Delivery of Gentamicin to the Rabbit Eye by Drug-Loaded Hydrogel Iontophoresis

Esther Eljarrat-Binstock,1 Frederik Raiskup,2 David Stepensky,3 Abraham J. Domb,1 and Joseph Frucht-Pery2

PURPOSE. To assess the corneal iontophoretic delivery of gentamicin by drug-loaded hydrogel probe, and to determine the resultant ocular disposition and elimination of the drug from the cornea and anterior chamber.

METHODS. Corneal iontophoresis of gentamicin sulfate was studied in healthy white rabbits by using drug-loaded disposable hydroxethyl methacrylate (HEMA) hydrogel disk probes and a portable mini-ion device designed in the authors’ laboratory. The iontophoretic treatment was performed with a current intensity of 1 mA for 60 seconds only. Three control groups were used: mock iontophoresis (no current) for 60 seconds, topical eye drops of fortified gentamicin (1.4%) every 5 minutes for 1 hour, and subconjunctival injection of 0.25 mL of 40 mg/mL gentamicin solution. The animals in the iontophoretic experimental groups were killed at predetermined time points. The gentamicin concentrations in the cornea and aqueous humor were assayed with a fluorescence polarization immunoassay. Analysis of the gentamicin eye pharmacokinetics was performed with a modeling approach.

RESULTS. Peak gentamicin concentrations in the cornea (365.1 ± 127.3 μg/g) and in the aqueous humor (29.4 ± 17.4 μg/mL) were reached at 0 and 2 hours after the iontophoretic treatment, respectively. The peak gentamicin concentrations after a single iontophoresis treatment were 12 to 15 times higher than those obtained after gentamicin injection or after topical eye drop instillation, and much higher than in mock iontophoresis. The concentration versus time profile of gentamicin in the cornea and the anterior chamber after iontophoresis was appropriately described by applying a two-compartment pharmacokinetic model.

CONCLUSIONS. A short iontophoretic treatment using gentamicin-loaded hydrogels has potential clinical value in increasing drug penetration to the anterior segments of the eye and maintaining therapeutic drug levels in the cornea for more than 8 hours. (Invest Ophthalmol Vis Sci. 2004;45:2543–2548) DOI:10.1167/iovs.03-1294

From the Departments of 1Medicinal Chemistry and Natural Products and 2Pharmaceutics, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel; and the 3Department of Ophthalmology, Hadassah University Hospital, Jerusalem, Israel.

This work is part of the PhD thesis of EE-B. Supported in part by grants from the Horowitz Foundation. Submitted for publication November 26, 2003; revised April 5, 2004; accepted April 9, 2004. Disclosure: E. Eljarrat-Binstock, None; F. Raiskup, None; D. Stepensky, None; A. J. Domb, None; J. Frucht-Pery, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Joseph Frucht-Pery, Department of Ophthalmology, Hadassah University Hospital, Jerusalem 91120, Israel; fruchtpery@md.huji.ac.il.

Gentamicin, an aminoglycoside antibiotic, exerts a potent bactericidal effect on pathogenic bacteria that cause a variety of eye infections, including bacterial keratitis, postoperative or posttraumatic endophthalmitis, and choroidal uveitis. However, the highly hydrophilic structure of gentamicin limits its permeability through biological membranes, resulting in low ocular bioavailability and posing a pharmacokinetic limitation to the drug’s reaching therapeutic concentrations at the site of action in the eye. The topical ocular bioavailability of gentamicin is especially limited in cases in which the infected areas are restricted to the posterior segments of the eye, and, to reach them, the drug must permeate the intact corneal epithelium. Intraocular permeability of gentamicin is further restricted because of common limitations of eye drop administration, including limited volume of the conjunctival sac (approximately 30 μL) and high tear turnover rate (approximately 1 μL/min). It has been determined that as much as 90% of the 50-μL dose administered in eye drops is cleared within 2 minutes, and only 1% to 10% of the administered dose penetrates to reach the inner eye. Therefore, a high frequency of administration of gentamicin eye drops (0.3% gentamicin) is required for treatment of most ocular infections, and fortified drops (0.8%–2.0% gentamicin) are applied in severe cases.

To achieve higher concentrations in the anterior or posterior segments of the eye, subconjunctival or intravitreal injections of gentamicin solution may be applied, respectively. Although intravitreal injections can deliver higher amounts of drug to a specific location in the eye, compared with eye drop instillation, their administration is painful, requires a physician, and is associated with severe complications such as perforation of the globe and scarring of the conjunctiva.

