PHARMACOKINETIC STUDIES OF CEFOPERAZONE AFTER BOLUS INJECTION IN PATIENTS WITH BENIGN PROSTATIC HYPERTROPHY

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We measured serum and prostate concentrations of cefoperazone (CPZ) following its intravenous administration to 53 patients with benign prostatic hyperplasia.

High concentrations of CPZ were sustained in serum. The drug's biological half-life ($T_{1/2\beta}$) was 133 min.

In patients who underwent retropubic prostatectomy, the concentrations of CPZ in the right and left lobes reached maximum values of 33.3 and 30.5 μg/g, respectively, at 8.6 min after administration. In the surgical capsule, the maximum concentration was 34.3 μg/g at 10.3 min. In patients who underwent transurethral resection, the concentration attained a maximum value of 39.8 μg/g at 2.3 min after administration. In all three patient groups, the concentration of CPZ in the prostate declined in parallel with that in serum. According to our findings concerning its bacterial inhibitory capacity and its penetration into prostate, CPZ may be effective against the bacteria that cause prostatitis and/or are detected in urine after operation for benign prostatic hyperplasia.

INTRODUCTION

In general, an antibiotic is administered according to its antimicrobial spectrum and ability to penetrate the affected organ. Recently, there have been many reports concerning the penetration of various antibiotics into specific tissues. ADACHI[1], SAKURAI[2], and RISTUCCIA[3] measured the concentrations of several antibiotics in the prostates of patients with benign prostatic hypertrophy (BPH).

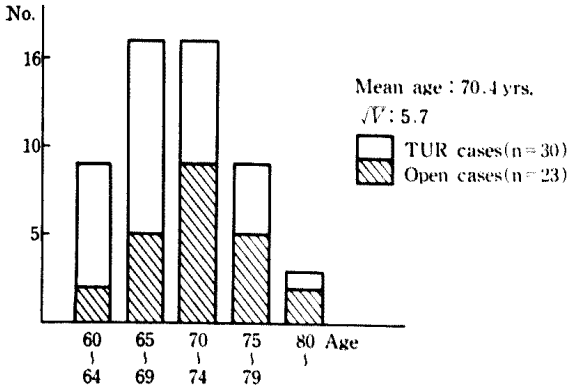
We previously reported that in the presence of BPH cefoperazone(CPZ) appears in high concentration in prostatic tissue and suggested that this agent is suitable for the treatment of bacterial prostatitis[4]. In the study reported here, we performed a pharmacokinetic evaluation of CPZ's penetrability into prostate.

PATIENTS AND METHODS

The subjects were 53 males with BPH admitted to the Yokohama Municipal Citizens Hospital, Kanagawa medical Center for the Adult, Fujisawa Municipal Hospital, and Yokohama Red Cross Hospital between January, 1982 and March, 1983. Their ages ranged from 60 to 83 years (70.4±5.7, mean±SD), as shown in Fig. 1. Kidney and liver functions were normal in all 53 patients.

A solution of 1 g of CPZ dissolved in 20 ml of saline was intravenously injected prior to surgery for BPH. The operative procedures were transurethral resection (TUR) or retropubic prostatectomy. Blood for determination of the serum CPZ concentration was drawn only once after prostatectomy. For determination of intraprostatic concentrations

Fig. 1 Age distribution and surgical procedure



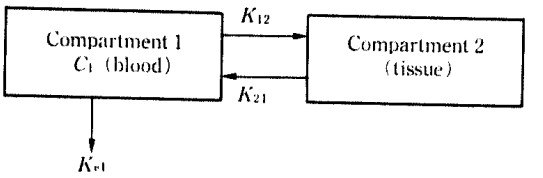
of CPZ, we used a fragments of prostatic tissue obtained by TUR or specimens from the prostatic capsule and each of the lateral lobes removed by open prostatectomy. The prostatic tissue was washed in a saline solution to eliminate blood and urine and frozen until the analysis was performed.

The prostatic tissue CPZ concentration was determined from the degree of inhibition of *Micrococcus luteus* (strain ATCC 9341) on a thin-layer disc containing nutrient fluid. The prostatic tissue was homogenized in a 1/15 M phosphate buffer (pH 7.0) and centrifuged at 3,000 rpm for 30 min. Using the supernatant, we measured the intraprostatic CPZ concentration by the same method as that used for serum. In the pharmacokinetic studies of the serum and intraprostatic CPZ concentrations obtained were from a single determination of each sample. The pharmacokinetic data were analyzed with a NEC ACOS 250 computer by the simulation and simplex method. Serum CPZ concentration was measured by a two-compartment model according to the calculation shown in Fig. 2. We employed the model in Fig. 3 to estimate the penetration of CPZ into prostatic tissue, which we considered to be related to its concentration in serum.

