Influence of renal insufficiency on the pharmacokinetics of cicletanine and its effects on the urinary excretion of electrolytes and prostanoids

N. FERRY¹, J. GEOFFROY¹, N. POZET², G. CUISINAUD¹, D. BENZONI¹, P. Y. ZECH² & J. SASSARD¹

¹Department of Physiology and Clinical Pharmacology (UA CNRS 606), Faculty of Pharmacy, Lyon and

²Nephrology Clinics (INSERM U 80), Hôpital E. Herriot, Lyon, France

1 The kinetics of a single oral dose (300 mg) of cicletanine a new antihypertensive drug with diuretic properties, and its effects on the urinary excretion of electrolytes and of the major stable metabolites of prostacyclin and thromboxane A₂ were studied in patients with normal renal function ($n = 6$), mild ($n = 9$) and severe ($n = 10$) renal insufficiency.

2 In normotensive subjects with normal renal function, cicletanine was rapidly and regularly absorbed, its apparent elimination half-life established around 7 h, and both its renal clearance (0.4 ml min⁻¹) and its cumulative renal excretion (0.85% of the administered dose), were low. Mild renal insufficiency did not significantly alter these parameters, while severe renal impairment reduced the renal clearance and the cumulative urinary excretion of cicletanine and increased its apparent elimination half-life (31 h). However the area under the plasma curve was not changed due to reduced plasma concentrations in these patients.

3 Cicletanine induced a rapid and marked (four fold as a mean) increase in the urinary excretion of water, sodium and potassium which lasted for 6 to 10 h, in subjects with normal renal function. Renal insufficiency did not alter the slope of the calculated plasma concentration-effects curves but reduced the maximum effect observed for water, sodium and potassium.

4 A single oral dose of cicletanine did not change the urinary excretion of 6-keto-prostaglandin F_{1α} and thromboxane B₂ in the three groups of patients studied, the basal values of which being found to be closely related to the creatinine clearance.

5 It was concluded that i) from a pharmacokinetic view point, the dosage of cicletanine should only be slightly reduced in patients with a glomerular filtration rate below 30 ml min⁻¹, ii) as with most of the diuretic agents, its natriuretic properties were markedly decreased in these patients and iii) an alteration in the renal synthesis of prostacyclin or thromboxane seems unlikely to participate in the pharmacological effects of cicletanine.

Keywords cicletanine diuretic antihypertensive drugs kinetics prostaglandins renal insufficiency

Introduction

Cicletanine (Figure 1) is a new antihypertensive furopyridine derivative which also exhibits diuretic properties. In contrast to the classical diuretics such as frusemide, amiloride and spironolactone, the renal effects of cicletanine do not seem to rely upon a direct inhibition of one of the various Na^+ carriers but rather upon a stimulation of the K^+ fluxes (Garay *et al.*, 1984). Since K^+ efflux has been demonstrated to be associated with a stimulation of prostaglandin (PG) biosynthesis (Dusing *et al.*, 1982) and that some PGs are vasodilator and natriuretic, namely prostacyclin (Levenson *et al.*, 1982), it was therefore hypothesized that the diuretic effect of cicletanine could be, at least partly, a prostacyclin dependent mechanism (Dorian *et al.*, 1984; Guinot *et al.*, 1985; Hornych *et al.*, 1986).

Since cicletanine could have to be given in hypertensive patients with renal impairment, the aim of the present work was to determine the influence of renal insufficiency on the kinetics of cicletanine and its effects on the urinary excretion of electrolytes and on the renal synthesis of prostacyclin and thromboxane.

Methods

Subjects

Six informed normotensive healthy volunteers and nineteen patients with renal insufficiency (chronic glomerulonephritis or interstitial nephritis) consented to be included in the study, the protocol of which having been approved by the local Ethics Committee. Patient exclusion criteria included cardiac, respiratory and hepatic diseases identified by careful clinical examination or routine biological tests as well as any condition requiring concomitant medication which might modify the PG biosynthesis or the drug disposition.

