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Distribution of Ciprofloxacin in the Dog Prostate and Various Tissues*

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Summary. The distribution in the dog prostate and other tissues of ciprofloxacin, a quinoline carboxylic acid derivative, was investigated in an experimental model. The concentrations in prostatic tissue, prostatic interstitial fluid (PIF), and prostatic secretion (PS) were lower than the corresponding plasma (P) concentrations, as would be expected for an acidic compound. The experiments were carried out under steady state conditions during intravenous infusion in one group of dogs and following gastric administration in another group. During steady state the ciprofloxacin concentrations were significantly higher in PS than in PIF, and the median PS/P ratios were significantly higher than the PIF/P ratios. These concentrations and ratios were compared with those of two other quinoline carboxylic acid derivatives, rosoxacin and norfloxacin. The concentrations of ciprofloxacin in prostatic tissue, PIF, PS, and urine were several times higher than the minimum inhibitory concentrations for most gram-negativve pathogens that cause bacterial prostatitis and urinary tract infections. Clinical trials of ciprofloxacin in these diseases are therefore indicated.

Key words: Ciprofloxacin, Bacterial prostatitis, Dogs.

Introduction

Chronic bacterial prostatitis is one of the most common causes of recurrent urinary infections in male patients [8]. The bacteria remain in prostatic secretion during therapy and reinfect the bladder when therapy is stopped. Treatment of chronic bacterial prostatitis has been rather disappointing. The best cure rates reported using long-term treatment with trimethoprim-sulfamethoxazole varied from 32% to 71% [7]. These results are probably due to poor drug penetration into the prostate [11].

Ciprofloxacin is a newly developed quinoline carboxylic acid. The best known member of this class of antibacterial agents, nalidixic acid, has long been used for treatment of urinary tract infections caused by gram-negative microorganisms. Nalidixic acid, however, has a relatively narrow antibacterial spectrum and low oral absorption. In contrast, ciprofloxacin has a broad antimicrobial spectrum comprising both gram-negative and gram-positive bacteria including *Pseudomonas aeruginosa* [12]. In vitro minimal inhibitory concentrations (MIC) generally range from 0.01–2 μg/ml [4, 10, 12]. Ciprofloxacin is well absorbed when administered orally [2]; therefore, it may have an important clinical role. The purpose of the present study was to evaluate the distribution of ciprofloxacin in prostatic tissue, secretion, and interstitial fluid, possibly forming the basis for clinical use of this drug.

Material and Methods

An experimental dog model, previously described in detail [6], was used. Eight mature male mongrel dogs with a median weight of 18.9 kg (range: 15.1–25.8 kg) were anesthetized by intravenously administered sodium thiopental. The prostate was exposed through a low paramedian incision, and a 10 × 6-mm multiperforated polyethylene tissue chamber with two connecting tubes (Engineering Industries, Verona, WI) was implanted in each lateral lobe of six of the dogs. Only one chamber could be implanted in two dogs because the prostate was too small. The connecting tubes were placed under the skin. Four weeks later, the dogs were anesthetized again, and the connecting tubes were exposed and cannulated to collect prostatic interstitial fluid (PIF). A vasectomy was performed and the bladder neck ligated to prevent urine contamination of prostatic secretion (PS) which was collected from a transurethrally inserted catheter. Urine was collected through a cystostomy. Four of the eight dogs also had a catheter introduced into the common bile duct to collect bile. Arterial blood samples were collected from a femoral artery cut down.

Four of the dogs received ciprofloxacin (10 mg/kg body weight) as an intravenous bolus injection, followed by constant infusion of ciprofloxacin (3 mg/kg/h) for 4 h in order to obtain steady state conditions. In the four other dogs, a single dose of ciprofloxacin

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(20 mg/kg body weight) was injected directly into the stomach through a small high midline abdominal incision, simulating oral administration of the drug. Pilocarpine (0.25 mg/kg) was given when needed to stimulate prostatic secretion. Samples of plasma, urine, PIF, and PS were collected before drug administration and at 30-min intervals for 4 h after ciprofloxacin was given. In the dogs receiving intravenous ciprofloxacin, bile samples were obtained at the same intervals. Samples of saliva were taken from all dogs. At the end of the study, the dogs were sacrificed and biopsies were taken from the following sites for bioassay of ciprofloxacin: kidney cortex, kidney medulla, liver, pancreas, bladder wall, prostate, testes, epididymis, and fatty tissue.

