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Trans-Scleral Controlled-Release of Drugs for Cataract Surgery

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1. Introduction

In the modern cataract surgery era, postsurgical inflammation is minimal, and a more comprehensive medical management strategy to treat such inflammation is still to be determined. Historically, corticosteroids have been the drugs of choice for the prevention or of postoperative ocular inflammation and are commonly used for several weeks. Surodex, an intraocular sustained release pellet of dexametasone has proven to be effective in eliminating the necessity for postoperative topical therapy, at the cost of potential movement and displacement side effects (Tan et al., 1999; Chang et al., 1999; Tan et al., 2001). In addition, there is no sufficient literature evidence to support its routine clinical acceptance. The sustained anti-inflammatory effects associated with the use of triamcinolone in the ophthalmic setting have prompted the authors to consider its therapeutic use for controlling post cataract surgery inflammation. A sub–Tenon’s capsule depot corticosteroid injection may satisfy all the requirements for an ideal anti-inflammatory strategy and may have distinct advantages for reducing complications related to patient noncompliance with eye drop administration.

Our published study comparing a single intraoperative sub-Tenon’s capsule injection of triamcinolone with conventional prednisolone eye drops substantiates a novel and more comprehensive anti-inflammatory strategy for cataract surgery (Paganelli et al., 2004). Consistent with other investigations (West, Behrens & McDonnell, 2005; Negi, Browning & Vernon, 2006) our results indicated that one 25-mg sub-Tenon’s capsule triamcinolone acetonide injection resulted in a therapeutic response and ocular tolerance comparable to 1% prednisolone acetate drops in controlling the signs and symptoms of ocular inflammation after cataract surgery. On the first post-operative day, all patients in both groups had anterior chamber cell and flare scores that gradually decreased over time. The parallel decreases in both groups suggested that triamcinolone is at least as effective as conventional prednisolone eye drops in reducing post-operative inflammation. As a result, a sub-Tenon’s
capsule injection of depot corticosteroid, an already accepted method for the treatment of various inflammatory ocular diseases, could be useful in the surgical arena. It provides a new way to eliminate patient self-medicating, avoiding problems with compliance and instruction. Furthermore, when this demonstration of the anti-inflammatory effects is coupled with its ability to treat cystoids macular edema and diabetic macular edema aggravated by cataract, (Yoshikawa et al, 1995; Thach et al., 1997; Walton, Wick & Greewald, 1999; Cardillo et al., 2005; Kim et al., 2008) a clear role for triamcinolone as a simple and more rational management strategy for post-cataract surgical inflammation begins to emerge.

One posterior sub-Tenon’s capsule triamcinolone injection also had ocular tolerance equivalent to prednisolone eye drops through 4 weeks of follow-up. There were no significant differences between the two treatment groups in the number of adverse events, changes in visual acuity (VA), or lack of response. The potential complications of sub-Tenon’s capsule injection of corticosteroids include inadvertent injection into the choroidal or retinal circulation, (McClean, 1975; Ellis, 1978; Morgan et al., 1988) globe perforation, (Giles, 1974; Schlaegel & Wilson, 1974; Schechter, 1985) and occlusion of the central retinal artery (Ellis, 1978), blepharoptosis, proptosis, orbital fat atrophy, delayed hypersensitivity reactions, strabismus, conjunctival hemorrhage, chemosis, and infection also have been reported (Ellis, 1974; Nozik, 1976; O’Connors, 1976; Mathias et al., 1978). Although both studies are not adequately powered to detect rare complications, these complications were not observed.

An increase in intraocular pressure (IOP) after topical or systemic administration of corticosteroids is of particular concern (Herschler, 1976). Patients who receive sub-Tenon’s capsule injections of corticosteroids may not respond to maximal anti-glaucomatous therapy and, therefore, may require surgical excision of the depot because of a persistently elevated IOP (Akduman et al., 1996). As increased IOP may be a function of the interaction between the disease itself and the use of topical or systemic corticosteroids - the role of posterior sub-Tenon’s capsule corticosteroids in ocular hypertension is not always clear. Therefore these concerns may not apply to patients who underwent surgery whose status in responding to corticosteroids is unknown. Following a posterior 40-mg triamcinolone sub-Tenon’s capsule injection, an incidence of increased IOP that was lower than expected was surprisingly observed (Paganelli et al., 2004). In our most recently study, only one eye (triamcinolone group) had an IOP that exceeded 25 mmHg, and the IOP returned to a normal level with topical antihypertensive drops (Paganelli et al., 2009). However, beyond our 28-day follow-up period, delayed onset of increased IOP must be considered. The depot formulation was placed forward under sub-Tenon’s capsule and, if an intractable IOP increase occurred, the remainder of the depot could have been easily removed.