We then applied a constant so that the square sum of the difference between the obtained value and the theoretical value would be minimal. In addition, the duration of serum and prostatic CPZ concentrations at each stage were computed in terms of the bacterial inhibitory concentration by the Newton-Raphson method. The area under the curve (AUC) was also computed by numerical integration according to Simpson's rule.

The dose required to sustain a given concentration in serum and in prostate for 1.5 hours was calculated by the golden section method.

Fig. 2 Two-compartment open model of serum CPZ concentration



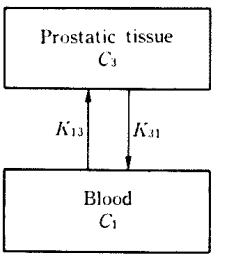
$$C_1(t)=\frac{W}{V(\alpha-\beta)}\left\{(K_{21}-\beta)\cdot e^{-\beta t}-(K_{21}-\alpha)\cdot e^{-\alpha t}\right\}$$

but

$$\alpha+\beta=K_{12}+K_{21}+K_{e1}$$
$$\alpha\cdot\beta=K_{21}\cdot K_{e1}$$

C_1 : Serum concentration (μg/ml)
V : Distribution volume of compartment 1(l)
K_{e1} : Elimination rate constant(hr^{-1})
K_{12}, K_{21} : Transition rate constant(hr^{-1})
W : Dose(mg)
t : Time(hr)

Fig. 3 Model of drug transport between serum and prostatic tissue



$$C(t)=\frac{W\cdot K_{13}}{V}\left\{\frac{(K_{21}-K_{31})}{(\alpha-K)(\beta-K)}e^{-K_{31}\cdot t}+\frac{(K_{21}-\alpha)}{(K_{31}-\alpha)(\beta-\alpha)}e^{-\alpha t}+\frac{(K_{21}-\beta)}{(K_{31}-\beta)(\alpha-\beta)}e^{-\beta t}\right\}$$

C_3 : Drug concentration (μg/g)
K_{13}, K_{31} : Transition rate constant (hr^{-1})

RESULTS

1. Serum CPZ concentration

The pharmacokinetic parameters are listed in Table 1. The distribution space was 5.7 L and the biological half-life 133 min. A simulation curve of serum CPZ concentration, shown in Fig. 4, yielded values of 105.5 μg/ml at 9 min (the minimum time point) and 26.0 μg/ml at 360 min (the maximum time point).

2. CPZ concentration in prostatic tissue

In Table 1 the prostatic pharmacokinetic data are subdivided according to preparation and tissue sample site.

With open prostatectomy, the maximum concentration in the right lobe, 33.3 μg/g, was attained

Table 1 Pharmacokinetic parameters

Serum

V (l)	K_{12} (hr^{-1})	K_{21} (hr^{-1})	K_{el} (hr^{-1})	α (hr^{-1})	β (hr^{-1})	$T_{1/2\,\beta}$ (min)	A_1 ($\mu g/ml$)	A_2 ($\mu g/ml$)
5.90	3.75	7.68	0.471	11.59	0.312	133	58.77	110.83

$C_{(t)}=A_1e^{-\alpha t}+A_2e^{-\beta t}$

Prostatic tissue

Prostatic tissue		K_{13} (hr^{-1})	K_{31} (hr^{-1})	t_{max} (min)	C_{max} (min)	B_1 ($\mu g/ml$)	B_2 ($\mu g/ml$)	B_3 ($\mu g/ml$)
Open surgery	Right lobe	4.83	17.0	8.6	33.3	−84.93	52.79	32.14
	Left lobe	4.44	17.1	8.6	30.5	−77.24	47.81	29.42
	Surgical capsule	4.26	14.0	10.3	34.3	−136.3	102.0	34.38
TUR		23.5	86.7	2.3	39.8	−48.55	18.39	30.15

