Pharmacokinetics of Ciprofloxacin in Elderly Patients

F. Kees[a], K. G. Naber[b], G. P. Meyer[c], and H. Grobecker[a]

Summary: *For perioperative prophylaxis 200 mg ciprofloxacin were administered as a short intravenous infusion to 17 patients aged 57—84 years before transurethral resection (TUR-P) or transvesicular enucleation (TVP) of the prostate. 13 patients were injected simultaneously with 2.5 g ioxitalamic acid i.v. to determine the kidney function. In 11 patients the plasma concentrations were assayed and the pharmacokinetic parameters calculated. At the end of infusion the concentrations of ciprofloxacin in plasma reached 4.2 ± 0.8 µg/ml and decreased after a fast distribution period (plasma half-life 0.20 ± 0.09 h) with a terminal half-life of 4.2 ± 1.3 h to 0.2 ± 0.09 µg/ml after 10 h. The apparent volume of distribution in steady state was 183 ± 45 % of body wheight, the plasma clearance 457 ± 146 ml/min/70 kg. The average concentrations in prostatic adenoma tissue were at all sampling times higher (2fold) than in plasma. The mean concentrations in prostatic secretion were about half of the respective plasma concentrations. High concentrations of the concomitantly administered ioxitalamic acid in prostatic secretion are considered as an indicator of urinary contamination. In those patients high ciprofloxacin concentrations in prostatic secretion are not reliable.*

Zusammenfassung: *Pharmakokinetik von Ciprofloxacin bei älteren Patienten*

17 Patienten im Alter von 57—84 Jahren erhielten 200 mg Ciprofloxacin als intravenöse Kurzinfusion (30 min) im Rahmen der perioperativen Prophylaxe vor transurethraler Resektion (TUR-P) bzw. transvesikularer Enukleation (TVP) der Prostata. Bei 13 Patienten wurden gleichzeitig 2,5 g Ioxitalaminsäure injiziert, um die Nierenfunktion zu bestimmen. Bei 11 Patienten wurden die Plasmakonzentrationen bis 10 h nach Injektion bestimmt und daraus die pharmakokinetischen Parameter berechnet. Die Konzentrationen von Ciprofloxacin im Plasma betrugen am Ende der Infusion 4,2 ± 0,8 µg/ml und fielen nach einer schnellen Verteilungsphase (Halbwertszeit 0.20 ± 0.09 h) mit einer Eliminationshalbwertszeit von 4.2 ± 1.4 h auf 0,20 ± 0,09 µg/ml nach 10 h ab. Das scheinbare Verteilungsvolumen im steady-state betrug 183 ± 45 % des Körpergewichts, die Plasma-Clearance 457 ± 146 ml/min/70 kg. Die Konzentrationen im Prostataadenomgewebe waren bei allen Patienten höher, im Mittel etwa doppelt so hoch wie die gleichzeitigen Plasmakonzentrationen. Sie fielen parallel zu diesen ab, waren aber bis 2,5 h nach Applikation noch höher als 1 µg/g. Die Konzentrationen im Prostatasekret betrugen etwa 20—100 % der gleichzeitigen Plasmakonzentrationen. Dabei wurde angenommen, daß hohe Konzentrationen von Ioxitalaminsäure im Prostatasekret auf Kontamination mit Urin hindeuten, weshalb die entsprechenden Ciprofloxacin-Konzentrationen als unzuverlässig eliminiert wurden.

Key words: *Ciprofloxacin, clinical pharmacokinetics · Ioxitalamic acid, clinical pharmacokinetics · Prostate, adenoma tissue, secretion*

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1. Introduction

Ciprofloxacin is a new quinolone carboxylic acid with a broad antibacterial spectrum against gram-positive and gram-negative bacteria (Cullmann et al. 1984, Sanders et al. 1987). A variety of publications deal with the plasma pharmacokinetics and tissue penetration of ciprofloxacin after oral administration, but a few only report on intravenous administration (c.f. Bergan 1987, Sörgel et. al 1987). The present study was performed to investigate the plasma pharmacokinetics of ciprofloxacin in elderly urological patients after intravenous administration and its penetration into prostatic adenoma tissue and secretion. Ioxitalamic acid, a renal contrast medium, was administered simultaneously as a marker of kidney function, and to detect possible urinary contamination of prostatic secretion.

