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The influence of renal insufficiency and haemodialysis on the kinetics of ciprofibrate

N. FERRY[1], N. BERNARD[1], N. POZET[2], E. GARDES[1], G. CUISINAUD[1], M. LABEEUW[2], P. Y. ZECH[2] & J. SASSARD[1]

[1]Department of Physiology and Clinical Pharmacology (CNRS URA 606), Faculty of Pharmacy, 8 Avenue Rockefeller, 69373 Cedex 08, Lyon and [2]Nephrology Clinics (INSERM U 80), Hôpital Edouard Herriot, Place d'Arsonval, 69437 Cedex 03, Lyon, France

1 The kinetics of the hypolipidaemic drug, ciprofibrate, were studied after a single oral dose (100 mg) in subjects with normal renal function ($n = 6$), patients with mild ($n = 6$) and severe ($n = 6$) renal insufficiency as well as in haemodialysed patients ($n = 5$).

2 Under fasting conditions, ciprofibrate, was absorbed rapidly in subjects with normal renal function, and its apparent elimination half-life was approximately 81 h. Both renal clearance (0.15 ml min^{-1}) and cumulative renal excretion (less than 7% of the administered dose) were low.

3 Mild renal insufficiency did not alter the pharmacokinetics of ciprofibrate, but severe renal impairment significantly reduced both its renal clearance and cumulative urinary excretion and increased the apparent elimination half-life.

4 A 5 h haemodialysis session did not lower the plasma concentrations of ciprofibrate.

5 It is concluded that, from a pharmacokinetic point of view, a reduction in the dosage of ciprofibrate should be considered in patients with a glomerular filtration rate below 30 ml $min^{-1}/1.73\ m^2$.

Keywords ciprofibrate pharmacokinetics renal insufficiency haemodialysis

Introduction

Racemic ciprofibrate, [(dichloro-2,2-cyclopropyl) -4-phenoxy]-2-methyl-2-propionic acid, belongs to a group of drugs used as hypolipidaemic agents (Wülfert *et al.*, 1976; Arnold *et al.*, 1979; Cayen, 1983; Sirtori & Franceschini, 1988).

The cyclopropyl substituent in ciprofibrate results in considerable chemical stability, very high potency (20 times that of clofibrate in man) and a prolonged plasma half-life (Edelson *et al.*, 1979). Clinical studies have shown that it is an efficient hypolipidaemic agent at dose levels much lower than clofibrate and fenofibrate (Brown *et al.*, 1979; Davignon *et al.*, 1982; Angelin *et al.*, 1984). Maximum plasma concentrations of ciprofibrate are attained within 2 h following a single oral dose to rats, rhesus monkeys, and man. The drug is eliminated slowly in all three species and the plasma elimination profile is best described by a two-compartment open model. The urine is the main route of excretion in monkeys and man, while the faeces are the predominant excretory route in rat. In human urine, about 73% of the drug-derived material is conjugated to glucuronic acid. At physiological concentrations, 99% of ciprofibrate is bound to rat, monkey, and human plasma proteins (Davison *et al.*, 1975).

Since hypertriglyceridaemia is a metabolic abnormality frequently associated with chronic renal failure (Bagdade *et al.*, 1976) and in conjunction with elevated cholesterol plasma levels represents an increased risk of coronary heart

Correspondence: Dr N. Ferry, Department of Physiology and Clinical Pharmacology, Faculty of Pharmacy, 8 Avenue Rockefeller, 69373 Cedex 08, Lyon, France

disease (Stamler, 1979), the aim of the present work was to determine the influence of renal insufficiency on the kinetics of ciprofibrate.

Methods

Subjects (Table 1)

Six informed healthy volunteers and seventeen patients with renal insufficiency consented to be included in the study, the protocol of which was approved by the local Ethics Committee. Exclusion criteria included cardiac, respiratory and hepatic diseases identified by clinical examination and routine biological tests.