$C_{(t)}=B_1e^{-K_{31}\cdot t}+B_2e^{-\alpha t}+B_3e^{-\beta t}$

Fig. 4 Simulated mean serum concentration of CPZ after 1 g intravenous injection

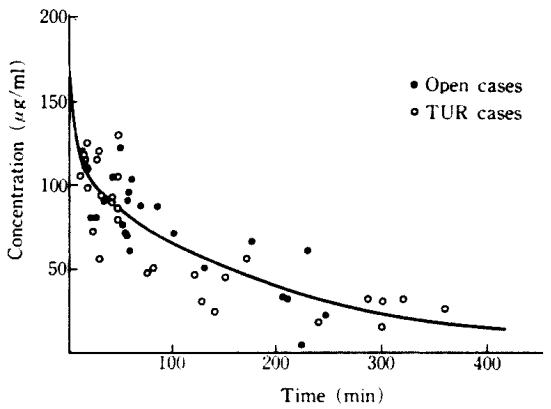


Fig. 5 Simulated mean right lobe concentration of CPZ after 1 g intravenous injection

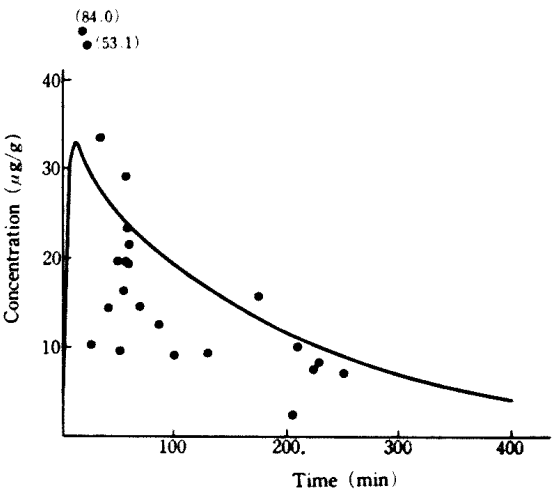
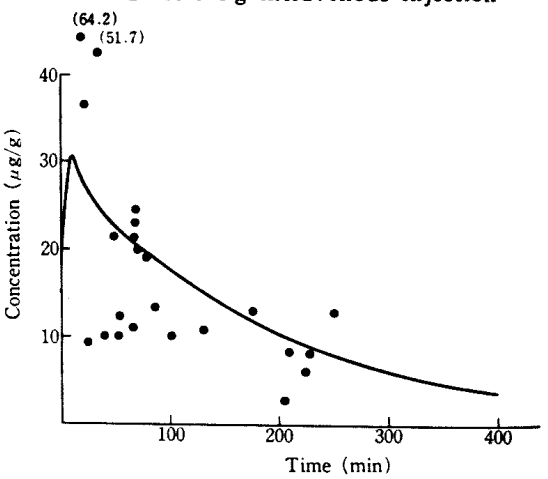


Fig. 6 Simulated mean left lobe concentration of CPZ after 1 g intravenous injection



at 8.6 min after administration. The K_{31}/K_{13} ratio was 3.52. The concentration in the left lobe reached a maximum of 30.5 $\mu g/g$, also at 8.6 min postadministration. The K_{31}/K_{13} ratio was 3.85. In the surgical capsule, the highest concentration was 34.3 $\mu g/g$ at 10.3 min. The K_{31}/K_{13} ratio was 3.29, which was smaller than that for the adenomatous lobes.

In the case of TUR, the maximum CPZ concentration, 39.8 $\mu g/g$, in resected adenomatous tissue occurred very soon—2.3 min—after administration. The K_{31}/K_{13} ratio was 3.69.

The simulation curves for CPZ concentration in prostatic tissue were derived from these data and are shown in Figs. 5-8. All four curves depict a similar course, with concentrations slowly declining after reaching the maximum.

Fig. 7 Simulated mean surgical capsule concentration of CPZ after 1 g intravenous injection

