Fleroxacin Pharmacokinetics in Aqueous and Vitreous Humors Determined by Using Complete Concentration-Time Data from Individual Rabbits

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Although composite data from separate subjects can be used to generate single-subject estimates, intersubject variation precludes rigorous ocular pharmacokinetic analysis. Therefore, a rabbit model in which sequential aqueous and vitreous humor samples were obtained following the administration of the quinolone fleroxacin was developed. Mean data from individual animals were used for pharmacokinetic analysis. Following direct intravitreal or systemic drug administration, sequential paracenteses did not alter pharmacokinetic constants or ocular penetration and were not associated with an increase in ocular protein; contamination of vitreous humor with blood was minimal (<0.1%). Following direct injection or intravenous administration, vitreous humor concentration-time data were best described by one- and two-compartment models, respectively. The maximum concentration and the penetration into the aqueous and vitreous humors were 1.54 and 0.5 μg/ml and 27 and 10%, respectively. Elimination rates from aqueous and vitreous humors and serum were similar following parenteral drug administration. Drug elimination following direct injection was rapid, and the elimination rate from the vitreous humor was not prolonged by the coadministration of probenecid. Our animal model provides a new approach to the rigorous examination of the ocular pharmacokinetics of quinolone antimicrobial agents in the eye.

Bacterial endophthalmitis is a severe and often blinding infection which occurs when the inner eye is seeded with microorganisms. The intraocular delivery and maintenance of therapeutic levels of antimicrobial agents into the eye, particularly the vitreous humor, continue to be vexing problems. Although intraocular drug administration in conjunction with vitrectomy preserves sight in many patients (3, 10, 11, 25, 29), this therapy is not successful in all patients. Intraocular drug administration can cause retinal damage (9, 27). Therefore, alternate or adjunct therapeutic modalities have been sought.

A major impediment to the development and assessment of improved drugs, delivery systems, and new approaches to therapy has been the imprecision with which intraocular pharmacokinetics are studied. Previous studies examining ocular pharmacokinetics have pooled data from different subjects to generate single-subject estimates. Unfortunately, when this approach is used to study pharmacokinetics in humans, it consistently yields inaccurate and imprecise estimates because of inter- and intrasubject variations (33).

Since pharmacokinetic data have fundamental implications for clinical trials, we developed a rabbit model in which sequential vitreous humor samples were obtained from individual subjects. Kinetic constants from each animal were then combined to generate population data (2, 21, 23, 26). Ocular and serum pharmacokinetics were compared. In these studies we examined the ocular pharmacokinetics of the quinolone fleroxacin. While there is limited information, fluoroquinolone penetration into the aqueous and vitreous humors ranges from 10 to 80% of that in the serum (4, 14, 15,

17, 31). This suggests that systemic fluoroquinolone administration might provide an effective and safer adjunctive or alternative therapy to the routine use of repetitive intraocular antibiotic injections.

(This study was presented in part at the Third International Symposium on New Quinolones, Vancouver, Canada, July 1990.)

MATERIALS AND METHODS

Animal model. Adult male New Zealand White rabbits (Hare Maryland Farms, Hewitt, N.J.) weighing 2.3 to 3.0 kg were used. Prior to experimental use, antibiotic-free feed (Lab Rabbit Chow HF5326; Purina Mills Inc.) and water were provided ad libitum. The rabbits were divided into four groups: the first two groups were used to examine the effects of multiple paracenteses on pharmacokinetic parameters, erythrocyte number, and protein content; subsequent groups were used to examine the kinetics of fleroxacin in the serum and aqueous and vitreous humors after intravenous or direct injection.

The animals were anesthetized with an intramuscular dose of ketamine hydrochloride (35 mg/kg of body weight) and xylazine hydrochloride (2.5 mg/kg) approximately 45 min prior to antibiotic administration. Anesthesia with supplemental intravenous ketamine, as needed, was maintained in the animals throughout the sampling period. A 24-gauge angiocatheter was inserted into a marginal ear vein to facilitate antibiotic administration, and a second catheter was inserted into the central artery of the contralateral ear to obtain serum samples.