The patients were divided into four groups according to their creatinine clearance (CL_{cr} ml $min^{-1}/1.73$ m^2) determined as a mean value over three 1 h periods: Group I: normal renal function (CL_{cr}: 89 to 133 ml $min^{-1}/1.73$ m^2, three women and three men aged 24–37 years, weighing from 48 to 73 kg); Group II: mild renal insufficiency (CL_{cr}: 39 to 60 ml $min^{-1}/1.73$ m^2, one woman and five men, aged 25–66 years, weighing from 52 to 70 kg); Group III: severe renal insufficiency (CL_{cr}: 11 to 30 ml $min^{-1}/1.73$ m^2, three women and three men, aged 37–60 years, weighing from 54 to 79 kg); Group IV: severe chronic renal insufficiency requiring routine haemodialysis (residual 24 h diuresis: 0–200 ml, one woman and four men, aged 44–70 years, weighing from 61 to 77 kg before dialysis).

Drug administration

Subjects fasted overnight and then received, at 08.00 h, a single oral dose of 100 mg ciprofibrate (Lipanor®, Winthrop Laboratories, Clichy, France) with 100 ml of tap water. A standard meal was allowed 4 h after dosing. In haemodialysed patients (Group IV), ciprofibrate was administered 24 h before starting a period of haemodialysis which had a mean duration of 5 h.

Blood and urine sampling

Heparinized blood samples (10 ml) were drawn before and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 32, 48, 56, 72, 80, 96 and 168 h after dosing. They were kept at 4° C, centrifuged within 2 h at 4° C and the separated plasma was frozen at −20° C. Seven urine samples were collected during the first 96 h after dosing. During the collection period, urines were maintained at 4° C, they were then homogenized, their volumes measured and three 5 ml aliquots were frozen at −20° C until assay.

For ethical reasons, only five blood samples were obtained from the haemodialysed patients. In these subjects 5 ml heparinized blood samples were drawn from the arterial line just before a period of haemodialysis, then 2 h after the start, at the end of the session (i.e. 24, 26 and 29 h after dosing), and finally just before starting the next period of dialysis (i.e. 78 h after dosing). In addition, a 5 ml blood sample was obtained from the venous line 2 h after the beginning of the haemodialysis. The haematocrit of each sample was measured and the separated plasma was stored at −20° C until assay for total proteins and ciprofibrate.

Analytical methods

Concentrations of total unchanged ciprofibrate were measured in plasma and urine using the high-performance liquid chromatographic method of Park *et al.* (1982) with minor modifications. Briefly, to 1 ml of the biological sample, a ciprofibrate analogue ([(dichloro-2,2-phenyl-3-cyclopropyl) -phenoxy] -2methyl-2-propionic acid) was added as the internal standard. After acidification, the samples were extracted twice with *n*-hexane. The purified extract was chromatographed on a Nucleosil C18 column using a mobile phase of phosphate buffer (pH = 3)-acetonitrile (47:53) at a flow of 1.8 ml min^{-1} and with ultraviolet detection at 232 nm. The limit of assay was 100 ng ml^{-1} in plasma and urine, with an interassay coefficient of variation less than 5%.

Calculations and kinetics analysis

Pharmacokinetic parameters Individual plasma drug concentration-time curves were fitted using a non-linear extended least squares multi-exponential regression program (SIPHAR® from SIMED, Créteil, France) developed for an IBM-PC computer. Owing to the lack of intravenous data, only the following parameters were calculated: apparent absorption half-life following oral administration ($t_{½abs.}$ h); lag time ($t_{lag.}$ h), the delay between oral administration and the apparent onset of absorption; maximum plasma concentration (C_{max}, μg ml^{-1}) and corresponding time (t_{max}, h); apparent elimination half-life ($t_{½.z.}$ h) derived from the terminal mono-exponential part of the curve; mean residence time (MRT, h) derived by statistical moment theory (Gibaldi & Perrier, 1982); area under the curve (AUC(0, 168), μg ml^{-1} h) using the linear trapezoidal rule; cumulative urinary excretion (Ae(0, 96), mg) and the renal clearance of the drug ($CL_{R.}$ ml min^{-1}) as the ratio: Ae(0, 96)/AUC(0, 96).

