THE CLEARANCE OF INTRAVITREAL GENTAMICIN

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Intravitreal gentamicin cleared significantly more rapidly from the uninflamed aphakic rabbit eye than the phakic control, with a half-life of 12 hours in the former and 32 hours in the latter. A similar difference was noted in aphakic and phakic eyes with an experimental *Staphylococcus aureus* endophthalmitis, but without the same level of significance. Human data from nine aphakic infected eyes undergoing reinjection or vitrectomy indicated that therapeutic levels of gentamicin are not consistently found 48 hours or more after the initial intravitreal injection.

Although intravitreal injection of gentamicin has been used for almost a decade in the treatment of postoperative endophthalmitis in humans,[1] our understanding of the dynamics of intravitreal gentamicin, as well as other antibiotics, has been based on data derived from studies in phakic, uninflamed rabbit eyes.[2,3] Such data may be misleading because the establishment of a communication between the vitreous and the anterior chamber might cause more rapid clearance of the antibiotic from the vitreous into the aqueous circulation.

We studied the clearance of gentamicin in phakic and aphakic rabbit eyes, both in the presence and absence of infection, to more closely approximate the most common setting for endophthalmitis in the postoperative aphakic patient. Additionally, gentamicin levels were obtained in a group of patients who underwent repeat intravitreal injections of antibiotics, a procedure that has been used with success in selected cases.[1] These data allow a critical evaluation of the duration of therapeutic gentamicin levels and a consideration of the optimal time for repeating intravitreal injections in those patients who require additional intravitreal antibiotic therapy.

MATERIAL AND METHODS

Thirty-one albino New Zealand rabbits (weighing 2 to 3 kg each) underwent lens aspiration in one eye; the unoperated eye served as the phakic control. Right and left eyes were done alternately, after the rabbits were under general anesthesia with intravenously administered pentobarbitol. A beveled 60-degree corneal incision was made, a sector iridectomy was performed, and the anterior lens capsule incised. A lens fragmentor was inserted and all visible lenticular material was irrigated from the anterior chamber. The posterior capsule was not intentionally incised. The wound was closed with resorbable sutures. The rabbits then received a subtenon's injection of 8 mg of triamcinalone acetonide and 4 mg of gentamicin subconjunctivally. The ani-

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mals were then observed for two to three months with regular slit-lamp examinations until the eyes were quiet. In the first part of the study, 13 of the monocularly aphakic animals received intravitreal injections of gentamicin into both eyes. A solution of 100 μg/0.1 ml was prepared by serial dilutions of stock solution of gentamicin. Proparacaine was applied topically to both eyes and a 30-gauge needle, mounted on a tuberculin syringe containing diluted gentamicin solution, was inserted 2 mm posterior to the temporal corneoscleral limbus, through the pars plana, with the bevel directed anteriorly. Before injection of the antibiotic, an anterior chamber paracentesis was performed to relieve any increase in intraocular pressure. Peyman and associates[2] demonstrated that gentamicin is cleared exponentially from the rabbit vitreous. By collecting data at fewer points (for example, three), more reliable figures could be obtained with a given number of animals. An exponential decay model allowed data to be plotted semilogarithmically to obtain a regression line. Rabbits were killed two, 24, or 48 hours after injection. We isolated the entire vitreous body for assay, using a modification of the technique described by Abel and Boyle.[4] The eyes were promptly enucleated, tagged with an identification label, and frozen in liquid nitrogen. Each globe was dissected, and vitreous was isolated and then placed in a graduated tube. The concentration of gentamicin was subsequently determined by radioimmunoassay technique and the concentrations per eye were calculated using the known volume of vitreous removed from the eye.

The second group of 18 rabbits was subsequently used to study antibiotic clearance in infected eyes. An endophthalmitis was consistently created in both eyes of each animal, using intravitreal inoculation of approximately 60 organisms of *Staphylococcus aureus*.[5] Thirty-two hours after infection, at which time clinical endophthalmitis was apparent, the eyes received 100 μg of gentamicin intravitreally. The rabbits were killed and studied in the same manner as the first, noninfected group.

