Pharmacokinetics of Levodopa and Carbidopa in Rats Following Different Routes of Administration

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This study examined the pharmacokinetics of levodopa and carbidopa in the rat after different modes of administration. The drugs were given simultaneously by the intravenous, intraarterial, oral, duodenal, and intraperitoneal routes, as single doses. The ratio of levodopa to carbidopa given was always 4:1. Two iv doses (5 and 15 mg/kg of levodopa) were given to test for nonlinearity. Three ip doses of levodopa were given (5, 7.5, and 15 mg/kg), and the 15 mg/kg dose was given in three volumes (2, 4, and 20 mL/kg). One oral dose and two intraduodenal doses of 15 mg/kg were given. The drugs were dissolved in saline in one of the intraduodenal doses and suspended in 1.8% methylcellulose in the other. The elimination of levodopa was nonlinear. There was a comparatively high degree of interindividual variability in absorption with the oral route, but this was substantially reduced when levodopa was given intraduodenally. There was also much less variability with the intraperitoneal route compared to the oral, and the degree of absorption was generally high. There was a significantly higher extent and slower rate of absorption when levodopa was administered ip in a large volume of vehicle. These results suggest that the oral route may not be the optimal method of delivering levodopa to patients who have a fluctuating response and that a continuous delivery system via the intraperitoneal or intraduodenal routes might be a better alternative.

KEY WORDS: levodopa; carbidopa; rat; pharmacokinetics; absorption.

INTRODUCTION

Levodopa is the drug of choice in the treatment of Parkinson's disease. It is a precursor to dopamine which is the active moiety in the treatment of this disorder. To prevent dopamine formation peripherally, and thereby avoid peripheral dopamine-related side effects, a dopa decarboxylase inhibitor, for example, carbidopa, is coadministered with levodopa. These inhibitors have markedly reduced the dose requirement in the treatment of the disease and the side-effect frequency has been lowered (1,2). The therapeutic window seems to be very narrow, especially at the later stages of the disease, and the patients experience a rapid switch between hyper- and hypokinesia (3,4). The response to levodopa in the early stages of the disease is very beneficial, but as the disease progresses the patients become very sensitive to the rapid fluctuations in plasma levodopa concentrations. This variability is explained by a combination of a high effective intestinal permeability (5) and a short elimination half-life. The high effective permeability implies that gastric emptying determines the absorption for drug in solution. This result indicates a need for improved drug delivery systems in the treatment of Parkinson's disease with levodopa, to obtain less fluctuating plasma concentrations and thereby possibly a more stable clinical effect. Levodopa has a short elimination half-life (about 1.5 hr in man) (6,7), and, therefore, a slow-release dosage form may be valuable. However, the present slow-release preparation of levodopa hitherto has not been successful in reducing the fluctuations satisfactorily. The oral route, however, does not seem to be the best mode of administering levodopa since erratic absorption dependent on gastric emptying occurs with this route (8,9). To avoid this, continuous infusion via the intraduodenal route has been utilized and shown to yield a good clinical response (10–12). Since levodopa has a low water solubility (66 mg/40 mL), maybe it could be infused in another vehicle.

Another alternative to oral administration could be intraperitoneal. This could have a large therapeutic potential since the gastric emptying is avoided. However, the factors influencing drug absorption from peritoneum have been poorly investigated. In this study we varied the doses of levodopa and the volume given intraperitoneally.

The main purpose of the present study was to investigate the pharmacokinetics of levodopa and carbidopa following potentially new routes of administration, with special emphasis on factors affecting absorption from the peritoneum and the small intestine. In parallel, the pharmacokinetics of both levodopa and carbidopa following intravenous and intraarterial administration was evaluated.

MATERIALS AND METHODS

Animals

Male albino Sprague–Dawley rats (ALAB, Sollentuna, Sweden), 80 days old, were used throughout the study. The weight of the rats was 300–350 g. The animals were allowed 3 weeks of acclimatization before entering the study. The rats were fasted overnight but with free access to water. This study was approved by the ethical committee of Uppsala University.

