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Ocular drug delivery: a comparison of transcorneal iontophoresis to corneal collagen shields

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Abstract

Topical administration of drugs to treat ocular disease is accomplished primarily by means of solutions, ointments, and suspensions. These are relatively inefficient as drug delivery systems; often only 1% of the available drug is absorbed by the eye. Two ocular drug delivery systems currently being studied are transcorneal iontophoresis and collagen shields. Transcorneal iontophoresis is intended to drive charged drugs by an electric current into the cornea. In a *Pseudomonas* model of bacterial keratitis, as well as in pharmacokinetic studies, ocular iontophoresis of gentamicin, tobramycin, or ciprofloxacin was superior to topical ocular drops for reducing *Pseudomonas* in the cornea. Both iontophoretic methods were shown to be safe and nontoxic to the rabbit corneal epithelium. The collagen shield, designed to prolong drug contact with the eye, is made from porcine scleral tissue that has been extracted and molded into a contact lens configuration. The shields can absorb the equivalent of drug present in 1–2 drops of a topical aqueous solution. Chemotherapeutic studies in an experimental *Pseudomonas* keratitis model showed that collagen shields containing gentamicin, tobramycin, or ciprofloxacin were equal to or better than frequent applications of fortified antibiotic drops for significantly reducing the bacteria in the cornea. The results gained from these experimental studies on corneal iontophoresis suggest the need for clinical trials.

Keywords: Iontophoresis; Collagen shield; Cornea; *Pseudomonas aeruginosa*; Rabbit

1. Introduction

Increased use of extended- and daily-wear soft contact lenses has led in the past several years to the rise in the instances of severe bacterial keratitis. *Pseudomonas aeruginosa*, a common opportunistic pathogen, has become one of the most frequently encountered etiologic agents of contact lens-associated corneal infection (Iglewski, 1989; Poggio et al., 1989; Laibson et al., 1993). *Pseudomonas* keratitis is the most devastating bacterial corneal infection, and like *Staphylococ-*

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cus aureus or pneumococcus keratitis, can terminate in loss of vision.

Superficial epithelial damage and hypoxia resulting from lens wear permit attachment of organisms to the corneal epithelium and subsequent penetration through the corneal stroma (Klyce and Beuerman, 1988). Proteolytic enzymes and cytotoxins released by *Pseudomonas*, as well as factors associated with the host immune response, lead to progressive destruction of the stroma and an ensuing corneal ulcer (Iglewski, 1989). Because of the severity of *Pseudomonas* keratitis, rapid diagnosis and prompt treatment are essential in preventing sight-threatening complications of the infection. Without appropriate treatment, irreversible corneal scarring, corneal perforation, and loss of sight may occur.

Current methods of drug delivery to the eye in the treatment of ocular infections include application of commercially prepared antibiotic drops, ointments, fortified topical drops and subconjunctival antibiotic injections. While useful in treating mild superficial ocular infections, commercial drops deliver ineffective concentrations of drug to deeper tissues affected by more serious corneal infections. In this case, fortified topical drops must be applied every 15–30 min for 48–72 h, an intensive regimen that is disruptive to the patient and often necessitates hospitalization for compliance with frequent therapy (Baum, 1986; Liesegang, 1988). Subconjunctival injections are painful, may cause damage to the eye, and result in inconsistent antibiotic concentrations in the cornea. Animal experiments comparing subconjunctival injections to administration of topical antibiotic drops have yielded contradictory results (Davis et al., 1979; Baum and Barza, 1983).

Two advances in ocular drug delivery are being tested in experimental models of bacterial keratitis that could overcome the problem of insufficient drug concentrations in the eye: transcorneal iontophoresis and corneal collagen shields. Ocular iontophoresis is designed to drive charged drug into the eye with a low electrical current, delivering high concentrations of drug to corneal epithelium, stroma, and aqueous humor (Shofner et al., 1989; Hill et al., 1993a). Corneal collagen shields containing antibiotic prolong the time of drug contact with the eye (Mondino, 1991; Hill et al., 1993b). In either method, efficacy of drug delivery to the cornea surpasses present chemotherapeutic methods of treating bacterial keratitis.