Fleroxacin, which was obtained from Roche Laboratories, Nutley, N.J., was dissolved with 1 N sodium hydroxide; the

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final solution was titrated to pH 8.6 with 1 N HCl. Prior to intravenous or intraocular administration, fleroxacin was reconstituted with sterile 0.9% NaCl or with balanced salt solution, respectively. A bolus intravenous infusion (10 mg/kg) was administered. Following intravenous administration, each animal received a 2-ml flush of 0.9% NaCl. For intraocular injection, following dilation with 1% atropine ophthalmic solution, under direct observation the needle tip was placed bevel up into the center of the vitreous cavity and 100 μg of fleroxacin in 10 μl was injected. Probenecid (20 mg/kg) was given intravenously over 5 min 2 h prior to the first ocular sample and every hour thereafter.

Sampling technique. Examination with a bilateral slit lamp was performed prior to antibiotic administration and again following each paracentesis. This was done to assess the eye for signs of inflammation and any changes in the depth or clarity of the anterior chamber or lens. All aqueous and vitreous humor samples were obtained by using aseptic technique. Care was taken to avoid tear fluid during sampling.

For aqueous samples, the experimental eye was exposed with a sterile lid speculum and fixated with forceps. Prior to aqueous paracentesis, 1 drop of 0.5% tetracaine hydrochloride was administered to the experimental eye, and then a tetracaine-soaked pledget was applied to the conjunctiva prior to fixation with forceps. Samples were obtained from the aqueous humor by using a sterile 30-gauge needle fused to a calibrated 20-μl capillary tube. This needle was gently inserted into the anterior chamber, and approximately 7 μl of aqueous humor was removed by the combined forces of positive intraocular pressure and capillary action. The paracentesis site was then examined with the slit lamp to ensure that the tract had sealed without leakage of aqueous humor.

For vitreous humor samples, the experimental eye was dilated with 1% atropine sulfate. The eye was fixated with forceps. A 28-gauge tuberculin needle was carefully inserted 4 mm from the limbus under direct visualization into the center of the vitreous cavity. Care was taken to avoid the lens. Sequential 20-μl vitreous humor samples were serially collected at times corresponding to the samples in the blood and aqueous humors. From a separate group of animals, we obtained sequential samples of vitreous humor for cell counts and protein determination. Erythrocytes were counted with a Spencer hemacytometer and protein concentration was measured by using the microtiter modification of the Lowry technique (bicinchoninic acid; Bio-Rad) with bovine serum albumin used as a standard.

Following the designated sampling periods (see figures), animals were sacrificed by administration of pentobarbital sodium (125 mg/kg) intravenously followed by bilateral pneumothoraces.

Antibiotic level assays. To determine fleroxacin levels in the serum and the aqueous and vitreous humors, a one-dimensional vertical diffusion microbiological assay was performed. Prior to analysis all samples were stored at 4°C. Serum and aqueous and vitreous humor samples were processed on the same day on which they were obtained. The one-dimensional assay is a modification of that described by Edberg and Sabath (13) that was adjusted to accommodate small samples. Blood samples were allowed to clot and were immediately centrifuged (Sorval GLC2B; Dupont, Newtown, Conn.) at 1,500 rpm for 15 min. An inoculum of 10^6 organisms per ml that was diluted 1:10 in molten nutrient broth (Difco) and that was adjusted to pH 8.0 with 1 N NaOH with 1% agar was poured into Wintrobe tubes (115 by 3 mm; Meteor, Vineland, N.J.) and allowed to harden. The

test organism was an *acrA* mutant of *Escherichia coli* (7). Alkaline pH and the use of mutants with alterations in the outer bacterial membrane increased the sensitivity of the biological assay (18). Five-microliter aliquots of serum or aqueous or vitreous humor were then pipetted onto the surface of the agar and incubated overnight at 37°C in an ambient air incubator. Zones of inhibition were read by using a magnifying eyepiece calibrated to 0.1 mm. Ten standards were prepared in rabbit serum ranging from 50 to 0.05 μg/ml. Regression curves for standards prepared in aqueous and vitreous humors were compared with those for standards prepared in serum, and the concentrations found in ocular compartments were adjusted accordingly. The coefficient of variation from day to day was 9.8%.

