Br. J. clin. Pharmac. (1989), **28**, 61–69

The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa

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1 The effect of age on the pharmacokinetics of levodopa administered alone and in the presence of carbidopa was investigated in young and elderly healthy volunteers.
2 The plasma clearance of levodopa following intravenous administration of 50 mg was 14.2 ± 2.8 (s.d.) ml min^{-1} kg^{-1} in the elderly compared with 23.4 ± 4.1 ml min^{-1} kg^{-1} in the young ($P < 0.01$) which resulted in a 49% greater area under the plasma concentration-time curve (AUC) in the older subjects ($P < 0.01$). The volume of distribution (V_{ss}) was lower in the elderly (1.01 ± 0.29 l kg^{-1}) than in the young (1.65 ± 0.39 l kg^{-1}) ($P < 0.002$).
3 Following oral administration of 250 mg of levodopa the AUC was 2512 ± 588 ng ml^{-1}h in the elderly compared with 1056 ± 282 ng ml^{-1}h in the young ($P < 0.002$). C_{max} was also significantly greater in the elderly ($P < 0.05$). The bioavailability of levodopa was significantly greater in the elderly (0.63 ± 0.12 compared with 0.41 ± 0.16, $P < 0.01$).
4 In the presence of carbidopa, the plasma clearance of intravenous levodopa (50 mg) was reduced in both age groups but remained lower in the elderly (5.8 ± 0.9 ml min^{-1} kg^{-1} compared with 9.3 ± 1.0 ml min^{-1} kg^{-1}; $P < 0.01$). This resulted in a 54% greater AUC in the older subjects ($P < 0.01$). The V_{ss} was also reduced in both age groups and the age related difference remained (0.62 ± 0.15 l kg^{-1} in the elderly compared with 0.93 ± 0.19 l kg^{-1} in the young; $P < 0.05$).
5 Following oral administration of 125 mg of levodopa in the presence of carbidopa, the AUC was significantly greater in the elderly (4530 ± 1034 ng ml^{-1} h compared with 2926 ± 542 ng ml^{-1} h, $P < 0.01$). This was due solely to the lower systemic clearance in the elderly because carbidopa abolished the age difference in the bioavailability of levodopa (0.85 ± 0.14 in the elderly compared with 0.86 ± 0.19 in the young).
6 The results indicate that decarboxylation is the age dependent component of the first pass metabolism of levodopa. The lower plasma clearance and V_{ss} in elderly subjects given carbidopa suggest that other aspects of the disposition are affected by age.

Keywords age levodopa carbidopa pharmacokinetics

Introduction

Levodopa is the naturally occurring precursor of dopamine, and it has become the mainstay of treatment for Parkinson's Disease owing to the poor penetration of the blood brain barrier by dopamine itself. Levodopa undergoes extensive peripheral metabolism – less than 1% of an oral dose being eliminated in the urine as unmetabolised levodopa (Abrams *et al.*, 1971). The main pathway of metabolism involves decarboxylation to dopamine by the enzyme L-

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aromatic amino acid decarboxylase (AAAD). This enzyme is widely distributed, with particularly high concentrations being found in the liver, gut and kidney. Dopamine is further metabolised by catechol-*O*-methyltransferase and monoamine oxidase to dihydroxyphenylacetic acid (DOPAC) and homovanillic acid. Other pathways of metabolism of levodopa such as *O*-methylation and transamination become quantitatively important when levodopa is administered with a peripheral decarboxylase inhibitor (Nutt & Fellman, 1984). This is now routine in clinical practice and has the effect of increasing the amount of unmetabolised levodopa available to cross the blood-brain barrier.

