

Ocular Kinetics of Pefloxacin after Intramuscular Administration in Albino and Pigmented Rabbits

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We determined the ocular kinetics of pefloxacin, a new fluoroquinolone, when administered by the intramuscular route to albino and pigmented rabbits. In serum of albino rabbits, the area under the concentration-time curve (AUC) for the experimental period was $31.4 \pm 1.07 \mu\text{g} \cdot \text{h/ml}$ (mean \pm standard deviation); the AUCs in the aqueous and vitreous humors were high (10.5 ± 1.90 and $12.4 \pm 3.79 \mu\text{g} \cdot \text{h/ml}$, respectively). Pefloxacin was found in the avascular ocular tissues ($30.15 \pm 3.79 \mu\text{g} \cdot \text{h/ml}$ in the cornea and $6.98 \pm 1.06 \mu\text{g} \cdot \text{h/ml}$ in the lens). In the vascularized tissues, the penetration ratio, defined as tissue AUC/serum AUC, was more than 1. The good intraocular diffusion of pefloxacin might be related to its low molecular weight and to its strong lipophilicity and could explain its clinical efficacy in the treatment of endophthalmitis. In pigmented rabbits, pefloxacin levels were high in the iris ($1525 \pm 328 \mu\text{g} \cdot \text{h/ml}$, versus $40.2 \pm 5.08 \mu\text{g} \cdot \text{h/ml}$ in albino rabbits) and chorioretina ($2600 \pm 422 \mu\text{g} \cdot \text{h/ml}$, versus $48.3 \pm 7.52 \mu\text{g} \cdot \text{h/ml}$ in albino rabbits), suggesting that it binds to the pigmentary apparatus.

Eye infections are rare but generally serious, often leading to the loss of vision since numerous ocular tissues consist of thin membranes which are rapidly destroyed by microorganisms.

When administered systemically, most antibiotics show poor ocular penetration, especially in the vitreous humor, since they must cross the blood-ocular barriers to reach the aqueous humor and retina before diffusing passively into the vitreous humor (8).

Pefloxacin [1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-methyl-1-piperazinyl)-quinoline-3-carboxylic acid] is a new fluoroquinolone. It has been shown to have exceptionally good diffusion in tissues (10). After systemic administration, it has been found in the aqueous humor and lenses of patients undergoing cataract extraction (6, 9, 13).

The purpose of this study was to assess the kinetics of pefloxacin in the different structures of the rabbit eye when administered by the intramuscular route. Albino and pigmented rabbits were used to determine the role of the pigmentary apparatus.

MATERIALS AND METHODS

Pharmacokinetic studies. Twenty-eight rabbits, each weighing approximately 2.5 kg, were used.

Fourteen albino rabbits (New Zealand White) and 14 pigmented rabbits (Fauve de Bourgogne) were given a single intramuscular injection of 50 mg of pefloxacin (Roger-Bellon Laboratories, Paris, France) per kg of body weight.

Blood samples were obtained prior to sacrifice by femoral artery puncture. The animals were killed with sodium pentobarbital 1, 2, 3, 5, 7, 9, or 11 h after antibiotic administration.

Aqueous and vitreous samples were aspirated by puncture with a 23-gauge needle mounted on a tuberculin syringe. The eyes were removed and cleaned of conjunctival tissue and blood to avoid contamination by blood. They were immedi-

ately stored at -80°C in order to minimize diffusion of the antibiotic (1).

Assay. Pefloxacin (mesylate dihydrate), norfloxacin (4803 P), and internal standard (4662 P) were obtained from Roger-Bellon Laboratories and were used to prepare the standard solutions. All reagents were obtained from Merck (Darmstadt, Germany). Pefloxacin and norfloxacin concentrations in serum and in aqueous and vitreous humors and the supernatants of ocular tissue homogenates were assayed by means of high-performance liquid chromatography (HPLC) with UV detection (12).

Pefloxacin and its main metabolite, *N*-desmethyl pefloxacin (norfloxacin), were assayed simultaneously. Separations were performed on a reversed-phase column (100 by 4.6 mm) (Nucleosil C8 3 μ ; SFCC, Neuilly-Plaisance, France). The mobile phase (pH 4.8) was prepared by mixing 260 ml of acetonitrile, 2 g of sodium acetate trihydrate, 2 g of citric acid monohydrate, 4 ml of triethylamine, 2 ml of formic acid, and 740 ml of water. All HPLC assays were carried out at room temperature with a 1-ml/min flow rate (116B model delivery system; Beckman).

