J. Pharm. Pharmacol. 1990, 42: 242–246
Received September 21, 1989

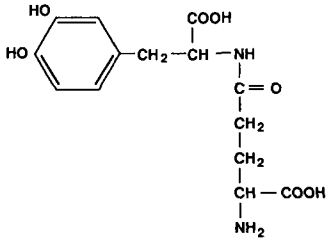
Pharmacokinetics, Bioavailability, Metabolism, Tissue Distribution and Urinary Excretion of γ-L-Glutamyl-L-dopa in the Rat

J. CUMMINGS, L. M. MATHESON, L. MAURICE AND J. F. SMYTH

Imperial Cancer Research Fund, Medical Oncology Unit, Western General Hospital, Edinburgh EH4 2XU, UK

Abstract—γ-L-Glutamyl-L-dopa (gludopa) is believed to be a dopamine prodrug specific for the kidney. Its pharmacokinetics have been studied in the rat given 50 mg kg^{-1} intravenously (i.v.) and 60 mg kg^{-1} intraperitoneally (i.p.). By the i.v. route, elimination followed apparent first order kinetics and was biphasic with a $t_{\frac{1}{2}}\alpha$ of 7 min and terminal half-life of 67 min. After i.p. administration absorption was rapid ($t_{\frac{1}{2}ab}$ 6 min), elimination was monophasic with a terminal half-life almost identical following i.v. dosing (65 min), and bioavailability was 40%. In tissues (liver and kidney) gludopa was biotransformed to four intact catecholic products (L-dopa, dopamine, DOPAC and γ-L-glutamyl-dopamine) which appeared quickly (peaks at 15 min) and which were almost completely cleared by 4 h. Dopamine was the major kidney metabolite accounting for 69% of total catechol content with an AUC 31 times greater than in liver where it accounted for only 34% of total catechols. In rat urine eight major metabolites (5·7% of the dose) and at least 12 minor metabolites were detected of all of which 85% was dopamine. A higher percentage of the dose was excreted as intact catechols in man (15·7%) but fewer metabolites were detected (L-dopa, dopamine, DOPAC). It is confirmed that gludopa is kidney specific in rat but that the pharmacological effects of dopamine are likely to be short lived due to rapid clearance. Gludopa appears to be less dopamine specific in man.

γ-L-Glutamyl-L-dopa (gludopa, I) is a di-peptide believed to be a dopamine prodrug specific for the kidney (Wilk et al 1979). Evidence in favour of this hypothesis has come largely from indirect measurements of biochemical indices such as tissue activities of the two enzymes that convert gludopa to dopamine: γ-glutamyl-transpeptidase (γ-GT, EC 2.3.2.2, Orlowski & Szewczuk 1961) followed by L-dopa decarboxylase (EC 4.1.1.26, Vogel et al 1970), and from tissue uptake of labelled [^{14}C]glutamyl amino acids (Orlowski & Wilk 1976), rather than by direct measurement of gludopa itself. Kidney specificity can be illustrated by comparing tissue levels of γ-GT: if the activity in kidney is ascribed a value of 100 then activity in pancreas is 8·3, intestine 0·95, brain 0·5, liver 3·9 and heart 0·05.



Molecular structure of γ-L-glutamyl-L-dopa (gludopa).

In experimental animals and in man infusions of gludopa mimic the pharmacologic effects of dopamine on the kidney by increasing renal blood flow and glomerular filtration rate, inducing natriuresis and diuresis and reducing plasma renin activity (Wilk et al 1979; Worth et al 1985). These responses can be partially blocked by both (+)-sulpiride, a DA_1 receptor antagonist and domperidone, a DA_2 receptor antagonist (Worth et al 1986; MacDonald et al 1987) whereas the close structural analogue γ-L-glutamyl-tyrosine is without effect on the kidney (Jeffrey et al 1988). After a 2 h infusion of 100 μg min^{-1} kg^{-1} gludopa to normal subjects, urinary excretion of dopamine increased 2500-fold (Worth et al 1985).

As a kidney specific dopamine prodrug, gludopa may have a therapeutic role in hypertensive and sodium retaining states. However, it has also been shown to ameliorate glycerol-induced kidney tubular necrosis and in this respect may be useful against drugs known to be nephrotoxic (Casson et al 1982). The present paper reports the pharmacokinetics and tissue distribution of gludopa and its catecholic metabolites in the rat, and its bioavailability and its comparative metabolism in man and rat.