To enhance the permeability of gentamicin to the intraocular sites of action, iontophoresis can be applied. Iontophoresis is a noninvasive technique in which direct contact between the ionized drug and the tissue is required, and a small electric current is used to enhance the penetration of charged molecules into the tissue. Iontophoresis is suitable for drugs that are charged at physiological pH, and the major factors that determine the drug’s tissue penetration are the molecular charge, the molecular weight, and the lipid solubility of the drug. Additional parameters that determine the drug’s penetration are the electric density, the drug concentration, and the duration of the iontophoresis procedure. Iontophoresis has been used in various fields of medicine—for example administration of local anesthetics, testing for cystic fibrosis by transcutaneous delivery of pilocarpine, administration of vidarabine to patients with herpes orolabialis, and fluoride administration to patients with hypersensitive dentin.

The first studies on iontophoresis in ophthalmology were performed in the early 1940s, and its major potential application has been identified as achieving inhibitory levels of antibiotic drugs in the eye for the treatment of bacterial endophthalmitis and keratitis. Gentamicin is a suitable candidate for ocular iontophoresis due to its charged chemical structure and low molecular weight, and ocular iontophoresis of gentamicin has been applied in several studies to enhance its penetration of the tissue.

Copyright © Association for Research in Vision and Ophthalmology

2543
Ocular iontophoresis of gentamicin in experimental animals produced high levels of gentamicin in the cornea and in aqueous humor and was associated with minimal toxicity. However, the experimental protocol in these studies may not be suitable in clinical settings because of the long period of iontophoresis (10 minutes) and levels of electric current at approximately 2 mA. Moreover, iontophoresis of drug solution applied in these studies necessitates prolonged contact between the cup containing drug solution and the cornea, which is technically clumsy, may cause mechanical injury to the cornea, and demands sterilization of the solution and cup before each treatment. It has been proposed that most of these drawbacks could be prevented by applying semisolid drug-loaded probes for iontophoresis application, such as an agar-gentamicin probe.14–16

Hydrogels are three-dimensional networks of hydrophilic polymers held together by association bonds or cohesive forces. We hypothesized that hydrogel probes would be suitable for gentamicin iontophoresis delivery because they can retain large quantities of gentamicin solution and can be directly applied to the cornea without need for sophisticated equipment. Hydrogels have been used for transdermal iontophoretic delivery of various drugs, and their ophthalmologic uses have been limited so far to application as contact lenses.19

The objective of the present study was to assess the corneal iontophoresis delivery of gentamicin using drug-loaded hydrogel probes, and to determine the resultant ocular permeability and disposition of the drug in vivo. The study was performed in preclinical settings, using rabbits as a common model to study ocular drug pharmacokinetics and a novel mini-ioniontophoresis device.

Materials and Methods

Gentamicin sulfate was obtained from Sigma-Aldrich (St. Louis, MO). All the other materials and agents were purchased from Sigma-Aldrich (Rehovot, Israel). All solvents were HPLC grade from BioLab (Jerusalem, Israel).

The Iontophoretic Device

The iontophoretic device that was applied in this study is a portable mini-ion device (designed in our laboratory) that can be operated by battery or by an external electric source (Fig. 1). A probe, with a cylindrical well attached that is 5 mm in diameter and 3 mm in depth, is used for insertion of the drug-loaded hydrogel disk 5 mm in diameter and 5 mm in height. The mini-ion device applies a variable electrical current in the range of 0.1 to 1.0 mA for preset periods from 10 to 120 seconds.

