Pharmacokinetics of Antiglaucoma Medications

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ABSTRACT
Pharmacokinetics may be simply defined as what the body does to the drug, as opposed to pharmacodynamics which may be defined as what the drug does to the body. This review is dedicated to the fate of antiglaucoma medications administered externally. A special focus is made on the preservatives used in the antiglaucoma medications. Although from a pharmacokinetic point of view, these preservatives may improve drug penetration but their ocular surface adverse effects cannot be ignored.

Keywords: Antiglaucoma medications, Ocular surface disorder, Pharmacokinetics, Preservatives.

INTRODUCTION
Glaucoma is a chronic disease of the eye which is a major cause of blindness all over the world.1 Management of glaucoma is a multipronged approach which involves simple observation and investigation to medical treatment, laser therapy and various types of surgery.

Since early times, ophthalmologists have been fighting this blinding disease, yet total cure is still not in sight. Surgical therapy was the mainstay earlier with surgeries, like trephination, iridencleisis, sclerectomies and sclerotomies in the past years. Surgical excellence too has come a long way, subscleral trabeculectomy with modulations—surgical and pharmacological. Laser trabeculoplasty, visco-canaliculostomy, nonpene-trating surgery and glaucoma drainage devices are the later additions in selected cases. In this era of rapid technological advances in surgical devices and procedures, it is no small wonder that we now understand aqueous dynamics of the human eye better. This is the result of untiring research for newer molecules to contain glaucoma, which is fueled by a tough competition in the pharma industry. The last word has not yet been written about the best drug ever. Fortunately, what has happened in the process is that now we are equipped with an ever expanding armamentarium of drugs at our disposal to mix and match to customize the treatment individually for our glaucoma patients. Intraocular pressure (IOP) being the sole modifiable factor in most cases, its management has been known to retard progression of glaucomatous damage1,2 as effectively as surgery in the least with fewer complications.3

Today medical therapy being the mainstay of treatment for a wide variety of glaucoma and particularly primary open angle glaucoma (POAG) requiring life time medication; a comparative knowledge of how the drugs are formulated, the additives and preservatives used to enhance the efficacy would be helpful. A practicing ophthalmologist should be familiar with the pharmacokinetics of the products being prescribed every day since claims of better drug performance by pharmaceutical companies by adding these additive looms at large and one should not get blinded by these claims. A brief review of the pharmacokinetics of commonly prescribed group of drugs has been prepared.

Pharmacokinetics: How the Drug reaches Inside the Eye?
To reach its receptor, often a drug needs to be administered away from its target tissue, with eye being a exception that drugs can be administered topically to reach the target receptors directly.

Pharmacokinetics deals with the absorption, distribution, metabolism and elimination of the drug.

In the eye, the concentration of the drug or its availability at the receptors depends on following factors:
1. Concentration and kinetics of drug in conjunctiva
2. Absorption across cornea and sclera
3. Rate of metabolism and elimination from the eye.

Kinetics in Conjunctival Cul-de-sac
As the drug is administered, it mixes with the tear film. Drug availability for absorption from the cornea and sclera also depends on:

a. Drop size: Average volume of tears in cul-de-sac is 7 to 9 μl; however, it can hold up to 30 μl. The size of average topical medications ranges from 25 to 56 μl, therefore, about half the drug is washed away at time of instillation
b. Drainage via nasolacrymal system which reaches its peak, minutes after instillation. The systemic toxicity mainly depends on this form of absorption.
Therefore, a very little amount of drug is available for absorption from cornea and sclera.

Absorption via cornea and sclera: Tear film is a trilayered structure with outermost layer made up of lipid followed by aqueous layer and mucin layer with lipid layer favoring the transport of lipid soluble (nonionized) drug and aqueous layer favoring absorption of water soluble (ionized) drug (Fig. 1). Cornea also contains a lipid-water-lipid with epithelium and endothelium containing more lipid being easily traversed by lipid soluble drugs and stroma being traversed by water soluble drugs. The absorption and transport of drugs across cornea depends on the fact that it should exist both in ionized and nonionized form with both forms in equilibrium one replacing the concentration of other to maintain equilibrium.

