Topically administered corticosteroids and treatment of inflammatory keratitis

Irrespective of its etiology, inflammation of the cornea is characterized by cellular invasion, primarily by polymorphonuclear leukocytes. Contained within the lysosomes of these inflammatory cells are substantial quantities of a number of hydrolytic enzymes, excessive amounts of which may be released, producing a degradation of normal corneal structure. Repair is effected by fibrous tissue replacement of the injured parenchyma (scarring); therefore, the degree of scarring is proportional to the degree of parenchymal destruction. The same inflammatory leukocytes, present both in the cornea and in the anterior chamber, also can irreversibly damage the corneal endothelium, causing edema and, subsequently, neovascularization. These phenomena all reduce corneal transparency and result in visual loss. Thus, while the usual mechanism for resolution of corneal inflammation is adequate for preservation of ocular structure, it leaves the eye badly compromised functionally.

Early elimination of the invading leukocytes may avoid or reverse these processes and allow preservation of normal tissue structure. Among presently available pharmacologic agents, corticosteroids most effectively accomplish this purpose. They produce an involution of inflammatory cells, suppress their migration to the site of injury, and inhibit their release of hydrolytic enzymes. Systemic administration, even in very high doses, puts relatively little drug into the cornea and anterior chamber at the expense of a host of toxic side effects. Lesser quantities of the drug can be used and therapeutically effective ocular levels obtained by the simple expedient of administering the drug locally, usually by topical application. While this virtually eliminates systemic side effects, use of the drug in this manner is by no means innocuous. A variety of ocular side effects (glaucoma, enhancement of microbial replication, etc.) has been well documented, making it obligatory that these agents be used in a manner that ensures maximal therapeutic benefit. This obligation is underscored by the need to eliminate the offending inflammatory cells as rapidly as possible if optimal preservation of corneal transparency is to be achieved.

Ophthalmic steroids vary in their ability to penetrate into and through the cornea. The factors responsible for these variations are complex and reflect both peculiarities of corneal structure and differences in the physical properties and methods of formul-
lation of different steroid bases and their derivatives. For example, the corneal epithelium and endothelium are lipophilic and resist penetration by water-soluble molecules. The stroma, on the other hand, is hydrophilic and resists penetration by fat-soluble molecules. Thus, a water-soluble corticosteroid preparation will penetrate readily into the hydrophilic corneal stroma if the epithelium is absent but will produce substantially lower corneal and anterior chamber drug levels if the epithelium is intact. If the steroid is to penetrate all layers of the cornea with facility, it generally must be of biphasic polarity, that is, it must have some degree of solubility in both aqueous and lipid media.

Phosphate preparations (e.g., dexamethasone phosphate, prednisolone phosphate) are highly soluble in aqueous solution and, as a result, the commercially available ophthalmic products are solutions. In contrast, alcohol and acetate preparations (e.g., dexamethasone alcohol, prednisolone acetate) are sparingly soluble in aqueous solution, a physical property requiring that the commercial ophthalmic formulations be suspensions. Suspensions are said to be superior to solutions, a claim based on the presence of steroid particles in the suspension and the assumption that these particles persist in the conjunctival cul-de-sac for prolonged periods. This is believed to increase the contact time between the drug and the eye, presumably permitting the drug to attain a higher concentration in ocular tissues and fluid than the comparable drug in solution. However, undoubtedly of equal importance is the fact that the steroid derivatives marketed as suspensions, the acetate and the alcohol, are biphasic in solubility (particularly the acetate) and, therefore, are better able to penetrate into and through the intact cornea.

In the experimental situation, a number of other factors clearly can be shown to influence the level a topically administered steroid achieves in the eye. These factors include the quantity of drug administered, its concentration, its pH, the frequency of administration, the position of the recipient, whether or not the recipient is anesthetized, the position and movement of the lids subsequent to drug administration, and the vehicle in which the drug is delivered to the eye. It is generally taught that any vehicle which prolongs the contact time between the drug and the eye will permit the drug contained in that vehicle to achieve a higher concentration in ocular tissues. All other things being equal, this thesis is probably correct. Therefore, at present, ointment bases should represent the optimal ophthalmic vehicle. However, the situation with respect to ophthalmic corticosteroids unfortunately is somewhat more complex. Comparison of experimental data obtained following administration of radiolabeled commercially available dexamethasone phosphate solution with that of the commercially available comparable ointment demonstrates that the ointment form produces lower corneal and anterior chamber levels than does the solution. The dexamethasone phosphate apparently does not partition rapidly from the petrolatum (used as the vehicle in the formulation of the commercial ointment) to the tear film, and so it is not readily available for penetration into the cornea. Thus, in this instance prolongation of contact time does not enhance the availability of the drug in the anterior segment of the eye.

These differences in the quantity of drug measurable in the cornea and anterior chamber suggest corresponding differences in the ability of ophthalmic corticosteroids to suppress inflammation in these locations. However, steroids differ in their anti-inflammatory potency, and these differences prevent the transposition of data on tissue levels of drug directly into data on relative pharmacologic effect. Until recently, even presumably logical suppositions were hazardous since no basic information was available on the anti-inflammatory potency of different steroids following topical administration to the eye. To obtain definitive information on the relative ability of
various ophthalmic steroids to suppress an ocular inflammatory response required a method to quantitate inflammatory processes in ocular tissues.