The increased susceptibility of elderly patients to levodopa associated side effects was noted in several early studies using levodopa alone (Godwin-Austen *et al.*, 1971; Broe & Caird, 1973; Grad *et al.*, 1974). This has remained a problem despite the introduction of peripheral decarboxylase inhibitors and considerably lower doses of levodopa are used in the elderly than in younger patients (Turnball & Aitken, 1983). Various physiological changes that occur as part of the normal ageing process may have consequences for drug pharmacokinetics (McAllister, 1986), but little information is available concerning the effect of age on the pharmacokinetics of levodopa.

In 1981, Evans *et al.* reported that the area under the plasma concentration-time curve (AUC) of levodopa was significantly greater in elderly compared with young volunteers following a single oral dose. However, as no data were obtained following intravenous administration the mechanism of this difference could not be given. The effect of the addition of a peripheral decarboxylase inhibitor on these age related changes in the pharmacokinetics of levodopa is unknown.

We have therefore undertaken studies to compare the pharmacokinetics of levodopa in young and elderly healthy volunteers following oral and intravenous administration of levodopa both alone and with a peripheral decarboxylase inhibitor.

Methods

The studies were approved by the local Ethics Committee and all subjects gave written informed consent. Details regarding the volunteers are summarised in Table 1. The twelve elderly subjects were recruited from a register of healthy elderly citizens who had previously indicated a willingness to participate in research projects. Different volunteers were used for the two studies (Table 1) apart from five elderly subjects who took part in both. Four of the 12 elderly were receiving regular medication. Three were taking the combined preparation of frusemide and amiloride (Frumil); in one instance with ibuprofen and in another with digoxin. The fourth patient was receiving digoxin and warfarin. These were withheld on the study days. The young volunteers were healthy medical students. None of the volunteers smoked.

The basic protocol was similar for the two studies (i.e., with and without carbidopa). All subjects received oral and intravenous levodopa on two different occasions, in random order and separated by at least 1 week. In both studies 50 mg of levodopa were administered intravenously in 100 ml of 0.9% saline over 5 min. In Study A (levodopa alone) a tablet containing 250 mg of levodopa was given orally. In Study B (levodopa + carbidopa) the oral dose of levodopa was reduced to 125 mg. For Study B, carbidopa was given 1 h before (100 mg) and 6 h after (50 mg) the oral and intravenous doses of levodopa. Subjects were studied after an overnight fast and remained recumbent for 1 h and fasted for 4 h after receiving levodopa, when a standard lunch containing 20g of protein was given. Blood samples (6 ml) were taken via an indwelling cannula for 8 h following oral and intravenous levodopa with additional samples taken at 12 h

Table 1 Volunteer characteristics

	Sex	*Age (years)*	*Weight (kg)*	*Lean body mass (kg)*	*Creatinine clearance (ml min^{-1})*
Study A (levodopa alone)					
Young $n = 8$	1F : 7M	21.8(20–23)	69.6(62.0–82.5)	59.3(39.9–70.2)	not available
Elderly $n = 9$	2F : 7M	71.0(68–75)	75.2(56.7–93.0)	58.7(45.8–65.3)	68(58–87)
Study B (levodopa + carbidopa)					
Young $n = 8$	4F : 4M	21.6(21–22)	67.1(57.3–87.3)	54.3(42.8–75.4)	127(102–150)
Elderly $n = 8$	4F : 4M	73.1(69–76)	70.0(49.5–98.0)	53.3(36.3–65.3)	64(51–87)

by single venepuncture, following oral administration. Multiple early samples (every 15 min for 2 h) were taken following oral levodopa in order to define the absorptive phase. Samples were analysed for levodopa and dihydroxyphenylacetic acid (DOPAC) by extraction with neutral alumina as described by Freed & Asmus (1979) and measurement by reverse phase high performance liquid chromatography with an electrochemical detector using a Waters μBondapak C18 column and a mobile phase consisting of 5mM octane sulphonic acid and 0.1mM EDTA in 8% v/v aqueous methanol adjusted to pH 3.2 with 0.07 M phosphate buffer. Standards, prepared using control plasma, were analysed with each batch of samples. Coefficients of variation for levodopa were ±5% at 100 and 200 ng ml^{-1} and ±3.5% at 1000 ng ml^{-1}.