Pharmacokinetic analysis. Pharmacokinetic analyses of plasma and aqueous and vitreous humor concentration-time data following systemic administration and direct ocular administration were performed by using an iterative, nonlinear, least-squares regression program, RSTRIP (Micromath Scientific Software, Salt Lake City, Utah). The most appropriate pharmacokinetic models were determined by using the coefficient of determination and the RSTRIP model selection criterion, which is a modified form of the Akaike (1) information criterion. Estimations for each exponential coefficient and time constants were computed with the standard deviations of each estimate, along with its 95% confidence range, which was calculated by using both univariate and support plane approximations for the bounds of the 95% confidence range. On the basis of the coefficient of determination and model selection criterion, aqueous and vitreous humor and serum antibiotic concentration-time data following intravenous administration were best fitted to a two-compartment model. Concentration-time data following direct injection into the vitreous body were best fitted to the monoexponential equation describing a one-compartment model. Other standard pharmacokinetic parameters were determined by using computer-generated primary coefficients and standard pharmacokinetic equations (15). Observed concentrations in serum and aqueous humor were used to determine maximum concentrations, times to reach maximum concentrations, and area under the concentration-time curves (AUCs).

Statistical analysis. Overall differences in pharmacokinetic parameters among rabbits were evaluated by analysis of variance. All statistical tests were performed by using the PC version of MINITAB (W. W. Norton, New York, N.Y.). The mean and standard deviation of each pharmacokinetic variable among all rabbits in a group were also calculated. In all tests the level of significance was fixed at 0.05. An analysis of variance test was conducted. The P values, when computed, were compared against the specified level of significance of 0.05. Decision on significance or nonsignificance was therefore dependent on the value of P in relation to the specified level of significance of 0.05. In the event that a test was found to be statistically significant, Tukey's test was used to detect the means that were significantly different.

RESULTS

Characterization of the animal model. Mean antibiotic concentrations within ocular compartments such as the anterior chamber and vitreous humor cavity are proportional to the AUC. In order to show that multiple paracenteses did not alter ocular pharmacokinetics, we examined the effects of serial sampling on both kinetic constants and percent
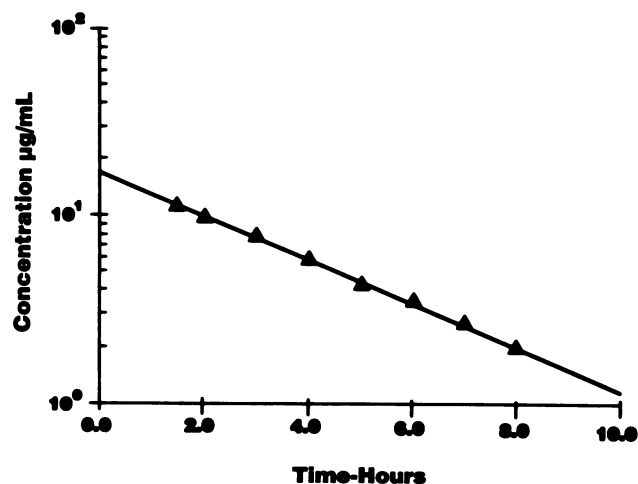
FIG. 1. Vitreous humor pharmacokinetics following direct injection into the center of the vitreous humor bodies of five rabbits. Following direct injection of fleroxacin, vitreous humor samples were obtained at 15- to 30-min intervals over an 8-h period by sequential aspiration with a 28-gauge needle.

FIG. 2. Comparison of the mean concentration-time data for 10 animals given fleroxacin intravenously. In one eye, serial vitreal paracenteses were performed in all subjects (solid line, open circles); in the contralateral eye a single (virgin) paracentesis was performed corresponding to each sample time (broken line, closed circles). Serum pharmacokinetic curves were constructed by using mean data for all animals (solid line, closed squares) or single concentrations in serum corresponding to individual animals from which virgin eye samples were obtained (broken line, closed triangles).

penetration. Initial studies examined the effect of paracenteses on drug elimination following direct and systemic drug administration; percent penetration was determined following systemic administration. We also measured the effect of serial paracenteses on cell count and protein concentration.