Experimental Procedure

Levodopa was administered via five routes in different doses. The doses given were two intravenous (iv) iv doses, one intraarterial (ia) dose, one oral (po) dose, five intraperitoneal (ip) doses, and two intraduodenal (id) doses.

- The iv doses were 15 and 5 mg/kg.
- The ia and the po doses were both 15 mg/kg.
- The ip doses were 15, 7.5, and 5 mg/kg in a volume of 2 mL/kg and two doses of 15 mg/kg in a volume of 4 and 20 mL.
- The id doses were also 15 mg/kg in either a volume of 2 mL/kg or in a suspension administered as 0.75 mL/kg.

There were six rats in each of the 11 groups.

The catheters for drug administration were implanted in

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the rats on the day before the experiment and a catheter was inserted into the carotid artery for blood sampling. In the iv studies a catheter was also implanted in one of the jugular veins, and in the ip and id studies a catheter was inserted into the peritoneum and duodenum, respectively. In the ia study, the arterial dosing catheter was thoroughly rinsed after administration and before the first sample was taken. The catheters were exteriorized at the back of the neck and there protected by a plastic hat. The dose solutions were sampled before administration to the first rat and after the last one and analyzed for levodopa and carbidopa content.

Blood (200 μL) was withdrawn 2, 5, 10, 15, 30, 60, 90, 120, 150, and 180 min after drug administration. The samples were centrifuged at 3000*g* and the plasma frozen immediately. The samples were kept at −20°C until analyzed.

Drugs and Chemicals

Levodopa and carbidopa were dissolved in 4 parts of 0.2 *M* HCl, neutralized with 1.5 parts of 7% $NaHCO_3$, and stabilized with 5% ascorbic acid, according to the amount of levodopa in the solution. The final pH of the solution was 6.0. The ratio of levodopa to carbidopa was 4:1 in all routes of administration. The carbidopa was a gift from MSD, USA. The suspension was made from milled Sinemet 25/100 tablets suspended in 1.8% MC-1500 to a concentration of 20 mg/mL by the Department of Pharmaceutics, Uppsala University, Uppsala, Sweden. All other chemicals were of analytical grade.

HPLC Analysis

Plasma concentrations of levodopa, carbidopa, and 3-*O*-methyldopa were determined using an HPLC method with electrochemical detection. The method was modified from a previously reported method (13).

The plasma was precipitated with 1 *M* trichloroacetic acid, then centrifuged and the supernatant injected into an electrochemical detector LC-4A with a glassy-carbon electrode. The mobile phase consisted of a 0.05 *M* phosphate buffer (pH 3.4) and methanol (92:8), with the addition of 0.6% 1 *M* trichloroacetic acid and 0.1% tetrahydrofuran. The flow rate was 1 mL/min, and the oxidation potential +0.7 V. Levodopa, carbidopa and 3-*O*-methyldopa were displayed on the same chromatogram. The coefficient of variation was 3% for the lowest standard of levodopa, 6.2% for carbidopa, and 3.5% for 3-*O*-methyldopa, and the limits of detection were 0.04, 0.05, and 0.05 μg/mL, respectively.

Pharmacokinetic Analysis

The area under the plasma concentration–time profile (AUC) and the terminal half-life ($t_{1/2}$) were calculated model-independently for levodopa and carbidopa, where AUC was calculated by the log-linear trapezoidal rule. Plasma clearance (CL) was calculated according to Eq. (1). The residual area after the last observed data point was calculated as C_{calc}/λ, where C_{calc} is the calculated concentration on the last sampling occasion, estimated from the log-linear regression, and λ is the corresponding terminal rate constant. The volume of distribution at steady state was calculated model-independently according to Eq. (2).

$$CL = \frac{Dose_{intravascular}}{AUC} \quad (1)$$

$$V_{ss} = \frac{Dose \cdot AUMC}{AUC^2} \quad (2)$$

where AUMC is the area under the first moment curve.

To compare the pharmacokinetics of the different doses, the dose-corrected AUC values for the different treatments were compared.