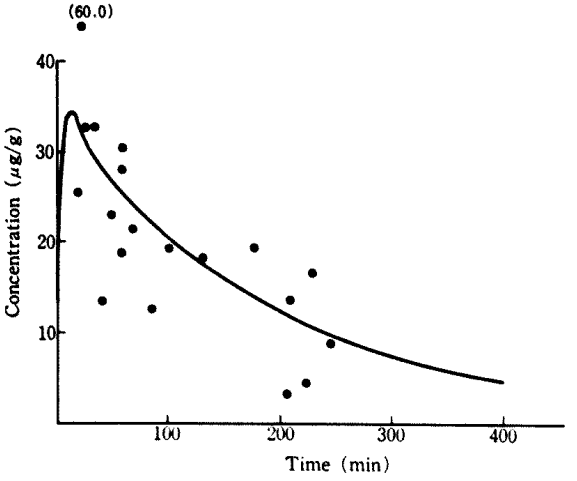
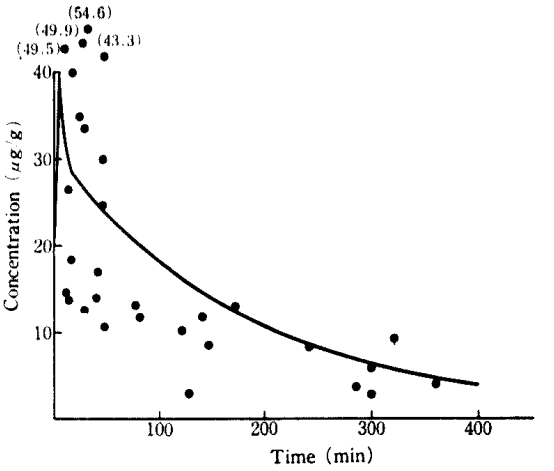


Fig. 8 Simulated mean TUR tissue concentration of CPZ after 1 g intravenous injection



3. Duration of minimal inhibitory concentration (MIC) of CPZ

The intervals during which the concentrations of CPZ in serum or prostatic tissue remained above the MIC are listed in Table 2. A concentration of 50 μg/ml of CPZ in serum was maintained for 2 hrs and 33 min. A level of 12.5 μg/g was detected in all prostatic regions for over 2 hrs. In the left lobe a concentration of 25.0 μg/g was sustained for 28 min ; the duration was longer—58 min—in the surgical capsule.

4. AUC (Table 3)

The AUC for several CPZ concentrations in serum and prostatic tissue is given in Table 3. The AUC for serum was large : 314.5 μg/hr/ml at 3.13 μg/ml and 160.9 μg/hr/ml at 25.0 μg/ml. In the prostate, at 3.13 μg/g, the AUC was large in the surgical capsule, with an average of 75.22 μg/hr/g, and small in left lobe, with an average of 61.40 μg/hr/g. However, at 25.0 μg/g, the AUC was small in all sites.

5. Dosage required to maintain MIC for 1.5 hours (Table 4)

The dosages required to maintain various concentrations of drug for 1.5 hours are listed in Table 4. In serum, a concentration of 100 μg/ml necessitated 1.44 g of drug. In the surgical capsule of the prostate, 1.18 g was required for a concentration of 25.0 μg/g and 2.35 g for a level of 50 μg/g.

DISCUSSION

Inflammation of the prostate is often encountered by clinicians. Patients with prostatitis range wide-

Table 2 Duration of MIC maintenance

MIC (μg/ml)	Serum (hrs)	Prostatic tissue (hrs)			
		Open surgery			TUR
		Right lobe	Left lobe	Surgical capsule	
0.20	20.3	16.3	16.0	16.5	16.1
0.39	18.1	14.1	13.9	14.4	13.9
0.78	15.9	11.9	11.6	12.1	11.7
1.56	13.7	9.70	9.41	9.91	9.49
3.13	11.4	7.46	7.18	7.68	7.26
6.25	9.22	5.24	4.96	5.46	5.04
12.5	7.00	3.01	2.72	3.22	2.82
25.0	4.77	0.76	0.47	0.97	0.59
50.0	2.55	—	—	—	—
100.0	0.36	—	—	—	—

Table 3 The area under the concentration/time curve

MIC (μg/ml)	Serum (μg·hr/ml)	Prostatic tissue (μg·hr/g)			
		Open surgery			TUR
		Right lobe	Left lobe	Surgical capsule	
0.20	355.7	98.77	90.07	105.3	93.74
0.39	352.0	95.81	87.25	102.4	90.95
0.78	345.5	90.78	82.33	97.3	86.02
1.56	334.0	82.45	74.22	88.8	77.86
3.13	314.5	69.18	61.40	75.22	64.92
6.25	282.7	49.76	42.87	55.13	46.13
12.5	232.8	24.78	19.66	28.80	22.36
25.0	160.9	2.82	1.30	4.20	2.63
50.0	72.4	—	—	—	—
100.0	6.73	—	—	—	—