Other authors have also confirmed our theory and similar results have been published applying a similar technique targeting operations in cataract and retina surgery (Negi, Browning & Vernon, 2006). Although we cannot draw definitive conclusions based on these initial findings, the results suggest further investigation is needed. A large phase III multicenter trial is being considered to evaluate this potential treatment. Investigation of the latest-generation fluoroquinolone formulation combined with non-steroidal anti-inflammatory drugs is currently underway in our laboratory and will be the next level of improvement for this suggested system.
This suggested anti-inflammatory approach provides the ophthalmologist with an alternative tool to costly controlled drug delivery and eliminates the need for patient self-medication, which avoids problems with compliance and instruction. Such an approach could be especially important in the third world, where topical medications may not be available after intraocular surgery.

2. Anti-infection prophylaxis for cataract surgery

The achievement of high antibiotic concentrations within infected tissue is important for a number of reasons. First of all, in order for the therapy to be effective, the necessary bactericidal concentrations to eradicate the pathogen must be achieved and maintained. The bactericidal activity of fluoroquinolone is largely concentration-dependent, which explains why peak concentration values and the 24-hour area under curve (AUC) are important determinants of individual drug activity (potency). Higher drug exposure and total dosages, as indicated by higher AUCs, may be associated with more effective eradication of the infecting organism (Paccola, Jorge & Barbosa, 2007). Second, the emergence of bacterial resistance to fluoroquinolone also appears to be concentration-dependent (Bui, Dang & Hwang, 1995; MacDonald, 2006). At fluoroquinolone concentrations above the minimum inhibitory concentration (MIC), the frequency of bacterial mutation increases exponentially as the concentration decreases. This means that the employment of fluoroquinolone that can result in tissue concentrations only modestly above the MIC could result in the development of antibiotic resistance to that specific fluoroquinolone (Bui, Dang & Hwang, 1995). Thus, the ability of a drug to produce high drug concentrations within infected tissues may facilitate enhanced antibacterial activity with a reduced likelihood of emergence of resistance. For a future and revolutionizing therapy, this required target could only be achieved by the development of an eye-specific antimicrobial agent or by an appropriate drug delivery approach engineered to enhance drug penetration (Velpandian, 2009).

3. Conventional antimicrobial strategy and its limitations

The route for local ophthalmic drug delivery remains the topical application of solutions at the surface of the eye as drops. Drug delivery to intraocular tissues by this approach, however, is limited by: (A) the significant barrier to solute flux provided by the corneal epithelium; and (B) the precorneal drug loss that occurs by way of the tear fluid turnover. Although a relatively small fraction of the dose applied topically reaches the intraocular tissues, the topical formulations can deliver therapeutic concentrations in tissues of the anterior segment, mainly because the administration of a high dose of the drug is necessary. It has been estimated that typically less than 5% of a topically applied drug actually permeates the cornea and eventually reaches intraocular tissues. The major portion of the instilled dose is absorbed systemically by way of the conjunctiva, through the highly vascular conjunctival stroma and through the lid margin vessels. Additionally, systemic absorption also occurs when the solution enters the nasolacrimal duct and is absorbed by the nasal and nasopharyngeal mucosa (Lang, 1996; Geroski & Edelhauser, 2001).