Data analysis

The maximum concentration (C_{max}) and the time of C_{max} (t_{max}) are the observed values. The terminal half life ($t_{½}$) was calculated by linear least squares regression analysis on the terminal slope of the log plasma drug concentration time curve. The area under the plasma drug concentration time curve (AUC) and the area under the first moment of the drug concentration time curve (AUMC) were calculated by the trapezoidal rule with extrapolation to infinity as described by Gibaldi & Perrier (1982). Pharmacokinetic parameters calculated were:

$$\text{Bioavailability } (F) = \frac{\text{AUC oral}}{\text{AUC i.v.}} \times \frac{\text{dose i.v.}}{\text{dose oral}}$$

$$\text{Clearance (CL)} = \frac{\text{Dose i.v.}}{\text{AUC}}$$

$$\text{Mean residence time (MRT)} = \frac{\text{AUMC}}{\text{AUC}}$$

Mean absorption time (MAT) = MRT (oral) − MRT (iv)

Volume of distribution at steady state (V_{ss}) = MRT (iv) × CL.

Lean body mass (lbm) was derived from skin fold thickness measurements as described by Durnin & Rahaman (1967).

Results are expressed as mean ± s.d.

Statistical analysis was by Wilcoxon's rank sum test, a P value of <0.05 was considered to be statistically significant.

Results

Study A levodopa alone

Following intravenous administration the plasma clearance of levodopa was 39% lower in the elderly subjects ($P < 0.01$) which was associated with a 49% greater AUC in this age group (Table 2). The V_{ss}, corrected for total body weight was also significantly lower in the elderly so that the $t_{½}$ did not differ between the two age groups. Correction of the V_{ss} for lean body mass reduced but did not abolish the age related difference ($P < 0.05$). The MRT was not affected by age.

Two young and nine elderly subjects exhibited multiple peaks in their plasma concentration-time curves following oral administration (Figure 1). The presence of these peaks is reflected in the large standard deviations for C_{max}, t_{max} and MAT reported in Table 2. The AUC for levodopa was 2.4 fold greater in the elderly subjects ($P <$

Table 2 Pharmacokinetic parameters following oral and intravenous administration of levodopa alone

Study A (levodopa alone)	*Young*	*Elderly*	P
Intravenous (50 mg)			
AUC (ng ml^{-1} h)	541 ± 140	806 ± 94	< 0.01
CL (ml min^{-1} kg^{-1})	23.4 ± 4.1	14.2 ± 2.8	< 0.01
V_{ss} (1 kg^{-1})	1.65 ± 0.39	1.01 ± 0.29	< 0.002
V_{ss} (1 kg^{-1} lbm)	1.89 ± 0.47	1.29 ± 0.34	< 0.05
$t_{½}$ (h)	1.3 ± 0.3	1.3 ± 0.2	NS
MRT (h)	1.2 ± 0.3	1.2 ± 0.2	NS
Oral (250 mg)			
C_{max} (ng ml^{-1})	1077 ± 577	1842 ± 901	< 0.05
t_{max} (h)	0.8 ± 0.6	0.9 ± 0.8	NS
AUC (ng ml^{-1} h)	1056 ± 282	2512 ± 588	< 0.002
$t_{½}$ (h)	1.5 ± 0.4	1.4 ± 0.3	NS
MRT (h)	1.8 ± 0.4	2.3 ± 0.7	NS
MAT (h)	0.6 ± 0.5	0.9 ± 0.7	NS
Bioavailability (F)	0.41 ± 0.16	0.63 ± 0.12	< 0.01

For abbreviations in this and subsequent tables, see under Methods.