Frozen eyes were dissected, and the ocular tissues were isolated (cornea, iris, lens, chorioretina, and sclera). After addition of 3 ml of 0.05 M sodium phosphate-citrate buffer (pH 5.8) and internal standard, each tissue was homogenized with an Ultra-Turrax mixer. After centrifugation, the whole supernatant was removed for assay. A one-step liquid-liquid extraction was performed with 7 ml of chloroform. After agitation and centrifugation at $1,000 \times g$ for 10 min, the lower organic phase was evaporated to dryness under nitrogen at 37°C . The dry residue was diluted in 100 μl of the mobile phase. An aliquot (5 to 20 μl) was injected into the chromatograph by using a Wisp 710B automatic injector (Waters). UV absorbance was monitored at 280 nm.

Peak surface measurements were used to establish calibration curves. Under these conditions, the retention times of pefloxacin, norfloxacin, and the internal standard were 1.89, 2.19, and 2.95 min, respectively. The lowest detection limit (concentration of antibiotic resulting in a signal-to-noise

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TABLE 1. Kinetics of pefloxacin in rabbit^a

| Tissue or fluid ^b | Mean AUC \pm SD ($\mu\text{g} \cdot \text{h}/\text{ml}$) | | Tissue AUC/serum AUC | | $t_{1/2}$ (h) ^c | |
|------------------------------|--|------------------|----------------------|-----------|----------------------------|-----------|
| | Albino | Pigmented | Albino | Pigmented | Albino | Pigmented |
| Serum | 31.4 \pm 1.07 | 29.9 \pm 1.54 | 1 | 1 | 2.01 | 2.61* |
| Aq. humor | 10.5 \pm 1.90 | 7.31* \pm 0.76 | 0.33 | 0.24* | 2.79 | 5.40* |
| Vitreous | 12.4 \pm 1.41 | 13.5 \pm 2.76 | 0.39 | 0.45 | 3.38 | 6.16* |
| Cornea | 30.1 \pm 3.79 | 24.5* \pm 4.44 | 0.96 | 0.82* | 2.96 | — |
| Lens | 6.98 \pm 1.06 | 7.32 \pm 0.70 | 0.26 | 0.24 | — | — |
| Iris | 40.2 \pm 5.08 | 1,525* \pm 327 | 1.28 | 51* | 2.06 | — |
| Ch. retina | 48.3 \pm 7.52 | 2,600* \pm 422 | 1.54 | 87* | 3.06 | — |
| Sclera | 84.1 \pm 31.9 | 207* \pm 17.2 | 2.68 | 6.94* | 4.01 | — |

^a Mean AUC was determined through the course of the experiment (11 h), and the tissue AUC/serum AUC ratio and half-life ($t_{1/2}$) in ocular tissues and humors in albino and pigmented rabbits were determined from 1 to 11 h after a single intramuscular injection of 50 mg of pefloxacin per kg. Asterisks indicate a statistically significant difference between albino and pigmented rabbits ($P < 0.05$).

^b Aq. humor, aqueous humor; vitreous, vitreous humor; ch. retina, chorioretina.

^c —, $t_{1/2}$ was too long to be evaluated during the course of the experiment (slope = 0).

ratio of 4) was 5 ng for pefloxacin and norfloxacin. Previous calibration curves of concentrations in tissue and serum showed no difference in slope or intercept and exhibited no difference due to tissue determination in yield and background. Therefore, serum standards were used routinely for the measurement of pefloxacin in ocular tissues. The assay precision was 4.8%. The intraday coefficient of variation was 2.8% for the pefloxacin high control (2,000 ng) and 6.8% for the pefloxacin low control (50 ng).

With regard to the limits of the method, when frozen eyes were dissected, a variable amount of pigment was noted to adhere to the sclera. In addition, the retina was not separated from the choroid. Contamination of the vascularized tissues by blood has been evaluated by hemoglobin microassays (sensitivity, 1 $\mu\text{g}/\text{mg}$). Its role in pefloxacin concentration determination has been considered negligible because of its very low presence in the eye (1.9, 3.5, and 0.56% in the iris, chorioretina, and sclera, respectively). Finally, norfloxacin levels might be underestimated since the extraction method was optimal for pefloxacin and suboptimal for norfloxacin.