A Michaelis–Menten differentiation equation was simultaneously fitted to the data from the two iv doses and the ia dose according to Eq. (3) using PCNONLIN (14).

$$\frac{dC_{(1)}}{dt} = k_{21} \cdot C_{(2)} - k_{12} \cdot C_{(1)} - \frac{V_{max} \cdot C_{(1)}}{K_m + C_{(1)}} \quad (3)$$

where $C_{(1)}$ is the concentration in the central compartment, $C_{(2)}$ is the concentration in the peripheral compartment, k_{21} and k_{12} are the rate constants describing the transfer of drug between the compartments, V_{max} is the maximal elimination rate (expressed as concentration/time), and K_m is the Michaelis–Menten constant. $1/C_{obs}^2$ was used as weighting. Dose/V_c was used as the starting condition, where V_c was a parameter calculated by the program.

A maximum clearance value was calculated using Eq. (3) as $Cl = V_m * V_c/K_m$.

The plateau concentration of the metabolite, 3-*O*-methyldopa, was calculated as the average concentration in each group at the three last data points (120, 150, and 180 min). The metabolite level was related to the AUC of levodopa by comparing the ratio of the dose-corrected plateau concentration of the metabolite to the dose-corrected AUC of levodopa for each dose.

Statistical Analysis

Differences in clearance, half-life and AUC were tested with one-way analysis of variance performed by StatView (BrainPower Inc., 24009 Ventura Blvd, Suite 250, Calabas, CA 91302, USA) coupled to FSD (Fisher's least significant difference) contrast test when testing more than two doses and Student's *t* test when comparing only two doses. The significance level was set at $P < 0.05$, unless otherwise stated. For the ip doses, the 15 mg/kg dose of levodopa administered in a volume of 2 mL/kg was used as reference dose.

RESULTS

Intravenous Doses

The mean plasma concentration–time profiles of levodopa following iv administration are shown in Fig. 1.

There was a dose-disproportional increase in the AUCs following the 5 and the 15 mg/kg iv doses (Figs. 1 and 4). V_{max} and K_m were estimated as 0.43 (SE = 0.06) μg/mL × min and 3.3 (SE = 0.6) μg/mL, respectively, and the initial volume of distribution, V_c, was 0.4 L/kg (SE = 0.03) (Table I). Clearance of levodopa was dose dependent, with a maximum clearance of 50 mL/min/kg. The half-life was about 48

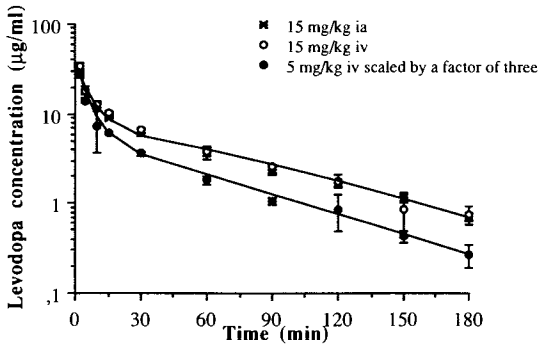

Fig. 1. Plasma concentration–time profiles of levodopa after the 5 mg/kg iv dose scaled by a factor of 3 for comparison with the larger 15 mg/kg iv dose and the 15 mg/kg ia dose. Each point is the mean ± SD for six rats. The symbols represent the mean ± SD and the solid lines represent the concentrations estimated from the computer fit of the Michaelis–Menten equation with a V_{max} of 0.43 μg/mL × min and a K_m of 3.3 μg/mL.

min for the iv and ia 15 mg/kg doses and 42 min for the 5 mg/kg dose, the half-life of the higher doses being significantly longer than the half-life of the small dose (Fig. 4). There was no statistical significant difference ($P > 0.05$) in either AUC or volume of distribution when levodopa was given ia compared to iv (Fig. 1). For the lower iv dose, V_{ss} was calculated as 1.6 ± 0.14 L/kg.