According to their creatinine clearance (CL_{CR} , ml min^{-1}), the patients were divided into the three following groups. Group I: normal renal function (CL_{CR} : 101 to 145 ml min^{-1} ; three men and three women, aged 23–34 years and weighing from 47 to 86 kg); Group II: mild renal insufficiency (CL_{CR} : 39 to 112 ml min^{-1} six men and three women, aged 20–66 years and weighing from 43 to 103 kg); Group III: severe renal insufficiency (CL_{CR} : 7 to 30 ml min^{-1} ; five men and five women aged 35–71 years and weighing from 42 to 70 kg).

Figure 1 Structural formula of cicletanine: 1,3-dihydro 6 methyl 7-hydroxy 3-(4-chloro phenyl) furo (3,4-c) pyridine.

Drug administration

Overnight fasted subjects received, at 08.00 h, a single oral dose of 300 mg of cicletanine, together with 100 ml of tap water. The first standardized meal was allowed 4 h after dosing.

Blood and urine sampling

Following a previously determined time-schedule, twelve 10 ml heparinized blood samples were drawn before and during the 72 h following dosing. Blood samples were kept at $+4^{\circ}\text{C}$, centrifuged within 2 h at $+4^{\circ}\text{C}$ and the separated plasma was frozen at -20°C until assay. Eight urine samples were collected during the 72 h of the study. In Group I subjects, one urine sample was obtained during the 12 h which preceded dosing while in Group II and III patients, values obtained during the last period studied (48–72 h) were considered as control (see **Results**) namely for CL_{CR} and the urinary PG excretion. During the collection period, urines were maintained at $+4^{\circ}\text{C}$, then they were homogenized, their volume and the pH measured and two 5 ml aliquots were frozen at -20°C until assay.

Analytical methods

Total unchanged cicletanine was measured in plasma and urine using our previously described (Cuisinaud *et al.*, 1985) high-performance liquid chromatographic technique. Urinary concentrations of 6 keto prostaglandin $\text{F}_{1\alpha}$ ($6\text{KPGF}_{1\alpha}$) and of thromboxane B_2 (TxB_2) the major stable metabolites of prostacyclin and thromboxane A_2 respectively, were measured by specific radioimmunoassays after a high-performance liquid chromatographic separation step (Benzoni *et al.*, 1982; Geoffroy *et al.*, 1985).

Calculations and kinetic analysis

Individual cicletanine plasma concentration-time curves were fitted using a multiexponential

Table 1 Mean ($\pm$ s.e. mean) glomerular filtration rate (GFR) and pharmacokinetic parameters of cicletanine in patients with normal renal function (Group I, $n = 6$), mild (Group II, $n = 9$) and severe renal insufficiency (Group III, $n = 10$) given a single oral dose of 300 mg.

	GFR (ml min^{-1})	C_{max} ($\mu\text{g ml}^{-1}$)	t_{max} (h)	$t_{1/2}$ (h)	AUC (0–72 h) ($\mu\text{g ml}^{-1} \text{h}$)	Cl_R (ml min^{-1})	CUE (0–72 h) (mg)
Group I	123 $\pm$ 9	20 $\pm$ 2	1.3 $\pm$ 0.1	7.4 $\pm$ 0.6	115 $\pm$ 19	0.42 $\pm$ 0.07	2.5 $\pm$ 0.4
Group II	66 $\pm$ 9	14 $\pm$ 2*	1.3 $\pm$ 0.2	12.4 $\pm$ 2.3	81 $\pm$ 13	0.65 $\pm$ 0.14	2.5 $\pm$ 0.4
Group III	16 $\pm$ 2	13 $\pm$ 2**	0.95 $\pm$ 0.2	31 $\pm$ 8**	109 $\pm$ 15	0.19 $\pm$ 0.1*	1.1 $\pm$ 0.4*

* $P < 0.05$, ** $P < 0.01$ vs Group 1.

regression analysis program that we developed for a HP9825 calculator (Hewlett-Packard). However, due to the lack of intravenous data, only the following clinically relevant parameters were calculated: maximum plasma concentration (C_{max} , $\mu\text{g ml}^{-1}$) and corresponding time (t_{max} , h); apparent elimination half-life ($t_{1/2}$, h) given by the linear regression calculated with the log plasma concentrations over the terminal mono-exponential part of the curve; area under the curve ($\text{AUC}_{0-72 \text{ h}}$, $\mu\text{g ml}^{-1} \text{h}$) using the trapezoidal rule and the renal clearance of the drug (Cl_R , ml min^{-1}) which was calculated as follows:

$$Cl_R (\text{ml min}^{-1}) = \frac{\text{cumulative urinary excretion (0–72 h) (CUE, } \mu\text{g})}{\text{AUC}_{0-72 \text{ h}} (\mu\text{g ml}^{-1} \text{min})}$$

Statistics

Data are expressed as mean $\pm$ s.e. mean and further statistical analysis used the non parametric Wilcoxon signed rank test.