Preparation of HEMA Gel Disks

Hydroxyethyl methacrylate (HEMA; 97% pure), ethylene glycol dimethacrylate (EDGMA, 98% pure), and deionized water (2.0, 0.04, and 6.5 mL, respectively) were mixed to produce a clear solution, under a stream of dry nitrogen. The following initiator solutions were added: 2% sodium persulfate Na2S2O8 (0.05 mL), 2% sodium metabisulfite Na2S2O5 (0.05 mL), and 2% ammonium ferrous sulfate Fe(NH4)2(SO4)2 (0.025 mL). The solution was rapidly mixed and divided into a Teflon tray with wells (5 mm height, 6 mm diameter) and was left to polymerize overnight at room temperature, under a nitrogen blanket in the dark. The obtained disks were immersed in 0.5 L of water with stirring, to clean the hydrogels of unreacted monomers, catalysts, and low-molecular-weight by-products. The purified hydrogels were frozen with liquid nitrogen and were dehydrated by lyophilization overnight to form sponge cylinders that were of a size similar to that of the wet cylinders. Two hours before use, the dried hydrogels were immersed in a 10% (wt/vol) gentamicin sulfate solution. The drug-loaded hydrogels were solid but soft, and had a cylindrical shape with dimensions of 5 × 5 mm. The hydrogels were weighed before and after immersion in the gentamicin solution, to evaluate the drug load of the hydrogel before use.

Animals

Healthy New Zealand White male rabbits (n = 58) weighing 2.0 to 3.0 kg were used in the study. The study conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Drug Administration

The animals were anesthetized by injection of ketamine and xylazine solution (intramuscularly, 25 and 2.5 mg/kg, respectively). Five groups of eight rabbits each underwent corneal iontophoresis with the mini-ion system with a hydrogel disk probe containing an average amount of 26.11 mg gentamicin sulfate (one eye per rabbit). Before the electrode was placed on the ocular surface, the eye was topically anesthetized with 0.4% benoxinate eye drops (Localin; Dr. Fischer Laboratories, Ltd., Bnei-Barak, Israel). The gentamicin-loaded hydrogel disk was inserted into the cylindrical opening edge of the iontophoretic device and placed onto the cornea. The complementary electrode was attached to the ear of the rabbit. Iontophoresis was performed on one eye by using a current intensity of 1.0 mA (5.1 mA/cm2) for 60 seconds. The experimental settings included three control groups of six rabbits each. One control group (group 6) was treated with mock iontophoresis, in the same way as described earlier, with the exception that no current was applied. Group 7 received topical eye drops of fortified gentamicin (1.4% wt/vol in water) every 5 minutes for 1 hour, and group 8 received a subconjunctival injection of 10 mg gentamicin (0.25 mL of 40 mg/mL gentamicin; Teva, Kfar-Saba, Israel) into the subconjunctival space.

Sample Collection

The animals in the experimental groups were killed immediately after the iontophoresis treatment and at 1, 2, 4, and 8 hours after treatment (groups 1–5, respectively) by an intravenous injection of a lethal dose of 2% pentobarbital. The animals in the control groups were killed immediately after the end of the drug administration period. The aqueous humor was collected by aspiration, and the corneas were excised. The volume of the aqueous humor and weight of the cornea were measured after their collection from the animals.

Gentamicin Assay

Cornea. After excision, the specimen was rinsed in 5 mL 0.9% NaCl solution, cut with a scalpel, and weighed. Each sample of the specimen was transferred into the microcentrifuge tube and 1.0 mL of 0.01 M phosphate-buffered saline (pH 7.4; Sigma-Aldrich) was added. The tubes were incubated for 18 hours at 37°C with oscillation at 100 rpm followed by centrifugation at 2000 rpm for 10 minutes. The
supernatant was collected (200 μL) and was assayed for gentamicin concentration using a fluorescence polarization immunoassay (TDx System Analyzer; Abbott Laboratories, Abbott Park, IL).

**Aqueous Humor.** Aliquots of 100 μL of the collected samples were diluted with 100 μL normal saline, and gentamicin concentrations were determined (TDx; Abbott Laboratories).

The TDx system analyzer is being used routinely by the Hadassah Hospital in Jerusalem for drug level detection in patient’s serum. For gentamicin, the detection limit of the TDx system is 0.1 μg/mL at a 95% confidence level and average recovery of 102.6% with precision of less than a 3% coefficient of variation (CV). The instrument was calibrated before each measurement according to the authorized gentamicin standard in the kit.

The concentration of gentamicin in the cornea was calculated as follows

\[ C_{\text{sample}} = \frac{(W_{\text{sample}} + V_{\text{buffer}}) \cdot C_{\text{buffer}}}{W_{\text{sample}}} \]  

where \( C_{\text{sample}} \) is the gentamicin concentration in the sample (micrograms per gram); \( C_{\text{buffer}} \) is gentamicin concentration in the buffer in micrograms per gram; \( W_{\text{sample}} \) is the weight of the sample in grams; and \( V_{\text{buffer}} \) is the volume of buffer in milliliters.