The total plasma clearance of carbidopa was about 30 ± 4 mL/min/kg and not dose dependent (Table II). The volume of distribution and hence the half-life were, however, dependent on either the dose or whether carbidopa was given iv or ia (Table II). When 3.75 mg/kg carbidopa was given ia, the volume of distribution was calculated as 1.1 ± 0.1 L/kg, compared to 1.6 ± 0.3 L/kg when 1.25 mg/kg was given iv ($P < 0.001$). The carbidopa concentrations following the high iv dose could not be included because of analytical circumstances.

Intraperitoneal Doses

The plasma concentration–time profiles of levodopa following ip administration are shown in Fig. 2.

The dose-corrected AUC (AUC/Dose) of levodopa was significantly lower following the 7.5 mg/kg ip dose than following the 15 mg/kg ip dose. When levodopa was administered ip in a large volume (20 mL/kg), the AUC/Dose was clearly increased, compared to the dose administered in 2 mL/kg, and the rate of absorption was slower, resulting in a lower C_{max}.

Table I. Pharmacokinetic Parameters of Levodopa, Estimated According to Eq. (3)[a]

	V_{max} (mg/mL × min)	K_m (mg/mL)	V_c (mL/kg)	k_{12} (min^{-1})	k_{21} (min^{-1})
Estimate	0.428	3.30	376	0.135	0.0386
SE	0.060	0.56	35	0.017	0.0036
CV (%)	14	17	9	12	9

[a] Parameters were estimated by fitting Eq. (3) simultaneously to the 5 mg/kg (iv), 15 mg/kg (iv), and 15 mg/kg (ia) doses.

Table II. Pharmacokinetic Parameters (Mean ± SD) of Carbidopa, Calculated Model-Independently

	Route of administration	
	ia	iv
Dose (mg/kg)	3.75	1.25
CL (mL/min × kg)	30 ± 4	31 ± 1.4
AUC/Dose [μg × min/mL/(mg/kg)]	8.4 ± 1.4	8.2 ± 1.0
$t_{1/2}$ (min)	32 ± 8	54 ± 17*
V_{ss} (L/kg)	1.1 ± 0.1	1.6 ± 0.3***
V_β (L/kg)	1.3 ± 0.3	2.3 ± 0.5**

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

The AUC/Dose values for the ip doses of carbidopa were significantly larger for the small ip dose (1.25 mg/kg) and the dose given in a large volume (3.75 mg/kg given in 20 mL/kg) compared to the 3.75 mg/kg dose given in 2 mL/kg (Table III). These values were even greater than the corresponding values for the intravascular routes. The half-life for the 3.75 mg/kg dose given in 20 mL/kg was also longer than the reference ip dose (3.75 mg/kg given in 2 mL/kg). Carbidopa concentration data from three rats were omitted for the ip dose of 1.87 mg/kg carbidopa because of analytical reasons.

Oral and Intraduodenal Doses

The plasma concentration–time profiles of levodopa following oral and duodenal administration are shown in Fig. 3.

For the oral dose, both the rate and the extent of absorption showed great variability. This variation was substantially reduced when levodopa was given id both as a water solution and in the 1.8% methylcellulose suspension (Fig. 3).

The AUC/Dose from the oral and duodenal solutions and duodenal suspension were the same, indicating a similar degree of absorption (Fig. 4). The bioavailability of the oral and duodenal doses can be calculated using the dose-corrected AUC value for either the large iv dose or the small one (AUC_{po}/AUC_{iv}). When the 15 mg/kg dose was used the bioavailability was 35%, and when the 5 mg/kg dose was used the bioavailability was 62%.

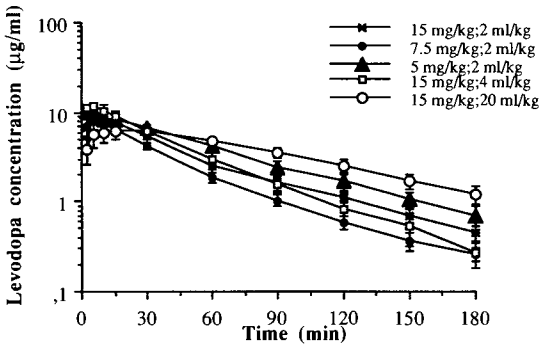

Fig. 2. Concentration–time profiles of levodopa after the ip doses. Each data point is scaled for comparison with the 15 mg/kg dose. Each point is the mean ± SD for six rats.