2. Materials and methods

2.1. Patients, administration and sampling

14 patients aged 57—84 years (median 74 years) with a body weight of 52—80 kg (median 72 kg), a height of 155—175 cm (median 168 cm), serum creatinine of 0.8—1.9 mg/dl (median 1.0 mg/dl), undergoing transurethral resection of the prostate (TUR-P) were administered intravenously with 200 mg ciprofloxacin as a 20—25 min infusion for perioperative antibiotic prophylaxis. Immediately before ciprofloxacin administration, 2.5 g ioxitalamic acid (5 ml Telebrix® N 300) was injected intravenously. Before administration, 15 min after start of the ciprofloxacin infusion, at the end, and after 0.17, 0.33, 0.50, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8 and 10 h, venous blood (ammonium-heparin Monovette®, Sarstedt, Nümbrecht, FR Germany) was withdrawn from a contralateral arm vein through an indwelling catheter (Braunüle, Braun, Melsungen, FR Germany). 1—2.5 h after start of the ciprofloxacin infusion, immediately before TUR-P, prostatic secretion was obtained by massage of the prostate, if possible. During surgery, tissue samples of the left, median and right lobe of the prostate were taken for determination of tissue concentrations. In addition, in three patients (no. 16—18, 85, 76, 81 years, 162, 170, 155 cm, 61, 70, 86 kg) undergoing TVP 16—18 h after ciprofloxacin infusion, prostatic adenoma tissue and secretion (squeezing out the enucleated tissue) was obtained.

2.2. Analysis

2.2.1. Reagents and chemicals

Ciprofloxacin with the respective metabolites, M1, M2, M3, M4, and norfloxacin were supplied by the respective manufacturers. Ioxitalamic acid (5-acetamido-N-(2-hydroxy-ethyl)-2,4,6-triiodo-isophtalamic acid) and as diagnostic agent meglumine ioxitalamate (Telebrix N 300) were obtained from Byk Gulden (Konstanz, FR Germany). Tetrabutylammonium hydrogensulfate was purchased from Fluka (Neu Ulm, FR Germany), all other chemicals (analytical or HPLC grade) from E. Merck (Darmstadt, FR Germany). Water was purified with a Milli-Q water purification system (Millipore, Eschborn, FR Germany).

2.2.2. Chromatographic system

All samples were stored at −70 °C until analysis and assayed by high-performance liquid chromatography (HPLC) employing a solvent delivery system M 6000A, an autosampler WISP 710B, an integrator M 730, and a system controller M 720 (all from Millipore Waters-Chromatography, Eschborn, FR Germany). A fluorescence detector was used (F 1000, ex. 280 nm, em 445 nm, Merck-Hitachi, Darmstadt, FR Germany) for the quinolones, and in series a photometric detector (M 440, 254 nm, Millipore Waters-Chromatography) for ioxitalamic acid combined with an integrator D 2000 (Merck-Hitachi, Darmstadt, FR Germany). For separation, a Novapak® C18 column (i.d. 150 × 4 mm, Millipore Waters-Chromatography) was used. The mobile phase consisted of 1000 ml water, 2.0 g tetrabutylammonium hydrogensulfate, 2.0 ml 87 % o-phosphoric acid, and 100 ml acetonitrile. Chromatograms are shown in Fig. 1.