Conventional ocular pharmacokinetic views have downplayed the possibility of any highly effective transfer of a drug from an eye drop to the aqueous and vitreous humor.
Widely accepted for conjunctival and corneal infection, new antibiotic drops are often exploited for prophylactic use without rationalizing the penetration characteristics in the drug development stage. Interesting, in the currently clinical scenario, in contradiction with the physiological processes involved in guarding the eye against xenobiotics, the newer fluoroquinolone have been marketed partly on the basis of their excellent ocular penetration after topical administration - but at the cost of extremely artificial supportive methods used in their development (Kim et al., 2005; Sollomon, Donnenfeld & Perry, 2005). A careful literature and methods review of the relevant studies will point to an unacceptable high antibiotic loading dose and single point measurement (usually at a short- and higher peak concentration-time point) which is used to demonstrate the potential of the newer-generation fluoroquinolones to overcome these barriers to drug delivery. Tested in a practical clinical setting, where a single drop is instilled ever four to six hours and poor patient compliance to the treatment is a common issue, even later generation antibiotics may face obstacles in reaching high and even more importantly sustained therapeutic levels. In support of our theory against topical antibiotic delivery in cataract surgery, our laboratory has elaborated a more simplistic and realistic investigation method to experimentally address the role of topical prophylaxis in the surgical scenario.

An aqueous humor bioactivity comparison of several fluorquinolones following a single topical drop delivery was carried out in our laboratory with the single purpose of evaluating quantitatively over time the bioactivity of ciprofloxacin 0.3%, levofloxacin 1.5%, gatifloxacin 0.3% and moxifloxacin 0.5% in the aqueous humor of rabbit eyes. For supportive methods, a total of 64 New Zealand rabbit eyes were topically treated with a commercially available formulation of ciprofloxacin 0.3%, levofloxacin 1.5%, gatifloxacin 0.3% and moxifloxacin 0.5% eye drops. Following an initial loading dose consistent with a single antibiotic drop the aqueous humor was sampled at 30 minutes, 1, 2 and 4 hours post-treatment. Biological activity was indirectly determined from the size of the zone of inhibition (ZOI) of filter paper disc soaked in 25μl of aqueous humor drawn from treated eyes and placed on an agar plate surface-cultured with Staphylococcus Epidermidis. To our amazement, but theoretically expected, although not significant, 0.5% moxifloxacin eye drops showed an initial (30 minutes and 1 hour post-treatment) trend towards superior aqueous bioactivity compared to all other tested formulations (Figure 1). At and following the second hour, the aqueous humor drawn from all treated eyes failed to demonstrate any bacterial inhibitory potential for the four tested formulations, since no zone of inhibition could be observed. The main conclusion of this method of antibiotic-bioactivity exploration is that sole reliance on the minimum inhibitory concentration and artificial pharmacokinetics studies as guides to antibacterial efficacy may be misleading and even newer-generation fluorquinolones failed to demonstrate a significant aqueous bioactivity using a dosing regimen that simulated prophylactic use after cataract surgery (Paganelli et al., 2010).

Despite surrogate studies showing that topical antibiotics decrease bacteria on the ocular surface and anterior chamber, and that some topical antibiotics can penetrate the cornea and the anterior chamber (Callegan et al., 2003; Price, Quillin & Price Jr, 2005; Sollomon, Donnenfeld & Perry, 2005), there has not been a prospective randomized study showing that topical antibiotics prevent endophthalmitis. Bioavailability has been touted in the literature, but its relationship to endophthalmitis in the human is unknown. In one rabbit
study, several drops of moxifloxacin administered preoperatively prevented endophthalmitis from developing (Kowalski et al., 2004). This was the first study to suggest that topical antibiotics alone can prevent endophthalmitis. Once an organism reaches the vitreous, however, topical application of antibiotics is probably not efficacious (Costello et al., 2006). Furthermore, in vitro susceptibility data and animal studies cannot be translated uniformly into a solid and reliable assessment of in vivo efficacy because of additional factors such as anatomic location and pharmacodynamics.

![Image of aqueous humor bioactivity](image)

Fig. 1. Aqueous humor bioactivity following the delivery of a single topical drop of moxifloxacin 0.5% evaluated quantitatively over time: (a) 30 minutes, (b) 1 hour, (c) 2 hours and (d) 4 hours post drop-instillation (Paganelli et al., 2010).