2. Iontophoresis of antibiotics

Transcorneal iontophoresis involves the application of a direct electrical current driving ionized antibiotic deeper into ocular tissues. Ideally, the drug is dissolved in water and is instilled into a cylindrical eye cup circumscribed by the corneal limbal area. A platinum electrode with a charge matching that of the drug is placed in contact with a drug solution in the eye cup. A second electrode of opposite charge is connected to the rabbit's ear. The electrical current is maintained at 0.8 mA for no more than 10 min. The direct current overcomes surface resistance of the corneal epithelium, driving the drug through the semipermeable corneal epithelium and into the corneal stroma and aqueous humor (Hill et al., 1993a).

The design of an iontophoretic system involves controllable direct electric flow that completes an electrical circuit in the body. The type and charge of electrode used for electric transfer is important. Platinum has been shown to be the best electrode; use of platinum electrodes essentially eliminates ionic release, electrode degradation, and toxicity. Electrode charge, whether anionic or cationic, depends on the charge of molecules in the drug itself. Therefore, the drug vehicle should have minimal extraneous ions. In experimental animal models, iontophoresis of diluents alone (antibiotic-negative vehicle controls) were neither toxic nor bactericidal (Hobden et al., 1988a, 1989, 1990a). The salt form of a drug has been preferred for iontophoretic delivery because of the high charge density and solubility. Other parameters, such as conductivity, pH, and ionic strength of the drug solution, should be determined before and after iontophoresis (Hill et al., 1993a). One of the earliest known studies of iontophoresis of solutions into the eye includes work involving iontophoresis of zinc salts and other solutions for

treatment of corneal ulcers (Duke-Elder, 1962). Fluorescein iontophoresis has also been used in studies of human aqueous humor pharmacodynamics (Jones and Maurice, 1966; Brubaker, 1982). In studies involving the effect of human ocular iontophoresis, no adverse effects have resulted, as evidenced by slit lamp examination of patient corneas.

Experimentation involving corneal iontophoresis of antibacterial agents has been performed primarily in experimental animal models of infection. Fishman et al. (1984) used iontophoresis to deliver gentamicin into the cornea, aqueous humor, and vitreous humor of uninfected aphakic rabbit eyes. Peak drug concentrations, 71 μg/ml in the cornea and 78 μg/ml in the aqueous humor, were obtained 30 min post-iontophoresis. Peak vitreous humor gentamicin concentrations (10.4 μg/ml) were obtained at 16 h, with drug concentrations above the minimal inhibitory concentration (MIC) maintained 24 h following iontophoresis. In addition, Grossman et al. (1990) showed that iontophoresis of 10% gentamicin dissolved in 2% agar resulted in higher and more sustained drug concentrations in the cornea and aqueous humor compared to concentrations obtained from subconjunctival injections.

Rootman et al. (1988a) first employed transcorneal iontophoresis of tobramycin in the treatment of experimental bacterial keratitis in the rabbit. Infection was induced by intrastromal injection of 1000 colony forming units (CFU) of *P. aeruginosa* resulting in growth of bacteria to 10^7 CFU per cornea by 22 h post-infection. Iontophoresis of tobramycin at 22 and 27 h post-infection resulted in a 6 log decrease in CFU per cornea compared to untreated controls, and rendered 67% of the corneas bacteriologically sterile 32 h after infection. Neither application of topical fortified drops nor subconjunctival injection of tobramycin resulted in bacteria-free corneas in the rabbit model. In pharmacokinetic studies comparing drug delivery by topical drops, subconjunctival injections, and iontophoresis, iontophoresis resulted in higher and more sustained concentrations in the corneal epithelium, corneal stroma, and aqueous humor (Rootman et al., 1988b). Furthermore, iontophoresis was demonstrated to be relatively safe. Minimal superficial disruption of the corneal epithelium and slight corneal epithelial edema were observed by scanning electron microscopy and slit lamp biomicroscopy (Rootman et al., 1988b).

