Brief Report: Pharmacokinetics of Ciprofloxacin in Young (healthy volunteers) and Elderly Patients, and Concentrations in Prostatic Fluid, Seminal Fluid, and Prostatic Adenoma Tissue following Intravenous Administration

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Ciprofloxacin has a broad antibacterial spectrum with favorable pharmacokinetic properties and can be administered orally as well as parenterally. Therefore, it has been used widely in the treatment of complicated nosocomial urinary tract infections and demonstrated to be suitable for therapy of bacterial prostatitis and for perioperative prophylaxis in urologic surgery.

In this study, the pharmacokinetics of ciprofloxacin after intravenous administration in younger volunteers and elderly patients were compared, and concentrations in prostatic and seminal fluid and in prostatic adenoma tissue following intravenous administration were determined.

MATERIALS AND METHODS

Study in Volunteers

Two groups of healthy male volunteers took part in the study.

Group 1

Twelve volunteers aged 19 to 33 years (median, 27 years) with a body weight of 67 to 83 kg (median, 79 kg) received a 30-minute intravenous infusion of 200 mg ciprofloxacin and a bolus intravenous injection of 2.534 g ioxitalamic acid (IOTA) (5 ml Telebrix 300^{R}, Byk Gulden, Konstanz). Venous blood samples were taken before, during (15 minutes), at the end of infusion, at 10, 20, 30, 45, 60, and 90 minutes, and at two, three, four, six, eight, 10, 12, and 24 hours after infusion. Prostatic secretion was obtained by massage of the prostate at 0.5, 1.0, 1.5 and 2.0 hours after the infusion (three subjects at each time). Urine was collected in portions: zero to four, four to eight, eight to 12, 12 to 24 hours.

Group 2

Twelve volunteers aged 25 to 33 years (median, 27 years) with a body weight of 68 to 84 kg (median, 76 kg) received an intravenous infusion of 200 mg ciprofloxacin and a bolus intravenous injection of 2.534 g IOTA. Group 2 was divided into three subgroups of four persons each: group 2a received a 30-minute intravenous infusion of ciprofloxacin and an intravenous bolus injection of IOTA. Prostatic and seminal fluid (split ejaculate) were obtained four hours after the infusion; group 2b received an intravenous injection of IOTA, an intravenous bolus injection of IOTA, and intravenous injection of 50 mg ciprofloxacin followed by a constant infusion of 150 mg ciprofloxacin over four hours. Prostatic and seminal fluid (split ejaculate) were obtained at the end of the infusion; group 2c received a 30-minute intravenous infusion of ciprofloxacin and eight hours after the infusion an intravenous bolus injection of IOTA. Prostatic and seminal fluid (split ejaculate) were obtained at 12 hours after the infusion.

In groups 2a and 2b, volunteers were not allowed to pass urine prior to sampling prostatic and seminal fluid. In group 2c, volunteers voided urine about one hour before sampling of prostatic and seminal fluid.

Study in Patients

There were two groups of male patients: group A and group B.

Group A

Group A consisted of 14 patients undergoing transurethral resection of the prostate. They were aged 57 to 84 years (median, 74 years) with a body weight of 50 to 80 kg (median, 72 kg), and a serum creatinine level of 0.8 to 1.9 mg/dl (median, 1.0 mg/dl). The patients received a 30-minute intravenous infusion of 200 mg ciprofloxacin and a bolus intravenous injection of 2.534 g IOTA. Venous blood samples were taken before, during (15 minutes), at the end of the infusion, at 10, 20, 30, 45, and 90 minutes, and at two, three, four, six, eight, and 10 hours after the infusion. Prostatic fluid and adenoma tissue samples were obtained 1.0 to 2.5 hours after infusion.

