eleven days after treatment. In two eyes, onset occurred between four and 25 days after treatment. In these seven eyes, pressure ranged from 24 mm Hg to slightly more than 50 mm Hg. (The upper limit of the Perkins tonometer is 50 mm. Hg.)

In one monkey, the pressure in one eye ranged from 6 to 16 mm Hg after two photocoagulation treatments. The eye was not inflamed. In a second monkey, the pressure in one eye was 20 mm Hg seven days after the second treatment. This subsequently fell to normal values. The pressure in the other eye of the same animal was 12 mm Hg seven days after the second treatment; it rose to 24 mm Hg by 30 days after the second treatment, but was normal at 40 and 50 days. No change of the optic nervehead from normal occurred in these three eyes.

Outflow facility, determined in vivo, was impaired in all treated eyes. The values obtained ranged from 0.02 to 0.11 /l min. -1 mm. Hg -1 (normal values: 0.33 to 0.75 /l min. -1 mm. Hg -1).

Histopathologic specimens have been prepared from the two control eyes and from four eyes which had developed elevated intraocular pressure and cupping of the optic nervehead. Preliminary examination has shown trabecular scarring with obliteration of the canal of Schlemm in the treated eyes (Fig. 1). In the retina, a selective loss of ganglion cells and thinning of the nerve fiber layer has been observed (Fig. 2). Cupping of the optic nervehead, with posterior bowing of the lamina cribrosa, has been verified (Fig. 2). No extensive cavernous degenerative change was seen in the optic nerves.

The experimental ocular hypertension presented here differs from previous models in several ways. First, the sustained elevation of intraocular pressure is produced by use of a noninvasive technique. Second, the mild to moderate initial inflammation, caused by the photocoagulation, is transient, usually lasting less than two weeks. Third, the primary alteration induced in the eye is localized to the region of the aqueous humor outflow pathways. That this experimental ocular hypertension is a glaucoma is indicated by the observed development of cupping of the optic nervehead and by the selective loss of retinal ganglion cells in histopathologic specimens.

Dr. Frank Macri reviewed and assisted in the preparation of this manuscript.

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Key words: experimental glaucoma, Rhesus monkey, perfusion, argon laser.

REFERENCES


Permeability of the isolated rabbit cornea to corticosteroids. DAVID S. HULL, JAMES E. HINE, HENRY F. EDELHAUSER, AND ROBERT A. HYNDIUK.

Isolated rabbit corneas were mounted in a perfusion chamber, and the corneal permeability of four tritiated corticosteroids was determined. With the epithelium intact, corneal permeability to dexamethasone sodium phosphate was significantly lower than to prednisolone sodium phosphate, prednisolone acetate, and flurometholone. With the epithelium removed, the corneal permeability to dexamethasone sodium phosphate and prednisolone sodium phosphate increased three- to four-fold while the corneal permeability
to prednisolone acetate and fluorometholone was unaffected.

Studies on corticosteroid penetration into the anterior segment of the eye have been limited to the topical application of the steroid to the surface of the cornea and the subsequent measurement of aqueous humor concentration. Potential problems with this technique include variations of blink rate, head position, and protein and tissue binding. In addition, the drug is constantly diluted in the tear film at variable and undetermined rates in the test animals. Different schedules of drug administration and quantitation of results probably also account for the variable results reported in aqueous humor corticosteroid levels.

Some studies have been unable to demonstrate measurable levels of dexamethasone sodium phosphate in the aqueous humor of rabbits after topical application of a single dose to an uninflamed eye. Others have reported measurable levels of dexamethasone in the anterior chamber after topical application. Following multiple topical applications, aqueous humor concentrations of approximately 1 μg per milliliter of dexamethasone and 6-methylprednisolone were measured by chromatography and spectrophotometry. Earlier reports, using less sensitive techniques, had reported aqueous humor levels ten- to fifteen-fold higher for the same drugs.

It was the purpose of this study to eliminate the previous variables by clamping the cornea in vitro and measuring the corneal permeability of four topical steroids used in the treatment of ocular inflammatory disorders. Materials and methods. Albino rabbits weighing approximately two kilograms were killed. The eyeball was enucleated complete with conjunctival sac and lids. The isolated corneas were then mounted in a Lucite block system with a corneal holder that had been modified according to the method of Dikstein and Maurice which prevents trauma to the corneal epithelium and distortion of corneal curvature during clamping. Six milliliters of glutathione bicarbonate Ringer’s solution (GBR), which has been shown to maintain endothelial function for up to six hours were added to the reservoir bathing either side of the cornea and circulated with an airlift siphon. The blocks were placed on a hotplate, and the temperature monitored and maintained at 37° C. with a Thermometer and thermistor in a 22-gauge needle (Yellow Springs Instrument Co., Yellow Springs, Ohio).