Table 1 Characteristics of healthy volunteers and patients with mild and severe renal insufficiency included in the study

Subjects	*Sex*	*Age (years)*	*Height (cm)*	*Weight (kg)*	*Plasma creatinine* ($\mu g\ ml^{-1}$)*	*Creatinine clearance* ($ml\ min^{-1}/1.73\ m^2$)*	*Diagnosis*
Group I							
1	M	30	172	60	13.1	112	
2	M	24	175	64	12.8	121	
3	F	35	163	69	10.9	94	
4	M	29	182	73	11.9	133	
5	F	33	160	48	7.2	131	
6	F	37	169	57	12.0	89	
Mean		31	170	62	11.3	113	
s.d.		5	7	10	2.2	20	
Group II							
7	M	25	169	68	35.9	39	Chronic glomerulonephritis
8	M	45	162	52	14.1	60	Chronic glomerulonephritis
9	F	31	151	62	11.6	45	Chronic renal artery stenosis
10	M	48	159	58	10.6	56	Chronic pielonephritis
11	M	59	160	70	24.0	49	Hypertensive nephropathy
12	M	66	167	61	17.3	48	Chronic renal artery stenosis
Mean		46	161	62	18.9	49	
s.d.		15	7	7	10	7	
Group III							
13	M	39	170	79	51.5	30	Subacute glomerulonephritis
14	M	60	162	58	46.8	21	Chronic glomerulonephritis
15	M	41	159	58	43.3	28	Diabetic hypertensive nephropathy
16	F	49	157	54	62.7	11	Polycystic kidney disease
17	F	48	165	58	40.0	19	Polycystic kidney disease
18	F	37	169	67	43.8	22	Chronic glomerulonephritis
Mean		46	164	62	48.0	22	
s.d.		10	5	10	8.1	7	

*Significantly different between Groups at $P < 0.001$ (Wilcoxon's test).

Haemodialysis clearance In addition to the elimination parameters, the haemodialysis plasma clearance (CL_D, ml min^{-1}) of ciprofibrate was estimated from venous and arterial drug concentrations corrected for protein content, haematocrit and the drug partition coefficient between plasma and red blood cells (Singlas & Lebelle, 1987).

Statistics Data are expressed as mean ± s.d. and further statistical analysis used a one way analysis of variance (ANOVA) and the non-parametric Wilcoxon rank sum test.

Results

Pharmacokinetics of ciprofibrate (Table 2)

The plasma concentration-time profile of ciprofibrate indicated rapid absorption followed by a biexponential decline in the three groups of patients (Figure 1a). In subjects with normal renal function ciprofibrate was absorbed rapidly ($t_{lag} = 0.29 \pm 0.17$ h; $t_{½abs} = 0.28 \pm 0.27$ h; $t_{max} = 1.3 \pm 0.7$ h) and showed little variability in C_{max} (24 ± 2 μg ml^{-1}, range 19–27 μg ml^{-1}). The apparent elimination half-life was between 56 and 104 h ($t_{½,z} = 81 \pm 16$ h), and renal clearance was low ($CL_R = 0.150 \pm 0.040$ ml min^{-1}, ranging from 0.096 to 0.20 ml min^{-1}).

Mild renal insufficiency did not alter significantly the pharmacokinetic parameters of ciprofibrate, except for an increase ($P < 0.01$) in the lag time (0.79 ± 0.22 h).

Severe renal impairment significantly decreased ($P < 0.05$) C_{max} (17 ± 4 μg ml^{-1}) and prolonged ($P < 0.05$) t_{max} (2.8 ± 1.8 h). There was a reduced renal clearance and an increase ($P < 0.01$) in the apparent elimination half-life of ciprofibrate (from 81 ± 16 h for Group I to 172 ± 66 h for Group III) and in the AUC(0, 168) (from 1370 ± 316 μg ml^{-1} h for Group I to 2445 ± 656 μg ml^{-1} h for Group III).

Creatinine clearance in the 18 subjects correlated inversely with the elimination half-life ($r = 0.64$; $n = 18$, $P < 0.01$) and the AUC(0, 168) of ciprofibrate ($r = -0.70$, $n = 18$, $P < 0.001$) and directly with C_{max} values ($r = 0.50$, $n = 18$, $P < 0.05$).

