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NOTES

Influence of Renal Failure on Intestinal Clearance of Ciprofloxacin in Rats

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Following intravenous doses, ciprofloxacin pharmacokinetics in control and nephrectomized rats were studied. There were no differences between control and nephrectomized rats for area under the concentration-time curve in plasma or biliary clearance. The intestinal clearance of ciprofloxacin was increased in nephrectomized rats. Intestinal elimination seems to compensate partially for the decrease in urinary excretion of ciprofloxacin in nephrectomized rats.

In humans, renal clearance of ciprofloxacin represents 67% ± 11% of total body clearance (5). Since metabolism and biliary excretion account for the elimination of 15 and 1% of the dose administered, respectively (1, 12), intestinal secretion of ciprofloxacin may be important. Sörgel et al. (17) confirmed the importance of intestinal secretion (10.6% following intravenous [i.v.] administration) in ciprofloxacin's overall disposition. Clinical studies carried out with patients with renal failure demonstrated a less pronounced decrease in ciprofloxacin total clearance than could have been expected from creatinine clearance values (5, 6, 8). This suggests the existence of compensatory mechanisms for ciprofloxacin renal elimination. Rohwedder et al. (13) identified the role of intestinal secretion in the elimination of ciprofloxacin in patients with impaired renal function.

In animals, the intestinal elimination of ciprofloxacin was extensively studied (9, 14, 16) with the ex vivo intestinal perfusion model used by Schanker et al. (15). We have developed two experimental models with biliary derivation (4) to evaluate the overall intestinal elimination of ciprofloxacin and the importance of its intestinal reabsorption in nephrectomized rats. To study the influence of renal failure on the intestinal secretion of ciprofloxacin, we used an experimental model of surgically induced renal failure (2). We then compared the intestinal elimination and the biliary excretion of ciprofloxacin in normal and nephrectomized rats following the parenteral administration of increasing doses of ciprofloxacin.

Materials and methods. Ciprofloxacin hydrochloride was a generous gift from Bayer (Puteaux, France). The intestinal perfusate solution was a potassium phosphate buffer (0.15 M) (Prolabo, Paris, France). The male Sprague-Dawley rats used in this study weighed between 250 and 300 g at the time of the experiment (Charles River, Saint Aubin Les Elbeufs, France).

Three weeks before the experiment, rats underwent an 80% nephrectomy (2). Control rats underwent laparotomy only. Animals were on a 20% casein dry food diet with a low sodium content. Rats were food deprived for 12 h prior to the experiments; during the night, water was given ad libitum.

To evaluate intestinal elimination, we used two distinct models. The first model, with an open-intestinal perfusion (14), allowed the quantitation of overall intestinal elimination (4). The second model, with intestinal loops, allowed the estimation of net intestinal elimination, taking into account both elimination and reabsorption processes. The isolated intestinal segment was rinsed and then filled with perfusate and ligated at both ends. After a 20-min equilibration period, ciprofloxacin was injected via the jugular vein. A predose blood sample was obtained to measure plasma creatinine levels. Blood samples, via the carotid artery, were then collected at regular intervals after the end of the ciprofloxacin injection. Rats were rehydrated by injection of saline via the jugular vein. Bile and perfusate effluent in the open-intestinal perfusion model were collected. In the intestinal loop model, overall loop contents were collected at the end of the experiment (i.e., after 120 min), and the sac was flushed with the perfusion solution.

Control and nephrectomized rats were compared in two experimental protocols in order to study overall and net intestinal elimination. Ciprofloxacin was administered at 5, 12.5, 25, and 50 mg/kg of body weight in control and nephrectomized rats; five animals were used per dose level.

For the ciprofloxacin assay, the high-performance liquid chromatography system was operated in the reversed-phase mode and coupled with fluorescence detection (14). Plasma creatinine was measured by an automated kinetic procedure according to the method of Jaffé (Hitachi 717; Boehringer Mannheim, Meylan, France).

The area under the concentration-time curve (AUC) in plasma over 120 min was calculated according to the trapezoidal rule (Siphar; SIMED, Créteil, France). Overall and net intestinal clearances and biliary clearance were obtained by dividing the amount of ciprofloxacin eliminated over 120 min through the appropriate route by the AUC in plasma.

The groups were compared by using a nonparametric Mann-Whitney test. Statistical significance was fixed at $P < 0.05$. To

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TABLE 1. Pharmacokinetics of ciprofloxacin over 120 min after administration of increasing i.v. doses to control and nephrectomized rats in the overall and net intestinal elimination models