Materials and Methods

Drug analysis techniques

Gludopa, its major metabolites L-dopa, dopamine, 3,5-dihydroxyphenylacetic acid (DOPAC) and γ-L-glutamyl dopamine (gludopamine) were measured in plasma, urine, liver and kidney by high-performance liquid chromatography (HPLC) with electrochemical detection. Gludopa was a kind gift from Professor Lee (Department of Clinical Pharmacology, Royal Infirmary of Edinburgh), was synthesized by UCB Bioproducts (Brussels, Belgium) and was >98% pure peptide (water content was 4·5%). Gludopamine was synthesized in our own laboratory enzymatically from dopamine and reduced glutathione by γ-glutamyl transpeptidase essentially according to the procedure described by Wilk et al (1979) for gludopa. All standards,

Correspondence to: J. Cummings, Imperial Cancer Research Fund, Medical Oncology Unit, Western General Hospital, Edinburgh EH4 2XU, UK.

reagents and chemicals used were available commercially and were of the highest grade obtainable. Full details of our HPLC methodology are contained in another report (submitted J. Chromatog). Essentially, the HPLC separation used a reversed phase C18 spherisorb ODS-2 5 μm column (25 cm by 4·6 mm internal diameter, Phase Separations, Deeside, Wales) and a mobile phase which consisted of 90% 50 mM sodium dihydrogen phosphate buffer (adjusted to pH 2·9 with 1M orthophosphoric acid) containing 250 mg L^{-1} heptane sulphonic acid and 80 mg L^{-1} EDTA in 10% methanol. Elution was isocratic at a flow rate of 1 mL min^{-1} and the column was at ambient room temperature. Detection was electrochemical using an ESA 5100A multi cell Coulochem detector (ESA, Bedford, USA) with a conditioning cell set at a voltage of +0·3V and a twin electrode analytical cell with the first electrode set at +0·1V and the second electrode set at −0·3V. Quantitation was by measuring peak heights in nA and referring to calibration curves run on the same day. Limit of detection for gludopa and its metabolites in plasma and urine was 40 pg mL^{-1} and in tissue was 10 ng g^{-1}.

Gludopa, its metabolites and dihydroxybenzylamine (DBA, internal standard) were extracted from plasma and urine according to Anton & Sayre (1962) by the use of minicolumns prepacked with 10 mg alumina (ESA), with the modification that catechols were finally eluted in 200 μL of 10% trichloroacetic acid (TCA) to achieve roughly equal recovery for all components. In control experiments the extraction efficiency of L-dopa was 65·8 ± 4·2% s.d.; gludopa, 60·3% ± 4·5% s.d.; dopamine, 58·5% ± 3·5% s.d.; DOPAC 60·2% ± 5·6% s.d. and DBA, 58·0% ± 1·8%.

Liver and kidney (approximately 0·5 g) were homogenized in 2 vol (w/v) of 5% TCA using a standard laboratory high speed blender. Homogenates (1mL), after addition of DBA, were filtered through YMT membranes (mol. wt cut off 30000) contained in an MPS-1 micro-ultrafiltration unit (Amicon, UK) by centrifugation at 1000 *g* for 30 min. Thereafter, tissue samples were ready for analysis. All samples were stored at −20°C, thawed at 0°C and kept cool throughout sample preparation.

Animal pharmacokinetic studies

All animal pharmacokinetic studies were performed with Wistar rats, ca 200 g, which were housed in the animal unit of the Western General Hospital. They were fed a standard laboratory diet, had free access to water and were maintained under constant conditions of temperature and a 12 h dark/light cycle. Gludopa was made up at a concentration of 50 mg mL^{-1} in 0·9% sodium chloride (saline) and rats were treated with 50 mg kg^{-1} for intravenous (i.v.) pharmacokinetics, tissue distribution and urinary excretion and 60 mg kg^{-1} for intraperitoneal (i.p.) pharmacokinetics. For i.p. pharmacokinetics two rats were killed at each of 5, 30, 45, 60, 90 min, 2, 4, 6, 8, and 24 h after drug administration and blood (approximately 2 mL) was collected. For i.v. pharmacokinetics four rats were killed at each of 15, 30, 60 min, 3, 4, 6 and 24 h after drug administration and blood, liver and kidneys collected. All blood was immediately centrifuged and plasma collected, tissues were immediately washed and samples stored at −20°C for not more than two months before analysis. A separate group of rats (n = 6) were housed in metabolic cages and administered gludopa, 50 mg kg^{-1} i.v. Urinary output over the first 24 h after drug administration was collected into round bottom vessels containing two drops of concentrated hydrochloric acid to prevent oxidation of catechols. Urine was also stored at −20°C for not more than 2 months before analysis.