2.3. Sample treatment

Plasma (500 µl) was mixed with 100 µl internal standard (10 µg/ml norfloxacin in 1.0 % Na_2EDTA, pH 7.0) and 2.0 ml methanol. After standing for 15—20 min at 4 °C the precipitated protein was separated by centrifugation (10 min, 4500 g). Prostatic secretion (100—200 µl) was treated similarly. Tissue was divided in two parts (200—600 mg) and dissected (20—30 mg pieces). One part was treated for 5 min in a stomacher no. 80 (Kleinfeld, Hannover, FR Germany) with 10 volumes 0.1 mol/l sodium phosphate, pH 7.0 (2 mmol/l Na_2EDTA, 100 ng/ml internal standard norfloxacin), and 500 µl of the eluate was ultracentrifuged (Centrisart I, cut off 20,000, Sartorius, Göttingen, FR Germany. Adsorption of the compounds at the ultrafiltration membrane did not occur). The other part was homogenized in 10—20 volumes of a mixture of 500 ml water, 500 ml methanol, 10 ml 70 % perchloric acid, 1 ml 87 % o-phosphoric acid containing 100 ng/ml internal standard norfloxacin (homogenization: 1—1.5 min, cooling with ice, ultra turrax homogenizer type TP-18-10 with stick SN 25N-10G, IKA, Staufen, FR Germany). After standing for 15—20 min at 4 °C the mixture was centrifuged (10 min, 4500 g). 5—10 µl of the respective supernatants were injected onto the column.

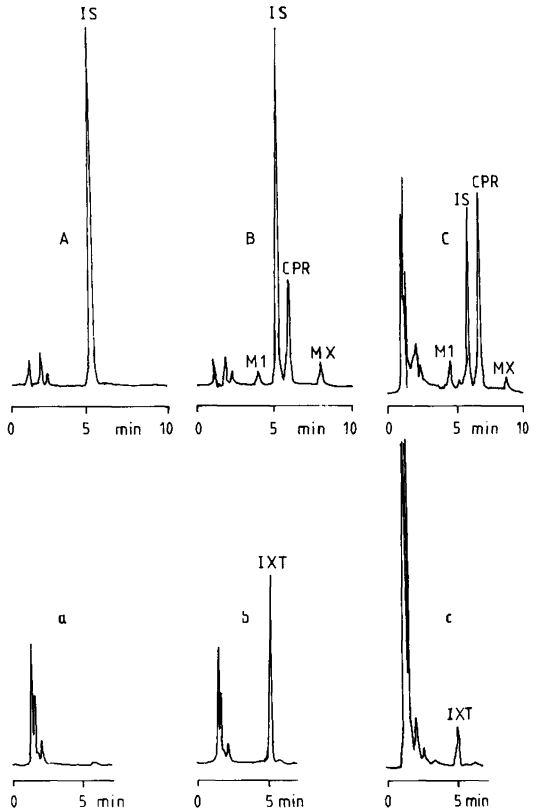

Fig. 1: Chromatograms of plasma (A, B), and prostatic adenoma tissue (C) of a patient (no. 10), before (A, a) and 1.5 h (B, b; C, c) after intravenous administration of 200 mg ciprofloxacin and 2.5 g ioxitalamic acid. A—C: Fluorescence at ex/em 280/445 nm. a—c: Absorbance at 254 nm. Abbr.: IS, internal standard, norfloxacin; CPR, ciprofloxacin; M1 and MX are metabolites of ciprofloxacin. IXT, ioxitalamic acid.

2.4. Evaluation of the assay

Linearity was checked in the range 0.2—5 µg/ml (ciprofloxacin), 0.02—0.05 µg/ml (M1) and 10—250 µg/ml (ioxitalamic acid) and was found satisfactory (coefficient of correlation better than 0.9990). The recovery of ioxitalamic acid from plasma was quantitative, that of norfloxacin (internal standard) and ciprofloxacin equal and amounted to about 90 %, whereas the recovery of metabolite M1 was 70 % only. The recovery of the internal standard norfloxacin from patients plasma was 93.1 ± 1.5 %, from tissue 82.6 ± 5.2 (stomaching) and 87.2 ± 5.2 (ultra turrax). Accuracy and reproducibility (3 assay days, 9 specimens) for spiked control plasma specimens (5, 2, 0.5 µg/ml for ciprofloxacin, 0.5, 0.2, 0.05 µg/ml for M1 and 50, 20, 5 µg/ml for ioxithalamic acid) was 100.8 ± 2.5 % for ciprofloxacin, 104.9 ± 1.8 % for M1, and 98.4 ± 3.5 % for ioxitalamic acid. The known metabolites of ciprofloxacin, M2, M3, M4, could not be quantified by the analytical procedure because of their differing chromatographic and fluorescing properties (c.f. Scholl et al. 1987).