**Pharmacokinetic Analysis**

Analysis of the pharmacokinetics of gentamicin after corneal iontophoresis was performed by using a modeling approach. The applied model consisted of two compartments attributed to the cornea and the anterior chamber (Fig. 2). The gentamicin transport between the compartments and elimination through the posterior segments of the eye was assumed to occur according to the first-order kinetic processes. The differential equations used to describe the pharmacokinetic model were as follows:

\[ \frac{dX_1}{dt} = -k_{12} \cdot X_1 + k_{11} \cdot X_2 \]  
\[ \frac{dX_2}{dt} = k_{12} \cdot X_1 - (k_{21} + k_{20}) \cdot X_2 \]

where \( X_1 \) and \( X_2 \) are the gentamicin amounts in the cornea and the anterior chamber, respectively, and the rate constants are \( k_{12} \) transport from the cornea to the anterior chamber, \( k_{21} \) transport from the anterior chamber to the cornea, and \( k_{20} \) elimination through the anterior chamber to the posterior segments of the eye.

The modeling was performed on computer (WinNonlin, ver. 4.0.1; Pharsight Corp., Mountain View, CA) applying the Gauss-Newton algorithm and 1/2 weighting. Both sets of concentration versus time data were analyzed simultaneously. The fitness of the applied model to the experimental data was assessed using Akaike (AIC) and Schwarz (SC) criteria.21

**Statistical Analysis**

The Kruskal-Wallis test with the Dunn post hoc test was used for statistical evaluation of the gentamicin concentration obtained in the studied groups. \( P < 0.05 \) was considered significant. All results are expressed as the mean ± SD.

**RESULTS**

The time course of mean gentamicin levels in the cornea and aqueous humor after transcorneal iontophoresis (groups 1–5), compared with the control groups (groups 6–8), are presented in Table 1 and in Figure 3. The peak level of gentamicin in cornea (563.1 ± 127.3 μg/g) was attained immediately after the termination of transcorneal iontophoresis. This concentration was 12 to 15 times higher than the gentamicin concentrations achieved after subconjunctival injection (30.01 ± 8.56 μg/g, \( P < 0.01 \)) or after eye drop instillation every 5 minutes for 1 hour (22.7 ± 14.8 μg/g, \( P < 0.001 \)), respectively. Moreover, the peak concentration of gentamicin in the cornea after iontophoresis was more than 100 times higher than the gentamicin concentration achieved immediately after mock iontophoresis (2.72 ± 2.1 μg/g, \( P < 0.001 \)). Gentamicin concentrations after the iontophoretic treatment remained significantly higher than the concentration achieved after mock iontophoresis (group 6) for at least 4 hours, and for 2 hours when compared with the eye-drops-treated group (group 7). Gentamicin concentrations in the cornea after transcorneal iontophoresis declined gradually, but measurable gentamicin concentrations were obtained over 8 hours after iontophoretic drug ejection.

After transcorneal iontophoresis, the gentamicin concentration in the aqueous humor increased initially and then declined. The highest concentration of the drug in the aqueous humor was detected at 2 hours after iontophoresis (29.4 ± 17.4 μg/mL). No significant differences were found in gentamicin concentrations in the aqueous humor immediately after the iontophoresis treatment (group 1, 3.0 ± 2.9 μg/mL) compared with those in mock iontophoresis (group 6, below detectable levels; eye drop instillation (group 7, 3.2 ± 2.1 μg/mL) or gentamicin injection (group 8, 3.2 ± 1.6 μg/mL). Nevertheless, bactericidal concentrations (the minimum inhibitory concentration [MIC] of 3 μg/mL) were maintained in the anterior chamber at least 4 hours after a single iontophoretic treatment.12 The applied pharmacokinetic model (Fig. 2) appropriately described the concentration versus time profile of gentamicin in the cornea and the anterior chamber after iontophoresis. The calculated pharmacokinetic parameters are summarized in Table 2, and the observed versus predicted concentration–time profiles are presented in Figure 3.