Pharmacokinetic analysis. Results were expressed per milliliter, assuming that tissue densities are approximately 1. Areas under the concentration-time curve (AUC) were calculated for the experimental period (0 to 11 h) by using the trapezoidal rule method. Half-lives were calculated by linear regression using a monoexponential model. For some tissues, the half-life could not be evaluated because the slope was zero. The peak concentration was considered to be reached within the first hour for all the tissues. The penetration ratio was defined as the tissue AUC/serum AUC.

Statistical evaluation. Comparisons of means were made by using Student's unpaired *t* test; *P* values less than 0.05 were considered significant.

RESULTS

Kinetics of pefloxacin in albino rabbits. The kinetics of pefloxacin in albino rabbits are shown in Table 1. In albino rabbits, the mean serum AUC was 31.4 $\mu\text{g} \cdot \text{h}/\text{ml}$. The mean peak level achieved in serum was 8.89 \pm 0.65 $\mu\text{g}/\text{ml}$ within 1 h after the injection. The half-life was short (2.01 h). The volume of distribution was large (3.8 liters/kg of body weight).

The level reached in the vitreous humor by the majority of antibiotics after a systemic administration is usually a few percent of the peak concentration in serum (2). The penetra-

tion into both the aqueous and the vitreous humors by pefloxacin was remarkably high, with penetration ratios of 0.33 and 0.39, respectively. The half-life of pefloxacin was 3.38 h in the vitreous humor and 2.79 h in the aqueous humor.

The penetration of pefloxacin into the cornea and lens was good (Table 2). As both are avascular tissues which establish exchanges with the aqueous and/or vitreous humor, their pefloxacin levels should be related to those in the humors. The cornea AUC/aqueous humor AUC ratio (2.88) showed a corneal accumulation of pefloxacin. The lens AUC/aqueous humor AUC and lens AUC/vitreous humor AUC ratios (0.67 and 0.56, respectively) showed a low diffusion in the lens. However, the half-life in the lens was too long to be evaluated over the course of the experiment.

High levels were found in the iris and in the chorioretina (Table 2), both of which are vascularized tissues; the iris/serum and chorioretina/serum penetration ratios were greater than 1.

Kinetics of pefloxacin in pigmented rabbits. The kinetics of pefloxacin in pigmented rabbits are shown in Table 1. In pigmented rabbits, the mean serum AUC was similar to that in albino rabbits, but the volume of distribution was significantly larger (5.25 versus 3.81 liters/kg) and the serum half-life was significantly longer (2.61 versus 2.01 h).

The main difference between albino and pigmented rabbits was in iris and chorioretina pefloxacin concentrations. In pigmented rabbits, the mean AUCs in these tissues were 38- and 54-fold higher, respectively, than in albino rabbits, and the half-lives were too long to be evaluated during the course of the experiment. These results suggest markedly greater uptake and retention of pefloxacin by pigmented tissues than by corresponding albino tissues.

The increased pefloxacin levels observed in the sclera were probably due to contamination by pigments during dissection.

Kinetics of norfloxacin. The kinetics of norfloxacin are described in Table 3. In albino rabbits, the mean norfloxacin AUC/pefloxacin AUC ratios were 0.48, 1, and 0.95 in the sera, aqueous humors, and corneas of albino rabbits, respectively. No norfloxacin was found in the vitreous humor or in the lens.

DISCUSSION

Intraocular penetration of drugs is limited by the blood-ocular barriers, one regulating exchanges between the blood