2.5. Pharmacokinetic calculation

The plasma level data were analysed by the open, two-compartment model using standard pharmacokinetic equations. Details of the procedure are given elsewhere (Kees et al. 1985).

3. Results

The mean plasma concentrations of ciprofloxacin and ioxitalamic acid are shown in Fig. 2, the mean values of ciprofloxacin including M1 and the unknown metabolite MX,

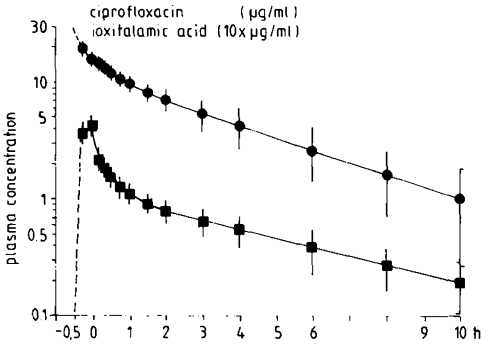

Fig. 2: Plasma concentrations (mean, standard deviation) of ciprofloxacin (■) and ioxitalamic acid (●) after intravenous infusion (0.5 h) of 200 mg ciprofloxacin in 11 elderly urological patients and bolus injection of 2.5 g ioxitalamic acid to 10 patients. (Patient 8 was not injected with ioxitalamic acid, because of possible allergic side effects.)

Table 1: Concentrations (mean, standard deviation) of ciprofloxacin and the metabolites M1 and MX in plasma of 11 elderly patients after intravenous administration of 200 mg ciprofloxacin.

Time (h)	Ciprofloxacin (µg/ml)	M1 (ng/ml)	MX[1] ("ng/ml")
– 0.25	3.63 ± 0.91	5.30 ± 3.54	
0.00[2]	4.15 ± 0.79	8.44 ± 3.43	47 ± 31
0.17	2.15 ± 0.49	9.32 ± 2.60	71 ± 38
0.33	1.73 ± 0.36	10.2 ± 3.09	114 ± 81
0.50	1.52 ± 0.33	10.8 ± 2.96	127 ± 60
0.75	1.20 ± 0.26	10.3 ± 3.33	156 ± 61
1.0	1.09 ± 0.23	9.81 ± 3.24	175 ± 67
1.5	0.87 ± 0.16	8.88 ± 2.71	191 ± 66
2.0	0.76 ± 0.18	8.33 ± 3.12	186 ± 67
3.0	0.61 ± 0.16	7.07 ± 2.46	159 ± 55
4.0	0.53 ± 0.16	6.45 ± 2.09	142 ± 56
6.0	0.38 ± 0.15	5.50 ± 1.67	113 ± 49
8.0	0.26 ± 0.10	4.83 ± 2.11	92 ± 46
10.0	0.20 ± 0.09	3.88 ± 1.40	76 ±46

[1] Apparent concentrations in terms of ciprofloxacin units.
[2] End of ciprofloxacin infusion.

evaluated as the parent compound ciprofloxacin, are depicted in Table 1. The mean maximum levels of ciprofloxacin at the end of the infusion were 4.15 ± 0.79 µg/ml, 1 h later on 1.09 ± 0.23 µg/ml and after 10 h 0.20 ± 0.09 µg/ml. During the same period the plasma levels of ioxitalamic acid decreased from 159.4 ± 15.2 µg/ml to 10.5 ± 7.9 µg/ml. As can be seen, the mean maximum plasma levels of the metabolite M1 were reached 0.5 h after the end of the ciprofloxacin infusion amounting to less than 1 % of the simultaneous ciprofloxacin concentrations, whereas the unknown metabolite reached its maximum 1.0 h later.