Additional pharmacokinetic studies by Hobden et al. (1988a) demonstrated the efficacy of iontophoresis in delivering high concentrations of tobramycin (600–800 μg/mg cornea) to uninfected, mock-infected, and *P. aeruginosa*-infected rabbit corneas. 5-times more tobramycin was delivered by iontophoresis than by bathing the cornea in an eye cup with drug to which no electrical current was applied. Iontophoresis also delivered 20-times more antibiotic than application of topical fortified tobramycin drops (1.36%).

Table 1
Viable bacteria per cornea 27 h post-infection after treatment with ciprofloxacin (Hobden et al., 1990a)

Group	Treatment	Conditions	CFU [a]
I	iontophoresis	0.8 mA × 10 min 25 mg/ml 22 h post-infection	0.25 ± 0.17
II	eye cup	10 min 25 mg/ml 22 h post-infection	1.18 ± 0.17 [b]
III	topical drops	7.5 mg/ml every 15 min for first hour, then every 30 min for 3 h	1.11 ± 0.17 [b,c]
IV	none	–	6.23 ± 0.14 [b]

[a] Log base 10 ± standard error of the mean.
[b] Significantly different from group I ($P \leq 0.008$).
[c] Not significantly different from group II ($P = 0.8$).

Hobden et al. (1989) demonstrated the efficiency of tobramycin iontophoresis in experimental aminoglycoside-resistant *P. aeruginosa* keratitis. A laboratory-developed drug resistant strain of *P. aeruginosa* (MIC, 31 μg/ml) was injected intrastromally into rabbit eyes. Iontophoresis of 2.5% tobramycin resulted in a 3 log decrease in CFU per cornea, demonstrating the potency of iontophoresis in delivering bactericidal concentrations for even a tobramycin-resistant strain of *Pseudomonas*. Furthermore, iontophoresis of the fluoroquinolone, ciprofloxacin (1 or 2.5%), was more effective in reducing the number of viable aminoglycoside-resistant *P. aeruginosa* per cornea more than 5 log units, compared to that of untreated controls (Table 1). Ciprofloxacin iontophoresis was also significantly more efficient in drug delivery and bacterial killing than application of 0.75% topical ciprofloxacin drops or use of an eye cup with 2.5% ciprofloxacin (Hobden et al., 1990a).

Iontophoresis has recently been shown to successfully deliver large complex glycopeptides to corneal tissues. Choi and Lee (1988) iontophoresed vancomycin, a high molecular mass antibiotic (1448 Da), recovering peak aqueous humor concentrations essentially equivalent to those delivered by subconjunctival injection (12.4 vs 14.7 μg/ml).

Transcorneal iontophoresis has been demonstrated as an effective antibiotic delivery system and is capable of efficiently killing *P. aeruginosa* growing in the rabbit corneal stroma. Iontophoresis of drugs for the treatment of bacterial keratitis is an experimental technique not presently used in the clinical setting. Transcorneal iontophoresis in experimental models has been demonstrated to be a safe and effective mode of antibiotic delivery to the cornea.

3. Corneal collagen shields

Corneal collagen shields were originally developed for use as therapeutic bandage lenses for damaged eyes following corneal surgery or other abrasive injury. The shields provide lubrication to the eye and protection from further epithelial trauma (Mondino, 1991; Hill et al., 1993b). Substitution of the collagen shield for the hydrophilic soft contact lens as a bandage lens has led to the suggestion of the use of the collagen shield as an effective ocular drug delivery system. Collagen shields containing antibiotic may prove effective in chemotherapy of ocular infections such as bacterial keratitis.

The corneal collagen shield is made of collagen extracted from porcine scleral tissue or bovine corium, purified, and processed into the shape of a contact lens. A single shield can absorb as much drug as is present in 1–2 topical antibiotic drops. Once applied to the eye, peptidases in ocular fluid degrade the collagen cross-links and the shield begins to dissolve. Dissolution times of shields vary from 12 to 72 h, and are dependent upon the amount of cross-linking produced by ultraviolet radiation exposure during manufacture. As dissolution progresses, the gradual release of antibiotic into tear film results in high drug concentrations reaching both the cornea and aqueous humor. Use of the shield as an antibiotic reservoir also lengthens the contact time between drug and infected tissue (Mondino, 1991; Hill et al., 1993b).