Results

Pharmacokinetics of cicletanine (Table 1)

As shown in Figure 2a, cicletanine appears to follow a two-compartment model in the three groups of normotensive patients. In subjects with normal renal function orally given cicletanine was rapidly (t_{max} ranging from 1 to 1.5 h) and regularly absorbed (C_{max} ranging from 14.3 to 27.1 $\mu\text{g ml}^{-1}$). Its apparent elimination half-life established between 5.8 and 9.9 h, and its urinary excretion was low and variable (renal clearance ranging between 0.15 and 0.62 ml min^{-1}).

Mild renal insufficiency did not alter the pharmacokinetic parameters of cicletanine, except for a significant ($P < 0.05$) decrease in the observed C_{max} . Severe renal impairment significantly reduced the renal clearance and the

Figure 2 Mean ($\pm$ s.e. mean) plasma concentrations (a) and cumulative urinary excretion (b) of cicletanine in patients with normal renal function ($n = 6$, $\square$ — $\square$), mild ($n = 9$, $\bullet$ — $\bullet$) and severe renal insufficiency ($n = 10$, $\blacktriangle$ — $\blacktriangle$) given a single oral dose of cicletanine.

cumulative urinary excretion of cicletanine, leading to an increase in its apparent elimination half-life. However it must be noted that, due to reduced plasma concentrations the $\text{AUC}_{0-72 \text{ h}}$ calculated in patients with severe renal insufficiency did not differ from that of subjects with normal renal function.

As indicated by Figure 2b, the urinary excretion of unchanged cicletanine was rapid but of low magnitude (0.85 $\pm$ 0.1% of the administered dose in 72 h).

In all the 25 subjects a positive relationship was found between the creatinine clearance and both the renal clearance ($r = 0.72$, $n = 25$, $P < 0.001$) and the cumulative urinary excretion ($r = 0.73$, $n = 25$, $P < 0.001$) of cicletanine.

Table 2 Mean ($\pm$ s.e. mean) urinary excretion in patients with normal renal function (Group I, $n = 6$), mild (Group II, $n = 9$) and severe (Group III, $n = 10$) renal insufficiency given a single oral dose of 300 mg of cicletanine.