Results

The gentamicin concentration in the rabbit vitreous, measured in micrograms per eye, was plotted on a logarithmic scale against the hours after injection of antibiotic into the vitreous body. Using an exponential decay model, a least squares regression line was obtained from the data. The data for the aphakic and the phakic eyes were compared in the first group of noninfected rabbits (Fig. 1), and in the second group of animals with experimental endophthalmitis (Fig. 2).

The clearance of gentamicin from the rabbit vitreous is equivalent to the slope of the line derived from plotting the

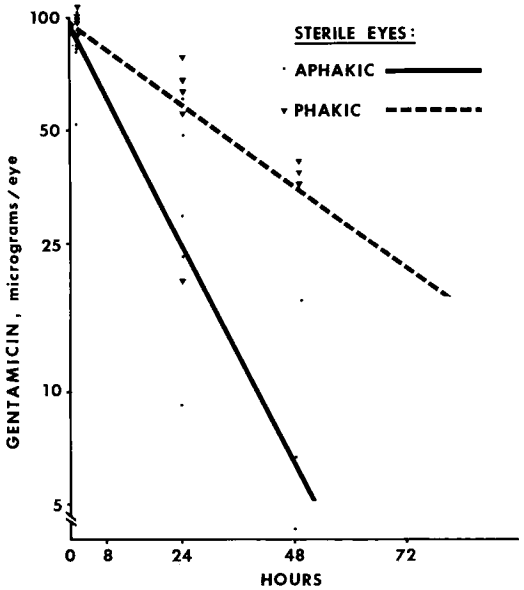

Fig. 1 (Cobo and Forster). The clearance of 100 μg of gentamicin injected into the midvitreous cavity of uninfected rabbit eyes.

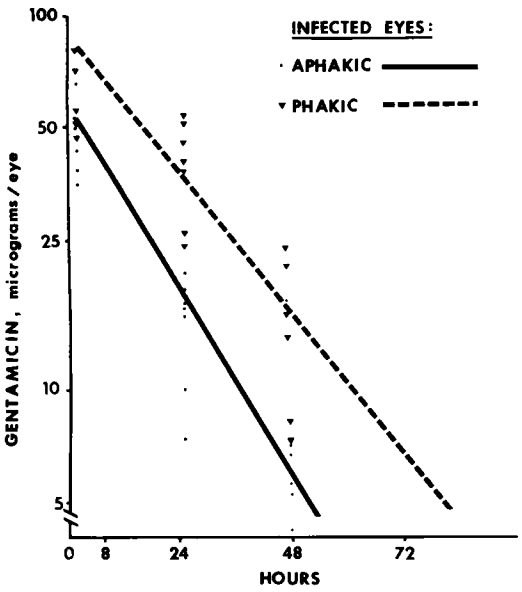

Fig. 2 (Cobo and Forster). The clearance of 100 μg of gentamicin injected into the midvitreous cavity of rabbit eyes infected experimentally with *Staphylococcus aureus*.

concentration of gentamicin per eye on the logarithmic scale against the time after injection (hours). In the noninfected model, gentamicin was cleared more rapidly from the aphakic eye than the phakic eye, with a half-life of 12 hours in the aphakic model compared to 32 hours in the control phakic eye ($P < .05$).

In the second group of animals infected with *S. aureus*, the difference in rate of clearance was less distinct. The half-life of gentamicin in the infected aphakic eye was 14 hours compared to 19 hours in the infected phakic eye ($.10 > P > .05$).

Gentamicin levels in vitreous fluid obtained from human eyes at the time of reinjection are listed in the Table, including the time that had elapsed from the initial intravitreal injection and the isolated organism. All eyes had aphakic endophthalmitis. Vitreous samples were obtained either by pars plana syringe aspiration or at the time of vitrectomy. The gentamicin level was determined by radioimmunoassay technique.