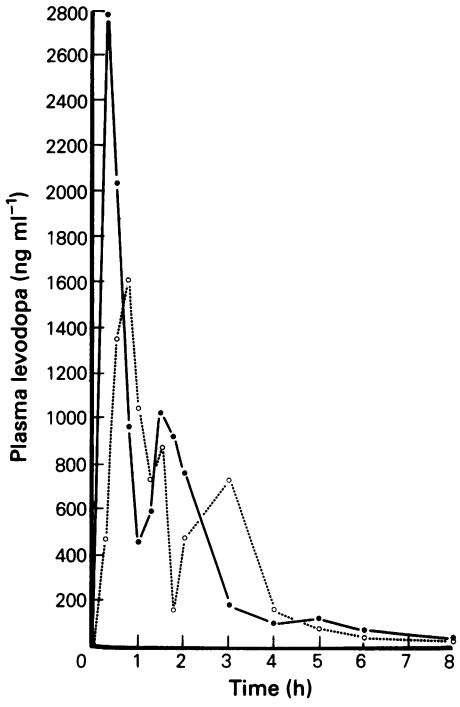

Figure 1 Plasma concentration-time curves for levodopa in two elderly volunteers given a single oral dose of 250 mg of levodopa.

0.01) and C_{max} was also higher ($P < 0.05$). The absolute bioavailability of levodopa was 53% greater in the elderly compared with the young ($P < 0.01$). The $t_{½}$ (derived using at least three data points which were log-linear) and MRT were similar in both age groups.

Study B levodopa plus carbidopa

The clearance of intravenous levodopa when given in combination with oral carbidopa showed a proportionally similar reduction in both age groups and therefore remained significantly lower in the elderly than in the young ($P < 0.01$) (Table 3). This resulted in a 54% greater AUC in the older subjects ($P < 0.05$). The V_{ss} (corrected for total body weight) was also significantly lower in the elderly subjects ($P < 0.05$), although correction for lean body mass removed the statistical significance of the difference between the age groups. The $t_{½}$ and MRT were similar in both groups.

Multiple plasma peaks occurred in four young and five elderly subjects following oral levodopa with carbidopa which again resulted in wide interindividual differences in C_{max}, t_{max} and MAT (Table 3). The AUC values were significantly greater in the elderly compared to the young ($P < 0.01$) but the addition of carbidopa abolished the age related difference in the bioavailability of levodopa found when it was given alone. The $t_{½}$ and MRT were similar in the two age groups.

The effect of the addition of carbidopa on levodopa kinetics within each age group.

(a) Intravenous levodopa The addition of carbidopa resulted in a 60% reduction in the plasma clearance of levodopa in both age groups ($P < 0.002$) (Table 4). In both age groups the addition of carbidopa was associated with a reduction in the V_{ss} ($P < 0.01$ in the elderly; $P <$

Table 3 Pharmacokinetic parameters following oral and intravenous administration of levodopa combined with carbidopa

Study B (levodopa + carbidopa	*Young*	*Elderly*	P
Intravenous (50 mg)			
AUC (ng ml^{-1} h)	1377 ± 219	2121 ± 230	< 0.01
CL (ml min^{-1} kg^{-1})	9.3 ± 1.0	5.8 ± 0.9	< 0.01
V_{ss} (l kg^{-1})	0.93 ± 0.19	0.62 ± 0.15	< 0.05
V_{ss} (l kg^{-1} lbm)	1.2 ± 0.3	0.9 ± 0.2	NS
$t_{½}$ (h)	1.5 ± 0.2	2.0 ± 0.5	NS
MRT (h)	1.7 ± 0.3	2.0 ± 0.4	NS
Oral (125 mg)			
C_{max} (ng ml^{-1})	1712 ± 769	1922 ± 563	NS
t_{max} (h)	1.4 ± 0.7	1.4 ± 0.7	NS
AUC (ng ml^{-1} h)	2926 ± 542	4530 ± 1034	< 0.01
$t_{½}$ (h)	1.6 ± 0.3	2.1 ± 0.4	NS
MRT (h)	3.1 ± 1.1	3.0 ± 0.4	NS
MAT (h)	1.4 ± 1.1	1.1 ± 0.6	NS
Bioavailability (F)	0.86 ± 0.19	0.85 ± 0.14	NS