	Group	Time after administration (h)										48-72
		-12-0	0-2	2-4	4-6	6-10	10-24	24-36	36-48	48-72		
Diuresis (ml min ⁻¹)	I	0.6 ± 0.1	4.2 ± 0.8	1.8 ± 0.4	1.6 ± 0.3	2.1 ± 0.4	0.8 ± 0.1	0.8 ± 0.2	0.8 ± 0.1	1.1 ± 0.1		
	II	—	1.8 ± 0.3	1.3 ± 0.2	1.6 ± 0.2	2.2 ± 0.3	1.5 ± 0.3	1.6 ± 0.3	1.3 ± 0.2	1.3 ± 0.1		
	III	—	2.5 ± 0.4	1.4 ± 0.2	1.3 ± 0.2	1.7 ± 0.3	2.1 ± 0.3	1.7 ± 0.3	2.0 ± 0.3	1.8 ± 0.3		
Sodium (μmol min ⁻¹)	I	83 ± 17	328 ± 21	281 ± 31	224 ± 19	227 ± 33	84 ± 8	61 ± 14	58 ± 12	82 ± 14		
	II	—	201 ± 28	120 ± 19	132 ± 15	157 ± 14	96 ± 17	78 ± 15	71 ± 10	63 ± 7		
	III	—	126 ± 19	72 ± 13	53 ± 7	58 ± 7	83 ± 12	57 ± 12	69 ± 11	50 ± 13		
Chloride (μmol min ⁻¹)	I	63 ± 11	394 ± 31	325 ± 35	277 ± 24	248 ± 29	84 ± 9	74 ± 16	52 ± 14	54 ± 16		
	II	—	227 ± 35	150 ± 22	164 ± 18	179 ± 16	97 ± 15	81 ± 16	62 ± 12	58 ± 9		
	III	—	121 ± 13	72 ± 13	55 ± 8	62 ± 5	76 ± 10	59 ± 9	52 ± 8	43 ± 10		
Potassium (μmol min ⁻¹)	I	26 ± 3	95 ± 22	81 ± 17	75 ± 11	80 ± 18	32 ± 2	65 ± 9	39 ± 6	55 ± 4		
	II	—	76 ± 14	55 ± 9	57 ± 9	66 ± 13	33 ± 4	42 ± 6	40 ± 5	38 ± 4		
	III	—	53 ± 6	33 ± 4	37 ± 5	40 ± 8	41 ± 5	39 ± 5	36 ± 4	34 ± 4		
Na/K	I	3.2 ± 0.3	3.9 ± 0.6	4.4 ± 1.1	3.1 ± 0.6	3.4 ± 0.9	2.7 ± 0.3	0.8 ± 0.2	1.5 ± 0.4	1.4 ± 0.2		
	II	—	3.3 ± 0.5	2.5 ± 0.5	2.7 ± 0.5	3.0 ± 0.5	3.0 ± 0.4	2.0 ± 0.3	2.1 ± 0.3	1.8 ± 0.2		
	III	—	2.3 ± 0.5	2.2 ± 0.4	1.6 ± 0.3	2.0 ± 0.5	2.2 ± 0.4	1.7 ± 0.4	2.2 ± 0.5	1.9 ± 0.7		
Calcium (μmol min ⁻¹)	I	3.8 ± 0.8	5.0 ± 1.1	2.5 ± 0.6	2.5 ± 0.9	3.6 ± 1.2	1.8 ± 0.4	2.2 ± 0.7	2.2 ± 0.4	2.4 ± 0.5		
	II	—	1.5 ± 0.4	6.6 ± 0.1	1.3 ± 0.3	1.5 ± 0.3	1.1 ± 0.3	1.0 ± 0.2	1.2 ± 0.2	1.2 ± 0.3		
	III	—	0.7 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1		
Magnesium (μmol min ⁻¹)	I	3.8 ± 0.6	3.3 ± 0.2	2.8 ± 0.5	2.9 ± 0.6	4.2 ± 1.0	2.6 ± 0.5	2.8 ± 0.5	3.0 ± 0.2	2.8 ± 0.2		
	II	—	2.8 ± 0.4	2.0 ± 0.2	2.6 ± 0.2	3.0 ± 0.3	2.2 ± 0.2	2.3 ± 0.4	3.1 ± 0.5	2.6 ± 0.2		
	III	—	2.8 ± 0.4	1.5 ± 0.2	1.4 ± 0.2	1.5 ± 0.3	2.1 ± 0.3	1.6 ± 0.2	1.8 ± 0.2	1.7 ± 0.3		
Osmolal Excretion (μosmol min ⁻¹)	I	595 ± 99	1378 ± 149	1048 ± 89	912 ± 67	978 ± 85	449 ± 58	553 ± 52	479 ± 24	529 ± 57		
	II	—	790 ± 126	552 ± 65	645 ± 58	715 ± 60	527 ± 81	560 ± 69	495 ± 39	475 ± 45		
	III	—	610 ± 76	361 ± 50	334 ± 43	336 ± 38	426 ± 44	351 ± 52	377 ± 41	330 ± 38		
Uric acid (μmol min ⁻¹)	I	3.7 ± 0.6	4.7 ± 0.8	3.1 ± 0.5	3.8 ± 0.3	4.6 ± 0.4	2.5 ± 0.4	4.0 ± 0.4	3.2 ± 0.3	3.4 ± 0.3		
	II	—	3.4 ± 0.7	2.2 ± 0.3	2.6 ± 0.3	2.7 ± 0.3	2.1 ± 0.4	2.5 ± 0.3	2.7 ± 0.4	2.5 ± 0.3		
	III	—	1.9 ± 0.2	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.4 ± 0.2	1.1 ± 0.1

Figure 3 Relationships between the plasma concentration (C_{mid}) of cicletanine and the urinary volume, sodium and potassium observed in patients with normal renal function ($n = 6$, $\square-\square$), mild ($n = 9$, $\bullet-\bullet$) and severe renal insufficiency ($n = 10$, $\blacktriangle-\blacktriangle$) during the 24 h following a single oral dose of cicletanine. C_{mid} are the plasma concentrations observed or extrapolated at the middle of the urinary collection periods. Data are mean $\pm$ s.e. mean.