All samples were frozen immediately and stored at −17 °C until bioassay. Tissue samples were homogenized in phosphate buffer. Ciprofloxacin concentrations were determined by disk diffusion using *Klebsiella pneumoniae* ATCC-10031 on neomycin assay agar as the test organism. Standard curves for plasma were generated from pooled dog plasma, and a phosphate buffer, pH 7.2, was used for standard curves for PIF, PS, urine, bile, and tissue.

Results

All tissue chambers but one yielded sufficient amounts of fluid (0.03–0.1 ml) every 30 min for bioassay. The fluid from both chambers in one dog was bloody; therefore, the results from this dog were excluded.

Table 1 shows the median values and ranges for ciprofloxacin in plasma, PS and PIF and the PS/P and PIF/P ratios from the four dogs receiving ciprofloxacin intravenously. The plasma concentrations measured 90 to 240 min after drug administration were used to calculate the mean concentration for the fluid/plasma ratios. Assuming that a steady state had occurred after 120 min, the median concentrations were significantly higher in PS than in PIF ($p \leqslant 0.05$, Mann-Whitney rank sum test), and the median PS/P ratios were significantly higher than the PIF/P ratios ($p \leqslant 0.01$). None of the fluid/plasma ratios exceeded 1.

Table 1. Concentrations of Ciprofloxacin (μg/ml) in plasma (P), prostatic secretion (PS), and prostatic interstitial fluid (PIF) after intravenous administration in four male dogs

	min after drug administration							
	30	60	90	120	150	180	210	240
Plasma	7.5[a] (5.6–11.0)	7.7 (4.8–9.2)	6.3 (4.3–7.5)	6.5 (3.9–9.9)	5.8 (4.1–7.0)	6.6 (3.8–8.5)	5.3 (3.6–7.5)	5.7 (3.6–7.6)
PS	2.0 (0.47–3.7)	3.4 (2.8–5.9)	3.4 (2.2–6.9)	4.1 (2.9–7.5)	4.3 (1.8–6.7)	3.6 (2.4–6.5)	3.0 (2.4–5.7)	3.2 (2.2–4.9)
PIF	1.8 (1.7–1.9)	3.5 (2.5–4.0)	3.1 (2.1–4.2)	2.4 (2.2–4.1)	3.0 (1.6–3.4)	2.3 (1.7–4.0)	2.4 (2.0–4.1)	2.6 (2.0–4.3)
PS/P	–	–	0.76 (0.29–0.92)	0.84 (0.47–1.0)	0.73 (0.37–0.89)	0.61 (0.53–0.87)	0.67 (0.31–0.76)	0.61 (0.40–0.67)
PIF/P	–	–	0.41 (0.26–0.43)	0.49 (0.29–0.53)	0.40 (0.33–0.44)	0.35 (0.31–0.52)	0.49 (0.27–0.53)	0.53 (0.27–0.56)

[a] Median (Range)

Table 2. Concentrations of Ciprofloxacin (μg/ml) in urine, bile, and saliva after intravenous drug administration in 4 male dogs

	min after drug administration							
	30	60	90	120	150	180	210	240
Urine	212[a] (8–1930)	358 (61–1168)	209 (75–1554)	165 (74–1013)	158 (123–1152)	201 (163–1596)	181 (41–1602)	83 (25–353)
Bile	30 (13–46)	39 (31–68)	44 (42–50)	40 (26–70)	61 (25–74)	63 (29–95)	93 (80–106)	75 (22–107)
Saliva	084 (0.61–1.3)	1.5 (0.7–1.7)	1.8 (1.4–3.3)	1.9 (1.3–4.6)	1.7 (1.1–4.7)	1.9 (1.6–6.9)	2.3 (1.7–3.6)	1.4 (1.1–5.2)

[a] Median (Range)