Unterman et al. (1988) first studied the pharmacokinetics of drug delivery by collagen shields. Corneal porcine collagen shields (Bio-Cor®, Bausch and Lomb, Clearwater, FL) hydrated with either 40 or 200 mg/ml tobramycin delivered much higher concentrations of drug to the cornea and aqueous humor of rabbit eyes than application of topical fortified tobramycin drops. No evidence of toxicity was observed with shields containing 40 mg/ml tobramycin, and only slight epithelial damage was found in eyes with shields containing 200 mg/ml tobramycin. Tobramycin concentrations contained within the shields before application (829 μg for 40 mg/ml tobramycin shields and 5525 μg for 200 mg/ml tobramycin shields) were much lower than the concentration of tobramycin in a single subconjunctival injection (20 mg). However, cornea and aqueous humor drug concentrations delivered by corneal collagen shields were significantly higher and much more uniform than that delivered by subconjunctival injection. Also, tobramycin con-

centrations in these tissues were well in excess of the MIC of most aminoglycoside-sensitive strains of *P. aeruginosa* (Unterman et al., 1988).

Collagen shield delivery of tobramycin has also been effective in the treatment of experimental *P. aeruginosa* keratitis in the rabbit. Hobden et al. (1988b) demonstrated that, after initiation of treatment 22 h post-infection, collagen shields hydrated with 4% tobramycin applied for 4 h were as effective against pseudomonads as 4% topical tobramycin drops applied every 30 min for the same period of time. The CFU per drug-treated cornea was reduced 4 to 5 log units with both treatments. Additional dosage of topical tobramycin drops to a drug-hydrated shield in situ was as effective in reducing the CFU per cornea as was periodic replacement of spent shields with fresh tobramycin-hydrated shields during therapy.

The efficacy of shields hydrated in tobramycin or gentamicin (1.4%) for *Pseudomonas* keratitis was found to be improved by supplemental antibiotic drops to shields in situ (Clinch et al., 1992; Silbiger and Stern, 1992). The chemotherapeutic efficacy of fortified tobramycin-hydrated collagen shields supplemented with fortified tobramycin (1.4%) drops every 4 or 6 h was superior to that of more frequent doses of topical fortified tobramycin (1.4%) drops applied directly to the cornea (Clinch et al., 1992). In a similar study, Callegan et al. (1994) compared the efficacy of tobramycin delivery by collagen shields vs topical tobramycin drops for the treatment of experimental antibiotic-sensitive *Staphylococcus aureus* keratitis. Tobramycin-hydrated shields supplemented with fortified tobramycin drops (1.36%) as infrequently as every 1, 2 or 5 h during the later stages of infection (10–20 h post-infection) sterilized all corneas. Corneal sterilization by topical drops was achieved only when drops were applied every hour. Shields and supplemental tobramycin drops or topical tobramycin drops alone applied every 1, 2 or 5 h resulted in aqueous humor concentrations that were not significantly different at each application interval. Tobramycin could not be detected in the aqueous humor 1 h after the conclusion of topical drop therapy consisting of a single drop at 10 h post-infection. Shields with a single supplemental drop applied immediately after the shield placement at 10 h resulted in an aqueous humor concentration of 8.3 μg/ml, a concentration significantly above the tobramycin MIC for this strain of *S. aureus* (Callegan et al., 1994).

Hobden et al. (1990b) demonstrated the use of shields hydrated with fluoroquinolone for the treatment of experimental aminoglycoside-resistant *Pseudomonas* keratitis. Application of shields hydrated with 25 mg/ml ciprofloxacin reduced the CFU per cornea approx. 4 log units compared to untreated controls. Only a 2 log decrease in CFU per cornea was attained with eyes treated with 40 mg/ml norfloxacin-hydrated shields (Table 2).