Pharmacokinetic analysis

Gludopa plasma concentration time profiles after i.v. administration were best fitted to a bi-exponential decline described by the equation:

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

where C is plasma drug concentration, A and B are constants and α and β are the apparent first order elimination rate constants. Gludopa plasma concentration time profiles after i.p. administration were best fitted to a mono-exponential decline with first order absorption described by the equation:

$$C = -Ae^{-k_{ab}} + Ae^{-\beta t}$$

where C is plasma drug concentration, A is a constant, K_{ab} is the apparent first order absorption rate constant and β is the apparent first order elimination rate constant. Experimental data were fitted to the above equations using the ELSFIT (Version 3·0 obtained from Dr L. Sheiner, University of California, San Francisco) computer program with a simple homoscedastic error model and weighting factor of $1/C^2$. All areas under the curve (AUC) for gludopa and its metabolites were calculated by the trapesoidal rule. Other parameters are defined as follows:

for i.v. $t_{\frac{1}{2}\alpha} = \frac{0{\cdot}693}{\alpha}$ $\quad t_{\frac{1}{2}\beta} = \frac{0{\cdot}693}{\beta}$

for i.p. $t_{\frac{1}{2}ab} = \frac{0{\cdot}693}{K_{ab}}$ $\quad t_{\frac{1}{2}\beta} = \frac{0{\cdot}693}{\beta}$

$$\text{bioavailability (F)} = \frac{AUC_{i.p.} \times Dose_{i.v.}}{AUC_{i.v.} \times Dose_{i.p.}} \times 100$$

Clearance (CL) = Dose/AUC

for i.v. volume of distribution (V_D) = Dose/A

Half-lives for metabolites were calculated graphically from the terminal portion of their concentration time curves.

Patient studies

Urine was collected in 4 h samples for 24 h in a group of four female cancer patients from the beginning of a 6 h infusion of 25 μg min^{-1} kg^{-1} (9 mg kg^{-1}) gludopa. The subjects were aged 64, 53, 59 and 59 years, and all had normal liver and kidney function. None was hypertensive, nor were they receiving nephrotoxic antibiotics. Each patient was undergoing cisplatin chemotherapy which was administered as a 1 h infusion of 100 mg m^{-2} in the middle of the gludopa infusion. Two had received two previous courses of cisplatin chemotherapy. The patients also received anti-emetic therapy during the present study; this was either dexamethasone and maxalon which was delayed until the end of the gludopa infusion (3 patients) or the anti-emetic Ondansetron GR38032F which is a 5-HT_3 receptor antagonist (1 patient). Urine was collected in plastic vessels containing 2 drops of concentrated hydrochloric acid to prevent oxidation of catecholamines. The total volume of the collection was measured, a 25 mL sample was taken for analysis and stored

at −20°C for not more than 2 months before analysis. Ethical approval was obtained for this study from the ethics committee of the Lothian Health Board.

Results

Gludopa pharmacokinetics

Plasma concentration time curves of gludopa after 50 mg kg^{-1} i.v. or 60 mg kg^{-1} i.p. are shown in Fig. 1 and the pharmacokinetic parameters derived from these profiles are contained in Table 1 along with the pharmacokinetic parameters of the two major metabolites detected in plasma (L-dopa and dopamine). Elimination of gludopa after i.v. administration was rapid and biphasic with an initial half-life of 7 min followed by a terminal half-life of 67 min. After i.p. administration elimination was also rapid but better described by a monophasic decline with a terminal half-life almost identical to that after i.v. administration (65 min). Absorption was rapid with a $t_{\frac{1}{2}ab}$ of 6 min and bioavailability was 39·8%. Only trace amounts of intact catecholic metabolites were present in plasma, but significantly higher dopamine concentrations were detected between 15 min and 2 h ($P < 0.01$, Student's t-test) after i.p. administration.

Kidney and liver concentrations of gludopa and its metabolites in rat after 50 mg kg^{-1} i.v.

