ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1984, p. 17–19
0066-4804/84/070017-03$02.00/0

Vol. 26, No. 1

Pharmacokinetics and Tissue Penetration of Enoxacin

R. WISE,* R. LOCKLEY, J. DENT, AND M. WEBBERLY

Department of Medical Microbiology, Dudley Road Hospital, Birmingham B18 7QH, United Kingdom

Received 18 January 1984/Accepted 9 April 1984

The pharmacokinetics of the quinolone enoxacin were studied after a 600-mg oral dose was given to each of six male volunteers. The levels of the compound were measured in serum, blister fluid, and urine. Absorption was variable, with peak levels (mean, 3.7 μg/ml) being attained between 0.75 and 3.0 h (mean, 1.9 h). The serum elimination half-life was 6.2 h, and 71.6% of the drug was recovered in the urine by 48 h. Enoxacin penetrated blister fluid well, the mean percent penetration being 78.4%.

Enoxacin (CI-919, AT-2266) is a member of the quinoline carboxylic acid group of antimicrobial agents. It has been shown to have high in vitro activity against a broad spectrum of organisms such as *Enterobacteriaceae* and *Pseudomonas aeruginosa*, including many strains that are resistant to aminoglycosides and broad-spectrum β-lactams (3, 7, 9, 10; I. B. R. Duncan, M. Skulnick, and P. W. Marshall, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 23rd, Las Vegas, Nev., abstr. no. 698, 1983). In general terms, it has a degree of antibacterial activity similar to that of norfloxacin. Enoxacin is absorbed from the gastrointestinal tract, and preliminary studies show that it reaches therapeutic levels in the blood (N. Mertz, T. Chang, J. R. Latts, J. R. Goulet, and G. J. Yakatan, 23rd ICAAC, abstr. no. 858).

The purpose of this study was to investigate the pharmacokinetic properties of this compound after oral administration and to determine its penetration into chemically induced blister fluid, which has been shown to be similar in composition to the exudate of a mild inflammatory reaction (11).

MATERIALS AND METHODS

Six healthy male volunteers were studied after approval had been obtained from Dudley Road Hospital Ethical Committee and written informed consent gained. These volunteers had previously received norfloxacin (1) and ciprofloxacin (4). They were aged 23 to 42 (mean age, 29.5 years); mean weight, 77.3 kg (range, 65 to 85 kg); mean height, 177.0 cm (range, 170 to 185 cm). Their past medical history was without significant episodes, and biochemical and hematological profiles were normal; in particular, tests of liver and renal function were normal. All underwent physical examinations the week before the study and were normal. Before each volunteer went to bed on the night before the study, two 0.2% cantharides-impregnated plasters (1 by 1 cm) were applied to the anterior surface of one forearm and taped in place. The subjects fasted from 10 p.m. on this evening. At 8 a.m. on the day of the study, they were given a single 600-mg oral dose of enoxacin (three tablets of 200 mg) with 300 ml of water. Thereafter, fluid was taken ad libitum. Solid food was taken after 2 h.

Blood was drawn through an intravenous cannula kept patent with 1-ml doses of heparin (100 IU/ml) at 0, 15, 30, 45, 60, and 90 min and 2, 3, 4, 5, 6, 8, 12, and 24 h after dosing. Urine samples were collected over 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 h after administration. At approximately 72 and 96 h after administration, the first early-morning specimen of urine was collected. The two blisters were sampled with a micropipette at 0, 30, and 60 min and then hourly to 6 h and at 8 and 12 h. The integrity of the blisters was maintained by spraying with a fast-drying plastic dressing. Approximately 25-μl samples of blister fluid were used to impregnate preweighed, sterile assay disks (6 mm) which were then reweighed to accurately measure the quantity of fluid obtained.

The antibiotic assays were performed, within an hour of sample collection, by using a plate diffusion assay; the test organism was *Escherichia coli* SCH 12655 (obtained from Schering Corp., Bloomfield, N.J.). The medium used was antibiotic medium no. 1 (CM327, Oxoid, Basingstoke, U.K.), pH 6.6. Standards were prepared by using human serum for serum samples, 70% human serum for blisters, and a 0.1 M phosphate buffer (pH 6.6) for urine. The plates were incubated in air overnight. The blister fluid assay plates were incubated at 30°C, and the serum assays were incubated at 37°C. Appropriate serum and blister standards and controls were used in each plate. The 95% confidence limit for the assay was ±14.5%. The lower limit of sensitivity for the assay was 0.1 μg/ml.

Repeat hematological and biochemical profiles were performed 24 h after dosing.