Table III. Dose-Corrected AUCs and Half-Lives of Carbidopa Following ip Administration (n = 6 in each group)

Dose (mg/kg)	Volume given (mL/kg)	AUC/Dose [μg × min/mL/ (mg/kg)]	$t_{1/2}$ (min)
3.75	2	4.1	17
		(0.5)	(5)
1.87	2	3.6	17
		(0.3)	(1)
1.25	2	10*,[a]	29
		(1.0)	(5)
3.75	4	4.9	19
		(1.3)	(5)
3.75	20	11*,[a]	35*
		(1.2)	(13)

[a] Significantly larger area than the areas after the intravascular doses.
* $P < 0.05$ according to ANOVA.

The rate of absorption was, however, faster with the duodenal route (both for the solution and the suspension) as shown by the increase in C_{max} and decrease in t_{max} (Fig. 5). The half-life of the duodenal solution was 35 min and the half-life of the suspension was significantly longer (52 min). Comparing the duodenal doses with the oral as reference, there were no significant differences among the half-lives of the three doses.

When given orally and id the plasma concentrations of carbidopa were below the limit of detection at almost all time points.

3-*O*-Methyldopa

The metabolite concentrations reached a plateau ($C_{max,met}$) after about 90 min and no decline in the concentrations was detected during the sampling period. There was a significant decrease in the plateau concentration of the metabolite following the iv dose of 5 mg/kg compared to the ia and iv doses of 15 mg/kg.

There was also a significant difference in the metabolite concentration following the 7.5 and 5 mg/kg and the 15 mg/kg in 20 mL/kg ip doses compared to the reference ip dose of 15 mg/kg in 2 mL/kg. These differences from the ip route vanished, however, when the plateau concentration of the metabolite was related to the AUC of levodopa, except for the 15 mg/kg in 20 mL/kg dose. For this dose, the ratio $C_{max,met}/AUC_{levodopa}$ was significantly reduced. The $C_{max,met}/AUC_{levodopa}$ for the different routes of levodopa administration are shown in Fig. 6.

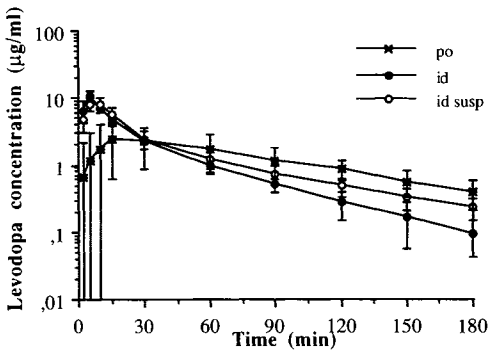

Fig. 3. Concentration–time profiles of levodopa after administration of the oral dose, duodenal solution, and duodenal suspension. Each point is the mean ± SD for six rats (five rats, duodenal suspension).

DISCUSSION

The evaluation of the pharmacokinetics of levodopa is complicated by the presence of carbidopa, since carbidopa influences both the absorption and the systemic elimination of levodopa (15,16). It has also been shown previously that the clearance and half-life of levodopa after an iv dose change with the dose of carbidopa coadministered (16). This perturbs the estimations of the pharmacokinetic parameters of levodopa administered by different routes, since the concentration–time profile of carbidopa depends on the route of administration. The local effect of the unabsorbed decarboxylase inhibitor can also have a major impact on the extent of absorption, especially from the small intestine. Therefore, it is difficult to characterize the pharmacokinetic properties of levodopa quantitatively.

Clearance of levodopa when carbidopa is given iv is reported as 45 mL/min/kg, compared to 86 mL/min/kg without carbidopa (16). Mearrick *et al.* reported a clearance of about 70 mL/min/kg when levodopa was given alone to rats (17). The half-life of levodopa in these two studies when no carbidopa was given was about 25 min.