Kidney and liver concentrations of gludopa and its four major catecholic metabolites are shown in Table 2 (kidney) and Table 3 (liver). The striking feature of the data for the kidney was the dramatic disappearance of gludopa by 30 min and the dramatic appearance of dopamine by 15 min at a concentration of 80 $\mu g\ g^{-1}$ which is at least six orders of magnitude higher than endogenous values. Significant concentrations of L-dopa, DOPAC and gludopamine were also present in the kidney, again appearing at their peak by 15 min. Dopamine alone accounted for 69% of total kidney catechols. Concentrations of all four metabolites fell quickly and by 6 h they were almost completely cleared (Table 2).

In the liver the picture was less dramatic although the same four metabolite species were present (Table 3). The parent drug was more abundant than in kidney but the concentrations of metabolites were much lower on an AUC basis; 14 times lower for L-dopa, 13 times lower for DOPAC and 31 times lower for dopamine which only accounted for 34·4% of total catechols. By 3 h gludopa and its metabolites were almost completely cleared with the exception of gludopamine which was still detectable at 6 h (Table 3).

Comparative urinary excretion of gludopa and its metabolites in man and rat

In rat urine eight major catecholic metabolites of gludopa were detected, four of these were identified as the major tissue products L-dopa, dopamine, DOPAC and gludopamine (Table 4). The other four unidentified products were quantitated using the standard curve of the catechol they eluted closest to during HPLC. Thus, M1 and M2 were quantitated using the L-dopa standard curve and M3 and M4 were quantitated using the dopamine standard curve. Apart from those eight major products at least 12 other minor products could be discerned on HPLC chromatograms. Of the total administered dose (50 mg kg^{-1} i.v.) 5·7% was recovered in urine as catechol-related species, with dopamine accounting for 85%.

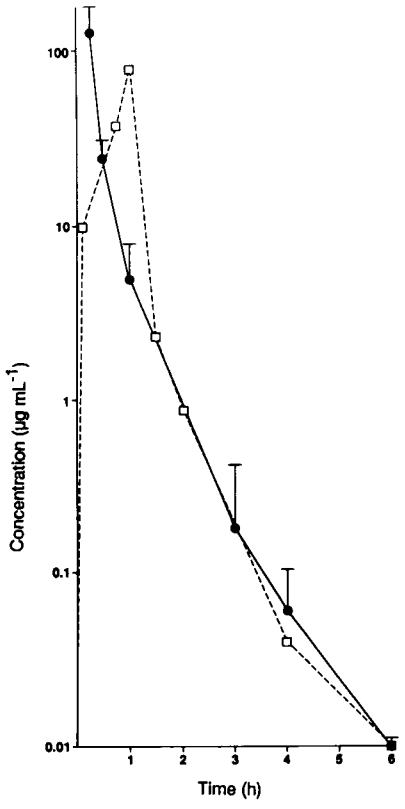


FIG. 1. Plasma concentration time profiles of gludopa in the rat after i.v. administration of 50 mg kg^{-1} (●–●, n = 4 ± s.d.) and i.p. administration of 60 mg kg^{-1} (□–□, n = 2).

Table 1. Pharmacokinetics of gludopa. Pharmacokinetic parameters were derived from the plasma concentration time profiles shown in Fig. 1 and from the plasma concentration time profiles of L-dopa and dopamine. All parameters are explained in Materials and Methods.

		Gludopa		L-Dopa		Dopamine	
Parameter	Unit	i.v.	i.p.	i.v.	i.p.	i.v.	i.p.
[b] C_0/C_{max}	$\mu g\ mL^{-1}$	125	80	0·34	0·29	0·18	0·73
[c] t C_{max}	min		60	30	30	30	30
AUC	$\mu g\ mL^{-1}\ h^{-1}$	109	52	0·25	0·24	0·12	0·55
AUC	% total AUC	99·7	98·5	0·2	0·5	0·1	1·0
$t_{\frac{1}{2}}\alpha$	min	7					
$t_{\frac{1}{2}}\beta$	min	67	65	6	17	ND[a]	12
$t_{\frac{1}{2}}ab$	min		6				
F	%		39·8				
V_D	mL	19					
CL	mL min^{-1}	1·5	3·8				

[a] Could not be determined.
[b] C_0 (i.v.) concentration at time zero, C_{max} (i.p. gludopa and metabolites) maximum concentration.
[c] tC_{max}, time to reach C_{max}.

