Blunt Trauma Drama, p. 114

July 15, 2012

REVIEW® OF OPTOMETRY

Part 1 of 2

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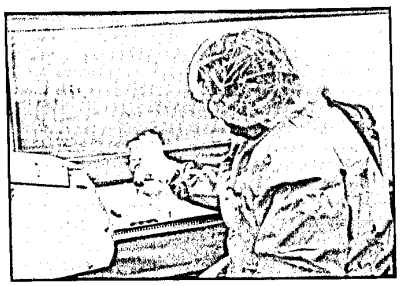


Mix It Up:
When to Call a Compounding Pharmacist, p. 30

ALSO INSIDE:

Consider Ortho-K for Myopia Control, p. 38

18th ANNUAL GLAUCOMA REPORT
New Thoughts on the Newly Diagnosed Glaucoma Patient, p. 53

Earn 2 CE Credits:
Optic Neuropathies: Glaucomatous vs. Non-glaucomatous, p. 58

Inside: Optometric Staff Continuing ation for ABO edit

Mix It Up:

When to Call a Compounding Pharmacist

Most medications that we require are readily available. But when they aren't, it's time to get creative. **By Jill C. Autry, R.Ph., O.D.**

The roots of medicinal compounding trace back to antiquity. In that era, copper compounds were concocted to treat headaches and a mixture of diluted snake venom was applied topically to stop bleeding.

The mixing and making of medications evolved from the first "healer," who compounded plant-based and herbal remedies around 4,000 B.C., to the multitasking professional we know today as a pharmacist. In fact, until mass drug manufacturing became commonplace in the 1950s, the neighborhood pharmacist mixed and molded almost all prescriptions made in the United States.

Today, although the need for compounding is far less common, there are still several situations when a compounded product may be your preferred choice. What do they offer that off-the-shelf products lack? At least four worthwhile variations:

• *Different strength.* The most common need for a compounded drug: The prescribed agent is not manufactured in a strength deemed necessary for the patient's condition, so the doctor needs a higher or lower concentration than what can be found in stock. For example, a terminally ill patient may need a medication delivered at half the typically prescribed strength, or a psoriasis patient may need a cream that is twice as strong as those made commercially. In such cases, the compounding pharmacist can purchase the raw materials and make the medication to match the needs of the patient.

• *Different form.* Another cause for calling upon a compounding pharmacist is when the prescribed medication does not come in the dosage form needed by the patient. This is common when making adult medications into suspensions for children, or for a cancer patient who cannot swallow a pill or capsule. The mixing of oral and intravenous medications into alternate dosage forms is also common in making ocular preparations, rectal

Photos: Jill Autry, O.D., R.Ph.

The neighborhood pharmacist of the 1950s mixed and molded almost all prescriptions. Today, we still need compounded drugs when manufactured ones won't do.

RESTASIS®
(cyclosporine ophthalmic emulsion) 0.05%
Sterile, Preservative-Free

INDICATIONS AND USAGE
RESTASIS® ophthalmic emulsion is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical antiinflammatory drugs or using punctal plugs.

CONTRAINDICATIONS
RESTASIS® is contraindicated in patients with active ocular infections and in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNING
RESTASIS® ophthalmic emulsion has not been studied in patients with a history of herpes keratitis.

PRECAUTIONS
General: For ophthalmic use only.

Information for Patients
The emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion.

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 1000 and 500 times greater, respectively, than the daily human dose of one drop (28 µL of 0.05% **RESTASIS®** BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes in vitro gave indication of a positive effect (i.e., induction of SCE).

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 15,000 times the human daily dose of 0.001 mg/kg/day) for 9 weeks (male) and 2 weeks (female) prior to mating.

Pregnancy-Teratogenic Effects
Pregnancy category C.

Teratogenic Effects: No evidence of teratogenicity was observed in rats or rabbits receiving oral doses of cyclosporine up to 300 mg/kg/day during organogenesis. These doses in rats and rabbits are approximately 300,000 times greater than the daily human dose of one drop (28 µL) 0.05% **RESTASIS®** BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Non-Teratogenic Effects: Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 30,000 and 100,000 times greater, respectively than the daily human dose of one drop (28 µL) of 0.05% **RESTASIS®** BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 17,000 and 30,000 times greater, respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 45,000 times greater than the daily human topical dose, 0.001 mg/kg/day, assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (15,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of **RESTASIS®** in pregnant women. **RESTASIS®** should be administered to a pregnant woman only if clearly needed.

Nursing Mothers
Cyclosporine is known to be excreted in human milk following systemic administration but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of **RESTASIS®** ophthalmic emulsion, caution should be exercised when **RESTASIS®** is administered to a nursing woman.

Pediatric Use
The safety and efficacy of **RESTASIS®** ophthalmic emulsion have not been established in pediatric patients below the age of 16.

Geriatric Use
No overall difference in safety or effectiveness has been observed between elderly and younger patients.

ADVERSE REACTIONS
The most common adverse event following the use of **RESTASIS®** was ocular burning (17%).

Other events reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Rx Only

ALLERGAN

Based on package insert 71876US14B Revised February 2010

U.S. Patent 5,474,979
Made in the U.S.A.

or vaginal suppositories, topical creams and lotions, or oral rinses.