Since the systemic elimination of levodopa is influenced by the plasma concentration of carbidopa, the reference AUC used for the bioavailability calculation becomes questionable. In the present study carbidopa was administered in the same solution as levodopa, making the estimation of the bioavailability of levodopa dependent on the bioavailability of carbidopa. The low plasma concentrations of carbidopa after the oral and duodenal routes compared to after the iv dose indicate low bioavailability of carbidopa with these routes. Hence, the systemic elimination of levodopa would not be influenced by the carbidopa dose when the drugs are given orally and id. This was also observed in the study by Leppert *et al.*, where no alteration in either half-life or AUC of iv levodopa was seen during duodenal administration of carbidopa (16). However, the half-life obtained in this study after oral and id administrations (35–52 min) is not significantly different from the half-life obtained from the iv doses, which contradicts the assumption of no systemic influence. It is possible that carbidopa can inhibit the decarboxylase enzymes in the liver during the first pass of carbidopa through the liver, which may affect the systemic liver extraction of levodopa.

Since levodopa is metabolized by several enzymes, the estimated V_{max} and K_m values are actually "hybrid parameters" for all the enzymes involved.

Since there was no difference in AUCs after iv and ia administration, there seems to be no major elimination of levodopa occurring in the lung (18).

When levodopa was administered ip in the large volume, the AUC was clearly increased and the rate of absorption was slower, resulting in a lower C_{max} and a longer t_{max}. A reason for this could be precipitation of levodopa when

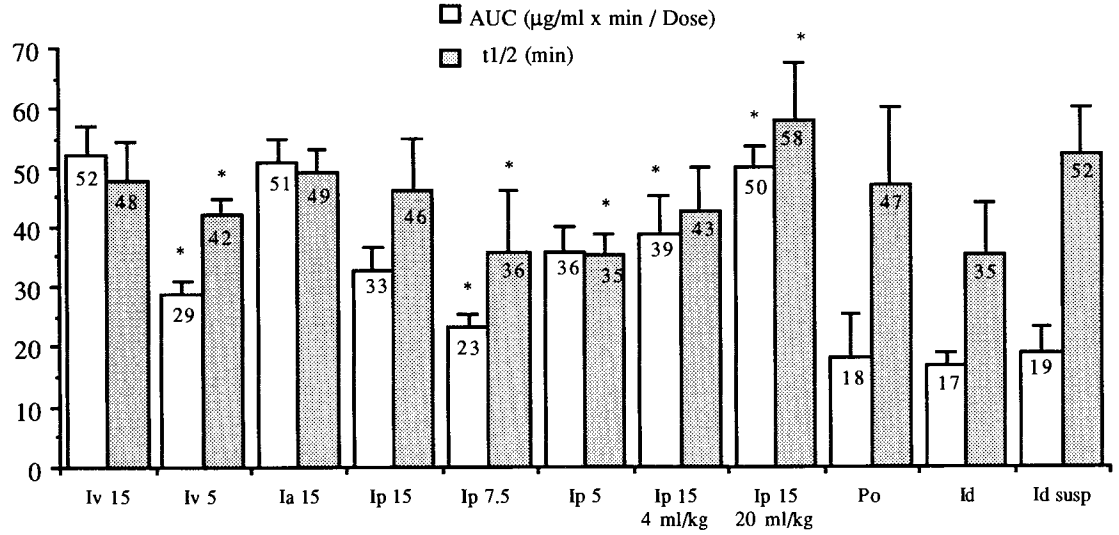

Fig. 4. Dose-corrected AUC and half-life of levodopa following the different modes of administration, calculated model-independently. (*) Significantly different from the reference dose for each route of administration as tested by ANOVA ($P < 0.05$).

given in smaller volumes, which would hinder the absorption. The absorption of water from the peritoneum is probably faster than the absorption of levodopa, and when smaller volumes are administered the water is soon absorbed, leaving levodopa undissolved. The larger volume would, however, keep levodopa dissolved during a longer time, facilitating the absorption. Another possibility could be that the fraction of the dose passing through the liver could be smaller because of uptake into blood vessels escaping the liver. This is possible since the whole peritoneal cavity will be covered by the solution (so-called belly bath) and the solution will be in contact with blood vessels other than those draining into the portal vein. The slower rate of absorption can be explained by (i) the lower concentration gradient, since the levodopa was more diluted when the larger volume was given, and (ii) the slow diffusion rate of levodopa in saline. On the other hand, a larger surface area is covered with the solution in this case, which would enhance the absorption rate.