Vitreous humor kinetics following direct drug administration into the center of the vitreous humor body in five animals were studied to determine whether an increase in the number of paracenteses altered the rate of drug elimination. Since the rationale behind these experiments was that if serial paracenteses caused an alteration in the kinetics of elimination, then the slope which describes the first-order elimination rate would vary as a function of aspiration number. As shown in Fig. 1, the concentration-time data over 8 h plotted semilogarithmically was linear with a correlation coefficient of 0.9991. On the bases of the model selection criteria and the coefficients of determination, elimination from the vitreous humor following direct injection was best fitted to a one-compartment model. There was no alteration in slope as the number of paracenteses increased, indicating that multiple vitreous humor aspirations did not alter the rate of drug elimination. This observation was significant at the 0.01 level. The initial equilibration time (diffusion from the center of the vitreous humor to the retinal surfaces) was 1.5 h (data not shown). Studies by others (12, 24) using data pooled from different subjects to measure antibiotic elimination from the vitreous body following direct injection also are best described by a one-compartment model.

To show that multiple paracenteses did not affect the percent penetration into the vitreous humor, we next examined drug concentrations following systemic administration. The mean concentration-time data for 10 animals given fleroxacin intravenously are shown in Fig. 2. In one eye, serial vitreal humor paracenteses were performed in all subjects; in the contralateral eye a single paracentesis in different subjects corresponding to each sample time was performed. We refer to the single vitreous humor samples in different animals as virgin eye points. Virgin samples were pooled to generate a single-subject estimate describing population parameters by using the naive pooled data approach
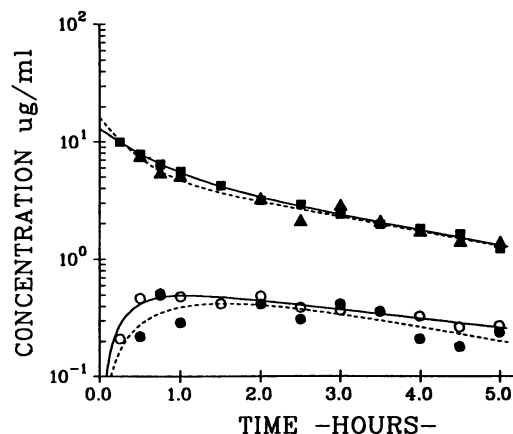
(33). These data are plotted semilogarithmically. The percent penetration based on the $AUC_{aqueous}/AUC_{serum}$ (mean drug concentration in aqueous humor/mean drug concentration in serum) following multiple paracenteses was compared with that for virgin eye points. In the latter calculations we compared the virgin pooled $AUC_{aqueous}$ data with the virgin pooled AUC_{serum} data to control for the intersubject variability inherent to this form of data analysis. The percent penetration for virgin eyes (8.7%) was similar to that for serially sampled eyes (9.8%). These data were significant at the 0.05 level and indicate that multiple paracenteses do not alter penetration into the vitreous humor. Moreover, despite the intersubject variation inherent in the pooled data method (33), the shapes and terminal elimination rates of the vitreous concentration-time curves are similar when virgin and sequentially sampled data are used. This supports the results of the direct injection studies showing that serial paracenteses did not alter kinetic constants.

