"Steroid-induced" mydriasis and ptosis

David A. Newsome, Vernon G. Wong, Thomas P. Cameron, and Richard R. Anderson

Pupil size, width of palpebral fissure, and intraocular pressure were followed in rhesus monkeys before and after treatment of one eye with dexamethasone phosphate in a vehicle mixture (Decadron), the vehicle mixture alone, some individual constituents of the vehicle, and pure dexamethasone in saline. Decadron and the vehicle alone produced relative pupillary dilation and ptosis, but dexamethasone in saline did not. Pupil and lid changes were not accompanied by a rise in intraocular pressure. The mydriasis and ptosis appeared to be caused by a direct myopathic effect of the vehicle.

Key words: pupil size, palpebral fissure width, intraocular pressure, dexamethasone phosphate, ptosis, mydriasis, myopathy.

It has been reported that topically applied steroid preparations can produce pupillary dilation, ptosis, and intraocular pressure changes in normal eyes. The mechanisms of the pupil and lid effects have not been elucidated, however. Some time ago, one of us (V. W.) noticed that intracamerally injected steroid preparations produced mydriasis and intraocular pressure alterations in rhesus monkeys. On the basis of these observations an investigation of "steroid-induced" ocular changes was undertaken.

Methods

Nine adult rhesus monkeys, 5 males and 4 females, were used, some for more than one experiment. The agents investigated were (1) Decadron (Merck, Sharp & Dohme) consisting of 0.1 per cent dexamethasone phosphate in a vehicle mixture, (2) the vehicle mixture alone,* (3) pure dexamethasone phosphate 0.1 per cent in sterile isotonic saline mixed freshly for each use, and (4) different agents contained in the vehicle mixture, namely (a) 0.2 per cent polysorbate 80, (b) 0.25 per cent phenylethanol, and (c) 0.05 per cent disodium edetate. Sterile sodium chloride solution (0.85 per cent) was used for control treatments. The solutions of polysorbate 80, phenylethanol, and disodium edetate were the same concentration as in the vehicle. All solutions were isotonic, and pH's were similar.

The animals were anesthetized with 8 mg. of phencyclidine hydrochloride (Seralyn) intramuscularly and one drop of 0.5 per cent Ophthaine topically in the eye to be treated. Two different routes of drug administration were employed:

Subconjunctival injection. 0.1 c.c. of either Decadron, vehicle, dexamethasone in saline, or polysorbate 80 was injected, in 0.1 c.c. amounts, through a 27 gauge needle under the conjunctiva of one eye at about the 11 o'clock position. The same amount of saline was injected into the other eye as a control.

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*The vehicle consists of an aqueous solution of sodium bisulfite 0.1 per cent, sodium citrate 2 per cent, sodium borate 0.3 per cent, creatinine 0.5 per cent, disodium edetate 0.05 per cent, phenylethanol 0.25 per cent, polysorbate 80 0.2 per cent, benzalkonium chloride 0.02 per cent, with the pH adjusted to 7.5 by hydrochloric acid.

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Anterior chamber perfusion. The eye was perfused through a 27 gauge needle placed through the cornea at the limbus anterior to the iris root with the tip over the inner ciliary-sphincter muscle zone of the iris. The needle was connected by polyethylene tubing to a 5 c.c. syringe. A Harvard pump was utilized to deliver test solutions into the eye at a rate of 3.0 nl per minute for 30 minutes; the second eye was similarly perfused with 0.85 per cent saline as a control. Solutions introduced into the eye by this method were Decadron, vehicle, dexamethasone in saline, polysorbate 80, phenylethanol, and disodium edetate. Each drug was administered only once to each animal.

Neosporin ophthalmic ointment was applied following each of the above procedures.

Pupillary diameter and the width of the palpebral fissure were observed and measured from photographs taken (1) before the administration of any drugs (2) and up to 80 days after treatment. The pictures were made before tranquilizing drugs were given. A 35 mm. Nikkorex camera equipped with an electronic flash unit was used. Lighting conditions under which the pupils were photographed were either diffuse room light (approximately 120 footcandles or 1,300 lux) or darkness. A millimeter scale was included in each photograph. The influence of such factors as the animal's state of arousal were minimized by having one treated and one control pupil. Measurement of drug-induced changes of pupillary size were made by comparison of the treated eye with its fellow control. Pupil measurements refer to the horizontal diameters in those photographs that showed the eyes looking straight ahead. In a few cases when no photograph with centrally positioned eyes was available the vertical pupil diameter was used.6

Intraocular pressure was followed daily by Schiötz tonometry. The same observer made all pressure readings. He was not informed of the nature of the drugs the animal had received until the completion of the experiments.