In the experimental keratitis studies, hydration of collagen shields with distilled water did not increase the CFU per cornea compared to untreated controls, indicating that collagen shields do not contribute to infection. Shields neither

Table 2
Viable *Pseudomonas aeruginosa* per cornea 27 h after inoculation (Hobden et al., 1990b)

Group	Solution delivered by collagen shield [a]	Number of corneas	Colony forming units [b]
I	ciprofloxacin 25 mg/ml	12	2.84 ± 0.15 [c,d]
II	norfloxacin 40 mg/ml	8	4.34 ± 0.11 [c,d]
III	tobramycin 40 mg/ml	8	6.58 ± 0.15 [e]
IV	solvent (sodium acetate)	4	6.42 ± 0.43
V	deionized water	4	6.66 ± 0.10

[a] Shields were on the eyes from 22 to 26 h post-infection.
[b] Log base 10 ± standard error of the mean.
[c] Significantly different from groups IV and V ($P \leq 0.0001$).
[d] Significantly different from all other groups ($P \leq 0.0001$).
[e] Not significantly different from groups IV and V ($P > 0.3$).

stimulated bacterial replication nor increased ocular inflammation during experimental bacterial infection. Collagen shield delivery of tobramycin and ciprofloxacin, especially with drops supplemented onto a shield already in place on the cornea, significantly reduced *P. aeruginosa* and *S. aureus* per cornea at a rate greater than that of topical drops alone. Pharmacokinetic and chemotherapeutic studies of antibiotic-hydrated collagen shields demonstrate that shields are safe and effective in delivering bactericidal drug concentrations to the cornea and aqueous humor during infection.

4. Conclusion

At present, there is no universal chemotherapeutic regimen for the treatment of bacterial keratitis and other severe corneal infections. The ideal therapeutic regimen would include not only rapid delivery and prolonged contact time between drug and ocular tissue, but also the availability of bactericidal drug concentrations in the area of infection. Application of topical fortified antibiotic drops deliver sufficient bactericidal drug concentrations to infected tissue; however, the drops must be applied very frequently, which is disruptive to the patient and hospital personnel. Subconjunctival injections do not deliver uniform drug concentrations to the cornea. The injections cause discomfort to the patient, and may result in damage to the eye.

Chemotherapeutic and pharmacokinetic studies of transcorneal iontophoresis show that iontophoresis of tobramycin and ciprofloxacin in the *Pseudomonas* keratitis rabbit model is superior to application of topical fortified drops and subconjunctival injection in delivering sufficient bactericidal concentrations to the cornea. Corneal collagen shields hydrated with tobramycin and ciprofloxacin also significantly reduce the number of bacteria per cornea in experimental bacterial keratitis models. These results are equal to, if not better than, application of topical drops alone. Both approaches are relatively safe, and neither has been toxic in the eye.

In the above-mentioned *Pseudomonas* keratitis studies, both iontophoresis and collagen shield application of ciprofloxacin were capable of killing viable bacteria in the cornea when treatment was initiated at 22 h post-infection. Compared to a 4 h application of collagen shields hydrated with 25 mg/ml ciprofloxacin, iontophoresis of 25 mg/ml ciprofloxacin for 10 min was superior in killing *Pseudomonas*, reducing the number of viable bacteria by approx. 6 log units ($P \leq 0.0080$). Collagen shield delivery of ciprofloxacin reduced pseudomonads per cornea by approx. 4 log units ($P \leq 0.0001$).

The increased incidence of bacterial keratitis provides a clinical situation in which the use of transcorneal iontophoresis of antibiotics may be indicated. In more severe cases where corneal scarring is evident, iontophoresis of other types of drugs such as anti-inflammatory agents could reduce or prevent sight-threatening complications. Use of the corneal collagen shield not only as a protective device, but also as a delivery system for a variety of drugs, indicates its use in the therapy of bacterial keratitis and other ocular infections. The ease of its application and convenience of its use makes the collagen shield a more attractive therapeutic tool than current regimens. The absence of side effects in both drug delivery methods indicates the safety with which both techniques could be used.

Further studies establishing the efficacy and safety of transcorneal iontophoresis and corneal collagen shields are needed in several areas. Experiments are needed to determine the ability of these techniques to deliver a variety of other chemotherapeutic agents, to treat other bacterial infections, to determine safety over an extended period of time, and to determine efficacy in humans. Future research and implementation of both modes of therapy could result in the use of transcorneal iontophoresis and corneal collagen shields as commonly employed technological advancements in ophthalmology.

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