While alterations in ocular physiology associated with serial paracenteses are important to a kinetic model only insofar as they alter pharmacokinetic parameters or percent penetration (neither occurred), we measured the effects of serial paracenteses on protein concentrations within the vitreous humor as a function of aspiration number. Protein concentration was taken as an indirect measurement of the putative effects on the blood-ocular barrier. To prevent the extravasation of lens protein, we attempted to avoid lens trauma; however, lens damage was observed in two eyes. In one instance, lens trauma occurred at the initial paracentesis and in another it occurred at the paracentesis at 4 h. Six eyes underwent serial paracenteses at the eight time points from 0.25 to 5 h (i.e., 48 samples were compared). In the two eyes with lens trauma, the mean protein content following trauma was 2,365 ± 1,566 mg%, whereas, excluding these eyes, the mean protein content was 205 ± 33 mg% (n = 36). The mean protein content in the initial samples was 104 ± 125 mg%, which did not differ from that in non-lens-traumatized,
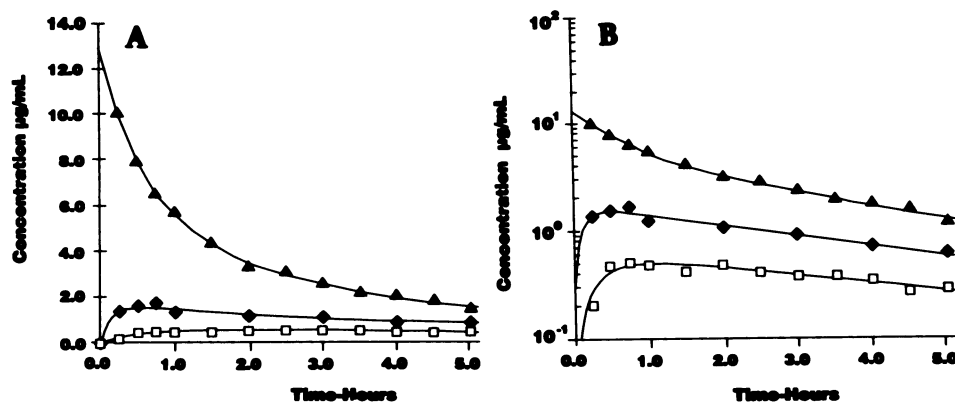
FIG. 3. Mean concentrations of fleroxacin in serum (triangles), aqueous humor (diamonds), and vitreous humor (squares) following intravenous administration. (A) Arithmetic depiction of fleroxacin concentration versus time in samples from 10 rabbits. (B) Data from panel A presented semilogarithmically.

sequentially sampled eyes. These data are significant at the 0.05 level.

To ensure that serial sampling was not associated with gross contamination with blood, we also measured erythrocyte counts in six eyes in animals with serial paracenteses. A grossly bloody tap was associated with >2,500 erythrocytes per mm³, corresponding to a blood/vitreous contamination factor of <0.1%. Only 5% of vitreous humor aspirates had >2,500 erythrocytes per mm³. The mean was 840 ± 414 erythrocytes per mm³.

Pharmacokinetics following intravenous administration. We next compared the pharmacokinetics of fleroxacin in serum and aqueous and vitreous humors using sequential data derived from 10 animals. Figures 3A and B show the mean levels in serum and aqueous and vitreous humors of animals given intravenous fleroxacin. These data are plotted arithmetically (Fig. 3A) to better visualize the relative penetrations of both drugs. Figure 3B shows, on a semilogarithmic plot, the data from Fig. 3A to permit a graphic comparison of the relationship between serum and aqueous terminal elimination rates. Observed and model-derived data points are given in Table 1, and derived kinetic parameters are given in Table 2. On the bases of model selection criteria and the coefficients of determination, the serum and aqueous and vitreous humor data were best fitted to a two-compartment

open model. The mean beta elimination in the serum was 0.296 ± 0.029, that in the aqueous humor was 0.216 ± 0.034, and that in the vitreous humor was 0.181 ± 0.037. Fleroxacin had a beta elimination half-life in serum of 2.34 h; the corresponding beta elimination half-lives in the aqueous and vitreous humors were 3.20 and 3.88 h, respectively. These values were not statistically different from one another. The mean maximum concentrations in the serum and aqueous and vitreous humors were 10.0, 1.69, and 0.51 μg/ml, respectively.

Pharmacokinetics following direct injection. To compare the rate of drug elimination following direct injection with that following systemic administration, we compared elimination rates following both routes. The pooled t test was used to compare these values. As noted above, elimination from the vitreous humor following direct injection was best fitted to a one-compartment model. Figure 4 shows elimination from the vitreous humor following both routes of elimination. The elimination rate constant and terminal half-life following direct injection were 0.250 ± 0.005 and 2.673 h⁻¹, respectively.

