Topical urea as a treatment for non-infectious keratopathy

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ABSTRACT. The purpose of this study was to evaluate topical urea ophthalmic ointment as an agent to promote epithelial healing. Corneal epitheliopathy and epithelial defects were chemically induced in rabbits. Urea ophthalmic ointment was administered to one eye and control ointment to the fellow eye. The rabbits were examined by a masked observer for eleven days and points were awarded for steps of improvement in their ocular surface disease. The eyes receiving the urea ointment improved an average of 5.73 points while the control eyes improved 4.2 points ($p < 0.0001$). In conclusion, topical urea dissolved in a bland ointment encourages corneal reepithelialization and limits epithelial damage after toxic injury to corneal epithelium.

Key words: urea - keratitis - allantoin - corneal epitheliopathy - ophthalmic ointment.

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The ocular surface is normally covered by nonkeratinized squamous epithelium, and is the most regularly arranged of all squamous epithelia in the body. Trauma, exposure, chemical toxicity, surgery, and infections can disrupt the ocular surface resulting in loss of epithelial cells and/or keratinization. Dry eye, inherited dystrophies, corneal degeneration, Meibomian gland dysfunction, infectious lid disease, allergies and other diseases can also cause such cell loss and keratinization. Following ocular surface damage, increased fibroblast activity and scarring may lead to visual loss (Baum 1971). Dry eye is a prominent cause of corneal keratinization in the United States today. Hence, most agents currently available for non-infectious keratitis or epithelial cell loss are directed towards the relief of dry eye.

Currently available ophthalmic solutions for relief of dry eye mimic physiologic tears (Gilbard et al. 1989). These solutions have generally been buffered to a physiologic pH, made isotonic or mildly hypotonic, and contain various synthetic polymers for improved viscosity and longer retention in the eye. No currently available commercial preparation is known to directly enhance hydration of the ocular surface or promote healing of the surface epithelium.

The hyperosmolarity of tears has been acknowledged as one explanation for the pathologic changes seen in dry eye, and the documentation of tear hyperosmolarity has been accepted as a diagnostic test for dry eye (Farris et al. 1983; Gilbard et al. 1978; Gilbard 1985; Beitch 1970). In previous research we discovered that patients requiring renal dialysis have hyperosmolar tears yet remain surprisingly asymptomatic for dry eye (Charlton et al.). In the normal dry eye state, tears become hyperosmolar due to evaporation of tears from the ocular surface and decreased tear production (van Haeringen 1981; Gilbard & Farris 1983; Rolando et al. 1983; Gilbard & Dartt 1982; Gilbard 1985). The hyperosmolarity in dry eye is due to high concentrations of ionic solutes such as sodium, potassium, and chloride ions. Renal dialysis subjects, however, have hyperosmolar tears secondary to high levels of urea (Thaysen & Thorn 1954; van Haeringen & Glasius 1977; Mastman et al. 1961). Hyperosmolarity alone, therefore, does not explain the dry eye state. It is more likely that hyperosmolarity due to *ionic* solutes explain the pathologic changes of dry eye. Urea, a nonionized chemical entity that has long been used in the treatment of dry skin and other keratinizing conditions of the skin, may be protective of the ocular surface in these renal dialysis patients. We speculated that urea may be beneficial to a damaged ocular surface as it is to skin.

Methods and Materials

Urea ophthalmic ointment was compounded by dissolving urea crystals in distilled water and incorporating the solution into an ophthalmic ointment vehicle consisting of white petrolatum, mineral oil, and anhydrase liquid lanolin (DuraTears, Alcon Laboratories). The final concentration of urea was 2.24% (1.63% is isotonic) (American Hospital Formulary Service Drug Information 1994). The final osmolarity of the preparation was 370 mOsm (300 mOsm is isotonic) (Gil-

bard & Kenyon 1985). This osmolarity was chosen to mimic the tear osmolarity of renal dialysis patients.