Pharmacokinetic analysis was performed by analysis of individual data and routine graphical methods (5, 6). The area under the serum concentration-time curve (AUC) was calculated by the trapezoidal method from 0 to 24 h with the addition of concentration at 24 h/K_e (elimination constant) to give $AUC_{0-\infty}$. The volume of distribution was calculated as (D · f)/B, where D is the dose, f is the fraction of drug absorbed, and B is the intercept of the monoexponential declining line of the β slope with the ordinate.

RESULTS

The results of the serum and blister fluid levels obtained are shown in Table 1, excretion data are shown in Table 2, and the derived pharmacokinetic data are shown in Table 3.

The rapidity of absorption of enoxacin varied, t_{max} ranging from 0.75 to 3 h and K_a varying from 0.97 to 3.1 h^{-1}. There was less individual variation in the maximum serum level, the mean being 3.7 μg/ml (range, 2.9 to 4.3 μg/ml). The difference between the maximum mean serum concentration (Table 1) and the mean maximum serum concentration, C_{max} (Table 3), was due to the considerable individual variations seen.

The drug penetrated blister fluid somewhat slowly, the maximum blister levels being obtained at a mean time of 3.3 h; again, there was considerable individual variation (t_{max} range, 2 to 5 h). The mean percent penetration of the drug into the blister fluid (calculated from individual ratios of

* Corresponding author.

TABLE 1. Concentrations of enoxacin in serum and blister fluid

Fluid	Vol no.	μg of enoxacin per ml of fluid at time (h) after administration											
		0.25	0.5	0.75	1.0	1.5	2	3	4	5	6	8	12	24
Serum	1	<0.1	0.8	2.8	3.9	3.7	3.2	2.6	2.2	1.8	1.8	1.3	0.8	0.2
	2	<0.1	0.8	0.7	1.4	2.3	3.7	2.6	2.4	2.1	2.0	1.4	1.1	0.4
	3	<0.1	0.3	1.3	1.4	2.1	2.6	2.9	2.3	2.1	2.0	1.7	1.0	0.3
	4	<0.1	<0.1	0.1	0.1	1.2	1.6	3.3	2.6	2.3	1.6	1.6	1.4	0.3
	5	0.3	4.2	4.3	3.7	3.0	2.7	2.1	1.4	1.2	1.0	0.9	0.5	0.1
	6	0.1	2.6	3.4	3.6	3.8	3.3	2.2	2.1	1.8	1.6	1.0	0.7	0.1
	Mean	0.07	1.7	2.5	2.4	2.1	2.9	2.6	2.2	1.8	1.7	1.3	0.9	0.2
	SD	0.12	1.6	1.5	1.6	1.0	0.7	0.4	0.4	0.4	0.4	0.3	0.3	0.1
Blister	1	NT[a]	<0.1	NT	0.6	1.6	3.1	2.8	3.0	2.8	2.4	2.1	1.2	
	2	NT	<0.1	NT	0.5	0.8	1.9	3.5	3.4	2.8	2.6	2.1	1.4	
	3	NT	<0.1	NT	0.5	0.5	1.2	3.1	3.3	3.0	2.4	2.3	1.4	
	4	NT	<0.1	NT	0.4	0.5	1.2	2.2	2.3	3.1	2.6	2.3	1.6	
	5	NT	<0.1	NT	1.7	2.1	2.8	2.0	2.0	1.5	1.3	0.9	0.6	
	6	NT	<0.1	NT	0.3	0.4	0.9	1.2	2.1	1.4	1.8	1.5	1.2	
	Mean		<0.1		0.7	1.0	1.9	2.5	2.6	2.4	2.2	1.8	1.2	
	SD				0.5	0.7	0.9	0.8	0.6	0.8	0.5	0.5	0.3	

[a] NT, Not tested.

maximum blister and maximum serum levels) was 81.1% (standard deviation, 21.4%). If the percent penetration is calculated on the basis of the ratio of the individual $AUC_{0-\infty}$ blister and $AUC_{0-\infty}$ serum, then a value of 113.4% (standard deviation, 3.8%) is obtained. The maximum level of enoxacin achieved in the blister fluid exceeded 2.1 μg/ml in all volunteers. The mean blister fluid levels exceeded the mean serum levels between 3 and 12 h (and probably longer).

The mean terminal elimination half-life of enoxacin in serum was 6.2 h (range, 5.1 to 7.6 h). The elimination half-life from blister fluid was longer at 7.2 h, the results being biased by one volunteer with an elimination half-life from blister fluid of 12.0 h. If this result was ignored, the mean was similar to that in serum, namely, 6.24 h. In all individuals, the drug levels in both serum and blisters exceeded 0.5 μg/ml 12 h after administration. The mean percentage of the recovered antimicrobially active drug in urine during the collection period is shown in Table 2, with a 0- to 48-h total of 71.6%. The levels of drug found in the urine showed great individual variations but exceeded 8.0 μg/ml in all volunteers in the 24- to 48-h sample. In the early-morning specimen of urine taken at ca. 72 h, the level exceeded 0.5 μg/ml in four of the six volunteers, and at 96 h the level was below 0.1 μg/ml in all but one volunteer.