Four eyes were studied histologically: one at five and one at ten days after perfusion with vehicle, one at ten days after perfusion with Decadron, and one saline control. The animals were killed with an overdose of intravenous sodium pentobarbital and the eyes were immediately enucleated and fixed in formalin. After being embedded in paraffin and sectioned, the tissues were stained by the usual techniques with hematoxylin and eosin and also periodic acid-Schiff (PAS), and examined with the light microscope.

Results

Effects on iris.

Decadron, pure steroid, and vehicle mixture. Both Decadron and vehicle mixture with no steroid produced pupillary dilation when administered by anterior chamber perfusion (6 of 6 experiments) but not by the subconjunctival route (4 experiments). No pupil changes were observed after perfusion with dexamethasone, the pure steroid, in saline (see Table I).

With anterior chamber perfusion with Decadron or the vehicle mixture, the pupil widened four to five minutes after the start of the perfusion and remained enlarged for an average of about 60 days. The anisocoria was greatest the first two to three days following perfusion, and then gradually decreased to a stable plateau. All mydriatic pupils reacted sluggishly to light immediately after the appearance of mydriasis. This sluggishness gradually diminished over the first seven days. The average difference in pupil size between treated and control eyes (they had been exactly equal before treatment) was 0.25 mm. in room light and 0.7 mm. in darkness as measured on the photographs.

When 15 per cent methacholine was instilled into both eyes of two animals three

Table I. Relation between route of administration and substance administered in production of mydriasis and ptosis

<table>
<thead>
<tr>
<th>Animal No.</th>
<th>Drug</th>
<th>Mydriasis</th>
<th>Ptosis</th>
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</tr>
<tr>
<td>576</td>
<td>Decadron</td>
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<tr>
<td>589</td>
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<td>Decadron</td>
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<td>744</td>
<td>Vehicle</td>
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<tr>
<td>663</td>
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<td>Phenylethanol</td>
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<td>576</td>
<td>Polysorbate 80</td>
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*Indicates presence of effect.
Fig. 1. Pupils before and three days after perfusion of the right anterior chamber with Decadron. Before treatment, pupils were equal (A1, B1); after treatment, there was a small anisocoria in room light (0.4 mm.) (A2) that became more pronounced in darkness (1.5 mm.) (B2).

Fig. 2. Lid position following anterior chamber perfusion (two monkeys). Twenty-four hours after the right anterior chamber of monkey A was perfused with Decadron there was a mild to moderate ptosis present (A2). Monkey B was treated with vehicle alone. Complete ptosis was present 24 hours later (B2). The usual degree of ptosis in our experiments was that seen in A2.

days after the anterior chambers had been perfused with the vehicle mixture, the treated eyes responded with about 1 mm. of constriction at 30 minutes in darkness, while the control eyes contracted about 1.5 mm. The pupillary responses of one animal were tested with topically applied 1 per cent hydroxyamphetamine, 4 per cent cocaine, and 2.5 per cent phenylephrine hydrochloride at 14, 21, and 28 days after treatment and the appearance of mydriasis without iritis. The amount of anisocoria did not change 30 minutes after both eyes had been treated with each of these drugs (Fig. 1).

After the vehicle mixture was perfused into an anterior chamber, 2+ cells and flare and moderate iris hyperemia were noted for the next five days. In one experiment with the vehicle mixture the iritis was severe enough to cause miosis; the pupil became mydriatic when the eye had quieted. With Decadron, however, any iritis was only minimal or absent. Regardless of the method of administration, the eyes that received saline showed no signs of irritation on slit-lamp and ophthalmoscopic examination, and no pupil or lid changes (Fig. 2).

**Individual vehicle components.** Perfusion of the eye with some of the individual components of the vehicle, namely poly-
sorbate 80, disodium edetate, and phenylethanol, produced no sustained pupillary changes. At the time of perfusion with both disodium edetate and phenylethanol there was a transient pupillary dilation that disappeared within half an hour and three to four hours, respectively.

**Lid effects.** Subconjunctival injection or anterior chamber perfusion of Decadron or of the vehicle mixture produced moderate to marked ptosis in 10 out of 11 experiments. The ptosis was present an average of eight days, and was accentuated when the animals were under the influence of Sernylan. Anterior chamber and subconjunctival administration of dexamethasone in saline, polysorbate 80, phenylethanol, and disodium edetate had no effect on the lids.

**Intraocular pressure effects.** Following anterior chamber perfusion with Decadron, the intraocular pressure was lowered, returning gradually to a preperfusion level in five to fourteen days. Intraocular tension returned to control levels in the saline-treated eyes after two to three days.

The vehicle mixture produced a fall in intraocular pressure averaging 10 mm Hg that lasted four to five days. The pure steroid, dexamethasone, in saline and the vehicle constituents tested separately produced an effect on the ocular tension similar to that of plain saline.