Intrinsic determinants influencing drug availability may include the factors like:

a. Intraocular circulation either to vascular system or aqueous outflow system
b. Drug binding, e.g. 80 to 85% of beta blockers are bound by melanin, while only 40% of pilocarpine has been reported to bind to melanin.

Other Factors influencing Drug Action

Vehicles

These may act as tools for increasing the viscosity of the formulation, thereby decreasing the loss from the conjunctival sac by minimizing the initial rapid drainage of drug. This effectively increases the drug-cornea contact time. Various vehicles used in glaucoma medication are polymers, like methyl cellulose, polyvinyl alcohol, ointments, suspension, such as pilocarpine gel and liposomes. They have the inherent quality of making the vision misty soon after instillation.

pH

Generally, weaker bases display a more nonionized form at higher pH. These absorb better at higher pH while weaker acids are absorbed more at lower pH. Most antiglaucoma medications are weaker bases, thus favorably amplifying their take-up.

Concentration

Drug efficacy can be enhanced to a limit by increasing the concentration. After a stage, the percentage of drug absorbed decreases and drainage via nasolacrimal system increases thereby increasing the systemic absorption through nasal mucosa and the toxicity. Using monkey as a model, greater percentage of 1% pilocarpine could be recovered from aqueous than 4% or 8%, after topical instillation.

Particle Size/Molecular Weight

This is generally not a factor influencing efficacy as ophthalmic drugs have molecular weight of less than 500 gm/mole.

Drop Size

As already pointed out, increasing the drop size beyond the maximum capacity of the conjunctival sac, as also the method of instillation, both determine bioavailability and onset of side effects.

Additives

Some additives are necessary for drug stability and decontamination, e.g. benzalkonium chloride serves this dual purpose with the added ability of decreasing the surface tension of the aqueous layer of the tear film, thus allowing more drug to mix with the tears.

Genetic Factors

The response of a drug is dependent on the receptor population based on the genetic makeup. Thus, clinically there can be responders (15% reduction of IOP from baseline at peak drug effect) and nonresponders (IOP did not decrease by 10%).

Metabolic Factors

a. Blood flow
b. Hormonal regulation
c. Neural regulation
d. Availability of nutrients
e. Age.

Pathological Conditions

a. Inflammation
b. Nonintactness of epithelium
c. Disrupted blood aqueous barrier
d. Concentration of aqueous humor.

Role of Preservatives in Glaucoma Medications

Preservatives are added to ophthalmic formulations to have antimicrobial effects in multidose bottles, thus keeping the drug safe from various microbes. This is mandated by FDA. Preservatives have two important functions:

a. To prevent decomposition of the active drug and
b. Provide sterility in multidose bottles.

Preservatives may be further classified as:

1. Detergents: These are the oldest preservatives in use. These act by disrupting the lipid component of the cell wall of microbes, destroying cell membrane and extruding all
organelles. The most prevalent example of this class is benzalkonium chloride, which is perhaps the most common used preservative even today.

2. **Oxidizing agents**: These act by oxidizing DNA, protein and lipid content of microbes and rendering them unharmed. Recently, formulated purite (stabilized oxychloro complex) and sodium perborate are important examples. This compound requires light protective packaging.

3. **Ionic buffers**: These are the most recently developed preservatives with good antifungal and antibacterial properties when exposed to cations, such as those that are normally encountered in the tear film of the eye, the substance becomes inactive. This is thought to induce reduce cytotoxicity to the ocular surface. An important example is SofZia, which is a combination of boric acid, zinc, sorbitol and propylene glycol.