Toxic keratitis was induced in 12 white New Zealand rabbits by administering 0.5% benzalkonium chloride solution twice daily for a total of 5 doses (Pfister & Burstein 1976). This dosage was found to give a keratitis lasting approximately 2 weeks. Following induction of the keratitis, the rabbits were examined at a slit-lamp for corneal clarity and lens clarity. Fluorescein 0.25% with Benoxinate HCl 0.4% (Fluress, Sola/Barnes-Hind) and a lid speculum were used to facilitate the examination. Intraocular pressure was measured utilizing gas tonometry at the beginning and completion of the study. This research was conducted in compliance with the Association of Research in Vision and Ophthalmology (ARVO) Statement for the Use of Animals in Ophthalmic and Vision Research. Since some discomfort to the animals was an unavoidable attribute of the study, all possible steps were taken to minimize this effect. The control group was designed to receive lubrication rather than no treatment at all. The duration of the study and the number of animals used were minimized. The local institutional review board approved both the study design as well as the care of the animals.

The ointment vehicle (DuraTears, Alcon) alone could not serve as the control because the ointment changed from clear to opaque with the addition of water. The anhydrous lanolin component of the vehicle allowed it to take up to 13% of its weight in solution, thus allowing the incorporation of the urea solution into the ointment. For the control ointment, a mildly hypotonic artificial tear preparation (HypoTears, IOLAB Pharmaceutical) was incorporated into the ointment vehicle so that the control and urea ointment were equally opaque. The same solution volumes (1.3 mls) were incorporated into both ointments. Following induction of keratitis, the rabbits were examined for the degree of keratitis and/or corneal epithelial defects. This examination was repeated every other day for eleven days by the same masked observer.

Each rabbit was randomly assigned to receive urea ointment in one eye and control ointment in the other eye. The ointment was administered twice daily for eleven days. Persons administering the ointment were masked.

At each examination, the corneas were graded according to the following scale:

Decrease in epithelial defect size by 30%
2 + keratitis
1 + keratitis
Trace keratitis
No keratitis.

One point was awarded for each step of improvement. It was possible to obtain more than one step of improvement between any two examinations (i.e., improvement from 3 + keratitis to 1 + keratitis from day 3 to day 5 would equal 2 points).

One eye of one rabbit was withdrawn from the study secondary to an abnormal response of the cornea to the benzalkonium chloride. The cornea became mildly vascularized and opaque at the periphery.

Results

All rabbits began the study with corneal epithelial defects in both eyes ranging in size from 30% to 80% of the corneal surface. Over the eleven day period, the eyes receiving the urea ointment improved an average of 5.73 points with a range of 4-7 points. The eyes receiving the control ointment averaged 4.2 points of improvement with a range of 2-5 points. This was statistically significant to P less than 0.0001 using a paired t-test.

The average pretreatment intraocular pressure of the eyes receiving urea ointment was 22.4 mmHg with a range of 18-35 mmHg. The average pretreatment intraocular pressure of the eyes receiving the control ointment was 24.8 mmHg with a range of 17-31 mmHg. On day eleven the average intraocular pressure of the eyes receiving the urea ointment was 18 mmHg with a range of 14-23 mmHg; the eyes receiving the control ointment had an average pressure of 19.2 mmHg with a range of 13-27 mmHg. This was not statistically significant.

No other extraocular or intraocular changes or abnormalities were noted in either group of rabbits upon completion of this study.

Discussion

The commonly accepted treatment of ocular surface disease such as dry eye and other causes of non-infectious keratitis has been to administer agents that mimic artificial tears. Such agents generally include near isotonic levels of monovalent cation salts, principally sodium and potassium ions. These preparations include agents which enhance viscosity and surface wetting. Tonicity, pH, and antimicrobial agents are also commonly added. No preparation is commercially available that has an active ingredient which directly enhances hydration and benefits the cells of the ocular surface.