Table 4 The effect of carbidopa on levodopa pharmacokinetics within age groups

	Without carbidopa Study A	*With carbidopa Study B*	P
(a) Intravenous levodopa			
Young			
CL (ml min^{-1} kg^{-1})	23.4 ± 4.1	9.3 ± 1.0	< 0.002
V_{ss} (1 kg^{-1})	1.65 ± 0.39	0.93 ± 0.19	< 0.002
$t_{½}$ (h)	1.3 ± 0.3	1.5 ± 0.2	NS
MRT (h)	1.2 ± 0.3	1.7 ± 0.3	< 0.05
Elderly			
CL (ml min^{-1} kg^{-1})	14.2 ± 2.8	5.8 ± 0.9	< 0.002
V_{ss} (l kg^{-1})	1.01 ± 0.29	0.62 ± 0.15	< 0.01
$t_{½}$ (h)	1.3 ± 0.2	2.0 ± 0.5	< 0.01
MRT (h)	1.2 ± 0.2	2.0 ± 0.4	< 0.002
(b) Oral levodopa			
Young			
t_{max} (h)	0.8 ± 0.6	1.4 ± 0.7	NS
MRT (h)	1.8 ± 0.4	3.1 ± 1.1	< 0.002
MAT (h)	0.6 ± 0.5	1.4 ± 1.1	NS
$t_{½}$ (h)	1.5 ± 0.4	1.6 ± 0.3	NS
F	0.41 ± 0.16	0.86 ± 0.19	< 0.002
Elderly			
t_{max} (h)	0.9 ± 0.8	1.4 ± 0.7	NS
MRT (h)	2.3 ± 0.7	3.0 ± 0.4	< 0.01
MAT (h)	0.9 ± 0.7	1.1 ± 0.6	NS
$t_{½}$ (h)	1.4 ± 0.3	2.1 ± 0.4	< 0.002
F	0.63 ± 0.12	0.85 ± 0.14	< 0.01

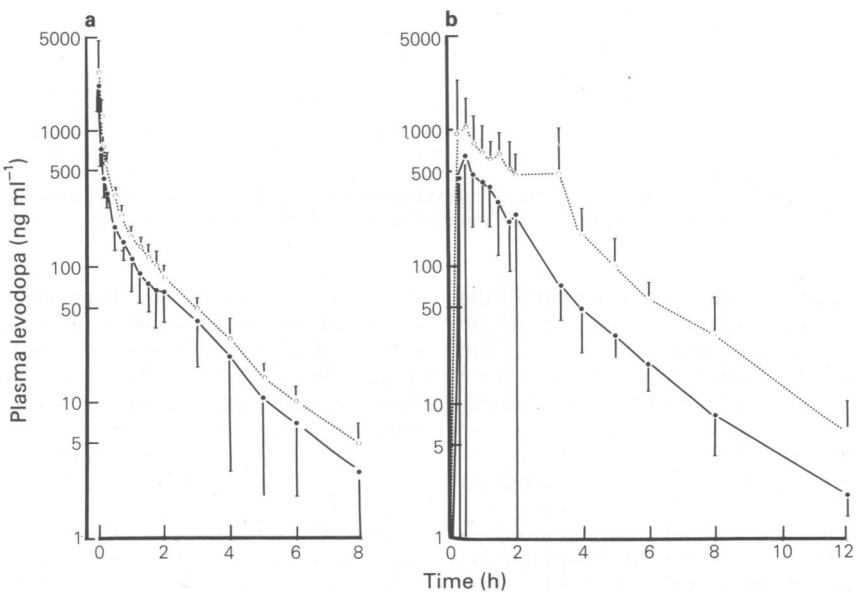

Figure 2 Plasma concentration-time curves for levodopa following intravenous (a) and oral administration (b) to young (●) and elderly (○) volunteers. The data are the means for eight volunteers with the s.d. indicated by vertical bars (Study A).