The AUCs were very similar for the serum and blister fluid data, and calculated volumes of distribution were high (ca. 100 liters). The value of these observations is uncertain in the absence of data concerning the distribution and metabolism of the drug, but they suggest that the drug is widely distributed throughout the tissues.

There were no adverse effects of the drug in any subject during this study, and the hematological and biochemical parameters did not vary significantly between the pre- and posttreatment samples.

TABLE 2. Enoxacin excretion

Serum vol no.	% of dose excreted (cumulative) at time (h) after administration				
	0–4	4–8	8–12	12–24	24–48
1	23.3	38.2	59.2	72.6	75.7
2	27.5	42.2	55.2	70.3	76.7
3	21.6	33.7	45.0	57.6	62.9
4	14.0	38.6	70.7	82.9	89.6
5	41.9	52.0	61.6	65.9	68.0
6	28.3	34.9	44.4	54.6	56.7
Mean	22.8	39.9	56.0	67.3	71.6
SD	13.6	6.6	10.1	10.4	11.6

DISCUSSION

The pharmacokinetics of enoxacin appear to accord with the limited available data. Mertz et al. (23rd ICAAC, abstr. no. 858) found the serum half-life to be between 3.1 and 7 h for oral doses of 200 to 1,600 mg and t_{max} to be between 0.5 and 3 h after dosing. They found the pharmacokinetics to be linear with dose over the range of doses tested, unlike norfloxacin (9), with which AUC and C_{max} declined relative to the dose.

Enoxacin appeared to be rapidly absorbed, the mean 1-h serum level being ca. 65% of the mean maximum serum level. There was, however, considerable individual variation, with two of the volunteers not achieving t_{max} until 3 h.

In the same group of six volunteers, C_{max} after 400 mg of norfloxacin given orally was 1.45 μg/ml (1), and after 500 mg of ciprofloxacin orally, C_{max} was 2.3 μg/ml (4). After adjusting for the lower doses of these two agents used, the mean C_{max} of enoxacin was 70% greater than norfloxacin and 34% greater than ciprofloxacin.

Studies in the same six volunteers showed that the serum half-life of enoxacin was considerably longer than that of norfloxacin (3.5 h [1]) or ciprofloxacin (3.9 h [4]). The longer serum half-life of enoxacin contributes to the greater C_{max} value for this agent. In addition, the urinary recovery of enoxacin, ca. 80%, was much greater than that of norfloxacin (30%) or ciprofloxacin (31%). Since a microbiological assay was used to measure enoxacin, it is possible that this agent was eliminated as a mixture of parent drug and microbiologically active metabolites, as is the case with norfloxacin (8). Preliminary information indicates that at least four metabolites of enoxacin are present in the urine (C. Siporin, Warner-Lambert, personal communication). Metabolism occurs in the piperazine ring to form oxo-, amino-,

TABLE 3. Pharmacokinetic parameters[a]

Vol no.	Serum						Blister fluid			
	T_{max} (h)	C_{max} (μg/ml)	$t_{1/2\beta}$ (h)	$k_{e\beta}$ (h^{-1})	$AUC_{0-\infty}$ (μg · h/ml)	k_a (h^{-1})	T_{max} (h)	C_{max} (μg/ml)	$t_{1/2\beta}$ (h^1)	$AUC_{0-\infty}$ (μg · h/ml)
1	1.0	3.9	5.1	0.14	27.8	0.43	2.0	3.1	5.6	31.5
2	2.0	3.7	7.6	0.09	33.5	0.53	3.0	3.5	7.3	39.0
3	3.0	2.9	7.4	0.09	32.0	0.38	4.0	3.3	6.8	35.7
4	3.0	3.3	6.2	0.11	32.7	0.70	5.0	3.1	6.8	36.7
5	1.5	3.8	5.6	0.12	25.6	0.23	2.0	2.8	12.0	35.3
6	0.75	4.3	5.2	0.13	20.9	0.18	4.0	2.1	4.8	19.3
Mean ± SD	1.9 ± 1.0	3.7 ± 0.5	6.2 ± 1.1	0.11 ± 0.02	28.8 ± 4.9	0.40 ± 0.19	3.3 ± 1.2	3.0 ± 0.5	7.2 ± 2.5	32.8 ± 7.1

[a] T_{max}, Time at which the maximum concentration (C_{max}) in serum or tissue fluid was achieved; $t_{1/2\beta}$, terminal elimination half-life in the serum and blister fluid; $k_{e\beta}$, overall elimination constant; $AUC_{0-\infty}$, area under the serum (blister fluid) concentration-time curve; k_a, absorption rate constant.

formyl-, and acetyl- compounds. The major metabolite would appear to be the oxo- derivative which is present in serum, according to specific high-performance liquid chromatography analysis, in approximately one-tenth the concentration of the parent compound. The other metabolites are not found in serum and only in traces in urine. The oxo-form has approximately one-tenth the microbiological activity of the parent compound.