4. Technological strategy of micro and nanoparticles for ocular trans-scleral drug delivery

Research and development in the area of pharmaceutical biotechnology has introduced an increasing number of therapeutic possibilities for medical treatment of many diseases, especially ocular diseases. The field of drug-controlled release represents a frontier area in medical science, involves a broad multidisciplinary approach, and has contributed decisively to improving human health. The systems offer clear advantages compared with conventional drug dosage forms, such as increasing the drug efficiency, reduced toxicity, increased patient compliance, improved safety and patient comfort (Zeimer & Goldberg 2001).

Sustained drug delivery devices offer an excellent alternative to solve many problems associated with patient use of postoperative drops in cataract surgery. These devices are made either from biostable (non-biodegradable, non-erodible), or from biodegradable (erodible) polymers. The erodible devices have an inherent advantage over the non-erodible systems in that as they degrade they gradually disappear from the site of implantation. The particles consist of drugs entrapped within a polymer, and are frequently classified by size into microparticles (> 1 μm) and nanoparticles (< 1 μm). According to physical structure, the microparticles are classified as microspheres and microcapsules. Microcapsules have a drug
core surrounded by a polymeric film, while in the microspheres the drug is dispersed through the polymeric matrix. The aim in the development of microspheres and microcapsules has been to develop long-acting injectable drug depot formulations with specific drug targeting and delivery optimization (Herrero-Vanrell & Refojo 2001). These systems have been under evaluation for ophthalmic drug delivery purposes for the past 20 years. Among the biodegradable polymers that have been investigated to make microparticles for drug delivery are gelatin, albumin, polyorthoesters, polyanhydrides, and polyesters, particularly polymers of polylactide acid (PLA), polyglycolic acid (PGA), and poly (lactide-co-glycolide) acid (PLGA). These polyesters have been most frequently used to make microspheres for subconjunctival and intravitreal drug delivery. Among the polymeric particles potentially useful for ocular drug delivery, the microspheres have been most commonly used, mainly due to the delivery possibility through conventional small-gauge syringes (Herrero-Vanrell & Refojo, 2001).

In our studies, the spray drying technique was used to produce biocompatible microspheres that were uniform in shape and size, sterilized by gamma radiation, and suitable for ocular administration. The great advantage of this methodology is that it produces dried microspheres of small size and free of solvent residues and other compounds needed in the emulsification methods. The mean particle sizes and encapsulation efficiencies were $1.03 \pm 0.30 \mu m$ and $97.86\% \pm 0.96\%$, respectively. These systems have proved to be suitable for subconjunctival and intraocular injection displaying pharmacokinetic profiles with high and prolonged drug concentration in aqueous and vitreous humors (Silva-Jr et al., 2008; Silva-Jr et al., 2009). Figure 2 shows the the images of the scanning electron microscopy of ciprofloxacin-loaded PLGA microspheres utilized in most of our studies.

Subconjunctival ocular drug delivery represents another attempt to elevate intraocular drug concentrations and minimize the frequency of dosing (Hosoya, Lee & Kim, 2005).

![Fig. 2. Scanning electron microscopy images of ciprofloxacin-loaded PLGA microspheres with drug/polymer proportions of (A) 1:1; (B) 1:2; (C) 1:3 and (D) 1:5 (w/w).](image-url)
Compared with direct intraocular injection, this approach is less risky to the patient and less invasive. Since sclera is much more permeable than conjunctiva, the formidable permeability barrier consisted of both cornea and conjunctiva can be avoided altogether in such approaches (Olsen et al., 1995; Hosoya, Lee & Kim, 2005). The advantage of subconjunctival implants as opposed to conjunctival injection of solution is the achievement of higher drug concentrations and sustained release of the drug in both aqueous and vitreous humor and even retinal areas (Gilbert et al., 2003). Dl-polylactide (PLA) nano- and microparticles containing budesonide (which inhibits the expression of vascular endothelial growth factor (VEGF) for the treatment of angiogenesis in the retina) are reported to afford sustained release of budesonide in vitro. Subconjunctival injection of PLA microparticles (3.6 μm) led to a much higher budesonide concentration in retina and vitreous humor over 14 days, compared with the solution form of dosing and PLA nanoparticle (345 nm) administration (Kompella, Bandi & Yalasomayajula, 2003). It was previously published that the collagen matrix and fibrin sealant provided a better controlled release of cisplatin and carboplatin, respectively, than the conventional drug solution, attaining higher drug concentrations after subconjunctival administration using rabbits in several ocular tissues including retina (Simpson et al., 2002; Gilbert et al., 2003). Trans-scleral delivery is a minimally invasive method that achieves targeted delivery of higher therapeutic levels of anti-infection and anti-inflammatory drugs to the anterior and posterior segments of the eye. This drug delivery modality exhibits linear kinetics of absorption and elimination, with potential to deliver a constant drug concentration. By bridging the potential of later generation antibiotics, trans-scleral delivery of biodegradable microparticles sits at the crossroads of patient comfort, treatment compliance, and enhanced safety.