TABLE 2. Concentrations of pefloxacin in serum and ocular tissues and humors^a

| Rabbits | Time (h) | Concn ($\mu\text{g/ml}$) of pefloxacin in: | | | | | | | |
|---------|-----------|--|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | | Serum | Vitreous | Aq. humor | Cornea | Iris | Lens | Ch. retina | Sclera |
| Albino | 1 | 8.89 \pm 0.65 | 1.66 \pm 0.86 | 2.61 \pm 1.12 | 4.81 \pm 2.19 | 7.88 \pm 2.00 | 0.60 \pm 0.26 | 8.20 \pm 3.70 | 12.11 \pm 6.6 |
| | 2 | 7.54 \pm 0.19 | 2.38 \pm 0.53 | 1.96 \pm 1.29 | 5.18 \pm 0.44 | 7.02 \pm 1.77 | 0.84 \pm 0.39 | 9.00 \pm 2.00 | 13.00 \pm 8.5 |
| | 3 | 4.32 \pm 0.06 | 2.18 \pm 0.58 | 1.83 \pm 0.42 | 4.33 \pm 0.39 | 6.12 \pm 2.43 | 1.14 \pm 0.49 | 8.70 \pm 3.00 | 9.00 \pm 5.20 |
| | 5 | 1.94 \pm 0.22 | 1.08 \pm 0.16 | 0.78 \pm 0.24 | 2.50 \pm 0.52 | 3.08 \pm 0.46 | 0.51 \pm 0.20 | 3.30 \pm 0.60 | 6.30 \pm 6.30 |
| | 7 | 1.59 \pm 0.33 | 0.82 \pm 0.15 | 0.41 \pm 0.13 | 1.89 \pm 0.59 | 2.45 \pm 0.80 | 0.57 \pm 0.18 | 2.60 \pm 2.00 | 6.30 \pm 7.10 |
| | 9 | 0.55 \pm 0.10 | 0.51 \pm 0.07 | 0.25 \pm 0.07 | 1.85 \pm 1.05 | 2.27 \pm 0.59 | 0.60 \pm 0.13 | 2.55 \pm 0.50 | 6.40 \pm 8.90 |
| | 11 | 0.29 \pm 0.07 | 0.25 \pm 0.04 | 0.27 \pm 0.11 | 1.18 \pm 1.48 | 0.61 \pm 0.79 | 0.47 \pm 0.05 | 1.11 \pm 0.40 | 7.50 \pm 12.7 |
| | Pigmented | 1 | 6.74 \pm 0.17 | 1.83 \pm 0.58 | 1.23 \pm 0.06 | 2.37 \pm 0.42 | 146 \pm 53 | 0.70 \pm 0.24 | 250 \pm 72 |
| 2 | | 6.08 \pm 0.23 | 1.80 \pm 0.59 | 1.27 \pm 0.65 | 2.78 \pm 0.04 | 117 \pm 51 | 0.60 \pm 0.28 | 185 \pm 34 | 17.2 \pm 5.8 |
| 3 | | 4.55 \pm 0.20 | 1.77 \pm 0.47 | 0.85 \pm 0.09 | 2.87 \pm 1.17 | 171 \pm 27 | 0.72 \pm 0.14 | 221 \pm 40 | 23.0 \pm 4.5 |
| 5 | | 2.22 \pm 0.59 | 1.49 \pm 1.04 | 0.58 \pm 0.13 | 2.17 \pm 0.41 | 127 \pm 8 | 0.76 \pm 0.09 | 167 \pm 102 | 21.1 \pm 5.7 |
| 7 | | 1.47 \pm 0.37 | 0.90 \pm 0.47 | 0.51 \pm 0.11 | 1.89 \pm 0.60 | 171 \pm 97 | 0.77 \pm 0.23 | 276 \pm 81 | 17.2 \pm 1.4 |
| 9 | | 1.25 \pm 0.26 | 0.99 \pm 0.55 | 0.49 \pm 0.04 | 2.62 \pm 1.88 | 158 \pm 51 | 0.63 \pm 0.13 | 352 \pm 157 | 22.4 \pm 3.5 |
| 11 | | 0.42 \pm 0.07 | 0.47 \pm 0.09 | 0.38 \pm 0.09 | 1.68 \pm 0.49 | 94 \pm 31 | 0.62 \pm 0.05 | 244 \pm 42 | 16.2 \pm 3.3 |

^a Concentrations of pefloxacin in serum and in ocular tissues and humors were determined after a single intramuscular injection of 50 mg of pefloxacin per kg. All values are the mean \pm standard deviation of four experiments. Aq. humor, aqueous humor; vitreous, vitreous humor; ch. retina, chorioretina.

and aqueous humor (the blood-aqueous barrier) and the other regulating exchanges between the blood and retina (the blood-retinal barrier) (8). Each of these barriers consists of a continuous layer of cells joined by tight junctions.

The blood-aqueous barrier is located primarily in the nonpigmented epithelium of the ciliary body. The blood-retinal barrier consists of two distinct elements: an inner barrier (the endothelium of the retinal vessels) and an outer barrier (the pigmented epithelium, which is the interface between the outer retina and the choriocapillaris). Diffusion into the vitreous humor from the intraretinal spaces is passive.

The tight junctions of the blood-aqueous barrier have been shown to be maculae occludentes of the "leaky" type, i.e., they become permeable when local inflammation or paracenteresis occurs. The tight junctions of the blood-retinal barrier have been shown to be zonulae occludentes of the "non-leaky" type; as a result, the blood-retinal barrier is less permeable than the blood-aqueous barrier (8).