4. **Slow release mechanism**: In a recent study, Thermo-sensitive polymer (poly-N-isopropylacrylamide (PNIPAAm) has been developed which undergoes phase transition when the temperature is raised to 32°C, the drug gets entangled into the mixture of polymer chains or the cross-linked hydrogel polymer and is slowly released for topical effect (at a higher temperature) making the drug long lasting. Results from the study done with epinephrine suggest the use of thermosensitive polymer solutions or hydrogels has potential in controlled release antiglaucoma ophthalmic drugs.

### SOME COMMON PRESERVATIVES DESCRIBED IN DETAIL (TABLES 1 AND 2)

#### Benzalkonium Chloride

The most common preservative in antiglaucoma preparations is benzalkonium chloride (BAK), a quaternary ammonium compound used in over 70% of the existing multidose bottles. Its concentration in glaucoma formulations ranges from 0.004 to 0.02%.

**Mechanism**

- It disrupts microbial cell membrane and denaturing proteins
- It reduces surface tension, helps penetration of drugs and improves IOP lowering effect.

**Advantages**

1. Very good preservative with good antifungal and antibacterial properties
2. Increases drug penetration
3. Most widely tested and tried.

**Side Effects**

Pathology of adverse effects:

- BAK promotes activation of lipoxygenases
- BAK is the most commonly used preservative in ophthalmic preparations, has a high affinity for membrane proteins and may accumulate in ocular tissues, inducing cell toxicity and/or cell death in a dose-dependent manner
- Synthesis, and secretion of eicosanoids, inflammatory mediators and cytokines such as IL-1α, IL-8, IL-10 and TNF-α, resulting in delayed hypersensibility and allergic reactions.

Mechanism of BAK toxicity:

- A detergent effect causing loss of tear film stability
- Direct damage to the corneal and conjunctival epithelium
- Immunoallergic reaction

Due to potential harmful effects of BAK, especially in chronic requirement in glaucoma, a search for preservatives with better safety profile was launched even as BAK remains widely used even today.

#### EDTA (Ethylenediaminetetra-acetic Acid)

It is a common chelating agent which is used for therapeutic purpose in cases of band shaped keratopathy. It is used as additive and preservative in several ophthalmic formulations for its preservative property.

**Mechanism**: Chelates trace metals and helps preserve the drug.

**Example**: Betagan (levobunolol).

#### Stabilized Oxychloro Complex

Stabilized oxychloro complex (Purite, Bio-Cide International Inc., OK, USA) first developed in 1990s is a oxidizing agent which causes damage to the DNA proteins and lipids of microbes and destroys them. Its efficacy has been thoroughly studied.

**Mechanism**

SOC dissociates into water, oxygen, sodium and chlorine free radicals. The chlorine free radicals inhibit microorganism protein synthesis within cells by way of glutathione oxidation, which causes microbe cell death.

Clinical examples brimonidine tartarate solution.

**Advantages**

1. Broad antimicrobial effects including antibacterial, antifungal and antiviral effects
2. Well tolerated by the ocular surface.

**Disadvantages**

1. Lack of long-term studies
2. Has to be kept in opaque bottles as on exposure to sunlight it breaks into its constituents.

#### SofZia

It is a recently developed preservative which is very gentle to the eyes and retains good antimicrobial activity.
Mechanism
When it comes to contact of cations in cul-de-sac, it is rendered inactive thereby reducing its toxicity. It contains boric acid, zinc, sorbitol and propylene glycol.

Advantages
a. Reduced conjunctival inflammation as compared to BAK
b. Decreased corneal epithelial changes
c. Better compliance and therefore better IOP control
d. Similar antimicrobial activity as BAK.

Disadvantage
Lack of long-term studies.

Polvinyl Alcohol (PVA) (Liquifilm)
Water-soluble synthetic polymer, resistant to temperatures up to 200°C.