As shown in Figure 1b, mild renal insufficiency slowed the urinary excretion of ciprofibrate but did not affect its extent, while severe renal insufficiency decreased non-significantly the excretion of ciprofibrate. In the three groups of subjects, the renal elimination of unchanged ciprofibrate appeared incomplete by 96 h after dosing.

Table 2 Mean (± s.d.) glomerular filtration rate (GFR) and pharmacokinetic parameters of ciprofibrate in patients with normal renal function (Group I, $n = 6$), mild (Group II, $n = 6$), and severe renal insufficiency (Group III, $n = 6$) given a single oral dose of 100 mg (for abbreviations see text)

Group	*GFR* (*ml min^{-1}*)	$t_{½abs}$ (*h*)	t_{lag} (*h*)	t_{max} (*h*)	C_{max} (*μg ml^{-1}*)	$t_{½,z}$ (*h*)	*MRT* (*h*)	*AUC(0, 168)* (*μg ml^{-1} h*)	Ae(0,96) (*mg*)	CL_R (*ml min^{-1}*)
Group I	113 ± 19	0.28 ± 0.27	0.29 ± 0.17	1.3 ± 0.7	24 ± 2	81 ± 16	111 ± 25	1370 ± 316	6.89 ± 1.69	0.150 ± 0.044
Group II	49 ± 7	0.33 ± 0.24	0.79 ± 0.22**	2.3 ± 0.5	22 ± 4	117 ± 36	160 ± 53	1759 ± 436	6.99 ± 2.06	0.149 ± 0.051
Group III	22 ± 7	0.77 ± 1.05	0.69 ± 0.34**	2.8 ± 1.8*	17 ± 4*	172 ± 66**	242 ± 93**	2445 ± 656**	4.67 ± 2.20	0.099 ± 0.061*

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

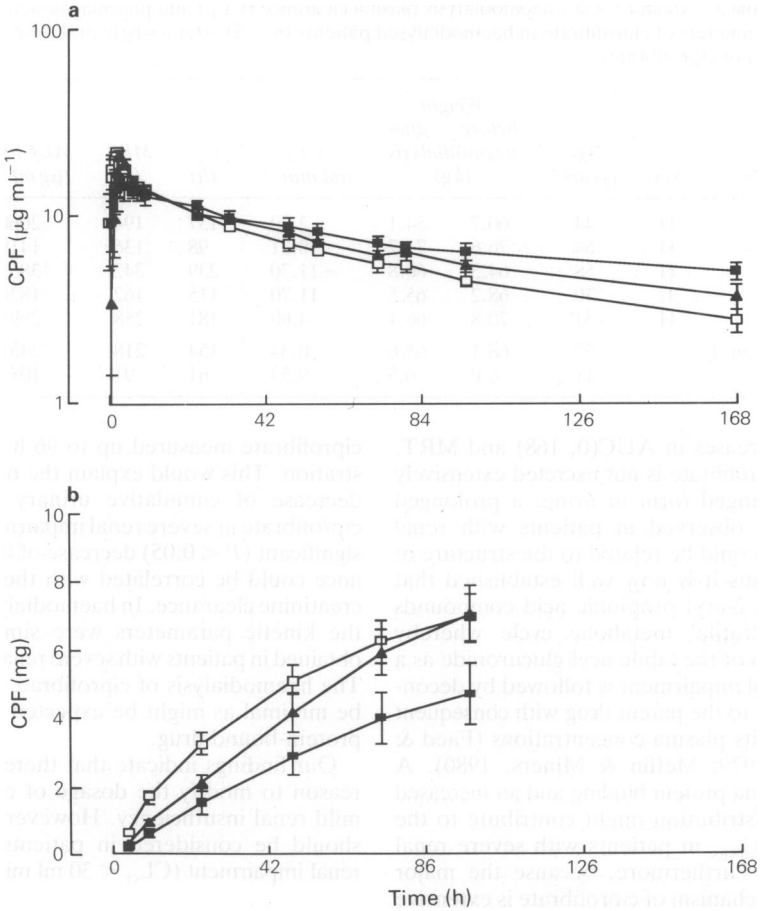

Figure 1 Mean (± s.e. mean) plasma concentrations a) and cumulative urinary excretion b) of ciprofibrate (CPF) in subjects with normal renal function ($n = 6$, □), and in patients with mild ($n = 6$, ▲) and severe renal insufficiency ($n = 6$, ■) given a single oral dose (100 mg) of ciprofibrate.

