa, for example the gut mucosa (Sasahara et al 1980b).

Carbidopa pretreatment reduced the proportion of available L-dopa metabolized to dopamine and subsequently to DOPAC and HVA after both intra-aortic and oral L-dopa. However, this was more apparent after intra-aortic dosing. This suggests that, after oral L-dopa, some DOPAC and HVA may be formed at a site protected from carbidopa. However, the accumulation of 3-OMD in plasma after oral L-dopa was greater following carbidopa suggesting that L-dopa was shunted from the AAAD to the COMT pathway. Nevertheless, the overall result of carbidopa pretreatment was an increase in the bioavailability of L-dopa, such that, in the clinical situation, a lower dose would give the same plasma concentrations of the drug.

The peripheral pharmacokinetics and metabolism of L-dopa have been described in the rat after both oral and intra-aortic administration. The profile of absorption and elimination of L-dopa was similar to that in man. The effect of carbidopa on the pharmacokinetic and metabolic handling of L-dopa in the rat has been shown to be similar to that in dogs and man (Sasahara et al 1980a, b; Nutt et al 1985) resulting in an increase in the bioavailability of L-dopa by both routes. This suggests further investigations into the pharmacokinetics of L-dopa could be performed in the rat at doses comparable with those used in the clinic. This could be of particular importance for the understanding of its pharmacokinetic and metabolic handling after chronic administration.

Acknowledgements

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