Group B

Three patients undergoing transvesical enucleation of the prostate, aged 77, 81, and 85 years with body weights of 61, 70, and 86 kg and with serum creatinine levels of 1.0, 1.0, and 2.9 mg/dl, respectively, received a 30-minute intravenous infusion of 200 mg ciprofloxacin and a bolus intravenous injection of 2.534 g IOTA. Venous blood and tissue samples were taken 16 to 18 hours after the end of the infusion. Prostatic secretion

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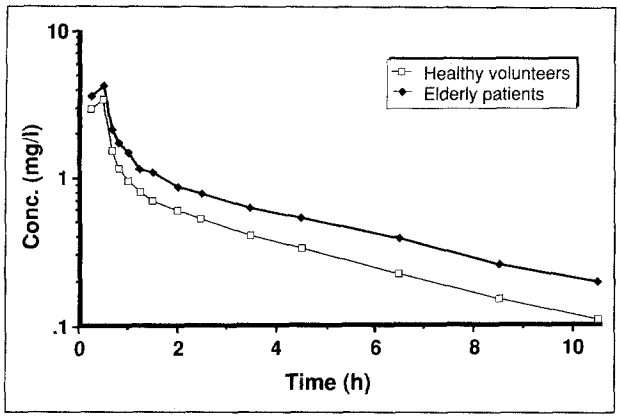

Figure 1. Mean plasma concentrations (conc.) of ciprofloxacin following a 30-minute intravenous infusion of 200 mg in 12 healthy volunteers and 11 elderly patients.

was obtained by manually exprimating tissue slices weighing about 1 to 3 g.

Concentrations of ciprofloxacin and IOTA were determined by high-performance liquid chromatographic methods [1]. Tissue samples were homogenized by an ultra turrax (IKA, Lauffen, Federal Republic of Germany). Pharmacokinetic parameters were calculated according to a model independent method. Statistically significant differences between the groups of volunteers (group 1) and patients (group A) were calculated using the Mann-Whitney rank sum test. A p value of less than 0.05 was considered significant.

RESULTS

Pharmacokinetics in Volunteers and Elderly Patients

Figure 1 shows the mean concentrations of ciprofloxacin in volunteers (group 1) and elderly patients (group A). In **Table I** the pharmacokinetic parameters of ciprofloxacin and IOTA for these two groups are listed. Elderly patients had higher maximal concentrations ($p < 0.05$), a larger area under the curve ($p < 0.001$), a smaller volume of distribution during steady state ($p < 0.05$) and during terminal elimination ($p < 0.001$), and a smaller total clearance ($p < 0.001$) as compared with volunteers. The higher maximal concentration and area under the curve can be explained partly because the mean body weight of the group of elderly patients (69.5 ± 9.1 kg) was lower than that of volunteers (76.0 ± 4.7 kg). There was, however, also a significantly smaller volume of distribution per body weight during terminal elimination ($p < 0.05$) and during steady-state ($p = 0.05$) in elderly patients as compared with volunteers. The reduction of total clearance of IOTA, which is almost exclusively excreted by glomerular filtration, is explained by reduction of renal function in elderly patients leading to prolongation of half-life of IOTA. In contrast, the half-life of ciprofloxacin increased only slightly, but not significantly in elderly patients.

Concentrations in Prostatic and Seminal Fluid and in Prostatic Adenoma Tissue

The concentrations of ciprofloxacin in prostatic and seminal fluid of volunteers are listed in **Table II**. One subject of group 1 (0.5 to 2.0 hours) and four subjects of group 2c (12 hours) showed IOTA fluid-to-plasma ratios far above unity and were therefore excluded from analysis due to urinary contamination. In the 18 remaining subjects, showing fluid-to-plasma ratios of 0.1 as maximum, the median concentrations of ciprofloxacin in prostatic fluid were in group 1 (0.5 to 2.0 hours) 0.16 mg/liter and in group 2 (four hours) 0.08 mg/liter with fluid-to-plasma ratios of 0.26 and 0.18, respectively. The median concentrations in seminal fluid (fraction 1/fraction 2) after four hours (12 hours) were 2.53/2.53 mg/liter (0.61/0.70 mg/liter) with plasma-to-fluid ratios of 5.8/7.1 (7.9/9.4).