Gentamicin’s half-life (\( t_h \)) in the anterior chamber and clearance to the posterior segments of the eye (CL) were calculated from the estimated value of the elimination rate constant of gentamicin transfer from the anterior chamber to the posterior segments of the eye (\( k_{20} \); Table 2), and were 2.07 hours and 1.73 μL/min, respectively. The calculation of clearance was based on the previously reported value of volume of the anterior chamber in rabbit (0.311 mL).22

**DISCUSSION**

Various approaches have been applied to achieving therapeutic concentrations of antibiotics in the cornea, aqueous humor, and vitreous humor of the eye. Subconjunctival, retrobulbar, intravenous, and intramuscular injections and topical drugs have been applied, but they do not produce adequate drug concentrations and are associated with a relatively high risk of complications and adverse effects.14

Iontophoresis is a noninvasive technique for drug administration to the eye that has been sporadically reported in ophthalmology, mainly for administration of antibiotic drugs for the treatment of bacterial infections.1,5,12–15 Gentamicin is suitable for iontophoresis, because it is charged at physiologic pH (three primary amines per molecule), possesses a low molecular weight, and is effective against a wide range of...
pathogenic Gram-negative and -positive bacteria. Gentamicin does not reach therapeutic concentrations in the eye tissue after regular topical administration (eye drops), because of its highly hydrophilicity and charge, leading to low permeability through biological membranes.

In our experiments, a short-term transcorneal iontophoresis of gentamicin produced drug concentrations in the cornea that were several times higher than those obtained in the control groups after mock iontophoresis, prolonged application of gentamicin eye drops, or gentamicin subconjunctival injection (Table 1). Despite the fact that the animals in the control groups were killed at only one time point (immediately after the end of the drug administration period), we compared the corneal concentrations obtained at the control groups with all iontophoretic experimental groups, hypothesizing that they are at their maximum concentrations. Although gentamicin concentrations in the aqueous humor observed in the control groups can increase with time and may get to their peak concentration 2 hours after treatment, we estimated it to be not more than 20% higher than the initial concentration in the cornea (5–6 μg/mL in our experiment). This hypothesis relies on published data on ocular pharmacokinetics of injected gentamicin and on gentamicin’s tendency to decline in the cornea after iontophoresis. Therefore, we can conclude that a short transcorneal iontophoretic treatment can induce drug penetration through the cornea and into the aqueous humor, achieving higher gentamicin concentrations than do the common eye infection treatments (eye drops or subconjunctival injection). The significantly higher gentamicin concentrations found in the cornea after a single iontophoretic treatment compared with mock iontophoresis, reveal the influence of the electric current and its importance in inducing drug penetration into the eye seg-

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Sampling Time (h)</th>
<th>Gentamicin Concentration in the Cornea (μg/g)</th>
<th>Gentamicin Concentration in the Aqueous Humor (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Iontophoresis</td>
<td>0</td>
<td>363.1 ± 127.3**††</td>
<td>0.6 ± 2.9</td>
</tr>
<tr>
<td>2</td>
<td>Iontophoresis</td>
<td>1</td>
<td>122.1 ± 47.1**†</td>
<td>9.4 ± 1.5</td>
</tr>
<tr>
<td>3</td>
<td>Iontophoresis</td>
<td>2</td>
<td>138.7 ± 119.6*</td>
<td>29.4 ± 17.4</td>
</tr>
<tr>
<td>4</td>
<td>Iontophoresis</td>
<td>4</td>
<td>47.8 ± 19.4†</td>
<td>13.7 ± 10.0</td>
</tr>
<tr>
<td>5</td>
<td>Iontophoresis</td>
<td>8</td>
<td>24.9 ± 6.1</td>
<td>0.9 ± 0.2</td>
</tr>
<tr>
<td>6</td>
<td>Mock Iontophoresis</td>
<td>0</td>
<td>2.7 ± 2.1</td>
<td>0.0%</td>
</tr>
<tr>
<td>7</td>
<td>Eye drops</td>
<td>0</td>
<td>22.7 ± 1.4</td>
<td>3.2 ± 2.1</td>
</tr>
<tr>
<td>8</td>
<td>Subconjunctival injection</td>
<td>0</td>
<td>30.0 ± 8.6</td>
<td>3.2 ± 1.6</td>
</tr>
</tbody>
</table>

Groups 1–5 (n = 8) received transcorneal iontophoresis with the mini-ion system with gentamicin-loaded hydrogel disk probe at current intensity of 1 mA (5.1 mA/cm²) for 60 seconds. Group 6 (n = 6) received transcorneal mock iontophoresis (no current) applying the Mini-ion system with gentamicin-loaded hydrogel disk probe for 60 seconds. Group 7 (n = 6) received topical fortified gentamicin drops (1.4% wt/vol in water) every 5 minutes for 1 hour. Group 8 (n = 6) received a subconjunctival injection of 0.25 mL containing 10 mg gentamicin. The animals in the experimental groups (groups 1–5) were killed at predetermined time points, and the animals in the control groups were killed immediately after the end of the drug administration.