Only 3 metabolites were detected in patient urine and these were identified as L-dopa, dopamine and DOPAC (Table 5). A higher percentage of the administered dose was recovered as intact catechols (15·7%) with a significant amount of gludopa being present and with a lower amount excreted as dopamine (35·3%).

Discussion

To-date, almost all pharmacological studies on gludopa have focused singly on its conversion to dopamine and its role as an antihypertensive drug (Wilk et al 1979; Worth et al 1985; Caillette et al 1988). Following the observation that gludopa

Table 2. Kidney concentrations ($\mu g\ g^{-1}$) of gludopa and its catecholic metabolites after 50 mg kg^{-1} i.v. (n = 4 ± s.d.).

Time (min)	L-Dopa	Gludopa	Dopamine	DOPAC	Gludopamine
0	0·01	0·00	0·00	0·00	0·00
15	2·78 ± 0·78	1·24 ± 0·53	80·21 ± 51	5·69 ± 0·53	8·43 ± 2·5
30	1·45 ± 0·74	0·00	21·42 ± 1·0	3·89 ± 1·12	7·87 ± 6·0
60	0·49 ± 0·25	0·00	1·04 ± 0·87	0·69 ± 0·10	0·84 ± 0·10
180	0·13 ± 0·13	0·00	0·04 ± 0·01	0·33 ± 0·01	0·24 ± 0·04
240	0·17 ± 0·13	0·00	0·03 ± 0·02	0·04 ± 0·02	0·01 ± 0·00
360	0·17 ± 0·06	0·00	0·01 ± 0·01	0·02 ± 0·01	0·00
1440	0·01	0·00	0·00	0·00	0·00
[a] AUC	2·46	0·00	29·48	4·31	6·47
[b] %	5·8	0·00	69·0	10·1	15·1

[a] Units, $\mu g\ g^{-1}\ h^{-1}$.
[b] Individual AUC expressed as % of total AUC.

Table 3. Liver concentrations ($\mu g\ g^{-1}$) of gludopa and its catecholic metabolites after 50 mg kg^{-1} i.v. (n = 4 ± s.d.).

Time (min)	L-Dopa	Gludopa	Dopamine	DOPAC	Gludopamine
0	0·01	0·00	0·00	0·00	0·00
15	0·38 ± 0·33	3·11 ± 0·10	1·74 ± 0134	1·17 ± 0·97	0·00
30	0·05 ± 0·03	0·25 ± 0·14	0·46 ± 0·08	0·03 ± 0·01	0·12 ± 0·03
60	0·01 ± 0·01	0·03 ± 0·03	0·28 ± 0·02	0·01 ± 0·01	0·11 ± 0·03
180	0·01 ± 0·01	0·01 + 0·01	0·01 ± 0·01	0·00	0·06 ± 0·03
240	0·01 ± 0·00	0·00	0·00	0·00	0·06 ± 0·03
360	0·01 ± 0·01	0·00	0·00	0·00	0·02 ± 0·01
1440	0·00	0·00	0·00	0·00	0·00
[a] AUC	0·17	0·91	0·94	0·32	0·38
[b] %	6·3	33·5	34·4	11·8	14·0

[a] Units, $\mu g\ g^{-1}\ h^{-1}$.
[b] Individual AUC expressed as % of total AUC.

Table 4. 24 h cumulative urinary excretion of gludopa and its catecholic metabolites in the rat after 50 mg kg^{-1}. Amounts are expressed as μg, M1–4 the unidentified metabolites were quantitated as described in Results.

	L-Dopa	Gludopa	Dopamine	DOPAC	Gludopamine	M1	M2	M3	M4
[a] Mean	18·3	3·28	475	37·5	1·13	17·8	0·32	3·5	4·5
s.d.	22	3·9	300	35	1·9	38	0·5	4	2·6
[b] %	3·3	0·6	84·6	6·7	0·2	3·2	0·1	0·6	0·8
[c] % dose	0·2	0·03	4·8	0·4	0·01	0·2	0·003	0·04	0·05
HPLC retention (min)	11·5	18·5	21·4	24	29·6	5·6	7·2	16·3	17·1

[a] n = 6.
[b] Individual amount expressed as % of the total amount excreted.
[c] Individual amount expressed as % of the dose administered.

Table 5. 24 h cumulative urinary excretion of gludopa and its catecholic metabolites in humans after 9 mg kg^{-1} (25 $\mu g\ min^{-1}\ kg^{-1}$ over 6 h). Amounts are expressed as mg.