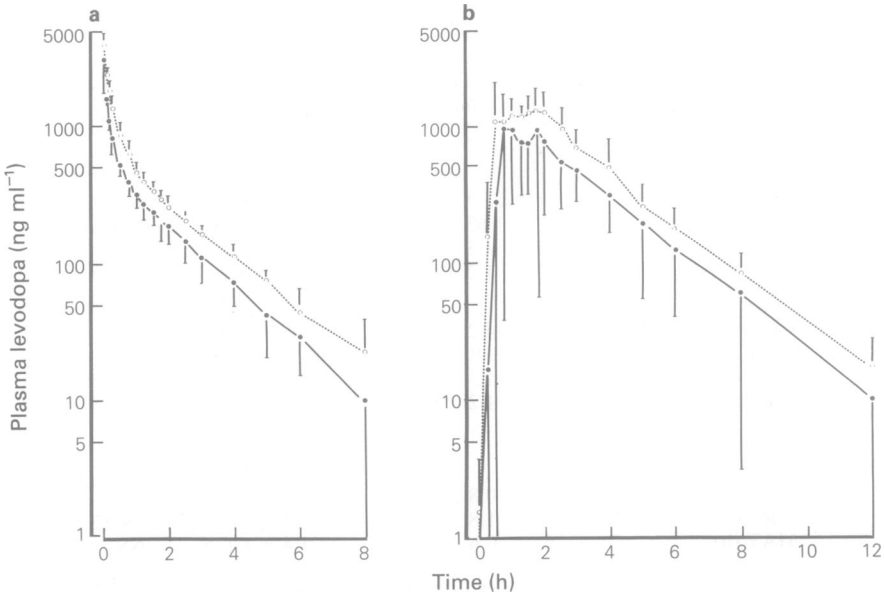

Figure 3 Plasma concentration-time curves for levodopa following intravenous (a) and oral (b) administration to young (●) and elderly (○) volunteers in the presence of carbidopa. The results are the mean for eight volunteers with s.d. shown by vertical bars (Study B).

Table 5 The effect of the addition of carbidopa on the area under the plasma concentration time curve for DOPAC.

	AUC DOPAC (ng ml^{-1} h) *levodopa alone*	*AUC DOPAC (ng ml^{-1} h)* *levodopa + carbidopa*	
Intravenous (50 mg levodopa)			
Young	56 ± 26	36 ± 22	NS
Elderly	74 ± 21	24 ± 11	$P < 0.002$
		levodopa + carbidopa	
Oral	*levodopa alone*	** (dose adjusted to 250 mg)*	
Young	1218 ± 608	286 ± 138	$P < 0.002$
Elderly	1365 ± 528	219 ± 117	$P < 0.002$

* The oral dose of levodopa was 250 mg when given alone and 125 mg when given with carbidopa. The data in Study B have therefore been doubled to allow for this difference in dose.

0.002 in the young). This was consistent for the group as a whole as well as the five elderly subjects for whom paired data were available (1.10 ± 0.28 l kg^{-1} Study A; 0.45 ± 0.19 l kg^{-1} Study B; $P < 0.01$). Carbidopa significantly increased the $t_{½}$ of levodopa in the elderly ($P < 0.01$) but not in the young. The MRT was prolonged significantly by the addition of carbidopa in both age groups ($P < 0.002$ in the elderly: $P < 0.05$ in the young). The addition of carbidopa did not significantly alter the AUC for DOPAC following intravenous administration of levodopa in either age group (see Table 5); DOPAC concentrations were low and close to the limit of detection.