The concentrations of prostatic fluid and adenoma tissue of patients are listed in **Table III**. Prostatic fluid results of two patients had to be excluded because of urinary contamination (prostatic fluid/plasma ratio of ioxitalamic acid was greater than 1 mg/liter). In the remaining seven patients of group A (1.0 to 2.5 hours)/group B (16 to 18 hours), the median concentrations were 0.62/0.06 mg/liter with a fluid-to-plasma ratio of 0.48/0.86. The median tissue concentration in group A/B was 1.87/0.13 μg/g with tissue-to-fluid ratio of 2.45/1.86.

TABLE I

Pharmacokinetic Parameters (model independent estimation) in 12 Young Volunteers and in 11 Elderly Patients after a 30-Minute Intravenous Infusion of 200 mg of Ciprofloxacin and after an Intravenous Bolus Injection of 2.534 g Ioxitalamic Acid*

	Volunteers*		Elderly Patients†	
	Ciprofloxacin	IOTA	Ciprofloxacin	IOTA
C_{max} (mg/liter)	3.43 ± 0.64‡	185 ± 19	4.15 ± 0.79‡	192 ± 26
AUC (mg × h/liter)	5.37 ± 0.72§	385 ± 36§	8.79 ± 2.73	595 ± 181§
$t_{1/2}$ (hours)	3.58 ± 0.54	2.25 ± 0.39‡	4.31 ± 1.38	2.97 ± 0.76‡
V_{dB} (liters)	194 ± 27§	21.6 ± 4.1‡	143 ± 29§	18.5 ± 2.0‡
V_{dss} (liters)	157 ± 25‡	17.2 ± 2.3	115 ± 29‡	16.5 ± 1.9
Cl_{tot} (ml/minute)	632 ± 75§	111 ± 12§	407 ± 104§	76.5 ± 21.2§
Cl_{ren} (ml/minute)	328 ± 96	112 ± 12	ND	ND
V_{dB}/BW (liters/kg)	2.52 ± 0.32‡	0.28 ± 0.05	2.09 ± 0.54‡	0.27 ± 0.05
V_{dss}/BW (liters/kg)	1.94 ± 0.29‡	0.22 ± 0.03	1.69 ± 0.52‡	0.24 ± 0.04
Cl_{tot}/BW (ml/minute · kg)	8.25 ± 1.7‖	1.45 ± 0.15‡	6.02 ± 1.90‖	1.12 ± 0.31‡

IOTA = ioxitalamic acid; C_{max} = maximal concentrations; AUC = area under the curve; $t_{1/2}$ = half-life; V_{dB} = volume distribution during terminal elimination; V_{dss} = volume of distribution during steady-state; Cl_{tot} = total clearance; Cl_{ren} = renal clearance; BW = body weight; ND = not done.
*Mean body weight 76.9 ± 4.7 kg.
†Mean body weight 69.5 ± 9.1 kg.
‡$p \leq 0.05$; § $p < 0.01$; ‖$p < 0.01$; (Mann-Whitney rank sum test) between the groups of volunteers and elderly patients.

TABLE II

Concentrations of Ciprofloxacin in Plasma and Prostatic and Seminal Fluid (split ejaculate) of Volunteers after Intravenous Infusion of 200 mg Ciprofloxacin

Time (hours)	Number of Subjects	Plasma Level (mg/liter)		Fluid Level (mg/liter)		Plasma Level (mg/liter)	
		Median	Range	Median	Range	Median	Range
				Prostatic			
0.5–2	10*	0.67	0.45–1.12	0.16	0.10–0.50	0.26	0.15–0.53
4	8	0.44	0.35–0.58	0.08	0.03–0.19	0.18	0.05–0.33
				Seminal (fraction 1)			
4	8	0.44	0.35–0.58	2.53	1.75–4.11	5.8	4.0–8.6
12	4	0.09	0.06–0.10	0.61	0.54–1.38	7.9	6.7–13.8
				(fraction 2)			
4	8	0.44	0.35–0.58	2.53	1.75–4.14	7.1	3.0–10.6
12	4	0.09	0.06–0.10	0.70	0.44–1.37	9.4	4.9–13.7

*One was excluded from evaluation because of urinary contamination (prostatic fluid/plasma ratio of ioxitalamic acid was greater than 1).