	L-Dopa	Gludopa	Dopamine	DOPAC
[a] Mean	24·5	7·75	30·98	24·48
s.d.	7·2	3·5	14·40	9·96
[b] %	28·0	8·8	35·3	27·9
[c] % dose	4·39	1·41	5·51	4·43

[a] n = 4.
[b] Individual amount expressed as a % of the total amount excreted.
[c] Individual amount expressed as a % of the dose administered.

could reverse glycerol-induced kidney tubular necrosis (Casson et al 1982), a new role emerged as a possible antidote to nephrotoxic drugs. Here, with the likelihood of co-administration of two compounds an understanding of the pharmacokinetics of gludopa and its conversion to dopamine in the kidney has become essential. We have performed the first pharmacokinetic studies on gludopa in the rat at dose levels similar to those effective in ameliorating glycerol induced nephrotoxicity and found that regardless of whether the drug was administered i.v. or i.p. it was cleared quickly from plasma with a short terminal half-life. Appearance of

dopamine in the kidney at maximum concentration was almost instantaneous, highlighting the kidney's high capacity to biotransform this drug and its subsequent elimination followed closely the clearance of the parent drug from plasma. Indeed, the actual values of plasma gludopa concentration and kidney dopamine concentration were similar. Thus, plasma pharmacokinetics reflect well the generation of dopamine in the kidney, and this observation may prove to be important in the clinical evaluation of the drug. However, these data also suggest that after a single i.v. or i.p. dose of gludopa possible beneficial effects of dopamine on the kidney are likely to be only short lived owing to its rapid elimination.

Presently, gludopa is administered clinically as an infusion which would normally require hospitalization, at least temporarily. If gludopa is to be an effective antihypertensive drug an oral formulation is necessary and this is currently under consideration (Lee 1988). From our studies three potential problems are envisaged with an oral formulation: 1, low bioavailability; 2, increased concentration of circulating dopamine and 3, short therapeutic response time.

At higher concentrations dopamine can stimulate both α- and β-adrenoceptors in the kidney (Goldberg 1972). Considering the dopamine levels achieved after gludopa administration (10^6 fold greater than normal) the possibility exists for a mixed receptor response. Stimulation of α-adrenoreceptors would cause kidney vasoconstriction which could result in drug/toxin retention. Our preliminary findings in rats with 50 mg kg^{-1} i.v. to counteract cisplatin nephrotoxicity suggests that this might indeed be happening since gludopa appeared to increase kidney concentrations of cisplatin rather than reduce them.

Clearance of gludopa and its four major metabolites from the liver appeared to occur by biotransformation to products not detected by our HPLC method since intact catecholamines are not excreted to any significant degree in bile and the four major metabolites were only present in trace amounts in plasma. Our HPLC method only detects intact catecholic species, not their *O*-methylated metabolites or products without adjacent hydroxyl groups. One of these products, the *O*-methylated metabolite of dopamine, vanillyl mandelic acid (VMA) has already been identified in the pancreas of rats in large amounts after an infusion of gludopa (Mizoguchi et al 1979). Gludopamine, a close structural analogue of gludopa, has also been shown to be cleared from tissues mainly through biotransformation (Kyncl et al 1979). Gludopamine differs significantly from gludopa as a prodrug in that it is only slowly hydrolysed to dopamine by γ-glutamyl-transpeptidase, due to the absence of the α-carboxyl group (Wilk et al 1979). In our studies 14–15% of total tissue catechols generated after gludopa administration was gludopamine. Its slow rate of hydrolysis is reflected by its persistence in the liver and its presence shows that gludopa itself can act as a substrate for dopa-decarboxylase. If each tissue can eliminate gludopa and its major catecholic metabolites L-dopa, DOPAC, dopamine, gludopamine and VMA (Mizoguchi et al 1979) by further metabolizing them, then urinary profiles of intact catechols must reflect biotransformation that occurred in the kidney itself. In man, only a small fraction of the administered dose was excreted as dopamine, and this would seem to imply that gludopa is not converted by the kidney to dopamine to the same extent in man as it is in the rat.