When administered by the systemic route, pefloxacin has been shown to be widely distributed in the tissues and fluids (10), including the cerebrospinal fluid (14) and brain (11). Some authors have reported that it penetrates into human aqueous humor (6, 9, 13). The purpose of our study was to

determine the ocular penetration, distribution, and elimination of pefloxacin in order to determine the mechanisms by which it diffuses into the different tissues.

Since we used pooled data from a population of rabbits, intra- and interanimal variations are high and are reflected by the relatively high standard deviations of the mean concentrations. This approach is not perfect, but it remains the only one available to evaluate the concentrations of drugs in tissue *in vivo*.

It is noteworthy that the penetration of pefloxacin into both the aqueous and the vitreous humors was high (30% of levels in serum). Most antibiotics show poor penetration into the aqueous humor and virtually no penetration into the vitreous humor (2). The capacity of pefloxacin to cross the blood-aqueous barrier and the blood-retinal barrier might be related to its biophysical properties. Pefloxacin has a low molecular weight of 333, is little bound by serum proteins, and is highly lipophilic. It has been shown to cross cell membranes readily in both directions (7).

The half-life of pefloxacin was longer in the vitreous than the aqueous humor since turnover is more rapid in the latter.

The cornea and lens are avascular tissues. The good exposure of the cornea to pefloxacin might be related to a diffusion of the drug from the aqueous humor and from the vessels located in the limbus.

Pefloxacin penetrates the lens by diffusion from the aqueous and vitreous humors. The lens is composed of several concentric layers of cells, the innermost of which show virtually no metabolic activity. Pefloxacin might thus penetrate through the lens cell membranes, and its long half-life might be a result of the slow metabolism of these cells. Alternatively, pefloxacin may bind to the lens proteins or ions.

Pefloxacin penetrated the vascularized tissues (the iris and chorioretina), since the penetration ratio in these tissues was greater than 1. In the clinical situation, steady state in serum is reached after six twice-daily systemic administrations. In light of these findings, it seems reasonable to suppose that ocular concentrations would also reach a plateau under these conditions.

Pefloxacin was found in the sclera; this tissue is not strictly vascularized but is crossed by numerous vessels. Moreover, several substances have been shown to diffuse

TABLE 3. Norfloxacin AUC/pefloxacin AUC ratio in ocular tissues in albino and pigmented rabbits^a

| Tissue or fluid | Norfloxacin AUC/pefloxacin AUC ratio in rabbits | |
|-----------------|---|-----------|
| | Albino | Pigmented |
| Serum | 0.48 | 0.55 |
| Aq. humor | 1 | 0.80 |
| Vitreous | 0 | 0 |
| Cornea | 0.95 | 0.64 |
| Lens | 0 | 0 |
| Iris | 0.37 | 0.02 |
| Ch. retina | 0.16 | 0.03 |
| Sclera | 0.23 | 0.09 |

^a Ratios were determined after a single intramuscular injection of 50 mg of pefloxacin per ml. Aq. humor, aqueous humor; vitreous, vitreous humor; ch. retina, chorioretina.

across the sclera from the chorioretina to the conjunctiva along a concentration gradient (5).

Pefloxacin appears to bind to the pigmentary apparatus, since its levels in the pigmented tissues (the iris and chorioretina) were several times higher in pigmented than in albino rabbits and since the half-lives in these tissues were also much longer in pigmented than in albino rabbits. This finding is not surprising since pefloxacin is lipophilic. In addition, chloroquine, which is a similar molecule, is known to bind to ocular pigments. Gentamicin binds with high affinity to the pigmentary apparatus and is inactivated (15); in contrast, clindamycin binds reversibly, thus providing a reservoir of active drug (3). We could not assess the activity of bound pefloxacin since the drug was assayed by HPLC. The high degree of binding to the pigmentary apparatus might induce a modification of pefloxacin kinetics. In the vitreous and aqueous humors of pigmented rabbits, its half-life was increased, although its AUC remained similar. This pharmacokinetic behavior suggests a slow release of pefloxacin from pigmented tissues with a simultaneous clearance resulting from the aqueous humor turnover.

In the same way, the increased volume of distribution in serum might be related to the binding of pefloxacin to other sites; its progressive release might explain its longer half-life in the serum of pigmented rabbits. The clinical implications of such binding remain to be demonstrated. Further studies of pefloxacin kinetics in Caucasian and black subjects would be of interest.