5. Subconjunctival delivery of antibiotic in controlled-release microspheres

Lack of commercial viability in conjunction with an absence of clarity or consensus about the mechanisms of ocular drug penetration and accurate drug delivery has translated into attenuated enthusiasm among pharmaceutical companies and researchers. This hinders the exploration of novel therapeutic approaches for the eye with appropriate newer molecules and better engineered drug delivery technologies. To the best of our knowledge our recently published investigations open up a new era offering the potential of no need for postoperative drops in cataract surgery (Paganelli et al., 2004; Paganelli et al., 2009; Cardillo et al., 2010). These studies gave new information and substantiated a novel and optimized antibiotic prophylaxis strategy using slow delivery technology. Superior vitreous penetration and immediately higher concentrations of antibiotic in the aqueous humor, when compared with the common practice of dosing eye drops 6-times-daily, both support and add rationale to the use of a slow-release trans-scleral drug delivery system in preventing endophthalmitis after cataract surgery. In addition, when this pharmacologic achievement is coupled with its ability to free the patient from the difficulties posed by topical administration, a clear role for this system as a simple and more comprehensive weapon for fighting postoperative infections begins to emerge.

By exploring superior sclera permeability and to avoid the rate-limiting barriers of the cornea and conjunctiva, subconjunctival routes may offer a promising alternative for enhanced drug delivery and tissue-targeting compared with topical routes (Clements &
Tailor, 1987; Behrens-Baumann & Martell, 1988; Barza, 1989; Starr & Lally, 1995; Prausnitz & Noonan, 1998). Confirming our premise, the controlled-release microsphere delivered therapeutic concentrations of antibiotic greater than the minimum inhibitory concentration for most common ocular pathogens up to 10 days after injection. The dosing regimen tested in this experimental investigation fits into a realistic clinical scenario and may provide a surrogate to assess achievable postoperative concentrations. Similar to previous studies (Gilbert et al., 2003; Kompella & Bandi, 2003; Kosoya, Lee & Kim, 2005) the parallel and higher aqueous and vitreous levels of ciprofloxacin-loaded microspheres, as opposed to the same concentration of ciprofloxacin in its free form after a single subconjunctival injection and to topical ciprofloxacin delivery, are considered a highly desirable pharmacological achievement. Furthermore, given the inherent advantages of intraoperative sustained-release antibiotics, particularly patient compliance and convenience, the studied system may achieve a breakthrough in the development of more successful treatment modalities, suggesting a possible new way to progress anti-infection prophylaxis in parallel with antibiotic drug development.

In an experimental rabbit model of endophthalmitis prophylaxis, we have demonstrated that prophylaxis with a biodegradable controlled-release system trans-scleral delivered through a single subconjunctival injection can reach sustained therapeutic levels in the anterior chamber that predictably reduced bacterial recovery and signs of clinical endophthalmitis (comparable to conventional topical drops). Extrapolating these findings to clinical settings, where typically patients are noncompliant with treatment, we could postulate and expect a superior performance for microspheres system over conventional postoperative drops. The frequency of application is important for attaining adequate antibacterial concentrations, and poor compliance also prevents the drops from reaching efficacious levels. Compliance with topical therapy was studied using an electronic device in ambulatory patients who underwent cataract surgery; all patients were noncompliant regarding total dose, time intervals, and premature discontinuation of therapy (Hermann, Ustundag & Diestelhorst, 2005).