(b) Oral levodopa The bioavailability of levodopa was increased significantly by carbidopa in both age groups. This effect of carbidopa was greatest in the young resulting in a doubling of the bioavailability of levodopa in this age group compared with a 35% increase in the elderly (Table 4). Consistent with the findings following intravenous administration, carbidopa prolonged the $t_{½}$ of levodopa only in the elderly subjects ($P < 0.002$) The MRT was increased by the addition of carbidopa in both age groups ($P < 0.01$ in the elderly; $P < 0.002$ in the young). The addition of carbidopa resulted in a significant (approximately 80%) decrease in the AUC for DOPAC in both age groups (Table 5).

Discussion

The systemic clearance of levodopa was 39% lower in elderly compared with young volunteers following intravenous administration of levodopa alone (Study A). The hepatic clearance of an intravenously administered drug may depend on liver blood flow as well as the intrinsic metabolising activity of the liver (Wilkinson & Shand, 1975). Apparent liver blood flow falls by 47% between the ages of 24–91 (Rawlins *et al.*, 1987); the effect of this is greatest for drugs with high hepatic clearance, which exhibit flow dependent kinetics (George, 1979). The systemic plasma clearance of levodopa is high (1621 ml min^{-1} in the young), and if the liver is the main site of clearance then changes in liver blood flow with age could account for the lower systemic clearance of levodopa in our elderly subjects. The contribution of extra hepatic tissues to the systemic clearance of levodopa is unknown but may also be age dependent since the blood supply to the intestine and kidney falls with age (Bender, 1965, 1968). Decarboxylase activity is widespread in extrahepatic sites, and an age related decline in renal and hepatic AAAD activity has been reported in animals (Awapara & Saine, 1975). It is not known if this occurs in humans although cerebral dopa decarboxylase activity is lower in the elderly (Gottfries, 1980).

Following oral administration of levodopa alone, the C_{max} was significantly greater in the elderly who also showed a 2.4 times greater AUC, thus confirming previous observations (Evans *et al.*, 1981). Despite the routine clinical use of oral levodopa over many years its bioavailability remains uncertain. Studies using radiolabelled levodopa indicated that 80–90% of the radioactivity from an oral dose is absorbed (Bianchine *et al.*, 1971; Abrams *et al.*, 1971). The oral bioavailability of only 41% in our young subjects indicates that extensive first pass metabolism occurs although the site of this cannot be determined from the present study. Comparison of the AUC of levodopa following oral, peripheral intravenous and rapid portal vein administration to dogs indicated that the intestinal wall was the major site of first pass metabolism (Sasahara *et al.*, 1981). Furthermore, a study of levodopa decarboxylation using an *in situ* rat jejunal preparation provided evidence that the gut rather than the liver was the major site of first pass metabolism (Iwamoto *et al.*, 1987). This study also demonstrated an age related decline in jejunal AAAD activity which was associated with a greater bioavailability of levodopa in elderly compared with young rats. A similar mechanism may be responsible for the 53% greater bioavailability observed in our elderly subjects. The higher oral bioavailability in this age group accounts for approximately half of the greater AUC in the elderly with the remainder being due to lower systemic clearance.

The contribution of AAAD activity to the altered pharmacokinetics of levodopa in the elderly was investigated in Study B. A total dose of 150 mg of carbidopa was used since inhibition of decarboxylase is reported to be maximal at a daily dose of 70–150 mg (Pinder, *et al.*, 1976). The extent of inhibition achieved can be estimated by comparison of the AUC for the dopamine metabolite DOPAC with that observed in Study A (after correction for dose). The degree of inhibition following oral levodopa (approximately 80%) was similar in both age groups. Comparison of the AUC for DOPAC after oral and intravenous administration indicates that it is formed mainly during absorption. Furthermore, the greater bioavailability of levodopa after carbidopa confirms that decarboxylation is the main pathway responsible for first pass metabolism.