Urinary water and electrolytes excretion (Table 2)

In subjects with normal renal function, a single oral dose of cicletanine induced a marked and rapid increase on the urinary excretion of water (two fold), sodium (four fold), chloride (six fold) and potassium (three–four fold). The maximum effect was observed within 2 h after dosing and disappeared 10 h thereafter. The urinary elimination of calcium, magnesium and uric acid was only slightly affected by cicletanine.

Expressed as absolute values or as the percent of the filtered load, the results showed that the effects of cicletanine on water, sodium and chloride excretion were reduced in patients with mild renal insufficiency and even more in those with severe renal impairment. The elimination

Figure 4 Mean ($\pm$ s.e. mean) urinary excretion of 6KPGF $_{1\alpha}$ and TxB $_2$ in patients with normal renal function ($n = 6$, $\square-\square$), mild ($n = 9$, $\bullet-\bullet$) and severe renal insufficiency ($n = 10$, $\blacktriangle-\blacktriangle$) given a single oral dose of cicletanine.

of potassium was also decreased in renally impaired patients but to a lesser extent than that of sodium and chloride.

Within the 24 h following dosing the elimination rate of water, sodium and potassium could be related to the plasma concentration of cicletanine observed or calculated at the middle of the urine collection periods.

As shown in Figure 3 renal impairment did not alter the slope of the relationship between plasma cicletanine and the excretion rate of sodium or potassium, but decreased the maximum effect which could be observed.

Urinary excretion of 6KPGF $_{1\alpha}$ and TxB $_2$

If one considers that between 48 and 72 h after dosing, the urinary excretion of 6KPGF $_{1\alpha}$ and TxB $_2$, as well as that of water and electrolytes, returned to normal. Figure 4 shows that a single oral dose of cicletanine did not alter the urinary elimination of these prostanoids in the three groups of patients studied. In addition, it appears clearly that the urinary excretion of 6KPGF $_{1\alpha}$ and TxB $_2$ is reduced in renally impaired patients. A highly significant relationship (see Figure 5) was found between creatinine clearance and the urinary excretion of 6KPGF $_{1\alpha}$ ($r = 0.84$, $n = 23$, $P < 0.001$) or TxB $_2$ ($r = 0.80$, $n = 23$, $P < 0.001$) measured in the urines collected between 48 and 72 h after dosing.

Figure 5 Relationship between creatinine clearance and the urinary excretion of 6KPGF_{1α} and TxB₂ in patients with normal renal function ($n = 6$, $\square$ — $\square$), mild ($n = 9$, $\bullet$ — $\bullet$) and severe renal insufficiency ($n = 10$, $\blacktriangle$ — $\blacktriangle$).

Discussion

In the present work the influence of renal insufficiency on the kinetics and the renal effects of a single oral dose of cicletanine was studied in order to calculate precisely the dosage adaptations which would have to be tested in renally impaired patients. In addition, the possible action of this new antihypertensive drug on the renal synthesis of prostacyclin and thromboxane A₂, two cardiovascular acting prostanoids, was evaluated.

In subjects with normal renal function, cicletanine was found to obey an open two-compartment model. After oral dosing, it was rapidly and regularly absorbed and exhibited an apparent elimination half-life of 7 h. These data are in good agreement with two previous studies devoted to cicletanine (Ipsen, 1984; Biomeasure, 1981). The renal clearance of cicletanine was low, which can be due to a high drug protein binding (93% unpublished data). This hypothesis is strengthened by the fact that, in some subjects, we measured cicletanine in saliva (data not shown), and found very low concentrations, a finding which was in accordance with a high protein binding as saliva concentrations reflect mainly the free plasma drug fraction (Adithan & Thangam, 1982).