The estimated pharmacokinetic parameters of ciprofloxacin and ioxitalamic acid are given in Table 2. The mean steady state volume of ciprofloxacin was calculated about twofold

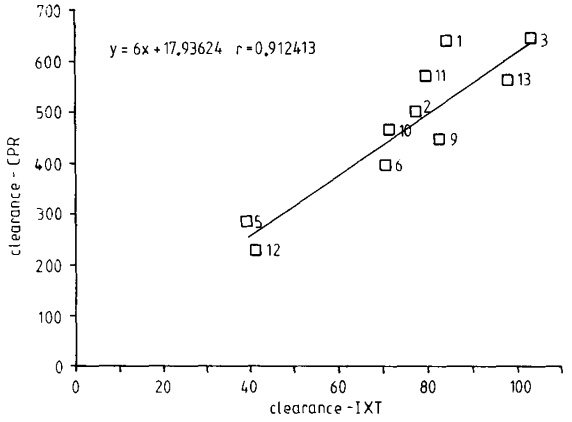

Fig. 3: Correlation between the plasma clearance (70 kg) of ciprofloxacin (CPR) and ioxitalamic acid (IXI) in elderly urological patients. The numbers mark the patients.

Table 2: Pharmacokinetic parameters of ciprofloxacin (Table 2a) and ioxitalamic acid (Table 2b) in elderly urological patients after intravenous administration of 200 mg ciprofloxacin as half an hour infusion, and bolus injection of 2.5 g ioxitalamic acid. Abbr.: SD, standard deviation; V_c, volume of the central compartment; V_{ss}, steady state volume of distribution; % b.w., percentage of body weight; AUC, area under the plasma concentration-time curve; Cl_t70kg, total body clearance normalized to 70 kg b.w.; t_α, plasma half-life of the fast distribution phase; t_β, terminal plasma half-life.

Table 2a

Pat.	B.w. (kg)	V_c (l)	V_{ss} (l)	V_{ss} %b.w.	AUC (mg/l h)	Cl_t (ml/min)	Cl_t70kg (ml/min)	t_α (h)	t_β (h)
1	56	30.3	97.8	175	6.51	512	640	0.20	2.85
2	67	22.1	99.4	148	6.95	480	501	0.15	3.12
3	65	23.0	95.3	147	5.58	597	643	0.13	2.45
5	80	25.1	102	128	10.3	324	284	0.19	4.37
6	78	26.1	120	154	7.52	443	398	0.15	3.80
8	74	55.8	151	204	11.4	292	276	0.43	6.87
9	77	35.7	151	196	6.73	495	450	0 13	4.02
10	66	26.0	139	211	7.55	441	468	0.12	4.28
11	52	41.8	146	281	7.86	424	571	0.19	4.55
12	73	38.2	109	149	13.9	240	230	0.26	5.85
13	75	64.2	165	220	5.52	604	564	0.25	3.63
Mean	69	35.3	125	183	8.17	441	457	0.20	4.17
SD	9	13.9	26	45	2.62	117	146	0.09	1.28
Median	73	30.3	120	175	7.52	443	468	0.19	4.28
Min	52	22.1	95.3	128	5.52	240	234	0.12	2.45
Max	80	55.8	165	281	13.9	604	643	0.43	6.87

Table 2b[1]

Pat.	B.w. (kg)	V_c (l)	V_{ss} (l)	V_{ss} %b.w.	AUC (mg/l h)	Cl_t (ml/min)	Cl_t70kg (ml/min)	t_α (h)	t_β (h)
1	56	12.4	15.6	27.9	593	67.3	84.1	0.59	2.93
2	67	8.66	14.2	21.2	540	73.9	77.2	0.35	2.52
3	65	8.99	13.2	20.3	418	95.6	103	0.48	2.00
5	80	8.43	16.7	20.9	888	44.9	39.3	0.35	4.70
6	78	9.26	15.0	19.2	506	78.8	70.7	0.39	2.53
9	77	13.4	18.0	23.4	440	90.7	82.4	0.44	2.48
10	66	12.0	19.0	28.8	592	67.4	71.5	0.59	3.75
11	52	12.8	16.7	32.1	677	58.9	79.3	1.13	3.90
12	73	11.0	14.8	20.3	929	43.0	41.2	0.42	4.15
13	75	10.3	14.9	19.9	379	105	98.0	0.57	2.17
Mean	69	10.7	15.8	23.4	596	72.6	74.7	0.53	3.10
SD	9	1.8	1.8	4.5	188	20.6	20.9	0.23	0.93
Median	73	11.0	15.6	21.2	592	73.9	79.3	0.48	2.88
Min	52	8.43	13.2	19.2	379	43.0	39.3	0.35	2.00
Max	80	12.8	19.0	32.1	929	105	103	1.13	4.70