Enoxacin penetrated well, if slowly, into the mild inflammatory exudate of the blister fluid. The mean percentage penetration, 81% (based on maximum blister and serum levels), was greater than the penetration of norfloxacin (67% [1]) or ciprofloxacin (57% [4]). The percentages of penetration, as measured by the ratios of the $AUC_{0-\infty}$, were 113% for enoxacin, 106% for norfloxacin, and 116% for ciprofloxacin.

The antibacterial activity of enoxacin has been studied against a wide range of pathogens (2, 3, 7, 10). In comparing the serum and blister fluid levels attained in this study with the in vitro activity of enoxacin, systemic (as opposed to urinary tract) infections caused by the majority of *Enterobacteriaceae*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*, requiring 90% MICs (MIC_{90}s) equal to or less than 1 μg of enoxacin per ml, might respond to treatment with an oral dose of 600 mg. *Staphylococccus aureus*, *P. aeruginosa*, *Serratia liquefaciens*, and *Providencia stuartii* are somewhat more resistant (1 μg/ml < MIC_{90} ≤4 μg/ml), and systemic infections might respond to a larger dose. *Streptococcus pneumoniae*, *Streptococcus faecalis*, and *Bacteroides* spp. require MIC_{90}s of 16 μg/ml and should probably be considered resistant unless a considerably higher dose can be employed. In the treatment of systemic infections, a twice-daily dosing frequency is suggested by this study. As urine levels in excess of 0.5 μg/ml were present for up to 72 h in the majority of volunteers after a single oral dose of 600 mg, the possibility of using a single dose in the treatment of simple cystitis could be clinically investigated.

ACKNOWLEDGMENT

We thank F. Gabbay for her advice and support.

LITERATURE CITED

1. **Adhami, Z., R. Wise, D. Weston, and B. Crump.** 1983. The pharmacokinetics and tissue penetration of norfloxacin. J. Antimicrob. Chemother. **13**:87–92.
2. **Chartrand, S. A., R. K. Scribner, A. H. Weber, D. F. Welch, and M. I. Marks.** 1983. In vitro activity of CI-919 (AT-2266) an oral antipseudomonal compound. Antimicrob. Agents Chemother. **23**:658–663.
3. **Chin, N.-X., and H. C. Neu.** 1983. In vitro activity of enoxacin, a quinolone carboxylic acid, compared with those of norfloxacin, new β-lactams, aminoglycosides, and trimethoprim. Antimicrob. Agents Chemother. **24**:754–763.
4. **Crump, B., R. Wise, and J. Dent.** 1983. Pharmacokinetics and tissue penetration of ciprofloxacin. Antimicrob. Agents Chemother. **24**:784–786.
5. **Gladtke, E., and H. M. Hattinberg.** 1979. Pharmacokinetics—an introduction, p. 58–59. Springer-Verlag, Berlin.
6. **Greenblatt, D. J., and J. Koch-Weser.** 1975. Clinical pharmacokinetics. N. Engl. J. Med. **297**:702–705.
7. **Nakamura, S., A. Mimami, H. Katae, S. Inoue, J. Yamagishi, Y. Takase, and M. Shimizu.** 1983. In vitro antibacterial properties of AT-2266, a new pyridonecarboxylic acid. Antimicrob. Agents Chemother. **23**:641–648.
8. **Osaki, T., H. Uchida, and T. Irikura.** 1981. Studies on metabolism of AM-715 in humans by high performance liquid chromatography. Chemotherapy (Japan) **24**(Suppl.4):128–135.
9. **Swanson, B. N., V. K. Boppana, P. H. Vlasses, H. H. Rotmensch, and R. K. Ferguson.** 1983. Norfloxacin disposition after sequentially increasing oral doses. Antimicrob. Agents Chemother. **23**:284–288.
10. **Wise, R., J. M. Andrews, and G. Danks.** 1983. In vitro activity of enoxacin (CI-919), a new quinoline derivative, compared with that of other antimicrobial agents. J. Antimicrob. Chemother. **13**:237–244.
11. **Wise, R., A. P. Gillett, B. Cadge, S. R. Durham, and S. Baker.** 1980. The influence of protein binding upon tissue fluid levels of six β-lactam antibiotics. J. Infect. Dis. **142**:77–82.