Properties
1. Polyvinyl alcohol has excellent film forming, emulsifying, and adhesive properties. It is also resistant to oil, grease and solvent
2. Used in eye drops and hard contact lens solution as a lubricant
3. It has no antimicrobial properties.

Chlorobutanol
1. Chlorobutanol is a widely used, very effective preservative in many pharmaceuticals and cosmetic products, e.g. injections, ointments, products for eyes, ears and nose, dental preparations, etc.
2. It has antibacterial and antifungal properties. Chlorobutanol is typically used at a concentration of 0.5% where it lends long-term stability to multi-ingredient formulations.

Polyquaternium
This compound is a member of cationic copolymers used as ingredient for antistatic and film-forming properties primarily in hair-care products and in skin and eye care products. These polymers are substantive to protein substrates and have water-binding property. It has the tendency of decreasing density of goblet cells thereby decreasing tear production.

Cap Designs
Innovative ideas to encourage compliance in glaucoma patients and hence, regard for their quality of life:
1. The compliance cap/reminder cap provides a method for tracking doses of eye drops. A window in the cap displays a number indicating which dose the patient is taking
2. Micropressor-assisted delivery: A sensor sensitive to pressure on the bottle used in study ensured 100% compliance
3. Metered drop: Measured amount of fluid is delivered into the eye.

COMMON GLAUCOMA DRUGS AND DISPENSING METHODS
1. Pilocarpine: comes as ophthalmic solution 1%, 2% and 4%
   Preservative: Benzalkonium chloride 0.01%.
   Inactives: Hypromellose 2910, boric acid, sodium citrate, sodium chloride (present in 1% only); hydrochloric acid and/or sodium hydroxide (to adjust pH); purified water
   pH: 3.5 to 5.5
   Osmolality: 290 to 350 mOsm
   Formulations: Drops, suspension, gel (once daily)
2. Timolol: 0.25% and 0.5%, timolol gel
   Preservative: Benzalkonium chloride 0.01%
   Inactive ingredients: Monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and water for injection
   pH: 7.0
   Osmolality: 274-328 mOsm
   Mode of dispensing: ISTALOL ophthalmic solution, 0.5% supplied in white malleable plastic (low density polyethylene or LDPE bottle with 15 mm LDPE yellow cap and 15 mm LDPE white dropper tip)
3. Brimonidine: 0.1%, 0.15% and 0.2%
   Preservative: Purite® 0.005% (0.05 mg/mL)
   Inactives: Sodium carboxymethylcellulose; sodium borate; boric acid; sodium chloride; potassium chloride; calcium chloride; magnesium chloride
   Osmolality: 250-350 mOsm/kg
   pH: 7.4 to 8.0 (0.1%) or 6.6 to 7.4 (0.15%)
   IOP lowering effect of brimonidine 0.15% and 0.1% (alphagan p 0.15% and 0.1%) is same as 0.2% solution (alphagan).
   Mode of dispensing: A opaque teal LDPE plastic bottles and droppers with purple high impact polystyrene (HIPS) caps.
4. Dorzolamide
   Preservative: Benzalkonium chloride 0.0075%
   Inactives: Hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide (to adjust pH) and water for injection.
   pH: 5.6
   Osmolality: 260-330 mOsm
   Method of dispensing: TRUSOPT ophthalmic solution 2% is supplied in an OCUMETER® PLUS container, a white, translucent, HDPE plastic ophthalmic dispenser with a controlled drop tip and a white polystyrene cap with orange label.
5. Latanoprost: Latanoprost ophthalmic Solution 0.005% (50 μg/mL)
   Preservative: Benzalkonium chloride, 0.02%
   Inactives: Sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injection
   pH: 6.7
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**Table 1: Common glaucoma drugs with preservatives**