[1] Note: Patient 8 was not injected with ioxitalamic acid because of possible allergic side effects.

of the body weight, whereas that of ioxitalamic acid was in accordance with previous results (Kees et al. 1985, Naber et al. 1986), about 20 % of the body wheight corresponding to the extracellular space. The mean plasma clearance of ciprofloxacin was 457 ± 146 ml/min/70 kg b.w., that of ioxitalamic acid 74.7 ± 20.9 ml/min/70 kg b.w., indicating slightly decreased renal function in the elderly patients. The plasma clearances were linear correlated with each other (Fig. 3). The half life of ciprofloxacin in the first distribution phase was markedly shorter (0.20 ± 0.09 h) than that of ioxitalamic acid (0.53 ± 0.23 h), but in the terminal phase somewhat longer (4.17 ± 1.29 h versus 3.10 ± 0.94 h).

In Table 3 the concentrations of ciprofloxacin and ioxitalamic acid obtained in prostatic adenoma tissue, secretion, and the concomitant plasma values are shown. The concentrations of the metabolites reached 0.5—2 % (M1) and 3—15 % (MX) of the respective ciprofloxacin concentration (not listed). Only mean values of the tissue levels are specified, because no significant difference could be found between the left, median and right lobe of the prostate. But it should be noted that intraindividually the concentrations in the three parts of the organ differed up to the factor 2, presumably mainly because of different composition of the tissue slices. The correlation between the concentrations of ciprofloxacin and ioxitalamic acid was satisfactory linear (homogenization by stomaching: r = 0.74; by ultra turrax: r = 0.86). At all sampling times the tissue levels exceeded the

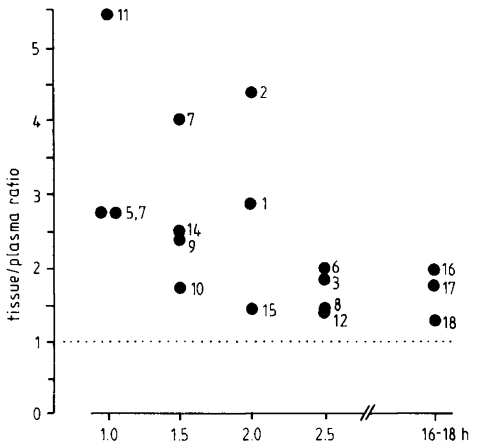

Fig. 4: Prostatic adenoma tissue over plasma ratio of ciprofloxacin in elderly urological patients after intravenous administration of 200 mg ciprofloxacin. The numbers mark the patients.

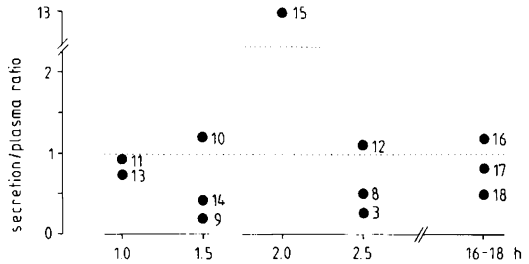

Fig. 5: Prostatic secretion over plasma ratio of ciprofloxacin in elderly urological patients after intravenous administration of 200 mg ciprofloxacin. The numbers mark the patients.