• *Different ingredients.* Some instances require the compounding pharmacist to remove or change the manufactured formulation. Inactive ingredients, such as preservatives or buffers, may cause toxicity or allergy in susceptible individuals. In this case, the pharmacist uses the active ingredient in the dosage required but removes the offending agent from the preparation without altering the pharmacological profile of the medication.

• *Different formulation.* Some compounds are even formulated to ease administration or promote compliance. This is an option when two or more medications are mixed together into a single dosage form. The most common of these combinations include dermatological preparations, which are usually prescribed separately but are more effective when applied together.

In ocular disease, many of the same reasons prompt an eye care practitioner to call the local compounding pharmacist for help. This article reviews the most commonly compounded ophthalmic preparations for specific conditions, the appropriate designations for use, and helpful hints for finding the right pharmacist nearby to put it all together.

Dry Eye

In its mildest form, dry eye causes episodic symptoms of burning, tearing, foreign body sensation and intermittent blur. For these patients, artificial tears and/or environmental changes may be all they need to relieve their symptoms. For patients with moderate dry eye, treatments such as Restasis (cyclosporine 0.05%, Allergan), punctal plugs, topical steroids and doxycycline are often added.

When we exhaust these more conventional treatments for a patient with moderate to severe dry eye, we can look to additional therapeutic options that need to be compounded:

• *Cyclosporine ophthalmic ointment.* This ointment, applied q.h.s. in severe dry eye patients, typically is used to supplement Restasis topical emulsion. It can be formulated as a 0.1% to 2% concentration. In severely damaged, low vision and/or phthisical eyes, the ointment may be substituted for the topical cyclosporine drop b.i.d. to q.i.d. for more contact time without the concern of associated blur.

• *Autologous serum.* This is used in severe aqueous-deficient dry eye to provide patient-specific protein-based protection to the ocular surface. Serum and

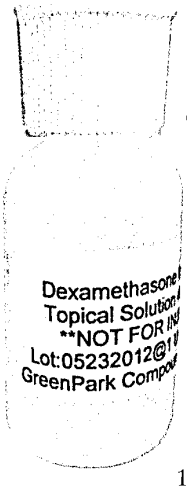
normal tears have many of the same components, including vitamin A, various growth factors and proteins (such as lactoferrin and lysozyme). To create the serum, the patient must make three to four blood donations a year; most clinicians ask for a 20% diluted serum to be instilled q.i.d. or more. Investigators also have tested this treatment for persistent corneal defects.[1]

• *Albumin drops.* Although not the preferred autologous serum-based derivative described above, albumin 5% artificial tears may be a suitable alternative tear supplement for several reasons. For one, it is easier to compound than autologous serum. Also, it avoids the need for the patient to make a blood donation. Last but not least, it's much cheaper than autologous serum.

Albumin may improve the tear film by providing mucin-like protection as well as anti-inflammatory action. Research on patients with Sjögren's syndrome found that albumin therapy inhibited the apoptotic enzyme caspase-3, and improved fluorescein and rose bengal scores in just four weeks.[2] (However, it was not statistically significant for tear break-up time or subjective symptoms.)

• *Transdermal testosterone cream.* Androgens play a role in dry eye through receptor activity in the lacrimal glands, the meibomian glands and the conjunctiva. Because androgen production decreases in older men and women as well as in autoimmune patients, clinicians are increasingly using topical, transdermal testosterone in a vanishing cream as a treatment for refractive dry eye in these patient populations. Various clinicians recommend a 3% to 5% concentration applied to the upper eyelids b.i.d. initially, then q.h.s.[3] Investigators also are testing compounded testosterone solution applied directly to the eye.[4]

• *Preservative-free steroids.* Many commercially available products for dry eye are available without preservatives, such as artificial tears and Restasis. Steroids are often an unavoidable part of our treatment regimen for dry eye, but unfortunately do not come in a preservative-free preparation.



Would your patient like a preservative-free steroid? Call your compounding pharmacist.

For patients who cannot tolerate preservatives, or if preservative-containing medications exacerbate their dry eye, the compounding pharmacist can make preservative-free products, such as 1% methylprednisolone ophthalmic drops. When necessary, other chronic medications, such as glaucoma drops or allergy treatments, can also be prepared preservative-free through compounding.

• *Acetylcysteine solution.* In various chronic ocular conditions—most notably severe dry eye—mucous filaments can form and attach to the cornea. This results in pain, foreign body sensation, photophobia and decreased vision. Initial treatment is to remove the filaments with forceps and, if necessary, apply bandage contact lenses. Next, aggressively treat the underlying dry eye and consider an ophthalmic solution of acetylcysteine drops. Mucomyst (acetylcysteine, Bristol-Myers Squibb) is used in patients with pulmonary conditions to reduce excess bronchial mucus. The compounding pharmacist can convert it into a 5% or 10% ophthalmic solution, which can be helpful in treating and preventing recurrences when used q.i.d.