The rapid drug elimination following direct administration is particularly important, since, for other antimicrobial compounds, intravitreal administration is considered the primary route of drug administration (3, 21). Therefore, to determine

TABLE 1. Fleroxacin levels in serum and aqueous and vitreous humors following systemic administration

Time (h)	Fleroxacin level (μg/ml) in:					
	Serum		Aqueous humor		Vitreous humor	
	Measured	Predicted	Measured	Predicted	Measured	Predicted
0.00			0.00	−0.002	0.00 ± 0.17	0.000
0.25	10.04 ± 1.21	9.98	1.37 ± 0.64	1.387	0.21 ± 0.27	0.281
0.50	7.88 ± 1.44	7.91	1.54 ± 0.61	1.544	0.46 ± 0.21	0.415
0.75	6.41 ± 1.25	6.49	1.69 ± 0.75	1.501	0.51 ± 0.21	0.474
1.00	5.61 ± 0.35	5.48	1.26 ± 0.51	1.429	0.48 ± 0.12	0.493
1.50	4.24 ± 0.94	4.19			0.42 ± 0.12	0.482
2.00	3.20 ± 0.72	3.40	1.10 ± 0.40	1.152	0.90 ± 0.01	0.449
2.50	2.95 ± 0.77	2.84			0.39 ± 0.12	0.412
3.00	2.43 ± 0.38	2.41	0.95 ± 0.24	0.928	0.37 ± 0.10	0.377
3.50	1.99 ± 0.23	2.07			0.36 ± 0.08	0.345
4.00	1.82 ± 0.36	1.78	0.73 ± 0.24	0.747	0.32 ± 0.12	0.315
4.50	1.63 ± 0.38	1.53			0.26 ± 0.09	0.232
5.00	1.23 ± 0.35	1.32	0.63 ± 0.24	0.602	0.27 ± 0.09	0.008

TABLE 2. Kinetic parameters of fleroxacin following intravenous administration[a]

Sample	β	$t_{1/2\beta}$ (h)	k_{el} (h^{-1})	AUC (mg · h/liter)	% Penetration	C_{max} (μg/ml)	T_{max} (h)	k_{12} (h^{-1})	k_{21} (h^{-1})
Serum	0.296	2.340	0.554	23.548	NA[b]	13.05	0	0.59	0.97
Aqueous humor	0.216	3.207	NA	7.964	27.109	1.54	0.503	NA	NA
Vitreous humor	0.181	3.878	NA	3.363	9.875	0.50	1.091	NA	NA

[a] β, elimination; $t_{1/2\beta}$, half-life at β phase; k_{el}, elimination rate constant; AUC, area under the drug concentration time curve; C_{max}, maximum concentration of drug in serum; T_{max}, time to maximum concentration of drug in serum.

[b] NA, not applicable; the constant could not be analyzed for the specific parameter indicated.

whether we could prolong the therapeutic effect of fleroxacin in the vitreous humor, we examined the effects of probenecid on quinolone elimination from the vitreous body. Probenecid is a benzoic acid derivative that inhibits the transport of organic acids across various epithelial barriers (e.g., renal tubular secretion, transport from the subarachnoid space into plasma, and biliary secretion). Systemic probenecid administration prolongs the half-life of β-lactam antibiotics in the vitreous humor because of a putative action on the retinal transport pump (6). Since the renal tubular secretion of fleroxacin in rabbits is markedly inhibited by probenecid (34), we examined the effect of systemically administered probenecid on fleroxacin elimination. Fleroxacin was injected directly into the vitreous humor. As shown in Fig. 5, probenecid at 20 mg/kg, a dose that prolongs the renal elimination of fleroxacin (34) and the vitreal elimination of β-lactams (5), had no effect on the rate of fleroxacin elimination from the vitreous humor.