Elimination model parameter	Group ($n = 5$)	Result at ciprofloxacin dose (mg/kg of body wt)[b]:				r[c], slope (P)
		5	12.5	25	50	
Overall						
AUC (mg · min/liter)	Controls	198.5 ± 31	412 ± 39	872.5 ± 72	1,969.5 ± 109	0.99, 39.9 (<0.001)
	N[a] rats	273 ± 40	447 ± 68	899.5 ± 84.5	2159 ± 347	0.97, 42.9 (<0.001)
Biliary amt (μg)	Controls	47.3 ± 5.2	110 ± 7.9	222 ± 40	428 ± 52	0.98, 8.4 (<0.001)
	N rats	49 ± 7.2	123 ± 17	205 ± 23	447 ± 64	0.98, 8.5 (<0.001)
Biliary clearance (μl/min)	Controls	240 ± 40	270 ± 40	260 ± 50	220 ± 40	
	N rats	180 ± 20	280 ± 20	230 ± 40	220 ± 70	
Intestinal amt (μg/cm^2)	Controls	0.21 ± 0.04	0.72 ± 0.16	1.14 ± 0.12	1.83 ± 0.2	
	N rats	0.57 ± 0.11**	1.07 ± 0.16*	1.52 ± 0.27**	3.42 ± 0.34**	
Intestinal clearance (μl/min · cm^{-2})[d]	Controls	1.10 ± 0.24	1.75 ± 0.24	1.31 ± 0.17	0.93 ± 0.07	
	N rats	1.97 ± 0.45**	2.40 ± 0.17**	1.69 ± 0.26*	1.62 ± 0.28**	
Net						
AUC (mg · min/liter)	Controls	198.0 ± 23	371 ± 59	952 ± 68	2,007 ± 181.5	0.99, 41.8 (<0.001)
	N rats	248.5 ± 39.5	468 ± 35	986.5 ± 149.5	1,954 ± 328	0.97, 38.5 (<0.001)
Biliary amt (μg)	Controls	49 ± 7.2	87 ± 13.5	227 ± 21	431 ± 44	0.99, 8.7 (<0.001)
	N rats	53.5 ± 4.5	117 ± 12	218 ± 23	479 ± 43	0.99, 9.5 (<0.001)
Biliary clearance (μl/min)	Controls	240 ± 50	250 ± 40	240 ± 30	220 ± 30	
	N rats	210 ± 50	250 ± 40	230 ± 50	250 ± 50	
Intestinal amt (μg/cm^2)	Controls	0.07 ± 0.02	0.14 ± 0.01	0.37 ± 0.08	0.93 ± 0.23	
	N rats	0.08 ± 0.02	0.31 ± 0.08**	0.61 ± 0.13*	2.17 ± 0.52**	
Intestinal clearance (μl/min · cm^{-2})[d]	Controls	0.35 ± 0.10	0.39 ± 0.05	0.38 ± 0.07	0.47 ± 0.13	
	N rats	0.34 ± 0.09	0.65 ± 0.13*	0.65 ± 0.12**	1.1 ± 0.13**	

[a] N, nephrectomized.
[b] Values are means ± standard deviations. * and **, $P < 0.05$ and $P < 0.01$ for controls versus nephrectomized rats, respectively.
[c] r, correlation coefficient between doses and ciprofloxacin AUC in plasma or biliary amount excreted.
[d] Intestinal clearance is expressed per unit of intestinal surface area (i.e., calculated from the length and internal diameter of the intestinal segment).

investigate the influence of the dose on AUC and biliary excretion, statistical analyses were based on linear regressions and correlation coefficients.

Results. Plasma creatinine levels were twofold greater in nephrectomized rats (96.5 ± 13.8 μmol/liter) than in normal rats (51.5 ± 7.2 μmol/liter).

AUCs were not significantly different between control and nephrectomized rats and were proportional to the dose administered.

The levels of biliary excretion of ciprofloxacin were not significantly different between normal and nephrectomized rats (Table 1). Biliary clearance values were constant, whatever the dose administered.

As deduced from the intestinal cumulative amounts eliminated and the intestinal clearance values (Table 1), nephrectomized rats eliminated more ciprofloxacin via the intestine than control rats at all doses but 5 mg/kg in the net intestinal elimination model.

Discussion. Renal failure in rats led to a 2-fold increase in plasma creatinine and a 10-fold decrease in ciprofloxacin's mean renal clearance (about 55 μl/min versus 600 μl/min in control rats [data not shown]). These results are in agreement with the data observed in humans with severe renal failure (8) and validate the experimental model of renal failure selected.

The investigation of ciprofloxacin pharmacokinetics showed that, for each dose, AUCs in plasma were similar in both groups, and there was a linear relationship between the dose administered (between 5 and 50 mg/kg) and AUCs in plasma.

Since plasma ciprofloxacin concentrations and biliary elimination were proportional to the dose administered, one can conclude that total and biliary eliminations of ciprofloxacin were not saturated at the doses investigated, as in humans (10). In the same way, there was no modification in ciprofloxacin renal clearance according to the same doses administered (data not shown).

The overall and net intestinal clearances of ciprofloxacin were significantly greater in nephrectomized rats than in control rats, particularly at 50 mg/kg (approximately twofold). Nouaille-Degorce et al. (11) also showed an increase of twofold in the nonrenal clearance of ciprofloxacin with the same model of renal failure in awake rats. These results are consistent with what has been found in humans (13) and suggest the existence of intestinal compensatory clearance mechanisms when renal function is compromised.

The investigation of overall and net intestinal fluxes with two models evidences the importance of reabsorption processes, with net intestinal clearances being two to four times lower than overall intestinal clearances.

The absence of proportionality between ciprofloxacin's overall intestinal elimination and the dose administered of between 12.5 and 50 mg/kg suggests the existence of active intestinal secretion mechanisms in addition to passive diffusion. The implication of active transport mechanisms in the intestinal elimination of ciprofloxacin was confirmed in vitro, in Caco-2 cells, when a saturable secretory efflux was evidenced (3, 7). However, further investigations are necessary to explain our results for the 5-mg/kg dose.

In conclusion, renal failure does not alter the biliary excretion of ciprofloxacin in the rat. In contrast, its intestinal elimination is increased, partially compensating for its decreased urinary excretion. The exact mechanisms underlying the increased intestinal elimination of ciprofloxacin in renal failure remain to be determined.

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