Table 4 Dose required to maintain MIC for 1.5 hours

MIC (μg/ml)	Serum (g)	Prostatic tissue (g)			
		Open surgery			TUR
		Right lobe	Left lobe	Surgical capsule	
0.20	0.0003	0.010	0.011	0.009	0.011
0.39	0.0006	0.020	0.021	0.018	0.021
0.78	0.011	0.039	0.043	0.037	0.041
1.56	0.022	0.078	0.086	0.073	0.083
3.13	0.045	0.16	0.17	0.15	0.17
6.25	0.09	0.31	0.34	0.29	0.33
12.5	0.18	0.63	0.69	0.59	0.66
25.0	0.36	1.26	1.37	1.18	1.32
50.0	0.72	2.51	2.74	2.35	2.65
100.0	1.44	5.02	5.49	4.71	5.31

ly in age, from adolescents to the elderly. If detected early, acute inflammation can be controlled with antibiotics. However, in some cases the inflammation is not cured but advances to a chronic state, and the treatment period may be prolonged, to no effect. The main problem is that few antibiotics reach the prostate in high enough concentration to exert a bacteriocidal effect on the prostatitis-causing organisms. Newly developed antibiotics are always studied for their efficacy against prostatitis, particularly in terms of their ability to penetrate the prostate. Their penetrative capacities should be evaluated in patients with prostatic inflammation, but in fact have generally been assessed in patients with prostatic adenoma, following drug administration and surgical excision. In this investigation we simultaneously measured the concentrations of CPZ in adenomatous tissue, the prostatic capsule, and serum.

MIYATA et al[5] reported that CPZ diffused satisfactorily into the prostate. We presented similar results[4] and suggested that CPZ is clinically effective. However, to data there have been no published reports on the pharmacokinetics of CPZ within prostate.

Our results are summarized as follows.

1) The CPZ concentration in right and left adenomatous lobes reached maximum levels of 30.5 μg/g and 33.3 μg/g, respectively, at 8.6 min after intravenous administration.

2) The CPZ concentration in the surgical capsule required somewhat more time—10.3 min—to attain its maximum of 34.3 μg/g, which was slightly higher than that in adenomatous tissue.

3) In adenomatous tissue resected by TUR, the maximum concentration was higher, 39.8 μg/g, and was reached earlier, at 2.3 min after drug administration, than in tissue resected by open surgery.

When the currently accepted criteria for antibiotic efficacy, which were derived from experiments with penicillin-G by EAGLE[6] and associates and from the study of cephaloridine and cephalothin by SHIMADA et al[7], are applied to CPZ, this agent demonstrates effectiveness against many bacteria that cause inflammation, since a serum concentration of 50 μg/ml is sustained for over 2 hrs, as shown in Table 2. This theory, however, concerns only serum antibiotic concentration and ignores the important element of drug concentration within the inflamed tissue—a factor that was addressed by SHIMADA et al[7].

It is clinically impossible to measure the concentration of an antibiotic in inflamed prostate ; nor can the concentration be assumed to be the same as that achived in benign prostatic hyperplasia. However, acute inflammation of the prostate may increase vascular perfusion and permeability, permitting antibiotics greater access to prostatic tissue. Therefore, applying our data to the inflamed prostate, we conclude that CPZ is effective against bacteria for which the MIC of CPZ is less than 12.5 μg/ml.

Escherichia coli and *Staphylococcus epidermidis* have been reported to be responsible for prostatitis[8~10]. *Serratia, Pseudomonas, Proteus, Enterobacter,* and *Klebsiella* species and *Streptococcus faecalis* are often detected in urine after operation for benign prostatic hyperplasia[11]. Although the MIC of CPZ against these bacteria is not lower than 12.5 μg/ml in every case[12], CPZ seems capable of controlling the majority of these organisms and is considered clinically useful.

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前立腺肥大症患者に Cefoperazone (CPZ) one shot 静注後の血中および前立腺組織移行濃度の薬動力学的解析

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CPZ 1g を前立腺肥大症患者 53 名の手術前に静注し，血清および摘出前立腺組織内濃度を測定し，薬動力学的解析を試みた。

血清濃度は高く維持され，生物学的半減期（$T_{1/2\beta}$）は 133 分であった。恥骨後式前立腺摘出術施行例の前立腺組織は左右両葉とも 8.6 分で最高濃度に達し，その濃度は 30.5 μg/g，33.3 μg/g であった。被膜は 10.3 分で最高濃度に達し，その濃度は 34.3 μg/g であった。経尿道的切除例では 2.3 分で最高濃度 39.8 μg/g に達していた。どの部位も血清濃度の低下とともに下降し，同様な濃度推移を示した。

時間曲線下面積および各部位の濃度の推移をみると，前立腺炎の起炎菌や前立腺肥大症の術後に検出される細菌に対して有効性が高いと判断された。