The cumulative urinary excretion of unchanged cicletanine measured up to 72 h after dosing was found to be low (less than 1% of the administered dose). This is also in accord with previous studies (Ipsen, 1984; Biomeasure, 1981) and is probably due to an extensive metabolism since most of cicletanine is conjugated (Dr Tarrade, personal communication).

Mild renal insufficiency did not significantly alter the kinetics of cicletanine. The renal clearance of cicletanine was slightly increased which was probably due to a lower protein binding in these patients. The same decrease in protein binding is also likely to account for the observed decrease in C_{max} .

With severe renal insufficiency, the apparent elimination half-life of cicletanine increased up to 30 h, as a mean, as a consequence of a significantly reduced renal clearance. These changes were significantly ($P < 0.001$) related to the glomerular filtration rate.

The effects of cicletanine on the urinary excretion of water, sodium and potassium were marked (four fold increase as a mean), rapid and lasted for 6 to 10 h, in subjects with normal renal function. As is usual with diuretics, renal impairment reduced the effect of cicletanine on those parameters. Interestingly, it was possible to relate the plasma concentration of cicletanine and the elimination rate of water, sodium and potassium. Using these relationships it appeared clearly that renal alterations reduced the maximum effects observed more than they changed the slope of the relationship between drug concentration and effect.

The urinary elimination of 6KPGF_{1α} and TxB₂, were measured using highly specific and sensitive techniques including a high-performance liquid chromatographic separation step, prior to their radioimmunoassay and used as an index of the renal synthesis of prostacyclin and thromboxane A₂ respectively. Indeed, intravenous infusion of prostacyclin and TxB₂ produces only minimal changes (less than 3%) in the urinary 6KPGF_{1α} and TxB₂ respectively (Zipser *et al.*, 1982) and, as recently reviewed by Ciabattini *et al.* (1987), the administration of sulindac which spares the renal cyclooxygenase activity results in a decrease of plasma but not urinary concentrations of 6KPGF_{1α} and TxB₂. Therefore, since the contribution of circulating PGs to the urinary levels seems negligible, and since plasma and urinary concentrations are largely unrelated, it appears valid to consider the urinary PGs as an index of their renal biosynthesis.

In these conditions, a single oral dose (300 mg) of cicletanine did not change the urinary excretion of 6KPGF_{1α} and TxB₂. A similar

observation was also made by Hornyh *et al.* (1985) who failed to disclose any significant modification in the urinary 6KPGF_{1α} in both normotensive and hypertensive patients. In contrast, Guinot *et al.* (1985) found an increased urinary 6KPGF_{1α} after acute and chronic treatment with cicletanine, but they used less specific techniques and moreover the reported increase was clearly dose-unrelated.

Therefore it appears that, a single oral dose of cicletanine does not alter the renal synthesis of prostacyclin and thromboxane A₂ and that its pharmacological effects are unlikely to rely upon the vasodilating prostacyclin. In addition such a conclusion is close to that emerging from the controversial results concerning most of the other groups of diuretics (Webster *et al.*, 1980; Olsen, 1983; Koopmans *et al.*, 1986).

It was interesting to observe that renal impairment was associated with a marked decrease in the production of prostacyclin and thromboxane by the kidney and that this decrease was significantly related to the glomerular filtration rate. Very few studies were devoted to relationships between kidney alterations and the urinary

excretion of prostaglandins. 6KPGF_{1α} but not PGE₂ was reported to be decreased in patients with renal insufficiency by Ciabatonni *et al.* (1984) and Mistry *et al.* (1986), while Patrono *et al.* (1983) found that the urinary TxB₂ was not affected in similar conditions.

In conclusion, after a single oral dose, cicletanine exhibits marked, concentration-related, diuretic effects. Mild renal insufficiency does not alter its pharmacokinetics. In patients with severe renal failure a slight reduction in its dosage should be suggested due to its prolonged half-life which was associated with decreased plasma concentrations. However the decrease in its diuretic action makes its use questionable in these patients.

Finally it appeared that pharmacological effects of cicletanine were unlikely to be related to a stimulation of the prostacyclin synthesis by the kidney.

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