Corneal Bacterial Keratitis

Within the first year of practice, most eye-care practitioners will encounter a bacterial keratitis that is so large, so central or so vision threatening that normal empirical treatment with topical fluoroquinolones does not meet the standard of care. The majority of these corneal ulcers are contact-lens related and, although we tend to think *Pseudomonas* in these cases, they can be caused by either gram-positive or gram-negative organisms.

In these cases, first culture the ulcer and then initiate fortified topical antibiotic therapy with one of the following:

• *Vancomycin 25mg/ml.* This covers a wide range of gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). It should be alternated every half-hour or hour with a gram-negative medication, such as ceftazidime or tobramycin.

• *Cefazolin 50mg/ml.* Like vancomycin, this first-generation cephalosporin also covers a wide range of gram-positive organisms, but is *not* effective against MRSA. It is well tolerated and is a good choice for pregnant patients who need intense antibiotic therapy (because fluoroquinolones are contraindicated).

• *Tobramycin 14mg/ml.* Although generally considered a medication that is active against gram-negative species, this aminoglycoside also works well against gram-positive organisms. It is often paired with vancomycin or cefazolin for comprehensive coverage.

How to Find a Compounding Pharmacist

Find a compounding pharmacist and develop a relationship *before* a unique case occurs so you'll be prepared if—or more likely when—the patient presents to your practice.

So, how do you find one?

- Ask your local dermatologist, oncologist or local retail pharmacist where they send compound prescriptions.
- Check professional websites, such as those for the Professional Compounding Centers of America (www.pccarx.com) or the International Academy of Compounding Pharmacists (www.iacprx.org), where you can enter your city/state/zip code to find a compounding pharmacist near you.
- When you do locate one, don't forget to make sure the compounding pharmacist makes ocular preparations; many are willing to mix common creams, ointments and oral dosage forms, but may decline to make the more involved ophthalmic preparations, which must meet more stringent guidelines.

Also, it is FDA Pregnancy Category B (no known risk to the fetus), so it can be compounded for the treatment of severe corneal infections in pregnant patients.

- *Ceftazidime 50mg/ml.* This third-generation cephalosporin is known for outstanding gram-negative coverage. Like tobramycin, ceftazidime is paired with gram-positive vancomycin or cefazolin and is alternated every 30 minutes to an hour for initial treatment.

The aforementioned are just a few of the most common fortified antibiotics. Other choices include amikacin, gentamicin and ceftriaxone.

Amoebic Keratitis

Acanthamoeba, one of the more formidable causes of keratitis, often results in the need for corneal transplantation. The infection is almost exclusive to contact lens wearers. Its diagnosis is often delayed because it can mimic bacterial, fungal or, more commonly, herpetic keratitis. Keep in mind that the amoeba can be resistant to treatment. This is why therapy definitely requires a compounding pharmacist, because the current recommended preparations are not commercially available in the U.S. Often, treatment involves a combined approach, including the use of a biguanide (either polyhexamethylene biguanide 0.02% or chlorhexidine 0.02%) combined with a diamidine (either hexamidine 0.1% or propamidine 0.1%).[5,6]

Band Keratopathy

This ocular degeneration is characterized by a 3 o'clock to 9 o'clock band deposition of calcium across the cornea. The calcium is found just under the epithelial surface, and tends to be concentrated in the intrapalpebral area due to increased tear tonicity and evaporation in this area. Band keratopathy can occur due to a variety of etiologies, but is most often seen in chronic inflammatory conditions, both systemic and ocular. The calcium band can cause visual acuity loss as well as chronic foreign body sensation, depending on its severity.

Treatment involves an ophthalmic solution of ethylenediaminetetraacetic acid (EDTA), an effective treatment due to its chelating effect on calcium and other metal ions.[7] Therapy starts with first debriding the epithelium and then applying a 2% EDTA compounded solution to the cornea for three to five minutes. Lastly, the calcium deposits are scraped away with a spatula and then a bandage contact lens is applied. Depending on severity, multiple applications and scrapings may be necessary over time to control the keratopathy.

Intravitreal Injections

Although intravitreal injections for macular degeneration are commonplace today, compounding pharmacists have been supplying various preparations of antibiotics and steroids for intraocular injection for years.

Today, the off-label use of the anti-VEGF Avastin (bevacizumab, Genentech), a systemic cancer therapy reformulated for intraocular use, is the most commonly compounded intravitreal preparation. It continues to be prescribed in lieu of the FDA-approved Lucentis (ranibizumab, Genentech) due to the extreme cost difference between the two products. (A single Lucentis injection costs approximately $2,000 while a shot of Avastin is closer to $50.)

A 2011 outbreak of endophthalmitis cases in Avastin-treated patients was traced to a single compounding pharmacy; this serves as an object lesson on the importance of demanding strict adherence to sterility protocols from your compounding pharmacies. (*See "Compounding Pharmacists Keep it Clean," page 36.*)

A new entrant to the anti-VEGF market, Eylea (aflibercept, Regeneron Pharmaceuticals), offers comparable efficacy to Lucentis but with less frequent dosing, especially in the first year of therapy. Depending on its cost, Eylea's reduced treatment regimen and manufacturing safeguards may temper enthusiasm for reformulated Avastin used off-label.

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