Table 3. Concentrations of Ciprofloxacin (μg/ml) in plasma, prostatic secretion (PS), prostatic interstitial fluid (PIF), urine, and saliva after oral administration in 4 male dogs

	min after drug administration							
	30	60	90	120	150	180	210	240
Plasma	0.72[a] (0–1.6)	1.2 (0.32–3.6)	1.7 (0.82–2.9)	1.9 (0.57–3.2)	2.0 (0.46–2.2)	1.6 (0.3–2.2)	1.7 (0.3–2.7)	1.6 (0.26–2.2)
PS	0.035 (0.03–0.62)	0.12 (0.045–0.38)	0.28 (0.26–1.1)	0.56 (0.30–1.1)	0.76 (0.29–1.9)	0.60 (0.41–1.7)	0.68 (0.09–0.83)	0.61 (0.30–1.8)
PIF	0.13 (0–0.42)	0.55 (0.28–1.3)	0.43 (0.26–2.0)	0.89 (0.21–2.5)	0.95 (0.25–1.7)	0.33 (0.17–1.6)	[b] (0.49–1.6)	0.52 (0.38–1.11)
Urine	6.3 (0–46)	40 (6.4–49)	31 (6.9–194)	36 (14–88)	37 (11–147)	30 (13–151)	40 (13–89)	25.3 (6.1–85)
Saliva	0.3 (0–0.2)	0.13 (0.05–0.36)	0.66 (0.12–0.74)	[b] (0.15–1.2)	[b] (0.2–0.67)	[b] (0.17–0.59)	[b] (0.21–0.41)	[b] (0.08–0.56)

[a] Median (Range)
[b] Only two observations

Table 4. Concentrations of Ciprofloxacin in various tissues at autopsy

Biopsy site	Ciprofloxacin i.v.		Ciprofloxacin Stomach Injection
	Concentration (μg/g Tissue)	Ratio Tissue:Plasma	Concentration (μg/g Tissue)
Prostate	3.95[a] (3.1–4.7)	0.58 (0.51–1.21)	2.0 (0.47–2.8)
Epididymis	7.35 (5.8–8.9)	1.66 (1.49–1.82)	2.5 (0.55–3.8)
Testis	5.0 (4.3–7.4)	0.95 (0.73–1.10)	1.34 (0.52–3.5)
Bladder	7.5 (4.9–10.3)	1.25 (1.19–1.34)	3.25 (0.57–5.1)
Kidney medulla	8.1 (7.1–9.2)	1.32 (1.16–1.95)	3.95 (1.0–6.6)
Kidney cortex	9.65 (7.1–12.4)	1.55 (1.27–2.44)	6.45 (1.2–7.5)
Liver	9.45 (8.9–9.6)	1.62 (1.21–2.28)	7.15 (0.7–9.4)
Pancreas	7.0 (6.0–7.8)	1.21 (0.78–2.00)	3.2 (0.77–4.8)
Fatty tissue	4.85 (4.4–6.6)	0.89 (0.66–1.18)	2.35 (0.26–5.0)
Bile (autopsy)	–	–	[b] (20–147)

[a] Median (Range)
[b] Only two observations

Concentrations of ciprofloxacin in urine, bile, and saliva after intravenous drug administration are shown in Table 2.

Median values and ranges of concentrations of ciprofloxacin in plasma, PS, PIF, urine, and saliva in dogs which received oral ciprofloxacin are shown in Table 3. Saliva was collected from only two dogs between 120 and 240 min after drug administration. Since no steady state occurred following intragastric administration of ciprofloxacin, the PS/P and PIF/P ratios were not calculated. During the 4-h study period, a median of 6.3% (range 2.0–18.3%) of ciprofloxacin was recovered in the urine.

Median concentrations and ranges of ciprofloxacin in the various tissues are shown in Table 4. Tissue/plasma ratios were calculated for only the four dogs which received ciprofloxacin intravenously.

Discussion

In a previous study, Crump et al. administered a single oral dose of 500 mg of ciprofloxacin in humans and found a mean maximum plasma level of 2.4 μg/ml at a mean time of 1.25 h after administration [2]. These data suggest that ciprofloxacin is widely distributed throughout the tissues, a finding that was confirmed in our study. Plasma concentrations following administration of ciprofloxacin into the stomach were lower than the concentrations found by Crump et al., although the dose was approximately three times that given to humans [2]. However, absorption of ciprofloxacin may have been impaired in our study because of the anesthesia and the surgical procedure.