Values for the excretion of gludopa as dopamine have already been reported in two separate patient studies (Worth et al 1985; Jeffrey et al 1988). In the first, 24·4% of the administered dose was recovered as dopamine during the first 12 h after an infusion of 125 μg min^{-1} kg^{-1}. In the second, 18% of the administered dose (10% on a w/w basis, equivalent to the measurements reported in this work) was recovered as dopamine 2 h after an infusion of 25 μg min^{-1} kg^{-1}. These values are much higher than our figure of 5·5% for dopamine after a similar dose. In these studies no data were presented on gludopa or its other metabolites and at least in one the possibility existed for an overestimation of excretion due to cross reactivity in the radioenzymatic dopamine assay with other catecholamine metabolites (Worth et al 1985). However, in those studies the subject population consisted of young, healthy adults rather than older patients with malignant disease and this may also account for the differences seen.

In summary, we have confirmed that in the rat gludopa is indeed a kidney-specific dopamine prodrug and shown from pharmacokinetic studies that as such its effect is likely to be short lived due to rapid clearance principally through metabolism. Gludopa would appear to be less dopamine specific in man although this conclusion must await confirmation by more detailed clinical pharmacokinetic studies.

References

Anton, A. H., Sayre, D. F. (1962) A study of the factors affecting the aluminium oxide-trihydroxyindole procedure for the analysis of catecholamines. J. Pharmacol. Exp. Ther. 138: 360–375

Caillette, A., Schmidt, M., Ehrhardt, J. D., Imbs, J. L. (1988) Metabolism and vascular effects of γ-glutamyl L-dopa on the isolated rat kidney. Clin. Exp. 10: 896

Casson, I. F., Anderson, C. K., Cope, G. F., Lee, M. R. (1982) The effect of dietry sodium chloride and γ-glutamyl-L-dopa on tubular necrosis following glycerol administration in the rat. Br. J. Exp. Path. 63: 426–431

Goldberg, L. I. (1972) Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol. Rev. 24: 1–29

Jeffrey, R. F., MacDonald, T. M., Lee, M. R. (1988) A comparison of the renal actions of γ-glutamyl-L-dopa and γ-L-glutamyl-L-tyrosine in normal man. Clin. Sci. 74: 37–40

Kyncl, J. J., Minard, F. N., Jones, A. I. (1979) L-γ-Glutamyl dopamine, an oral dopamine prodrug with renal selectivity. In: Imbs J. L., Schwartz J. (eds) Peripheral Dopaminergic Receptors, Pergamon Press, Oxford pp 369–380

Lee, M. R. (1988) Dopamine prodrugs. In: Bell C., McGarth B. (eds) Peripheral actions of dopamine, McMillan Press, London pp 207–218

MacDonald, T. M., Jeffrey, R. F., Freestone, S., Brown, J., La, M. R. (1987) D-Sulpiride antagonizes the renal effects of γ-L-glutamyl-L-dopa in man. Br. J. Clin. Pharmacol. 23: 612P-613P

Mizoguchi, H., Orlowski, M., Wilk, S., Green, J. P. (1979) γ-Glutamyl-L-dopa and γ-glutamyl dopamine: effect on plasma glucose levels. Eur. J. Pharmacol. 57: 239–245

Orlowski, M., Szewczuk, A. (1961) Colorimetric determination of γ-glutamyl transpeptidase activity in human serum and tissues with synthetic substrates. Acta. Biochem. Pol. 8: 189–200

Orlowski, M., Wilk, S. (1976) Metabolism of γ-glutamyl amino acids and peptides in mouse liver and kidney in vivo. Eur. J. Biochem. 71: 549–555

Vogel, W. H., McFarland, H., Prince, L. N. (1970) Decarboxylation of 3,4-dihydroxyphenylalanine in various human adult and fetal tissues. Biochem. Pharmacol. 19: 618–620

Wilk, S., Mizoguchi, H., Orlowski, M. (1979) γ-Glutamyl-L-dopa: a kidney-specific dopamine precursor. J. Pharmacol. Exp. Ther. 206: 227–232

Worth, D. P., Harvey, J. N., Brown, J., Lee, M. R. (1985) γ-L-glutamyl-L-dopa is a dopamine prodrug, relatively specific for the kidney in normal subjects. Clin. Sci. 69: 207–214

Worth, D. P., Harvey, J. N., Brown, J., Worral, A., Lee, M. R. (1986) Domperidone treatment in man inhibits the fall in plasma renin activity induced by intravenous γ-L-glutamyl-L-dopa. Br. J. Clin. Pharmacol. 21: 497–502