<table>
<thead>
<tr>
<th>Brand names (drug)</th>
<th>Preservatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alphagan</td>
<td>BAK 0.005%</td>
</tr>
<tr>
<td>Alphagan-P (brimonidine tartrate 0.1% and 0.15%)</td>
<td>Purite (SOC) 0.005%</td>
</tr>
<tr>
<td>Azopt (Brinzolamide 1%)</td>
<td>BAK 0.01%</td>
</tr>
<tr>
<td>Betagan (Allergan)</td>
<td>BAK + PVA 0.005%</td>
</tr>
<tr>
<td>Betoptic S</td>
<td>BAK 0.01%</td>
</tr>
<tr>
<td>Cosopt</td>
<td>BAK 0.0075%</td>
</tr>
<tr>
<td>Lumigan (bimatoprost 0.03%)</td>
<td>BAK 0.05%</td>
</tr>
<tr>
<td>OptPranolol (metipranolol 0.3%)</td>
<td>BAK 0.004%</td>
</tr>
<tr>
<td>Rescula (Novartis)</td>
<td>BAK 0.015%</td>
</tr>
<tr>
<td>Timoptic (Merck)</td>
<td>BAK 0.01%</td>
</tr>
<tr>
<td>Timoptic XE (Merck)</td>
<td>Benzododecinium bromide 0.012%</td>
</tr>
<tr>
<td>Travatan (travoprost 0.004%)</td>
<td>BAK 0.015%</td>
</tr>
<tr>
<td>Travatan Z (travoprost 0.004%)</td>
<td>Ionic buffered system–SofZia</td>
</tr>
<tr>
<td>Trusopt (Merck)</td>
<td>BAK 0.0075%</td>
</tr>
<tr>
<td>Xalatan</td>
<td>BAK 0.02%</td>
</tr>
</tbody>
</table>

**Table 2: Types of preservatives in glaucoma medications**

<table>
<thead>
<tr>
<th>Preservatives</th>
<th>Examples</th>
<th>Generic names</th>
<th>pH</th>
<th>Osmolality (mmol/kg)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>SolZia–borate, sorbitol, propylene glycol, zinc</td>
<td>Travatan Z</td>
<td>Travoprost (0.004%)</td>
<td>5.7</td>
<td>290</td>
<td>Less hyperemia, less irritation</td>
<td>Newer agent, requires more studies</td>
</tr>
<tr>
<td>Benzalkonium chloride 0.15%</td>
<td>Travatan Betagan Timolol Misopt</td>
<td>Travoprost (0.004%) Levobunalol Timolol Dorzolamide</td>
<td>6</td>
<td>290</td>
<td>Very effective antimicrobial</td>
<td>Irritation, conjunctival hyperemia, low compliance</td>
</tr>
<tr>
<td>Purite (0.005%)</td>
<td>Stabilized oxychloro complex</td>
<td>Alphagan-P Brimonidine (0.1% or 0.15%)</td>
<td>7.4-8</td>
<td>250-350</td>
<td>Well-tolerated by the ocular surface</td>
<td>Congestion corneal epithelial damage</td>
</tr>
<tr>
<td>EDTA</td>
<td>Betagan</td>
<td>Levobunalol</td>
<td></td>
<td></td>
<td>Inactive trace amounts of heavy metals which aids in the preservation of the solution</td>
<td>Few studies documenting the chronic side effects</td>
</tr>
<tr>
<td>Polyquaternium 0.001%</td>
<td>Brimo 0.15%</td>
<td>Brimonidine Tartarate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Osmolality:** 267 mOsmol/kg

**Mode of dispensing:** 2.5 mL solution in a 5 mL clear low density polyethylene bottle with a clear low density polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap.

6. **Bimatoprost:** Ophthalmic solution 0.03%

   **Preservative:** Benzalkonium chloride 0.05 mg/mL

   **Inactives:** Sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH

   **pH:** 6.8 to 7.8

   **Osmolality:** 290 mOsmol/kg

   **Mode of dispensing:** Opaque white low density polyethylene ophthalmic dispenser bottles and tips with turquoise polystyrene caps.
REFERENCES