Pefloxacin is a hydroxyquinoline. Some of these compounds are known to induce a loss of visual acuity by causing retinal alterations and vascular abnormalities (4). At present, despite the widespread clinical use of pefloxacin no ocular toxic effects have been reported, even in long-term therapy, as in the case of osteomyelitis.

Norfloxacin, the main metabolite of pefloxacin, was also assayed. The norfloxacin AUC/pefloxacin AUC ratio in serum was higher in rabbits (about 0.50) than in it was in humans (about 0.05) (12). In the eye, norfloxacin was found mainly in the aqueous humor and cornea but not in the vitreous humor. This distribution might be explained by the lower lipophilicity of norfloxacin and might have an additional antibacterial effect.

Pefloxacin, a new fluoroquinolone, shows exceptionally good penetration of the eye when administered by the systemic route. Since its molecular weight is low and since it is highly lipophilic, pefloxacin easily crosses the cell membrane. It thus crosses the blood-aqueous and blood-retinal barriers and reaches high levels in the aqueous and vitreous humors.

The clinical implications of pefloxacin binding to the pigmentary apparatus remain to be determined.

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REFERENCES

1. Abel, R. J., and G. L. Boyle. 1976. Dissecting ocular tissue for intraocular drug studies. *Invest. Ophthalmol. Visual Sci.* **15**: 216-219.
2. Barza, M., and J. Baum. 1987. Ocular pharmacology of antibiotics, p. 1-14. *In* T. D. Duane and E. A. Jaeger (ed.), *Biomedical foundations of ophthalmology*. Lippincott Co., Philadelphia.
3. Barza, M., A. Kane, and J. Baum. 1982. Marked differences between pigmented and albino rabbits in the concentration of clindamycin in iris and in choroid-retina. *J. Infect. Dis.* **139**:203-208.
4. Bernsmeier, H., U. Weber, and R. Trapp. 1987. Quinine poisoning: acute and chronic changes of the visual system. *Concepts Toxicol.* **4**:110-114.
5. Bill, A. 1980. Drainage of intraocular fluids, p. 179-193. *In* J. Cunha-Vaz (ed.), *Blood-retinal barrier*. Plenum Press, New York.
6. Bron, A., D. Talon, B. Delbosc, J. M. Estavoyer, F. Prost, and M. Montard. 1986. La pénétration intracamerulaire de la péfloxacine chez l'homme. *J. Fr. Ophthalmol.* **9**:317-321.
7. Carlier, M. B., B. Scorneaux, A. Zenebergh, and P. M. Tulkens. 1987. Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 622.
8. Cunha-Vaz, J. 1980. Sites and functions of the blood-retinal barriers, p. 101-117. *In* J. Cunha-Vaz (ed.), *Blood-retinal barrier*. Plenum Press, New York.
9. Denis, F., J. P. Adenis, M. Mounier, and M. Monassier. 1987. Etude du passage de la péfloxacine chez l'homme et le lapin. *Humeur aqueuse et vitré. Pathol. Biol.* **35**:772-776.
10. Fourtillan, J. B. 1986. Comportement pharmacocinétique de la péfloxacine chez l'homme. *Rev. Med. Interne* **7**:185-195.
11. Korinek, A. M., M. Guggiari, G. Montay, R. Grob, M. Rivierez, and P. Viars. 1986. Program Abstr. 1st Int. Symp. New Quinolones, abstr. 225.
12. Montay, G., and J. P. Tassel. 1985. Improved high performance liquid chromatographic determination of pefloxacin and its metabolite norfloxacin in human plasma and tissue. *J. Chromatogr.* **339**:214-218.
13. Salvanet, A., A. Fisch, C. Lafaix, G. Montay, P. Dubayle, and F. Forestier. 1986. Pefloxacin concentrations in human aqueous humor and lens. *J. Antimicrob. Chemother.* **18**:199-201.
14. Wolff, M., B. Regnier, C. Daldoss, M. Nkham, and F. Vachon. 1984. Penetration of pefloxacin into cerebral fluid of patients with meningitis. *Antimicrob. Agents Chemother.* **26**:289-291.
15. Young, P., M. Barza, A. Kane, and J. Baum. 1979. Radioactive and bioassay of intraocular antibiotics. *Arch. Ophthalmol.* **97**: 717-720.