Since adverse events are an important concern with any new dosage form, it is also important to ensure that the system chosen for prophylaxis following cataract surgery is safe and well-tolerated, eliminating any potential toxic effects. The biocompatibility of periocular microspheres of biodegradable polymers has been extensively investigated. In vivo there were no drug or procedure-related adverse events and no inflammatory cells or fibrous tissue response at the site of injection was observed. Clinically, in addition to its minimally invasive and pharmaceutically acceptable nature, no drug or procedure-related adverse events occurred (Paganelli et al., 2009; Cardillo et al., 2010).

Pharmacokinetic profiles of aqueous and vitreous humor in rabbit eyes using 0.2 mg/0.1mL of ciprofloxacin microspheres or 2 mg/0.1mL of free ciprofloxacin were compared to a single drop of 0.3% ciprofloxacin six times a day. In 45 rabbits, Staphylococcus aureus was injected into the anterior chamber and 15 were randomly chosen to receive 1 drop of 0.3% ciprofloxacin every 4 hours during 24 hours, 15 received drops of basic salt solution (BSS), and 15 received ciprofloxacin microspheres. After 24 hours endophthalmitis score were recorded, aqueous and vitreous humors were cultured and histology was performed. The subconjunctival administration of non-encapsulate ciprofloxacin exhibited a rapid absorption and permeation between aqueous and vitreous humors, with sharp decay within 6 hours of application (Fig. 3).
Fig. 3. Comparative pharmacokinetic profiles between the aqueous and vitreous humors after subconjunctival injection of the non-encapsulated ciprofloxacin (2mg/0.1ml). Key: (□) aqueous humor, (○) vitreous humor.

Compared to ciprofloxacin solution injection and ciprofloxacin eye drops, drug levels in the microspheres group showed an immediate and sustained trend towards increased aqueous and vitreous penetration (Fig. 4). A distinct pharmacokinetic trend was observed when the microsphere group was compared with the topical administration group. In the 8 hour-period studied for this group in the design, an immediate higher intraocular antibiotic level was found in the microsphere group, except for the fifth hour that demonstrated comparable measurements. At this time point, one hour prior to sampling, an extra drop of ciprofloxacin was instilled, following the pre-established schedule of one loading drop every 4 hours (Fig. 4).

Fig. 4. Comparative pharmacokinetic of ciprofloxacin in the aqueous humor after the single subconjunctival injection of CP (ciprofloxacin)-loaded PLGA microparticles (2mg/0.1ml) (●) and topical CP eye drops 0.3% (○).

Comparing the aqueous concentration following a single subconjunctival injection of the ciprofloxacin-loaded microspheres to the regular ciprofloxacin formulation, a statistically significant difference in favor of the microspheres group was noticed immediately following
drug administration and sustained throughout the entire study period. The system allowed sustained aqueous humor concentration of ciprofloxacin in the therapeutic range for most common ocular pathogens (2μg/mL) for up to 8 days (Fig. 5).

Fig. 5. Comparative pharmacokinetic of ciprofloxacin in the aqueous and vitreous humors subconjunctival administration of 2mg/0.1ml of CP-loaded microparticles. Key: (□) aqueous humor, (O) vitreous humor.

In contrast to the ciprofloxacin microspheres and solution groups, no measurable levels of ciprofloxacin could be detected in the vitreous cavity following topical administration. Assessing the vitreous concentration, a statistical significant difference in favor of the microspheres group was immediately noticed following drug administration and sustained throughout the entire study period.

6. Conclusions

Our scientific observations suggest that a trans-scleral antibiotic delivery system is both effective and may help to eliminate patient noncompliance. By freeing the patient from the hassles and expenses of topical therapy post cataract surgery, a new anti-inflammatory and anti-infection paradigm in modern cataract surgery has been introduced, meriting further consideration. In parallel to antibiotic development, exploiting the routes for trans-scleral delivery or circumventing the cornea-conjunctival barriers will be the key to an ultimate anti-infection strategy in the modern cataract surgery era. While the challenges are formidable, the experimentally and clinically tested systems hold promise for new paradigms in dosing anterior segment drugs. However, no study will provide the final answer regarding optimum antibiotic prophylaxis in this continually developing field. Advances in antimicrobial therapy and modes of delivery make this a dynamic area and highlight the need for continued investigation and periodic guideline reviews to keep pace with new developments to optimize patient care.

7. References


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