The half-life was also increased when levodopa was administered ip in the large volume, possibly because of a decrease in clearance. Since the concentration of carbidopa was higher on this occasion than during any other route or dose given, it is possible that the systemic inhibition of the elimination of levodopa is more pronounced. It is not likely that the absorption is rate limiting for the elimination of levodopa since the t_{max} is only 23 min, indicating a rapid rate of absorption in relation to the elimination half-life of levodopa.

For the 7.5 mg/kg ip levodopa dose given in 2 mL, quite the opposite was noted, the AUC being smaller and the half-life shorter, which might suggest a higher clearance for this dose. A reason for this might be the nonlinear elimination or a lower degree of decarboxylase inhibition. On the other hand, this would indicate a higher degree of bioavailability for the smallest dose (5 mg/kg) since the AUC/Dose for this dose is comparable with the reference ip dose.

The absorption rate is rapid from the small intestine (t_{max} = 5–8 min when given id). The absorption after oral

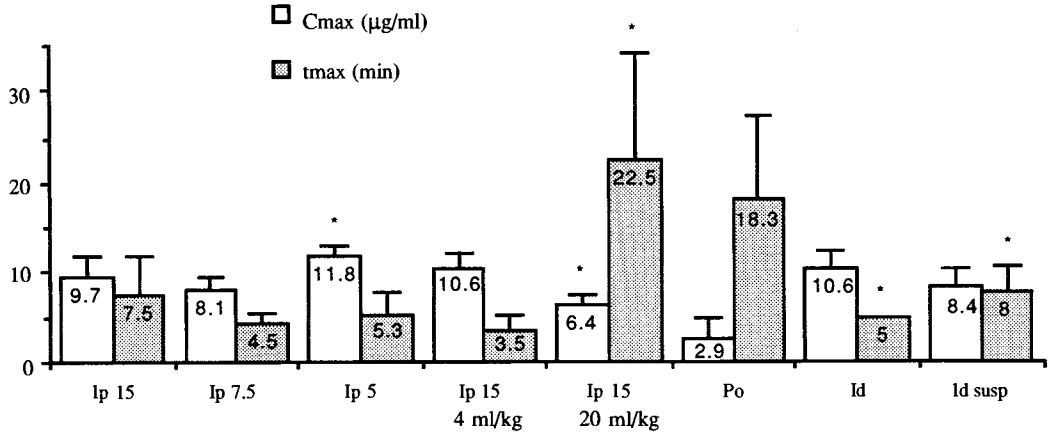

Fig. 5. Dose-corrected C_{max} and t_{max} of levodopa following different modes of administration, calculated model-independently. C_{max} is scaled as $C_{max} \times 15$/Dose. (*) Significantly different from the reference dose for each route of administration as tested by ANOVA ($P < 0.05$).

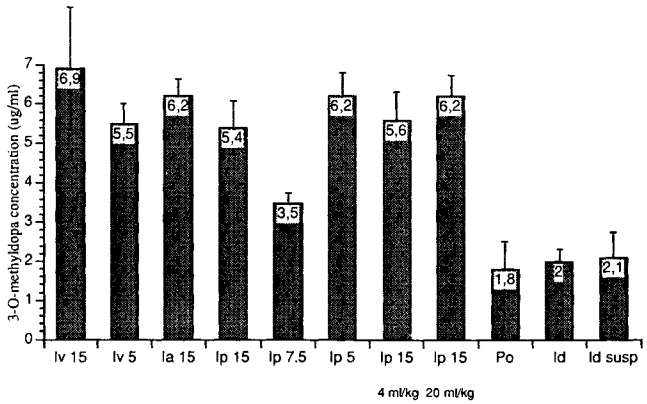

Fig. 6. Dose-corrected AUC and half-life of 3-*O*-methyldopa following the different modes of administration, calculated model-independently. (*) Significantly different from the reference dose for each route of administration as tested by ANOVA ($P < 0.05$).

