Pharmacokinetics of piroximone after oral and intravenous administration to patients with renal insufficiency

J. P. FAUVEL¹, N. BERNARD², M. LAVILLE¹, N. POZET¹, J. SASSARD² & P. Y. ZECH¹

¹Department of Nephrology, Edouard Herriot Hospital, Lyon, France and ²Department of Physiology and Clinical Pharmacology, URA CNRS 1483, Lyon, France

The pharmacokinetics of piroximone (PI) were determined in patients with renal failure (inulin clearance less than 50 ml min⁻¹ per 1.73 m²) using two protocols: (a) 10 patients received a single i.v. infusion of 0.5 mg kg⁻¹ PI and the data were compared with those from seven healthy subjects receiving the same regimen; (b), a single oral dose of either 25 or 50 mg PI was given to 20 patients. PI concentrations were assayed by h.p.l.c. in plasma and urine over 48 h. After i.v. administration to healthy subjects PI was distributed rapidly and eliminated with a mean half-life of 1.3 ± 0.2 h. The urinary recovery of unchanged PI was 64% of the dose. In the patients the extent of renal elimination of PI was decreased (-78%) in relation to the degree of renal insufficiency as assessed by inulin clearance ($r = 0.97$, $P < 0.0001$). Mean $C_{\max}$, AUC and $t_{1/2,z}$ values after i.v. infusion were increased by 47%, 127% and 77%, respectively, in comparison with healthy subjects. Similar results were obtained after oral administration. Until chronic dosing studies are undertaken, PI dosage should be adapted in relation to renal function.

Keywords piroximone pharmacokinetics renal insufficiency

Introduction

Piroximone is a cardiotonic agent acting by specific inhibition of cAMP phosphodiesterase type III. Phosphodiesterase inhibitors may be an alternative to catecholamines in the treatment of advanced congestive heart failure because they are effective even when β -receptors are down regulated. Piroximone (PI) improves left ventricular function by decreasing afterload and by a positive inotropic action [1,2]. The pharmacokinetics of PI have been studied in healthy subjects as well as in patients with congestive heart failure at dosages ranging from 0.2 to 2 mg kg⁻¹ after i.v. and oral administration. Kinetics are linear with dose and are not influenced by cardiac failure. Oral bioavailability is greater than 80% [3,4]. The terminal elimination half-life is short (1.7 ± 0.3 h) and urinary excretion of unchanged drug is the main route of elimination (68 ± 5% of an intravenously administered dose) [4]. We have studied the kinetics of PI in renal patients having a wide range of glomerular filtration rate after i.v. and oral administration.

Methods

PI pharmacokinetics were studied after either i.v. (first protocol) or oral administration (second protocol). Seven healthy volunteers (34 ± 6 years; creatinine clearance CL_{cr} : 120 ± 18 ml min⁻¹ per 1.73 m²) and ten patients with mild to severe renal insufficiency (50 ± 9 years; inulin clearance CL_{inul} : 31 ± 15 ml min⁻¹ per 1.73 m²) were included in the first protocol. Twenty patients with mild to severe renal insufficiency (52 ± 6 years, CL_{inul} : 16 ml min⁻¹ per 1.73 m²) were studied in the second protocol.

None of the subjects had cardiac, pulmonary or liver disease. Patients did not receive any antibiotics or antiinflammatory drugs at least 8 days before the study. Blood pressure, heart rate, and electrocardiogram were monitored throughout the study. The study was approved by the local ethics committee and written consent was given by each individual.

Drug doses were administered after an overnight fast. For the first protocol, each subject received a 10-min i.v. infusion of a 0.5 mg kg⁻¹ dose of PI, 1.5 mg ml⁻¹ in 0.9% w/v sodium chloride. In the second

study the patients were given 25 mg or 50 mg single oral PI doses. Venous heparinized blood samples were drawn and urine collected over 24 h. Samples of plasma and urine from the oral study were assayed for PI by solvent extraction followed by reversed phase h.p.l.c. This method allowed the measurement of PI up to 10 h after dosing. For the i.v. protocol, an improved h.p.l.c. method was used allowing measurements up to 24 h [5]. Standard pharmacokinetic parameters were derived after fitting the data with a two-compartment open model using the Siphar® program.

Results are expressed as mean $\pm$ s.d. Individual data were submitted to a two-way analysis of variance (with subject and group as source of variation) and to a nonparametric test applied to unpaired series (Mann and Whitney) between groups. A *P* value of < 0.05 was considered as significant.

Results

Mean plasma concentrations of PI are shown in Figure 1 and mean pharmacokinetic parameters are listed in Table 1.