DISCUSSION

An understanding of ocular pharmacokinetics is important in optimizing the therapy of bacterial endophthalmitis. Effective treatment of endophthalmitis requires that therapeutic antimicrobial levels be achieved and maintained within the vitreous humor cavity. Most studies simply describe drug penetration in the eye to determine whether therapeutic concentrations are achieved. While composite data from different subjects are occasionally pooled (11, 21, 23, 36), this approach to pharmacokinetic analysis is limited because of intersubject variation (33). Penetration of many antibiotics is marginal following systemic drug administra-

tion. We modified our anterior chamber model (24) to permit the analysis of complete concentration-time data in the vitreous humor. We studied a quinolone antimicrobial agent since quinolones penetrate into ocular tissue better than many other drugs (4, 14) and have excellent activity against ocular pathogens (19, 20). The quinolone fleroxacin is slightly less active than ciprofloxacin but has a longer half-life in humans (12). Preliminary studies suggest that quinolones, in combination with other antimicrobial agents, can be successfully incorporated into the therapy of bacterial endophthalmitis (22, 31).

Drug concentrations were measured by a microbiological assay modified to accommodate 5-μl samples rather than by high-pressure liquid chromatography (HPLC). The biological assay and HPLC are equivalent in sensitivity (0.01 μg/ml), but the latter requires 500 μl of fluid. As a result, the biological assay was used in these studies since, considering sample size constraints, it is two orders of magnitude more sensitive than HPLC. Both assays are equivalent despite the fact that one fleroxacin metabolite is biologically active (16).

Traumatic paracenteses which aspirate the entire anterior chamber volume may compromise the integrity of the blood-ocular barrier and thereby increase the penetration of drugs (30). Therefore, in order to develop an in vivo ocular pharmacokinetic model that permitted repeated vitreous humor paracenteses from the same animal but that did not
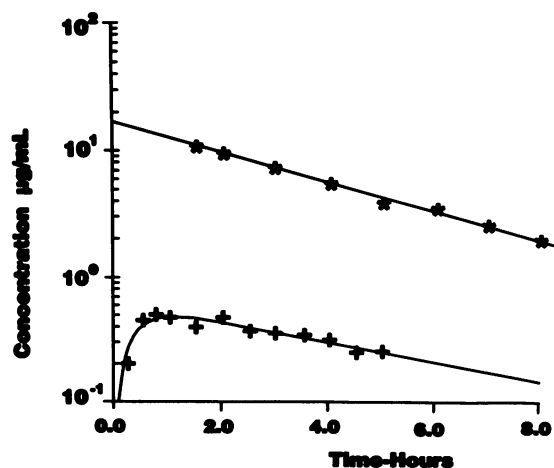

FIG. 4. Semilogarithmic plot showing fleroxacin concentrations in the vitreous humor following direct (asterisks, 5 animals) and systemic (pluses, 10 animals) administration.
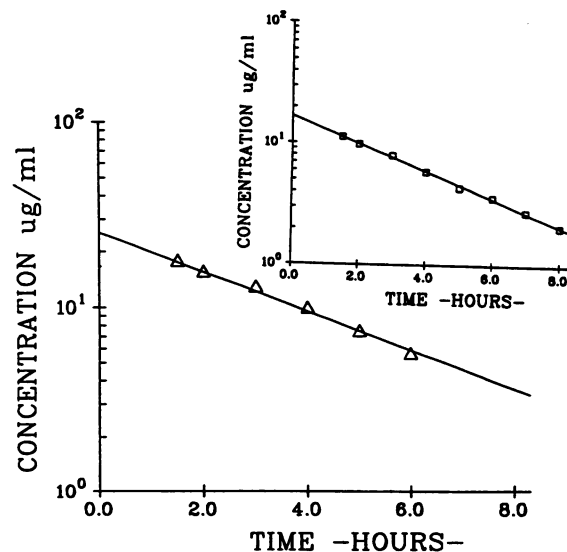

FIG. 5. Semilogarithmic plot showing fleroxacin concentrations in the vitreous humor following direct injection into the vitreous humors of five animals. These animals were also given probenecid (20 mg/kg) intravenously beginning 2 h prior to the administration of fleroxacin. The inset shows data for five animals given fleroxacin in the absence of systemically administered probenecid.