concomitant plasma levels (Fig. 4). The median ratio was 1.68 (range: 1.11—4.24) after stomaching and 2.18 (range: 1.41—5.43) after ultra turrax homogenization. In prostatic secretion the concentrations of ciprofloxacin were generally lower than in plasma (Fig. 5). Assuming high concentrations of ioxitalamic acid as indicative for urinary contamination (Naber et al., in press), patient 10, 12, and 15 have to be eliminated. The median concentration in the remaining six patients undergoing TUR-P was 45 % (range: 21—94 %) of the concomitant plasma concentration. In the three patients undergoing TVP, where urinary contamination of tissue and secretion during sampling can be excluded, 16—18 h after drug administration the concentrations of ciprofloxacin in tissue were 180, 130, and 200 %, respectively, and in prostatic secretion 80, 50, and 120 % of the concomitant plasma concentration (Table 3).

Table 3: Concentrations of ciprofloxacin and ioxitalamic acid in plasma, prostatic adenoma tissue and prostatic secretion of elderly patients after intravenous administration of 200 mg ciprofloxacin and 2.5 g ioxitalamic acid. (—.— = no sample or no drug administration; ST = stomaching, UT = ultra turrax homogenization).

Pat.	Time (h)	Ciprofloxacin				Ioxitalamic acid			
		Plasma (µg/ml)	Prostate			Plasma (µg/ml)	Prostate		
			Secr. (µg/ml)	Tissue			Secr. (µg/ml)	Tissue	
				ST (µg/g)	UT (µg/g)			ST (µg/g)	UT (µg/g)
5	1.0	1.26	—.—	2.71	3.46	105	—.—	49.3	80.1
11	1.0	1.07	1.01	4.54	5.81	113	9.1	74.9	83.5
13	1.0	0.87	0.62	1.80	2.41	78.5	25.5	55.7	57.4
7	1.5	0.65	—.—	2.18	2.61	77.3	—.—	51.4	45.1
9	1.5	0.75	0.16	1.61	1.79	80.5	4.3	30.3	36.9
10	1.5	0.80	0.96	1.05	1.41	98.9	64.3	31.7	35.3
14	1.5	1.54	0.63	2.58	3.87	150	18.9	67.7	87.5
1	2.0	0.68	—.—	1.14	1.95	111	—.—	30.1	56.2
2	2.0	0.65	—.—	2.10	2.86	98.5	—.—	30.2	55.3
15	2.0	1.14	14.8	1.26	1.65	116	177	52.8	53.1
3	2.5	0.55	0.14	0.89	1.02	90.8	16.3	14.4	29.2
6	2.5	0.64	—.—	2.16	1.28	88.3	—.—	31.9	25.8
8	2.5	0.82	0.39	1.32	1.19	—.—	—.—	—.—	—.—
12	2.5	1.23	1.32	1.60	1.73	132	104	42.0	30.5
17[1]	16.0	0.072	0.058	0.096	0.129	—.—	—.—	—.—	—.—
18[1]	17.0	0.087	0.042	0.108	0.115	—.—	—.—	—.—	—.—
16[1]	18.0	0.230	0.273	0.436	0.466	—.—	—.—	—.—	—.—

[1] Transvesicular enucleation of the prostate.

4. Discussion

Ciprofloxacin is a quinolone carboxylic acid whose clearance pathways in man include renal, as well as significant metabolic clearance with the formation of several metabolites (c.f. Borner et al. 1984, Bergan 1987). Four of these have been identified in urine (Gau et al. 1986). Because of multiple clearance pathways for ciprofloxacin, the effect of declining renal function on overall serum clearance is difficult to predict. Therefore, in our investigation the patients were injected intravenously with ioxitalamic acid, a renal contrast medium, which is eliminated by glomerular filtration only (Kees et al. 1985). There was a good linear correlation between the plasma clearances of ciprofloxacin and ioxitalamic acid, whereas only a bad linear correlation was found between the plasma clearances of ciprofloxacin and creatinine (Drusano et al. 1987). Our results confirm the superiority of intravenous ioxitalamic acid and similar compounds as marker of renal function over measurement of creatinine. The intercept of the regression line with the y-axis at positive values reveals the partial non-renal clearance of ciprofloxacin.