The steroids utilized in this study were tritiated prednisolone sodium phosphate—activity, 6.39 μCi per milligram (63.9 μCi per milliliter); fluorometholone—activity, 3.19 μCi per milligram (3.19 μCi per milliliter); prednisolone acetate—activity, 7.72 μCi per milligram (77.2 μCi per milliliter); and dexamethasone sodium phosphate—activity, 5.34 μCi per milligram (53.4 μCi per milliliter). Evaporation techniques were used to demonstrate that the tritium label was intact for each corticosteroid. In each experiment paired rabbit corneas were utilized, one with the epithelium intact and the paired cornea with the epithelium removed. The labeled corticosteroid was placed in the GBR solution perfusing the epithelial side of the cornea. The amount added to the chamber was corrected to be the equivalent of 100 μl of a one per cent solution for each drug.

Serial samples of 100 microliters were removed from each chamber at hourly intervals. Samples were then placed in 15 c.c. of scintillation counting solution consisting of 80 Gm. of naphthalene, 5 Gm. of PPO (2,5 diphenyloxazole), and 50 mg. of POPOP (1,4 bis-[2-(5-phenyloxazolyl)] benzene) and made up to a full liter with dioxane. Samples were counted in a Nuclear Chicago Unilux II liquid scintillation counter at one per cent error. Counts were corrected for background, and quenching was determined using an external standard. The average corticosteroid flux was calculated hourly, and was found to be linear over four hours by regression analysis.

Results. With an intact corneal epithelium, the three corticosteroids—prednisolone sodium phosphate, prednisolone acetate, and fluorometholone, all penetrated the cornea equally. The cornea was significantly less permeable to dexamethasone sodium phosphate than to the other three corticosteroids (Table 1).

When the corneal epithelium was removed, the diffusion rates of dexamethasone sodium phosphate and prednisolone sodium phosphate, both water-soluble, increased three- to four-fold. By comparison, corneal permeability of the lipid-soluble corticosteroids, prednisolone acetate, and fluorometholone, did not increase when the epithelium was removed (Table 1). This suggests that, clinically, the removal of the epithelium will enhance penetration of the two water-soluble steroids and not the two lipid-soluble steroids. It should be noted that with the epithelium removed the corneas increased in thickness, and they showed a weight gain of 25 to 40 per cent in four hours.

In most studies on drug penetration, the data are expressed in micrograms of drug per gram of tissue or per milliliter of aqueous. We have also expressed the diffusion rate in nanomoles per square centimeter of cornea per hour (Table 1). This takes into account differences in the molecular weight of the respective drugs and, therefore, reflects the number of molecules of corticosteroid potentially available for therapeutic purposes.

Comment. Application of the in vitro method
for determining corneal penetration is potentially useful for drug evaluation. It eliminates all other factors and permits the comparison of the corneal permeability of the drugs tested as the only variable.

Tritiated dexamethasone sodium phosphate (Decadron) was supplied by Merck Sharp and Dohme, Inc., West Point, Pa. Tritiated prednisolone sodium phosphate (Inflamase Forte) was supplied by Cooper Laboratories, Inc., Cedar Knolls, N. J. Tritiated prednisolone acetate (Prednefrin Forte) and tritiated fluorometholone (FML) was supplied by Allergan Pharmaceuticals, Irvine, Calif.

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Key words: corticosteroids, dexamethasone sodium phosphate, prednisolone sodium phosphate, prednisolone acetate, fluorometholone, diffusion rate, cornea, and drug penetration.

REFERENCES


10. Lenticular and fundus changes induced by the intraocular infusion of sodium aspartate. WILLIAM S. BARON.

Gross changes in the in vivo primate eye are reported which result from the intraocular infusion of 100 mM sodium aspartate at a rate of 0.25 c.c. per hour. Within 30 minutes after starting the infusion, there is an extraordinary vasospasm of the retinal vasculature, and within 3 hours, there is the formation of a posterior cataract which looks like lamellar separation.

The observations reported here were arrived at quite by accident during the course of doing late-