alter drug kinetics, we obtained small samples of aqueous and vitreous humors. The result was a relatively atraumatic sampling. To determine whether multiple vitreous humor paracenteses altered the rate of drug elimination, we examined the terminal elimination rates following direct injection of fleroxacin into the center of the vitreous body and that following systemic drug administration. Following systemic drug administration, serum and aqueous and vitreous humor terminal elimination rates were parallel (Fig. 3B), despite the fact that there were progressively more paracenteses over time. If serial paracenteses had caused an alteration in the blood-vitreous humor barrier, then vitreous humor fleroxacin levels would approach that in the aqueous humor and, eventually, that in the serum. These data indicate that serial paracenteses have no effect on the rate of fleroxacin elimination from the vitreous humor following administration by either route. We have previously described and validated (24) an anterior chamber pharmacokinetic model using constants derived from complete aqueous humor and serum concentration-time data.

To establish that serial paracenteses did not affect the blood-ocular barrier and, hence, the penetration of drug into the vitreous humor from the serum, the percent penetration data from single virgin vitreous humor concentration-time points was compared with those from subjects undergoing multiple serial vitreous humor aspirations. While the data describing the sequentially obtained virgin eye concentrations in different animals are less reliable than those in serially sampled animals because of interanimal variation, the degree of penetration was nevertheless found to be virtually identical in both groups. While there was a slight increase in vitreous humor protein content and a minimal amount of bleeding into the vitreous body, neither altered the pharmacokinetic behavior or the validity of our model. However, since gross bleeding (>2,500 erythrocytes) may be associated with increased drug penetration (unpublished data), these samples were excluded from analysis.

In subsequent studies we examined the pharmacokinetics of fleroxacin following intravenous and direct injection into the vitreous body. These studies were performed to further confirm the validity of our animal model and to show the utility of standard kinetic models by using population data in describing ocular pharmacokinetics in the vitreous and aqueous humors. The kinetics of fleroxacin following intravenous administration in the serum and aqueous and vitreous humors was described by a two-compartment open model in which absorption, distribution, and elimination followed first-order kinetics. Despite the expected differences in the concentrations of drug in the serum of individual animals, the interanimal kinetic coefficients were remarkably similar. As seen with other antimicrobial (24) and antifungal (36) compounds, drug elimination rates from the aqueous humor were similar to those from the serum. Pharmacokinetic data following direct injection into the vitreous body was described by a one-compartment model in which the rate of drug elimination followed first-order kinetics. Using composite pooled data, other investigators have also suggested that drug elimination from the vitreous body after direct administration follows first-order kinetics (8, 35). The half-life of elimination for fleroxacin following direct injection was more rapid than that following systemic administration. However, the rate of elimination from the vitreous humor following both routes was extraordinarily rapid relative to that for other antimicrobial agents (28) and was not shortened by the coadministration of probenecid. In rabbits, the elimination of fleroxacin is more rapid than that in humans

because of the increased metabolism and active tubular secretion which is blocked by probenecid (20, 34). Rapid entry and elimination of fleroxacin in the vitreous humor indicates that elimination occurs through the retina (23).

While these experiments were performed in uninfected animals, they provide the basis for studies examining the association between ocular pharmacokinetics and efficacy in infected animals. Importantly, even in noninflamed eyes, fleroxacin concentrations in the aqueous and vitreous humors following a single intravenous dose were in excess of the MICs for many ocular pathogens. Inflammation and the achievement of a steady state in serum both appear to increase drug penetration into the vitreous humor (23). New investigational quinolones have excellent activity against the gram-positive pathogens (19, 26, 32, 35) that are most commonly isolated in bacterial endophthalmitis (11, 25, 29). These observations, in conjunction with results of our pharmacokinetic studies, suggest that the fluoroquinolone antimicrobial agents may have a role in the prophylaxis and therapy of bacterial endophthalmitis. Results of our studies also provide a basis for examining the relationship between the structure-activity relationships and/or the physicochemical properties of drugs and ocular pharmacokinetics.

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