Penetration of drugs into the prostate depends on the same mechanisms that generally determine drug passage across biological membranes [11]. This process in the prostate is thought to be passive. Differences in the pH levels of plasma and PS are important because of the phenomenon of ion trapping. When steady state conditions occurred, the highest drug concentration (i.e., charged plus uncharged) will be on the side of the membrane where most drug ionization occurs. The pH of dog PS is approximately 6.4; consequently, a weak acid such as ciprofloxacin (pK_{a1} = 6.0; pK_{a2} = 8.8) [9] should be trapped on the plasma side and neither the PS/P nor the PIF/P ratio should exceed 1.0. Our results from four dogs in which ciprofloxacin was given intravenously under steady state conditions are in accordance with this.

There is some evidence that the drug concentration in prostatic interstitial fluid may be of greater improtance than the drug concentration in prostatic secretion. In a experimental study of chronic prostatitis in dogs, inflammatory changes were found mainly in the interstitial tissue and not in the acini, as in acute prostatitis [1].

Rosoxacin and norfloxacin are two other quinoline derivatives studied in this same experimental dog model [5]. Ciprofloxacin provided higher PS/P and PIF/P ratios than rosoxacin and a higher PS/P ratio than norfloxacin, but there was no significant difference between the PIF/P ratios of ciprofloxacin and norfloxacin.

The potency of an antimicrobial agent is determined both by its pharmacokinetic properties and by its antimicrobial activity. Both ciprofloxacin and norfloxacin have very low in vitro MICs, but the mean ciprofloxacin MIC is approximately one to four dilution steps lower than the mean norfloxacin MIC [4, 10, 12]. If a therapeutic index in a specific tissue or fluid is defined as the ratio of concentration to MIC, ciprofloxacin appears to be the more potent of these quinoline derivatives.

A basic assumption in dog experiments designed to study the diffusion of drugs into the prostate is that the pH of human prostatic secretion is similar to that of the dog (about 6.5). Fair and Cordonnier [3], however, found that the prostatic secretion of normal men is slightly alkaline, with a pH of approximately 7.3. Further, they found that the pH of prostatic secretion from men with prostatic infection is increased markedly (mean pH = 8.34). Since the pH gradient is crucial to the ion-trapping phenomenon, results obtained in dogs can only be applied to humans with caution.

In conclusion, ciprofloxacin might be valuable in treatment of bacterial prostatis and urinary tract infections. Clinical trials seem justified because of ciprofloxacin's broad antibacterial spectrum and its ability to penetrate prostatic interstitial fluid and secretion in sufficient concentrations.

References

1. Baumueller A, Madsen PO (1977) Experimental bacterial prostatitis in dogs. Urol Res 5:211–213
2. Crump B, Wise R, Dent J (1983) Pharmacokinetics and tissue penetration of ciprofloxatin. Antimicrob Agents Chemother 24:784–786
3. Fair WR, Cordonnier JJ (1978) The pH of prostatic fluid: a reappraisal and therapeutic implication. J Urol 120:695–698
4. Fass RJ (1983) In vitro activity of ciprofloxacin (Bay 09867). Antimicrob Agents Chemother 24:568–574
5. Jensen KM-E, Madsen PO (1983) Distribution of quinoline carboxylic acid derivatives in the dog prostate. Prostate 4:407–414
6. Madsen PO, Baumueller A, Hoyme U (1978) Experimental models for determination of antimicrobials in prostatic tissue, interstitial fluid and secretion. Scand J Infest Dis, Suppl 14: 145–150
7. Meares EM (1980) Prostatitis syndromes: new perspectives about old woes. J Urol 123:141–147
8. Meares EM, Stamey TA (1968) Bacteriologic localization patterns in bacterial prostatitis and urethritis. Invest Urol 5: 492–518
9. Miles Pharmaceuticals Medical Research (1982) Informational material for the investigational drug ciprofloxacin (Bay 09867). Investigator's brochure. West Haven, CT
10. Muijtjens HL, van der Ros-van de Repe J, van Veldhuizen G (1983) Comparative activities of ciprofloxacin (Bay 09867), norfloxacin, pipemidic acid, and nalidixic acid. Anitmicrob Agents Chemother 24:302–304
11. Stamey TA, Meares EM, Winningham DG (1970) Chronic bacterial prostatitis and the diffusion of drugs into prostatic fluid. J Urol 103:187–194
12. Wise R, Andrews JM, Edwards LJ (1983) In vitro activity of Bay 09867, a new quinoline derivative, compared with those of other antimicrobial agents. Antimicrob Agents Chemother 23: 559–564

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