Discussion

Experimental clearance data provide an estimate of the duration of therapeutic levels for a given, nontoxic dose of an intravitreally administered antibiotic. Additionally, clearance data are a guide in selected cases where the physician may wish to intervene with either vitrectomy or reinjection of antibiotic. Such data have generally been derived from

TABLE

Vitreous gentamicin concentrations in infected human patients

Patient No.	Time After Injection (hrs)	Vitreous Gentamicin Concentration (μg/ml)	Organism
1	20	0.90	*Citrobacter diversus*
2	31	>20.00	*Aspergillus flavus*, *Staphylococcus epidermidis*
3*	36	8.00	*S. aureus*
4	37	5.00	*S. epidermidis*
5*	44	6.75	*Enterococcus* Group D
6*	48	3.50	*S. epidermidis*
7*	48	0.25	*Klebsiella pneumoniae*
8*	48	10.00	*Streptococcus viridans*
9	52	3.50	*S. aureus*

*These samples were obtained at the time of subsequent vitrectomy.

uninflamed phakic animal models. This study indicates that gentamicin is cleared more rapidly in the aphakic rabbit eyes. Presumably, removal of the lens allows intravitreally administered antibiotic to diffuse more readily into the anterior chamber where such drugs may be more rapidly cleared through the aqueous circulation. Although studies in the infected model again demonstrated more rapid clearance in the aphakic eyes, the values for drug half-life were much closer in the phakic and aphakic eyes and the difference was not statistically significant as it was in the uninfected eyes.

If all other factors are equal, experimental clearance data for the intravitreal injection of 100 μg of gentamicin may be extrapolated from the 1.5-ml rabbit vitreous body to the 4-ml human vitreous body. Using half-life figures from the uninflamed eyes, where a significant difference was demonstrated between phakic and aphakic clearance rates, we estimated that the gentamicin level would reach the minimum therapeutic level of 4 μg/ml after 32 hours in the aphakic eye compared to 87 hours in the phakic eye. Comparison with data obtained from humans at first glance demonstrated the variability expected in the clinical setting and the problems of strict reliance on animal data. However, we then divided the group into those with values obtained less than 48 hours and those with values obtained more than 48 hours after the initial injection. Only one of four samples obtained after 48 hours contained a minimum inhibitory concentration of gentamicin, compared to four of five samples obtained before 48 hours. We cannot account for the unexpectedly low value in Patient 1 or the high level in Patient 2 other than sampling error or a technical error in the determination of antibiotic levels.

These data from experimental animals and humans indicate that therapeutic levels of antibiotic are maintained for 24 to 48 hours after the initial intravitreal injection of antibiotic in aphakic eyes. An optimal time for reinjection of antibiotic in a selected aphakic case may be between 36 and 48 hours. Although we have no human data on the clearance of gentamicin in phakic eyes, experimental animal data indicate that the drug may be cleared more slowly in these eyes. It may be reasonable to postpone reinjection in the phakic eye to 72 to 96 hours after initial injection to avoid potentially toxic intravitreal levels.

References

1. Forster, R. K., Abbott, R. L., and Gelender, H.: Management of infectious endophthalmitis. Ophthalmology 87:313, 1980.

2. Peyman, G. A., May, D. R., Ericson, E. S., and Apple, D.: Intraocular injection of gentamicin. Toxic effects and clearance. Arch. Ophthalmol. 92:42, 1974.

3. Zachary, I. G., and Forster, R. K.: Experimental intravitreal gentamicin. Am. J. Ophthalmol. 82:604, 1976.

4. Abel, R., and Boyle, G. L.: Dissecting ocular tissue for intraocular drug studies. Invest. Ophthalmol. 15:216, 1976.

5. Cottingham, A. J., and Forster, R. K.: Vitrectomy in endophthalmitis. Arch. Ophthalmol. 94:2078, 1976.