Haemodialysis plasma clearance of ciprofibrate

As indicated in Table 3 the haemodialysis plasma clearance of ciprofibrate was low ($CL_D = 0.34 \pm 8.7$ ml min^{-1}) reflecting similar venous and arterial plasma drug concentrations, which did not decrease significantly during the period of haemodialysis. In the interval between two haemodialysis sessions the slow decrease in plasma concentrations of ciprofibrate was described by an apparent elimination half-life of 154 ± 56 h, a value similar to that observed in severe renal insufficiency.

Discussion

In subjects with normal renal function, C_{max} was reached rapidly and showed little variation between subjects, the urinary excretion of unchanged drug was low and the apparent elimination half-life was between 56 h and 104 h. These data are in agreement with those from previous studies (Davison *et al.*, 1975; Edelson *et al.*, 1979) except for the value of the apparent elimination half-life. Previously studies were extended to only 70 h after the dose and consequently the calculation of the elimination half-life would have been influenced by the distribution phase, thereby giving rise to lower values ($t_{½,z}$ 26 to 42 h).

Mild renal insufficiency did not alter significantly the kinetics of unchanged ciprofibrate. In severe renal insufficiency, its apparent elimination half-life was increased two-fold in association with a significantly ($P < 0.05$) reduced renal clearance. The change was correlated significantly ($P < 0.01$) with the glomerular filtration rate, as

Table 3 Mean (± s.d.) haemodialysis plasma clearance (CL_D) and pharmacokinetic parameters of ciprofibrate in haemodialysed patients ($n = 5$) after a single oral dose (100 mg) of ciprofibrate

Subjects	*Sex*	*Age (years)*	*Weight before haemodialysis (kg)*	*Weight after haemodialysis (kg)*	CL_D *(ml min^{-1})*	$t_{1/2,z}$ *(h)*	*MRT (h)*	*AUC(0,78) (μg ml^{-1} h)*
1	H	44	60.7	54.1	−2.70	137	194	2060
2	H	64	76.6	71.7	−0.21	98	136	1419
3	H	58	64.3	60.8	−11.70	239	342	3863
4	F	70	68.2	65.5	11.70	115	162	1820
5	H	51	70.8	66.1	4.60	181	258	2995
Mean		57	68.1	63.6	0.34	154	218	2431
s.d.		11	6.0	6.5	9.53	61	91	1083

were the increases in AUC(0, 168) and MRT. Although ciprofibrate is not excreted extensively as the unchanged form in urine, a prolonged half-life was observed in patients with renal failure. This could be related to the structure of the drug. Thus it is now well established that analogues of 2-aryl propionic acid compounds undergo a 'futile' metabolic cycle whereby accumulation of the labile acyl glucuronide as a result of renal impairment is followed by deconjugation back to the parent drug with consequent elevation of its plasma concentrations (Faed & McQueen, 1979; Meffin & Miners, 1980). A lowered plasma protein binding and an increased volume of distribution might contribute to the decrease in C_{max} in patients with severe renal impairment. Furthermore, because the major clearance mechanism of ciprofibrate is extensive conjugation with glucuronic acid (Davison *et al.*, 1975), a decreased renal clearance would result in increased conjugation and therefore a low and incomplete urinary recovery of unchanged ciprofibrate measured up to 96 h after administration. This would explain the non-significant decrease of cumulative urinary excretion of ciprofibrate in severe renal impairment while the significant ($P < 0.05$) decrease of its renal clearance could be correlated with the value of the creatinine clearance. In haemodialysed patients, the kinetic parameters were similar to those obtained in patients with severe renal impairment. The haemodialysis of ciprofibrate was found to be minimal as might be expected with a highly protein-bound drug.

Our findings indicate that there is no kinetic reason to modify the dosage of ciprofibrate in mild renal insufficiency. However, lower doses should be considered in patients with severe renal impairment ($CL_{cr} < 30$ ml min^{-1}/1.73 m^2).

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