Rabbit eyes with chemically induced epithelial defects and keratitis improved more rapidly when urea ophthalmic ointment was administered as compared to a control ointment. This is not surprising considering the pharmaceutical properties of urea in dermatologic preparations. Urea is known to soften keratin, promote hydration of the corneum skin layer, and promote skin epithelialization. Urea also has solvent action on fibroblasts which decreases scarring (Ashton et al. 1970; Hellgren & Larsson 1974; Swanbeck 1968; Raab 1990; Banerjee et al. 1990; Physicians Desk Reference 1990). Urea has both mucolytic and antibacterial activity (American Hospital Formulary Sevice Drug Information 1994; Ashton et al. 1970). It also has some analgesic properties consisting of an antipruritic, cooling sensation when applied to skin (Raap 1990; Budavari et al. 1989). Our study indicates that urea may soften keratin and promote epithelialization on the ocular surface as well.

Hyperosmolar solutions applied to the corneal surface of rabbits have been shown to produce the same pathologic findings as dry eye (Gilbard et al 1984). Despite being hyperosmolar, the urea ointment did not induce dry eye findings but rather promoted resolution of the ocular surface damage. This is further evidence of the protective and healing activities of urea on the

ophthalmic surface. Dry eye patients have been described to benefit subjectively and objectively from using an autologous serum preparation. The serum preparation was felt to work through its lubricating ability, natural viscosity, and the emulsification of mucous secretions (Fox et al. 1984). The mucolytic and lubricating activity may be due to the urea that is present in serum.

The eye surface offers a formidable barrier to drug penetration. The tear film is hydrophilic followed by a corneal 'sandwich' of epithelium/stroma/endothelium which is hydrophobic/hydrophilic/hydrophobic. Small lipophilic drug molecules have the best absorption, thus illustrating that the epithelium and to a lesser extent the endothelium are extremely effective structures in preventing drug absorption. Urea is known to be an organic solvent if used in sufficient concentration. In fact, 8M urea has been shown to dissolve skin (Ashton et al. 1970). If used in smaller amounts, urea has been shown to enhance drug penetration through skin (Banerjee et al. 1990; Nishihata et al. 1990). Skin is a mixture of hydrophobic and hydrophilic structures much like the cornea. Proposed mechanisms by which urea works include solubilization and removal of intercellular lipids. Urea also splits keratin intramolecular hydrogen bonds (Raap 1990). Because of the similarities of skin and cornea, urea would be expected to enhance the ocular penetration of certain drugs.

Urea readily diffuses across the ocular surface and would gain entrance into the eye (Bleeker et al. 1968), potentially increasing the osmolarity of the internal eye fluids as compared to circulating blood. This may set up an osmolarity gradient which would attract fluid into the eye and raise intraocular pressure. Increased intraocular pressure was not manifest in our study; however, it could become a problem with more chronic use of topical urea.

Because of its ready absorption into the eye, urea itself might not be the ideal agent (Bleeker et al. 1968). Rather, a urea derivative that decreases ocular penetration yet retains surface activity is likely to be the best agent. Urea derivatives which deserve further testing include urea-D glucuronic acid, allantoin, urotanic acid or urea complexed to glucose (Budavari et al. 1989; Gennaro et al. 1990). Urea compounded in the hyperosmolar state was used in this study in an effort to mimic the tears of renal dialysis patients. Hyperosmolar preparations of ionic salts, however, have been shown to induce pathologic changes in the ocular surface (Gilbard et al. 1984). A better concentration of urea may exist than the one used in this study. Urea and urea derivatives deserve testing over a wide range of osmolarities.

The inherent properties of urea give it a wide variety of potential therapeutic uses in treating common eye problems. These problems would broadly include causes of keratitis such as dry eye, contact lens related keratitis, recurrent erosion syndrome, bullous keratopathy, filamentary keratitis, toxic keratopathy, and post-surgical keratoconjunctivitis. Corneal abrasions might also benefit from urea. Ocular surgeries for which topical urea might enhance postoperative healing include glaucoma, cataract, and corneal surgeries. Glaucoma surgery in particular would benefit from the ability of urea to decrease fibroblast activity, thus promoting and maintaining the desired conjunctival bleb formation. Ocular penetration by drugs may also be enhanced by urea. Urea or one of its derivatives may be a promising new ophthalmic treatment.

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