Human tears contain a biochemically complex mixture of proteins, mucins (glycoproteins), and lipids (oils). They contain several hundred components that can be separated into two categories: (1) factors that help maintain the stability of the tears and (2) those that protect and support the ocular surface. The protective ingredients of tears fight inflammation and infection. Some of the most abundant proteins in tears, such as lysozyme and lactoferrin, suppress the growth of microorganisms. Human tears also contain growth factors, such as epidermal growth factor, which is responsible for helping the corneal epithelial cells divide. Mucins act to reduce friction from the eyelids, and they also coat and lubricate the surface of the eye to make it comfortable.

Tears are essential to the health of the ocular surface—particularly the cornea—which does not have its own blood supply. Without a good tear film that contains healthy constituents, the ocular surface may not be as optically clear and smooth as it should be.

ARTIFICIAL TEARS

The only similarity between artificial and human tears is that they both contain water. A few preparations contain electrolytes that are similar to those found in human tears (ie, sodium and potassium). Theoretically, electrolytes may be a valuable component of an artificial tear product; however, this has not been well elucidated, and there are no studies in this area.

Beyond that, all ingredients in artificial tears are man-made. Manufacturers of products available in the United States, for instance, are permitted to use only the ingredients included on a relatively small list approved by the Food and Drug Administration (FDA). If the available products on the market are taken as a whole, one would find they all include roughly 90% the same ingredients. Artificial tear compounds may include one or two inert molecules, creating some products that are unique. Systane Lubricant Eye Drops (Alcon Laboratories, Inc., Fort Worth, Texas), for example, contain a guar protein. Blink Tears Lubricating Eye Drops (Abbott Medical Optics Inc., Santa Ana, California) include hyaluronic acid, a natural sugar molecule.

Currently, not a lot of science supports specific formulations of artificial tears. They have been shown to improve symptoms in patients and, to a certain degree, they do minimally improve the ocular surface.1 It is important to note that the effects of the drops last only for 10 to 15 minutes, and patients often use them excessively. For patients who instill artificial tears frequently, unpreserved formulations are better and safer. That is a major consideration for patients who use tears more than four times a day. Aside from the preservative issue, it is an individual preference as to which formulations feel best to the patient. There are few head-to-head comparisons; therefore, for most patients, it is a matter of trial and error.

CURRENT USES, NEEDED ADVANCES, AND BARRIERS TO DEVELOPMENT

Artificial tears are used by patients with a variety of ocular surface conditions and tear dysfunctions—the spectrum of which is large and growing. These include patients with meibomian gland dysfunction or blepharitis, individuals who do not blink, and those with a pterygium or pinguecula who are at risk for focal dry eye. There are many ocular surface conditions in which there is alteration in tear flow or spread and more rapid drying, for which artificial tears are often used.

A major advance in artificial tears would be for a company to create a near-physiologic replacement that includes supportive and protective factors that naturally occur in healthy human tears.

TAKE-HOME MESSAGE

- Effects of eye drops last for 10 to 15 minutes, and patients often use them excessively.
- Without a good tear film, the optical surface may not be as clear and smooth as it should be.
- Artificial tears only minimally improve the ocular surface.

(Continued on page 50)
As patients age, dry eye syndrome (DES) becomes one of the main reasons for consulting an ophthalmologist. Data from epidemiologic studies indicate that approximately 14% of the population 48 years of age and older have some level of DES. Treatment encompasses a variety of approaches, but today topically administered lubricants remain the mainstay of therapy. The ideal topical lubricant varies among patients; however, most available lubricants do not stay on the ocular surface for more than 10 or 15 minutes.

**IMPROVED MUCOADHESION**

One of the most important prerequisites for successful topical lubrication is a long residence time on the ocular surface, which can limit the need for frequent instillations and lead to better patient compliance. A promising approach is chitosan-N-acetylcysteine eye drops (Croma Pharma GmbH, Leobendorf, Austria). This biopolymer formulation consists of chitosan, a polycationic polysaccharide derived from alkaline deacetylation of chitin, which has high biocompatibility and low toxicity, and N-acetylcysteine, a derivative of the amino acid L-cysteine, which is a reducing agent with antioxidant activity. The N-acetylcysteine is covalently bound to the polymeric backbone of chitosan.

Most important, the chitosan has been chemically modified by immobilization of sulhydryl-bearing ligands on the polymeric backbone, a technique that is usually referred to as thiomer technology. This introduction of thiol groups leads to significantly improved mucoadhesive properties compared with corresponding unmodified polymers. Chemically speaking, the formation of disulfide bonds between thiol groups of the thiomer and cysteine-rich subdomains of glycoproteins of the mucous gel layer are responsible for the improvement in mucoadhesion. These bonds lead to adhesion of the modified chitosan to the ocular surface and, in turn, to a long residence time on the ocular surface.

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The technology exists to develop such a formulation, but it is cost-prohibitive. For each added ingredient, the FDA would require that the company undertake additional clinical efficacy studies. Considering that the artificial tears on the market do well and are relatively simple to manufacture, industry would have to identify a significant financial benefit to bringing a natural tear replacement product to the market.

**POINT OF INVESTIGATION**

Current evidence suggests that treating patients earlier with therapies that might help to prevent further loss of their ability to produce tears might be beneficial. Tear deficiency conditions should not be allowed to go untreated for too long. Extensive damage to the tear-producing cells or glands may not be reversible. That is one of the considerations with using topical cyclosporine (Restasis; Allergan, Inc, Irvine, California); it regenerates goblet cells that produce the mucous layer.

The goal is to identify patients who are at risk and treat them to preserve their ability to make their own tears. I am involved in a study of the natural history of dry eye. My colleagues and I are trying to establish that, if patients are left untreated, the disease does get worse. With that confirmed, we can move on to more extensive studies.

**PRECLINICAL, CLINICAL STUDIES**

Chitosan-N-acetylcysteine eye drops have been tested in preclinical and clinical studies to determine ocular residency time in vivo. In a preclinical study, radioactively labeled chitosan-N-acetylcysteine eye drops were applied to rabbit eyes. This experimental setting showed that even a single drop remained on the ocular surface 22 hours after application.4 In two preclinical proof-of-principle studies, the effect of topically applied chitosan-N-acetylcysteine eye drops was investigated in dry eye mouse models. Evaluation of dry eye biomarkers such as IL-1, IL-10, IL-alpha, and TNF-beta suggested that chitosan-N-acetylcysteine eye drops may have some protective ocular surface properties, indicated by decreased ocular surface mRNA expression.4,5

Preceding first use in humans, preclinical data demonstrated good safety and tolerability of chitosan-N-acetylcyesteine. Mild cytotoxicity was observed at high concentrations, most likely caused by the high viscosity of the test product. Acute oral toxicity at a dose of 1,000 mg/kg was tested in a rat model, with no observed toxic effects and no mortality.

Two phase 1 clinical studies were performed. In the first cohort, a single administration of chitosan-N-acetylcysteine was tested in three increasing concentrations (0.1%, 0.05%, and 0.025%). Each concentration was administered in six patients, for a total of 18 administrations. Investigators concluded that the overall tolerability of chitosan-N-acetylcysteine was excellent. In the second cohort, safety was tested after two-times-daily instillation in a group of 12 healthy patients. Again, the study revealed an excellent safety profile.

**CONCLUSION**

Results of preclinical and clinical studies of chitosan-N-acetylcysteine eye drops indicate excellent tolerability and prolonged resident time on the ocular surface. This indicates that chitosan-N-acetylcysteine eye drops have the potential to be a promising new approach to treat symptoms of DES.

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