Aqueous outflow facility in monkeys and the effect of topical corticoids

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The ocular effects of topically applied dexamethasone 21-phosphate and subconjunctivally administered methylprednisolone acetate were investigated in three monkey species. The duration of treatment lasted for three months. There was no significant change in intraocular pressure, outflow facility, or pupil size.

Topically applied corticoids were shown to produce in man an increase in intraocular pressure, a reduction in outflow facility, and dilatation of the pupil. In addition, important differences in this respect were depicted between the normal and glaucomatous eye. These findings suggested an extensive search for a suitable laboratory animal in which these effects may be reproduced and their mechanism definitively investigated.

This presentation will be limited to studies of the effect of topically applied dexamethasone 21-phosphate, 0.1 per cent (Decadron, Merck Sharp & Dohme), and subconjunctivally administered methylprednisolone acetate (Depo-Medrol, Upjohn) in three monkey species: Macaca mulatta (rhesus), Macaca nemistrina (pigtail), and Macaca cynomolgus (cyno). The results indicate that such application for three months failed to produce a significant change in intraocular pressure, aqueous outflow facility, or pupil size.

**Sample and Procedure**

The sample consisted of two groups: treated and untreated. The untreated group included 36 rhesus, 27 pigtails, and 25 cynos. The treated group comprised two categories: one in which topical applications of dexamethasone, 0.1 per cent, was investigated and this included 16 rhesus, 12 pigtails, and 13 cynos; and, another in which methylprednisolone acetate (40 mg. per cubic centimeter) was injected subconjunctivally, and included 10 rhesus and 10 cynos.

All animals were selected from amongst healthy adult monkeys with a minimum weight of 5 kilograms. These animals showed no evidence of cataract or of injury or inflammation in the anterior segment. The treated group was examined gonioscopically with the Zeiss hand slit lamp and a specially designed gonio lens to fit the monkey eye in order to insure absence of peripheral anterior synechiae in the chamber angle.

The treatment regimen consisted of the following: In the first group, 2 drops of dexamethasone, 0.1 per cent ophthalmic solution, were applied...
Fig. 1. The needle gun consists of a stainless steel cylinder 13 cm. long and 1.5 cm. in diameter. It houses a spring-driven stainless steel rod whose free end is fused to one side of the perpendicularly mounted rectangular needle carrier. The top of the needle carrier (A) has two tracks intersecting at right angles; the anteroposterior track accommodates the needle shaft, and the other accommodates the stainless steel disc fused to the needle shaft. The disc is circular and is 3 mm. in diameter and 1 mm. thick. On the sides of the rectangular needle carrier (B) are two retaining flat springs that maintain the needle in its groove by pressing down upon the disc. Its lower end has a spring-loaded stylus which, when pushed, releases the needle from the needle carrier (G). In the cocked position, the needle carrier is flush with the open end of the cylinder. The needle tip is approached to the eye at the limbus and the gun is aligned to insure proper direction of the needle shaft into the anterior chamber (D). The trigger is pushed and the spring-loaded rod is driven, carrying the needle into the anterior chamber (F). Its forward travel is limited to 1 cm. by an appropriate stop. The needle spring is then pushed, releasing the needle shaft (I). This procedure permits accurate controlled cannulation of the anterior chamber without manipulation of the eye. (D, F, I are top views; C, E, H are side views, A, B, G are details of needle carrier.)

to the right eye three times daily. For this, the animal was caught and restrained by one person, while another applied the eye drops. This regimen was continued for three months in the animals to be reported in this presentation. In the second group, the monkey was given an intramuscular injection of 1 mg. per kilogram of the cataleptic drug, phencyclidine. Five to 10 minutes after injection, the monkey became cataleptic and could be manipulated safely without exhibiting any resistance. The topical anesthetic, proparacaine, 0.1 per cent, was then applied to the right eye.
and an 0.1 to 0.15 c.c. of methylprednisolone acetate was then injected subconjunctivally in the upper temporal quadrant. This injection was repeated at intervals of 12 to 15 days until the end of the three month period. All animals received a minimum of five injections. The untreated group was not placed on any therapy.