* Significantly higher compared to group 6 (mock iontophoresis), P < 0.001.
† Significantly higher compared to group 7 (eye drops), P < 0.001.
‡ Significantly higher compared to group 8 (injection), P < 0.01.
§ Significantly higher compared to group 7 (eye drops), P < 0.05.
∥ Significantly higher compared to group 6 (mock iontophoresis), P < 0.05.
¶ Below the detection limit of the TDx system.
Gentamicin Delivery by Hydrogel Iontophoresis

The estimated values were obtained by pharmacokinetic analysis of gentamicin concentrations following corneal iontophoresis using a two-compartment pharmacokinetic model (see Figure 2). The gentamicin transport between the compartments and elimination to the posterior segments of the eye was assumed to occur according to the 1st order kinetic processes.

The rate constant of gentamicin transport are: $k_{12}$ transport from the cornea to the anterior chamber, $k_{21}$ transport from the anterior chamber to the cornea, and $k_{20}$ elimination from the anterior chamber to the posterior segments of the eye.

The time course of gentamicin concentration in the anterior segments of the eye after corneal iontophoresis was successfully described by the two-compartment pharmacokinetic model (Figs. 2, 3). More complex models, with additional (reservoir) compartments and/or drug transport processes, that were applied previously to determine the disposition in the eye of different drugs did not provide a better description of the experimental data observed for gentamicin. According to the modeling results, the elimination of gentamicin from the cornea occurs predominantly through the anterior chamber, and the contribution of other possible elimination pathways (through the sclera, back to the precorneal area, or enzymatic metabolism) is negligible. The values of the calculated pharmacokinetic parameters (Table 2) indicate that the rate-limiting step of elimination of gentamicin from the anterior segments of the eye is by drug transport from the anterior chamber to the posterior segments of the eye (with $k_{20}$ rate constant; Table 2, Fig. 2).

Gentamicin’s $t_{1/2}$ in the anterior chamber after an iontophoretic treatment of 1 mA for 60 seconds (2.07 hours) was found to be similar to its $t_{1/2}$ after topical eye drop administration (1.9 hours), as reported by Schoenwald. However, gentamicin’s $t_{1/2}$ was higher than the $t_{1/2}$ of aqueous humor turnover ($t_{1/2} = 46.2$ minutes)$^{15,16}$ and gentamicin’s clearance from the anterior chamber (CL = 1.75 μL/min) was less than aqueous humor’s clearance by bulk flow (CL = 4.67 μL/min)$^{15,16}$ These data indicate that gentamicin’s molecules may be bound, to a certain degree, to the eye tissues and are characterized by prolonged retention in the anterior segments of the eye.

Aminoglycoside antibiotics are characterized by a concentration-dependent bactericidal effect over a wide range of concentrations. In addition, exposure to aminoglycosides has a prolonged effect on bacteria (the postantibiotic effect) that persists for several hours, despite the decline of the drug concentrations below the MIC.$^{24,25}$ Thus, higher concentrations of gentamicin, compared with the MIC, are expected to produce rapid and potent bactericidal effects.

It has been determined that the MIC of gentamicin against the Pseudomonas aeruginosa species is approximately 3 μg/mL$^{17,18}$ and the MICs in 94% of 1142 isolated bacteria strains were 10 μg/mL gentamicin or less.$^{26}$ Because gentamicin concentrations in the cornea and the aqueous humor observed after iontophoresis in the present study (Table 1) were mostly higher than those MICs, potent bactericidal effects in these tissues are probable. In contrast, gentamicin eye drops produced lower concentrations and was thought to produce limited pharmacodynamic effects, despite a higher total dose of the drug. In addition, higher local concentrations of gentamicin, with a lesser extent of systemic exposure to the drug, is thought to provide additional beneficial effects, particularly during prolonged therapy, including fewer systemic adverse effects$^{27}$ and a reduced rate of emergence of drug-resistant mutants.$^{28}$ The efficacy of delivering gentamicin by iontophoresis, as described in the current study, was demonstrated in rabbits infected with Pseudomonas aeruginosa (Frucht-Pery J, Raiskup F, Mechoulam H, Shapiro M, Eljarrat-Binstock E, Domb AJ. Iontophoretic treatment of experimental Pseudomonas keratitis in rabbit eye using gentamicin-loaded hydrogel. Submitted).