I.v. administration

In healthy subjects, plasma PI concentrations declined biexponentially with a short apparent terminal half-life of 1.3 ± 0.2 h. Urinary excretion was virtually complete at 24 h after dosing and represented 64% of total elimination. No significant changes were observed either in blood pressure or heart rate and no major adverse event was noted with the exception of headache in one subject.

In the patients, all pharmacokinetic parameters with the exception of the volume of distribution (V_{ss})

Figure 1 Mean ($\pm$ s.d.) plasma concentrations of piroximone after (a) i.v. infusion of 0.5 mg kg^{-1} to seven healthy subjects ($\square$) and 10 patients ($\blacksquare$) with renal impairment, (b) oral administration of 25 mg ($\circ$) and 50 mg ($\bullet$) piroximone to 20 patients with renal impairment ($N = 10$ for each dose).

were correlated with renal function, $C_{\max}$, $r = 0.71$, $P < 0.01$; MRT, $r = 0.92$, $P < 0.001$ and AUC, $r = 0.90$, $P < 0.001$ negatively; CL, $r = 0.94$, $P < 0.001$ positively and $t_{1/2,z}$, $r = 0.86$, $P < 0.01$ reciprocally.

Table 1 Pharmacokinetic parameters of piroximone in healthy volunteers ($n = 7$) and patients with renal impairment ($n = 10$) after intravenous administration and in patients with renal impairment after oral administration of 25 mg ($n = 10$) or 50 mg ($n = 10$)

	V_{ss} (l)	$C_{\max}$ (nmol ml ⁻¹)	$t_{1/2,z}$ (h)	MRT (h)	AUC (nmol ml ⁻¹ h)	CL (ml min ⁻¹)	Urinary recovery (%)	CL_R (ml min ⁻¹)	CL_{NR} (ml min ⁻¹)
<i>First protocol: i.v. piroximone</i>									
Healthy subjects									
Mean	45.4	4.48	1.32	1.20	3.87	632	64.4	406	225
CI 95%	37.5–53.4	3.70–5.28	1.16–1.47	1.06–1.33	3.36–4.38	550–713	58.1–70.6	351–462	171–279
Renal patients									
mean	46.5	6.57*	2.33*	2.55*	8.77*	302*	26.2*	85.6*	216
CI 95%	38.2–54.7	5.65–7.49	2.09–2.57	2.25–2.85	7.35–10.19	245–359	18.7–33.7	50.8–120.4	183–249
<i>Second protocol: oral piroximone</i>									
Renal patients, 25 mg									
mean		1.77	2.90	3.51	5.41	—	16.9	75.2	—
CI 95%		1.37–2.17	2.08–3.72	2.70–4.32	4.58–6.24		7.8–26.0	28.6–121.8	
Renal patients, 50 mg									
mean		2.18	2.37	3.73	8.26†	—	15.8	91.6	—
CI 95%		1.69–2.67	1.86–2.88	2.80–4.67	6.45–10.06		9.8–21.8	49.2–134.1	

*Significant vs healthy subjects $P < 0.05$; †significant vs 25 mg of PI $P < 0.05$. Clearance values are corrected per 1.73 m^2 .

Urinary recovery of PI in the patients averaged $26.2 \pm 10.5\%$ of the dose at 24 h. The renal clearance of PI was significantly related to CL_{inul} ($r = 0.97$, $P < 0.0001$). Extrarenal elimination was not significantly increased but became the major pathway of elimination in patients with renal insufficiency. No significant adverse event was noted except headache in one patient.

Oral administration

Absorption of PI appeared to be rapid and the terminal elimination half-life (2.6 h) was short in spite of renal insufficiency. Urinary recovery of unchanged PI was $16.4 \pm 10.5\%$ irrespective of the dose. Despite similar renal function, patients receiving 50 mg of PI had mean C_{max} and AUC values less than twofold higher than those in patients receiving 25 mg. Neither $t_{1/2,z}$ nor MRT were influenced by the dose. There was no reciprocal relation between $t_{1/2,z}$ and CL_{inul} in spite of the wide range of renal function in the patients

(from 7 to 49 $ml\ min^{-1}$ per $1.73\ m^2$). A positive significant linear relation ($r = 0.71$, $P < 0.0005$) was found between renal clearance of PI and CL_{inul} . Subjective adverse events were noted in four patients (anxiety, $n = 2$; insomnia, $n = 2$; nausea, $n = 1$; headache, $n = 1$; thoracic constriction, $n = 1$) and were mild and brief.

Discussion

PI has a rapid elimination half-life and a clearance which is mostly renal under normal conditions. Extrarenal elimination becomes important only when renal function is impaired. In renal insufficient patients, PI was well tolerated. PI half-life increased in relation to renal impairment. However, the pharmacokinetic of PI appeared not to be linear. Until chronic dosing studies are undertaken, PI dosage should be adapted in relation to renal function.

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