At the end of the treatment period, the animals were anesthetized with intravenous Nembutal. They were given just enough Nembutal to eliminate the corneal reflex. The animals were then placed on their back with their extremities extended and tied down to the perfusion table. A 27 gauge needle cannula was then introduced into each anterior chamber with a needle gun similar in objective to that reported by Sears* (Fig. 1). The cannulas were connected to a servoperfusor for determination of steady-state pressure and outflow facility. Outflow facility was determined with the constant pressure servoperfusion technique* by finding the rate of fluid inflow from the servoperfusor into the eye which was required to maintain constant, a pressure level 20 mm. Hg higher than that of steady-state intraocular pressure. This was determined separately in each eye; right and left eyes were randomly alternated as to which was done first. The perfusion fluid was normal saline to which glucose, 1 Gm. per liter, was added.

Results

General observations. The monkeys tolerated well the above outlined treatment. There was no clinical evidence of systemic or local complication. The slit-lamp examination failed to reveal any opacification or neovascularization of the cornea, or any evidence of cataractous changes in the lens. The pupils, on gross inspection before and during anesthesia, failed to show the anisocoria reported in the human.

Effect on intraocular pressure. The steady-state intraocular pressure level ranged between 8 and 21 mm. Hg in this preparation. The values of the average intraocular pressure for the three species fell in the range of 14 and 15 mm. Hg. The difference between the right and left eye in the control group examined never exceeded 6 mm. Hg and had an average value which did not differ significantly from zero (0). The results in the treated group were identical with those of the untreated group. Thus, no significant increase in the intraocular pressure of the treated eye could be detected in this preparation.

Effect on outflow facility. The distributions of outflow facility values in the control group appear in Fig. 2. The distributions are quite similar for the three species investigated. Outflow facility values of the treated groups did not differ significantly from those of the control group. The ratio of outflow facility in the right eye to that of the left eye was calculated for both treated and untreated groups. The distributions of this ratio in the untreated group and that subjected to topical application of dexamethasone appear in Fig. 3. It is apparent that in this preparation the values of this ratio vary over an undesirably large range. The mean values in the control and in the treated groups, however, did not differ significantly from each other or from unity, indicating that no significant change in outflow facility was found in the treated eye. The same held true for the group treated with subconjunctival injection of methylprednisolone acetate.
Effect of topical corticoids

Fig. 3. Frequency distribution of the ratio $C_{O.U.}/C_{O.S.}$ in the control groups (light stippling) and in animals treated with dexamethasone, 0.1 per cent three times a day, to the right eye for three months in three monkey species. The mean ratio and the standard deviation of the mean are indicated for each group. The abscissa indicates the per cent ratio of $C_{O.U.}/C_{O.S.}$. The ordinate marks the number of animals.

Comments

Failure of the monkey species to demonstrate any of the ocular effects of topically applied corticoids that are so readily elicited in the human subject is disappointing. The monkey is, in general, considered a good experimental model of the human eye. Ocular penetration of the topically applied corticoid is not likely to differ drastically from that in man. On the other hand, there is no biologic index to assess or ascertain this penetration since the pupil size did not change in the monkey. Nembutal anesthesia may be considered as a factor that might have masked a corticoid effect on the intraocular pressure; it seems unlikely that it also masked an effect on outflow facility. However, experiments in which the monkey is first sacrificed before the perfusion are in progress to elucidate the possible effect of this factor.

On the other hand, Lieb reports that he succeeded in obtaining the corticoid-induced ocular hypertension in the rabbit only after he increased their intake of sodium phosphate. This intriguing finding implies that animals that are resistant to ocular corticoid effects may become sensitive to those effects by providing appropriate conditions. Studies of the corticoid effects in the monkey under conditions in which various dietary constituents are modified are in progress and will be reported in future publications.

REFERENCES