An experimental model which permits quantitation of corneal inflammation has been described. Replicating leukocytes are radiolabeled systemically with intravenously administered tritiated thymidine and, subsequently, during a corneal inflammatory response, they are chemotactically attracted to that site. The amount of radioactivity in the cornea is measured, providing a direct means of quantitating the degree of white cell infiltration and therefore the degree of corneal inflammation. Topical administration of corticosteroid produces a decrease in corneal radioactivity that is proportional to the decrease in invading labeled leukocytes. This, then, provides a direct measure of the anti-inflammatory effectiveness of the preparation.

Using this experimental model, the therapeutic efficacy in inflammatory keratitis of a number of widely used, commercially available ophthalmic corticosteroids was investigated. These experiments document that once they gain access to the site of inflammation, topically administered corticosteroids differ in their ability to suppress an inflammatory reaction. Among the corticosteroids studied to date, prednisolone acetate 1.0 per cent ophthalmic suspension has proved to be the most effective topical anti-inflammatory agent when the epithelium of the inflamed cornea is intact. In the absence of the corneal epithelium, prednisolone acetate 1.0 per cent ophthalmic suspension again produces the greatest mean reduction in leukocytic infiltration of the cornea although here one cannot demonstrate a statistically significant difference between its effect and that produced by either dexamethasone phosphate 1.0 per cent ophthalmic solution or dexamethasone alcohol 0.1 per cent ophthalmic suspension. Thus, overall, prednisolone acetate 1.0 per cent is the most effective of the agents studied for suppression of corneal inflammation.

These same experiments also demonstrate that modification of the derivative of a given steroid base alters its anti-inflammatory properties as measured by suppression of leukocyte invasion. The phosphate derivative of both of the steroid bases studied (dexamethasone and prednisolone) is a less effective anti-inflammatory agent following topical administration to the eye than other derivatives of the same steroid base. More specifically, topically administered prednisolone acetate 1.0 per cent is a more potent anti-inflammatory drug in the cornea than is prednisolone phosphate 1.0 per cent. Similarly, dexamethasone alcohol 0.1 per cent is a more effective anti-inflammatory agent in the cornea than is dexamethasone phosphate 0.1 per cent, both when the epithelium is intact and when it is absent. This differential in anti-inflammatory effect occurs despite greater corneal penetration by dexamethasone phosphate in both instances. The reason for the difference in therapeutic effectiveness is obscure, but clearly it is independent of the variability in drug penetration.

Thus, multiple factors contribute to the ability of a topically administered corticosteroid to gain access to the cornea and anterior chamber and to suppress inflammation once there. Many permutations and combinations of these factors are possible, and the combination capable of producing the optimal therapeutic response is not known. However, each of these variables seems to be readily accessible to experimental study, and each could be manipulated in the manner that would produce the greatest clinical advantage if the ophthalmologist had that information. The optimal use of each variable, therefore, must be scientifically defined if corticosteroids are to be used to gain maximum clinical benefit (i.e., preservation of normal structure and function with the minimal incidence and severity of toxic side effects). It is anticipated that the experimental data gleaned from animal studies will pro-
vide a basis for establishing more valid
guidelines than currently exist for the
clinical therapy of inflammatory keratitis.

Howard M. Leibowitz
Allan Kupferman
Boston University
School of Medicine
Boston, Mass.

REFERENCES
1. Leibowitz, H. M., and Kupferman, A.: Bio-
availability and therapeutic effectiveness of
topically administered corticosteroids, Trans.
Amer. Acad. Ophthalmol. Otolaryngol. 79: 78,
1975.
2. Cox, W. V., Kupferman, A., and Leibowitz, H.
M.: Topically applied steroids in corneal dis-
ease. II. The role of drug vehicle in stromal
absorption of dexamethasone, Arch. Ophthal-
3. Leibowitz, H. M., Lass, J. H., and Kupferman,
A.: Quantitation of inflammation in the cornea,

Conflicts of interest and vision research

Two years ago the Trustees of the Asso-
ciation for Research in Vision and Oph-
thalmology, recognizing that situations
could occur that would interfere with the
quality and objectivity of visual research,
established a Committee on Guidelines for
Clinical Investigation. The committee’s
charge was to determine possible situations
that could produce conflicts of interest in
clinical research on drugs and devices, to
formulate a set of ethical principles to
avoid such conflicts of interest, and to
recommend mechanisms whereby both the
investigator and the public could be pro-
tected from conflicts of interest.

At present, members of the committee
are Thomas D. Duane, Philadelphia, Pa.;
Phillip P. Ellis, Denver, Colo.; Paul Hen-
kind, Bronx, N. Y.; Herbert E. Kaufman,
Editor of INVESTIGATIVE OPHTHALMOLOGY,
Gainesville, Fla.; Irving H. Leopold, repres-
enting the Committee on Drugs, of the
American Academy of Ophthalmology and
Otolaryngology; Albert M. Potts, Chair-
man of the Trustees of ARVO, Chicago,
Ill.; Robert D. Reinecke, Secretary of
ARVO, Albany, N. Y.; and Bernard
Schwartz, Boston, Mass., Chairman of the
Committee.

The committee’s basic philosophy was
that the onus should be on the investiga-
tor to avoid a situation that produces a
conflict of interest, thus, obviating as much
as possible any “policing” effort.

The committee considered a number
of situations where possible conflicts of
interest could occur. These range from a
direct financial interest of the investigator,
or the investigator’s family, to an indirect
interest by other individuals engaged in
the research project, by the institution,
or department which may be sponsoring
the research.

The committee also considered that there
should be no interference with the finan-
cial privileges enjoyed by an individual
for the rights and rewards for inventions.
The committee recognized that there was
a limited number of capable investigators
in ophthalmology and visual research and