Carbidopa resulted in a 60% reduction in the systemic clearance of levodopa in both age groups but the age related difference in clearance persisted. This suggests that factors other than AAAD activity may be age dependent. The systemic plasma clearance of levodopa remained relatively high in the young in the presence of carbidopa (621 ml min^{-1}). The reduction in regional blood flow which occurs with age (Bender, 1965; Rawlins *et al.*, 1987) may therefore contribute to the lower clearance of levodopa in the elderly in the presence of carbidopa. Alternatively the activity of other metabolic pathways e.g. *O*-methylation (which become more important in the presence of a decarboxylase inhibitor) may decline with age. Previous clinical studies have indicated that the addition of carbidopa allows a 60–80% reduction in the oral dose of levodopa (Pinder *et al.*, 1976). In the present study oral administration of levodopa with carbidopa was associated with a 5.6 fold greater AUC of levodopa per unit dose in the young and a 3.6 fold greater AUC in the elderly compared with levodopa alone. This was due to a lower systemic clearance of levodopa in both age groups and a greater effect on bioavailability in the young. Carbidopa abolished the age differences in bioavailability and related C_{max}; thus, decarboxylation is the age dependent component of the first pass metabolism of levodopa.

An unusual pharmacokinetic feature of levodopa is the occurrence of multiple plasma

drug peaks following single oral doses. These have been reported in 40–100% of subjects when levodopa is given alone (Evans *et al.*, 1981; Wade *et al.*, 1974). The presence of multiple peaks necessitates frequent blood sampling during the absorptive phase to avoid errors in AUC measurement but also prevented calculation of absorption rate constants. These peaks were responsible for the wide interindividual variations in C_{max}, t_{max} and MAT.

Animal studies indicate that skeletal muscle is the major reservoir for levodopa – as is the case for other amino acids (Romero *et al.*, 1973). The decline in lean body mass which occurs with age (Forbes & Renia, 1970) may therefore account for the lower V_{ss} observed in the elderly subjects in both studies. Indeed, correction of the V_{ss} for lean body mass reduced the age related differences in both studies. The protein binding of levodopa is negligible (Hinterberger & Andrew, 1972) so that the fall in serum albumin that occurs with age (Woodford-Williams *et al.*, 1964) would not affect V_{ss}. Previous reports on the effects of carbidopa on the V_{ss} of levodopa have been inconclusive. Nutt *et al.*, (1985) found inconsistent changes in the V of levodopa administered as an infusion (2 h or > 20 h) with and without carbidopa. Kaakkola *et al.* (1985) reported an increase in V when the ratio of oral levodopa to carbidopa was altered from 10:1 to 4:1 (although in this case the calculation of V required assumptions regarding bioavailability). An unexpected finding in our studies was that carbidopa administration was associated with a significant reduction in the V_{ss} in both age groups. Possible mechanisms would be interference with the tissue uptake of levodopa by either carbidopa itself or by a product of one of the other metabolic pathways of levodopa such as the 3-*O*-methyl metabolite. An alternative explanation, consistent with the data in this paper, is that the V_{ss} may be concentration dependent.

Because V_{ss} and clearance of levodopa were lower in the elderly compared with the young, in both studies, there were no significant differences in the terminal half-lives or mean residence times between the two age groups. Therefore there appears to be no pharmacokinetic basis for the current widespread practice of giving levodopa less than three times daily in elderly patients (White & Barnes, 1981).

In conclusion we have demonstrated that age is an important determinant of the pharmacokinetics of levodopa when given alone and in conjunction with a peripheral decarboxylase inhibitor. These findings may explain the increased incidence of levodopa side effects in the elderly although changes in pharmacodynamic response may also contribute.

We thank W. Larby for skilled technical assistance, Susan O'Toole for nursing assistance and Hazel Killham for secretarial support. We are grateful to Roche Products Ltd for supplies of the oral and intravenous formulations of levodopa and to Merck, Sharp and Dohme Ltd for carbidopa tablets.

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(Received 7 November 1988, accepted 17 February 1989)