administration hence becomes very sensitive to factors affecting gastric emptying, e.g., diet, osmolality, and pH of gastric content, and volume given in relation to the inter digestive myoelectric migrating complex (IMMC) (19). The interindividual differences were significantly reduced after administration via the duodenal route compared to the oral, indicating that gastric emptying could be responsible for much of the erratic absorption observed in patients with Parkinson's disease. It is interesting to note that there was no difference in either rate or extent of absorption between the solution and the suspension administered id. This implies that a suspension of levodopa could be an alternative formulation when given to Parkinson's patients by id infusion. This would solve the problem of the large volume needed when levodopa is to be administered continuously, i.e., as a solution. The use of this route would be substantially simplified, since the concentration can be much higher, and hence the volume the patients have to carry much smaller. Both levodopa and carbidopa are chemically stable in this formulation (20).

The low oral bioavailability observed in this study, despite concomitant administration of carbidopa, can be explained by the fact that the rats were not pretreated with carbidopa. Huebert *et al.* found that after 5 days of carbidopa treatment (5 mg/kg daily), the oral bioavailability increased about three times, assuming the volume of distribution of 1.4 L/kg obtained in the present study (15). This is an approximation since the elimination is nonlinear. Carbidopa inhibits the dopa decarboxylase enzymes by scavenging the enzyme's pyroxidal phosphate cofactor. It is possible that this effect persists much longer than does carbidopa itself.

There was a significant difference in volume of distribution of carbidopa between the low iv dose and the higher ia dose (1.1 vs 1.6 L/kg). The size of the volume of distribution of carbidopa is the same as the volume calculated for the small dose of levodopa, 1.6 L/kg. Carbidopa is bound to plasma proteins only to 36% (21), and since the volume of distribution is about 1 L/kg, this indicates that the binding to tissue proteins is about 70–80% $\{f_{bT} = 1 - [f_u \times V_T/(V_{ss} - V_P)]$ (22)$\}$, where f_{bT} is the fraction bound in the tissues, f_u is the fraction unbound in plasma, V_T is the volume of tissue, and V_P is the volume of plasma. It is possible that levodopa interacts with the same tissue proteins as carbidopa, thereby displacing carbidopa from the tissue proteins at higher doses of levodopa and carbidopa. This would cause a decrease in the volume of distribution at higher concentrations.

The ratio of the concentration of metabolite 3-*O*-methyldopa at plateau to the AUC of levodopa was significantly higher when the smaller dose of 5 mg/kg was given. This is an indication of 3-*O*-methyldopa being part of the saturable metabolism of levodopa, assuming that there is no capacity limitation of the elimination of 3-*O*-methyldopa. There was also a significant decrease in the ratio $C_{max,met}/AUC_{levodopa}$ when levodopa was administered as 15 mg/kg in 20 mL/kg ip. The reason for this might be that the concentration of metabolite was still increasing at the last sample taken. It is interesting to note that the pharmacokinetics of all three entities measured in this study are affected when the large volume of 20 mL/kg is administered ip. It is possible that some physiological properties change when this large volume is placed in the peritoneum. Since the solution given was isotonic, it will be absorbed into the bloodstream and hence can affect the systemic elimination of the chemicals.

During the sampling period used in the study the metabolite concentrations did not start to decline but remained at a plateau, supporting the fact that 3-*O*-methyldopa has a much longer half-life than levodopa. It has been speculated that this metabolite could contribute in a negative fashion to the effect of levodopa (23), but the different routes of administration tested in this study indicated no route being of any advantage over another.

The conclusion drawn from this study is that the oral route is certainly not the best one for levodopa therapy even though it is convenient, since it exhibits large variation in both rate and extent of absorption.

Since absorption from the peritoneum and duodenum is rapid, a continuous delivery system via either of these routes could be tested in clinical practice. This could be beneficial to those patients with Parkinson's disease, who have large fluctuations in response and who are sensitive to the rapid changes in plasma levodopa concentrations obtained with intermittent levodopa dosing by the oral route.

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