**Histologic findings.** Under the light microscope, the tissues of one eye treated with Decadron by perfusion and two eyes treated with vehicle by perfusion were not grossly different in staining reactions or in morphology from those of the control eye.

**Discussion**

Armaly first reported in detail the pupillary dilation that can accompany the topical administration of corticosteroid preparations. He described patients in whom the treated pupil became at least 1 mm. larger than its fellow pupil, with the difference in size exaggerated in dim illumination. The light reactions of the enlarged pupil appeared normal. This relative dilation ap-

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Fig. 3. Pupillary light reflexes before and after topical steroids (A1 and A2), with sympathetic stimulation (C), and with decreased parasympathetic innervation (D). The patient had normal light reactions before Decadron was applied to the left eye q.i.d. (A). After one month of Decadron treatment, the left pupil (solid line in B) had become 0.6 mm. larger than the right (dashed line in B), but the time-amplitude profile of the reactions had not changed.* Increased sympathetic tone that causes such an increase in pupil size (after 1 per cent hydroxyamphetamine, solid line in C) also alters the shape of the light reaction in such a way that the normal eye would appear to have a sympathetic deficiency (dashed line, C). Decreased parasympathetic innervation also causes mydriasis (less in darkness than in light), but the amplitude and speed of the light reflex are decreased (solid line in D).

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*This study was done by Dr. S. M. Fodos while at the National Institutes of Health; his current address is the Department of Ophthalmology, Washington University, St. Louis, Mo.
appeared after at least two weeks of therapy, and was reversible by stopping the medication. Miller and associates investigated this effect in detail, and added pupillographic confirmation of Armaly's observation that the light reflexes of the relatively dilated eye were not appreciably altered. They suggested that steroids in some way weaken the intrinsic muscles of the eye.

Our experiments involving intracameral perfusion of the dexamethasone preparation and the Decadron-vehicle mixture produced a small but definite anisocoria that increased in magnitude in low illumination. The cause of this pupillary dilation can be ascribed to the vehicle. Eyes treated with Decadron and with vehicle alone displayed similar pupil and lid effects, while the pure steroid dexamethasone left the pupils unchanged.

Just how the vehicle produced the pupillary changes observed is not clear at present. Sphincter ischemia can produce pupillary dilation, as in an episode of acute intraocular hypertension. This explanation is made unlikely by the finding that the intraocular pressure was never above pretreatment levels at the time the pupil changes were observed.

Alteration in the innervation of the iris muscles, either a net increase in sympathetic, or net decrease in parasympathetic sphincter tonus, can produce a widening of the pupil. The fact that the pupils remained dilated for an average of six weeks after a single application of steroid preparation or of the vehicle mixture makes a direct sympathetic stimulatory action or a direct parasympathetic inhibition unlikely. Pupillography before and during topical corticosteroids has confirmed the development of the dilation (Fig. 3, A and B) but has shown no alteration in the reflex time-amplitude pattern that would indicate either sympathetic stimulation (Fig. 3, C) or parasympathetic weakness (Fig. 3, C). Furthermore, tests two weeks and longer after treatment did not show supersensitivity to adrenergic or to cholinergic compounds (phenylephrine and mecholyl), nor did they point to an increased amount of norepinephrine in the iris (hydroxyamphetamine and cocaine).

A direct toxic effect of the drugs on the iris muscles could produce the reactions observed. Weakening of the muscles could explain our observation that the light reactions of the treated eyes were initially impaired, along with the response to strong, topical methacholine.

The in vitro experiments of Kern and Macri also support the possibility of a toxic influence. In their experiments, isolated strips of iris sphincter had a lower resting tension and poorer response to pharmacologic stimulation when steroid preparations or vehicle were present in the muscle bath, and postulated that the surface-active agents in the vehicle altered membrane characteristics of the muscle cells, impairing their function. However, surface-active agents (polysorbate 80, phenylethanol, disodium edetate) used alone under our conditions do not produce pupil and lid changes in living monkeys. Perhaps the combination of agents in the vehicle mixture is necessary before any effects can be seen.

The ptosis produced seemed also to depend on a malfunction of the muscle fibers of the levator as opposed to a neurogenic effect. The ptosis was seen in conjunction with mydriasis. If increased sympathetic tone were invoked to explain the findings, one would expect lid retraction, not drooping. How the substances administered via the anterior chamber reached the levator fibers to produce the observed ptosis is not clear.

In the experiments reported here, pupillary dilation and ptosis occurred at a time when the intraocular pressure was reduced. The nature of the pressure-lowering effect observed, which persisted after all inflammatory processes had subsided, is beyond the scope of this communication.

Since these experiments did not employ instillation of the agents, the effects observed are not directly comparable to the clinical situation for which an acceptable
animal model has not yet been developed. A study of the effects of the vehicle mixture and of pure dexamethasone in saline applied topically to human eyes is in progress.

REFERENCES