Of the four known metabolites of ciprofloxacin in man (Gau et al. 1986), M1 is simply to determine in plasma simultaneously with the parent compound because of its similar chromatographic behaviour and intense fluorescence (c.f. Awni et al. 1987). Surprisingly, metabolite MX, which also exhibits favourable chromatographic and fluorescent behaviour, has been not yet mentioned (Gau et al. 1985, 1986). In a recent study (Myers and Blumer 1987) more attention is directed to the fluorescent metabolites of ciprofloxacin, but the metabolites are not all identified. Because of differing chromatographic procedures the compound MX, found in our work, cannot be assigned to any metabolite found by Myers and Blumer (1987). Even if the structure may not very differ from that of M1 or ciprofloxacin iteself, quantification is not allowed, especially because of the very variable fluorescence properties of ciprofloxacin and its metabolites (Scholl et al. 1987). Therefore, our data express only the percentage of MX in terms of ciprofloxacin fluorescence. Further studies are necessary to elucidate the structure of metabolite MX.

Compared to pharmacokinetic results in young healthy volunteers (c.f. Bergan 1987, Bergan et al. 1987) in the elderly patients the plasma clearance was decreased and half-life increased at about 30 % (28 versus 40 l/h, 4.2 versus 3 h), like in patients with impaired renal function (Drusano et al. 1987). Because of partial non-renal clearance of ciprofloxacin, the differences were smaller than in the case of ioxitalamic acid, whose mean clearance in the patients investigated was only 60 % of that in young volunteers (c.f. Kees et al. 1985), and whose plasma half-life was prolonged at 70 %.

With respect to ioxitalamic acid, the plasma half life of ciprofloxacin in the α-phase was shorter, indicating faster distribution of ciprofloxacin into several tissues. Accordingly, the highest levels in prostatic adenoma tissue were already found at the first sampling time, namely 1 h after start, i.e. about half an hour after the end of infusion. For perioperative prophylaxis intravenous administration of ciprofloxacin can be recommended because of reliable antibacterial tissue levels already 0.5—1 h after administration in contrast to oral administration (Dahlhoff 1987). In all cases the assayed tissue concentrations exceeded the plasma levels both after stomaching and after ultra turrax homogenization, and did not show the large variability found in a previous study (Dahlhoff 1987). Even if by ultra turrax homogenization somewhat higher tissue levels were assayed, stomaching is

also a useful method for disintegrating prostatic tissue (c.f. Kees et al., in press).

The concentrations in prostatic secretion were rather scattered showing a secretion-plasma ratio of 0.2 to 13. When high concentrations of the simultaneously administered ioxitalamic acid were correctly taken as indicative for urinary contamination, and therefore the three patients 10, 12 and 15 were eliminated correctly, the plausible concentrations of ciprofloxacin in prostatic secretion after single administration are lower than in plasma. In prostatic adenoma tissue and secretion of the patients undergoing TVP, where contamination with urine during sampling can be excluded, the tissue-plasma and secretion-plasma ratios 16—18 h after ciprofloxacin administration were similar to those in the other patients. Accumulation was observed neither in tissue nor in secretion. With regard to observations in healthy volunteers where it was found difficult to obtain prostatic secretion free of urine, especially after having voided (Naber et al., in press), we conclude that the high concentrations in prostatic secretion (up to 30fold the plasma concentration) 12—24 h after oral administration of ciprofloxacin published by Dahlhoff (1987) were presumably caused by urinary contamination.

In conclusion, after single intravenous injection of 200 mg ciprofloxacin in elderly patients the mean concentrations in prostatic adenoma tissue were doubled with respect to the concomitant plasma levels, and in prostatic secretion we observed about half the plasma concentration. In the investigated period up to 2.5 h after administration of ciprofloxacin the tissue concentrations were above 1 µg/ml, high enough for use of intravenous ciprofloxacin for perioperative prophylaxis during TUR-P.

5. References

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