As a result of a better understanding of the unique pharmacodynamic properties of gentamicin and the mechanisms responsible for its toxicity, a new method of once-daily doses is administered in various hospitals for systemic treatment of infections. The iontophoretic treatment can promote the use of this once-daily method in therapy for eye infections.$^{29}$

With respect to the clinical applicability of the hydrogel-based iontophoresis, the results presented in this report demonstrate the ability of iontophoresis to deliver doses of charged drugs to different segments of the eye by using a convenient, easy-to-operate device with a disposable drug-loaded hydrogel. Other complementary studies (to be published) have shown high effectiveness in treating eye infections, and a preliminary toxicity study revealed no permanent damage to the cornea.$^{30}$

**Acknowledgments**

The authors thank Marvin Shapiro for the analytical assay of gentamicin with the TDx System Analyzer (Abbott Laboratories).

**References**

9. Gangarosa LP, Hill JM, Thompson BL, Leggett C, Rissing JP. Ionto-
phoresis of vidarabine monophosphate for herpes-orolabialis. J In-
10. Gangarosa L, Park N. Practical considerations in iontophoresis of
11. Selinger E. Iontophoresis with contact lens type and eyecup
electrodes: some points of the theory and technic of ion transfer.
12. Fishman PH, Jay WM, Rissing JP, Hill JM, Shockey RK. Iontophore-
sis of gentamicin into aphasic rabbit eyes. Invest Ophthalmol Vis
13. Barza M, Peckman C, Baum J. Transscleral iontophoresis of genta-
icin in monkeys. Invest Ophthalmonol Vis Sci. 1987;28:1033–
1036.
14. Grossman R, Chu DF, Lee DA. Regional ocular gentamicin levels
after transcorneal and transscleral iontophoresis. Invest Ophthal-
Shapiro M. Efficacy of iontophoresis in the rat cornea. Graefes
gentamicin in the rabbit cornea following iontophoresis to the
17. Banga AK, Chien YW. Hydrogel-based iontotherapeutic delivery
devices for transdermal delivery of peptides/protein drugs. Pharm
18. Fang JY, Hsu LR, Huang YB, Tsai YH. Evaluation of transdermal
iontophoresis of enoxacin from polymer formulations: in vitro skin
permeation and in vivo microdialysis using Wistar rat as an animal
19. Kishida A, Ikada Y. Hydrogels for biomedical and pharmaceutical
applications. In: Dumitriu S, ed. Polymeric Biomaterials. 2nd ed.
20. Frangie JP. Clinical pharmacokinetics of various topical ophthal-
21. Gabrielson J, Weiner D. Pharmacokinetic and Pharmacody-
namic Data Analysis: Concepts and Applications. Stockholm:
22. Schoenwald RD. Ocular drug delivery: pharmacokinetic consider-
23. Worakul N, Robinson JR. Ocular pharmacokinetics/pharmacody-
24. Craig WA. Antibiotic selection factors and description of a hospi-
tal-based outpatient antibiotic therapy program in the USA. Eur
25. Craig WA. Pharmacokinetic/pharmacodynamic parameters: ratio-
1998;26:1–12.
26. Insler MS, Helm CJ, George WJ. Topical vs systemic gentamicin
penetration into the human cornea and aqueous-humor. Arch
27. Freeman CD, Nicolau DP, Belliteau PP, Nightingale CH. Once-daily
dosing of aminoglycosides: review and recommendations for clinical
28. Blaser J, Stone BB, Groner MC, Zinner SH. Comparative study with
enoxacin and netilmicin in a pharmacodynamic model to deter-
mine importance of ratio of antibiotic peak concentration to MIC
for bactericidal activity and emergence of resistance. Antimicrob
29. Schumock GT, Raber SR, Crawford SY, Naderer OJ, Rodvold KA.
National survey of once daily dosing of aminoglycoside antibiotics.
30. Eljarrat-Binstock E, Raiskup F, Frucht-Pery J, Domb AJ. Hydrogel
probe for iontophoresis drug delivery to the eye. J Biomater Sci