TABLE III

Concentrations of Ciprofloxacin in Plasma, Prostatic Fluid, and Adenoma Tissue in 14 Patients (group A) Undergoing Transurethral Resection and in three Patients (group B) Undergoing Transvesical Enucleation of Prostatic Adenoma after 30-Minute Intravenous Infusion of 200 mg Ciprofloxacin

Group	Time (hours)	Number of Subjects	Plasma (mg/kg)		Prostatic Material (mg/kg)		Prostatic Material/Plasma	
			Median	Range	Median	Range	Median	Range
					Prostatic Fluid			
A	1.0–2.5	7*	0.82	0.55–1.54	0.62	0.14–1.01	0.48	0.21–1.20
B	16–18	3	0.09	0.07, 0.23	0.06	0.04, 0.27	0.86	0.44, 1.17
					Prostatic Tissue			
A	1.0–2.5	14	0.81	0.55–1.54	1.87	1.02–5.81	2.45	1.41–5.43
B	16–18	3	0.09	0.07, 0.23	0.13	0.12, 0.47	1.86	1.33, 2.04

*Two were excluded from evaluation because of urinary contamination (prostatic fluid/plasma ratio of ioxitalamic acid was greater than 1 mg/liter).

COMMENTS

After a 30-minute intravenous infusion of 200 mg ciprofloxacin, plasma concentrations can exceed 3 mg/liter. Because of its large apparent volume of distribution, good tissue penetration can be assumed. The ciprofloxacin volume of distribution during steady-state ($p < 0.05$) and during terminal elimination ($p < 0.001$) are significantly smaller in elderly patients than in volunteers. However, this was not true for IOTA, which distributes only into the extracellular space. The terminal half-life between younger volunteers and elderly patients was not significantly different, despite significantly ($p < 0.001$) lower total plasma clearance per body weight in patients. According to our studies, dosage adjustments in elderly patients are not necessary despite expected reduction of renal function in this age group, which can be demonstrated by the significantly ($p < 0.001$) smaller total plasma clearance of IOTA.

In contrast to other studies [2,3], concentrations determined in prostatic fluid in healthy young volunteers and in patients did not exceed plasma concentrations, if urinary contamination can be identified by means of IOTA. As has been shown by other authors, the concentrations in seminal fluid [3] and in prostatic tissue [4,5] exceeded plasma concentrations by several-fold. Due to the broad spectrum, the favorable pharmacokinetics, and the sufficiently high concentrations in prostatic, seminal fluid, and prostatic adenoma tissue, ciprofloxacin, parenterally administered, is well-suited for the therapy of complicated and nosocomial urinary tract infections, as well as for bacterial prostatitis and perioperative prophylaxis in urologic surgery.

REFERENCES

1. Sörgel F, Muth P, Mahr G, Manoharan M: Pharmacokinetik und Analytik von Gyrase-Hemmern. 2. Hochdruckflüssigkeits-chromatographische Analytik (HPLC) von Gyrase-Hemmern in biologischem Material. In: Naber KG, Adam D, Grobecker H, eds. Gyrase-Hemmer II. Fortschritte der Antimikrobiellen und Antineoplastischen Chemotherapie. FAC 6-10. Munich: Futuramed, 1987; 1963–1986.

2. Boerema JBJ, Dalhoff A, Debruyne FMA: Ciprofloxacin distribution in prostatic tissue and fluid following administration. Chemotherapy 1985; 31: 13–18.

3. Dalhoff A, Weidner W: Diffusion of ciprofloxacin into prostatic fluid. Eur J Clin Microbiol 1984; 4: 360–362.

4. Eickenberg H-U, Dalhoff A: Quinolones and their kinetics in the prostate. In: Weidner W, Brunner H, Krause W, Rothauge CF, eds. Therapy of prostatitis. Munich, Bern, Vienna, San Francisco: W. Zuckschwerdt, 1986; 45–49.

5. Grabe M, Hellstern S, Forsgren A: The effects of a short and a prolonged perioperative course of ciprofloxacin in TUR compared with a control group without antibiotics (abstr 179). In: Proceedings of the International Symposium on New Quinolones, Geneva, July 17 to 19, 1986.