Acute Effects of Dexamethasone on Intraocular Pressure in Glaucoma

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The effects of 3 mg orally administered dexamethasone on the intraocular pressure (IOP) were examined in four patients with primary open-angle glaucoma hospitalized for this study. Plasma-free glucocorticoid activity was measured by a radioreceptor assay. Diurnal rhythms of IOP and plasma-free glucocorticoid activity were detected prior to administration of dexamethasone. The plasma-free glucocorticoid activity rose two- to threefold in the 30-min period following steroid administration and then declined throughout the rest of the day. IOP was approximately 2 mmHg higher in the 0-4-hr period and approximately 5.5 mmHg higher in the 4-8-hr period following the pharmacologic doses of dexamethasone compared with similar periods on control days. The increase in the IOP was highly significant ($P < 0.006$) in the latter time period. These findings suggest that the glucocorticoids may have a greater role in regulating IOP than generally has been appreciated. Invest Ophthalmol Vis Sci 26:170-175, 1985

Glucocorticoid hormones are known to have a variety of effects on mammalian tissues, including those on metabolic, immunologic, inflammatory, and hemodynamic functions. The influence of these steroids on ocular tissues has been of interest following observations that prolonged administration of topical or systemic glucocorticoids could increase intraocular pressure (IOP) in susceptible individuals.1-4 The glucocorticoid excess state of spontaneous Cushing syndrome also has been reported to be associated with the increased IOP.6

The elevation of IOP after 3-6 weeks of steroid therapy has been well documented in both normal populations and in patients with primary open angle glaucoma (POAG), but there have been conflicting assessments concerning the possibility of a more rapid effect on IOP. Linner first reported that topical administration of prednisolone to normal volunteers raised IOP within 2.5-6 hr.6 Subsequently, Kimura reported IOP to be increased 5-9 hr following administration of 20 mg of oral hydrocortisone to subjects with POAG.7 On the other hand, Spaeth did not observe a rapid increase in IOP following oral dexamethasone.8 The relationship between endogenous cortisol levels and the diurnal rhythm of IOP also has been the subject of a number of investigations.9-11 These studies suggested that a 3-4-hr time lag existed between the diurnal cortisol and IOP patterns. Although this evidence appeared to support the concept of a rapid glucocorticoid effect in IOP, Weitzman et al11 concluded that the relationship was not due to a direct steroid effect, based on the administration of systemic dexamethasone to one patient with pigmented glaucoma. In this study, we conducted a double-masked investigation to examine the possibility of glucocorticoids rapidly influencing IOP. A reversal of the normal afternoon decrease in IOP and a significant increase in the IOP following dexamethasone administration as compared with similar time periods on control days was found.

Materials and Methods

Four volunteers (ages 36-62; three women, one man) with POAG were studied. All had complete ophthalmologic examinations prior to hospitalization. Three patients had a positive family history for glaucoma and all had bilateral optic disc and visual field changes typical of POAG. They did not have other ocular, medical, or surgical problems except for one patient who had mild hypertension.
controlled by hydrochlorothiazide. In this patient diuretic therapy was maintained throughout the study. All patients were receiving topical agents to reduce IOP in both eyes; these were discontinued 1 week prior to hospitalization and for the duration of the study. No patient was taking oral medication for IOP control.

The patients were hospitalized for 5 days in the General Clinical Research Center, University of California, San Francisco. Prior approval of the Committee on Human Experimentation had been given and informed patient consent was obtained.

During day 1, IOP was measured and blood samples were obtained at intervals corresponding to those in the testing period to familiarize patients with these procedures. Testing began at 12 PM of day 2 and consisted of a 24-hr control period (control day 1). A crossover design was employed. On day 3, patients were given orally either 3 mg of dexamethasone or placebo at 12 PM and again at 8 PM. The time of the first dose of dexamethasone was selected to be within an interval based on previously reported data in which the intraocular pressure was most likely to be decreasing; thus, any acute effects of the steroid, if they occurred, might interrupt the usual drop in IOP. On the next day, subjects given placebo received dexamethasone and subjects given dexamethasone received placebo. This was done in a double-masked fashion. The day on which the subject received placebo was considered to be control day 2 (day 3 for patients 2 and 4; day 4 for patients 1 and 3). We considered the IOPs on control day 1 and control day 2 independently because of the possibility that administration of dexamethasone to two of the patients prior to control day 2 could influence our results.

To determine if the glucocorticoid might exert a rapid influence on IOP, it was important to consider that IOP shows (1) a diurnal rhythm, (2) a tendency to fall spontaneously upon hospitalization, and (3) may have moment-to-moment variations. For these reasons, multiple IOP readings were most likely to be at frequent time intervals around the clock. An Alcon pneumatonometer was employed to provide a permanent record of IOP readings at 1 AM, 2 AM, 4 AM, 7 AM, 10 AM, 12 PM, 2 PM, 4 PM, 6 PM, 8 PM, 10 PM, and 12 AM on each day. A 1:8 dilution of 0.5% proparacaine hydrochloride in sterile water was used for topical anesthesia. IOP measurements were performed after the patients were supine for at least 5 min; this controlled for positional variations and facilitated measurements during the night. Recorded IOP values were the mean of two consecutive readings. Twice daily, sitting measurements also were obtained with both the pneumatonometer and a Goldmann applanation tonometer. Measurements with the two techniques never differed by more than 2 mmHg, with the pneumatonometer readings consistently lower. The pneumatonometer was used because it records graphically the IOP and is convenient for measurements of supine patients.

Blood samples were taken at 12 PM, 1 PM, 6 PM, 8 PM, 10 PM, 12 AM, 1 AM, 2 AM, 4 AM, 7:30 AM, and 10 AM through a heparin lock (#19 needle) inserted in an arm vein with aseptic technique at the beginning of each day. To provide a more accurate assessment of fluctuating steroid concentrations, each sample consisted of a pool of three blood samples taken 10 min apart. The anticoagulated samples were centrifuged at 900 × g for 10 min and the plasma was removed.

Plasma-free glucocorticoid activity was measured by a radioreceptor assay reported in detail elsewhere. Briefly, 3H-dexamethasone was equilibrated with plasma and incubated with cultured rat pituitary tumor cells (GC line). The free steroids in the plasma competed with the 3H-dexamethasone for binding to glucocorticoid receptors in the cells. Free glucocorticoid activity then was quantified with the use of standard known amounts of dexamethasone. This assay measures all steroid hormones in the sample that bind to the glucocorticoid receptor; the free glucocorticoid hormone level determined by this assay provides a useful index of the ability of a given plasma sample to induce glucocorticoid-regulated effects. Dexamethasone and cortisol were the major glucocorticoid hormones applicable to the present study.

During the hospitalization, patients were maintained on an ad lib diet. Blood pressure was measured prior to IOP measurements. No day-to-day differences after the control day and no effect of dexamethasone on the blood pressure were detected. Patients slept well even after being awakened for IOP measurements.

The data were analyzed using a repeated measures analysis of variance and Scheffe's multiple range test. Since multiple observations of IOP were performed on the same eyes, the repeated measures analysis of variance provided the appropriate statistical model in our experimental design to examine the effect of dexamethasone, as well as other potential factors that could influence IOP. Since there were two separate control days in addition to the day of dexamethasone administration, Scheffe's test provided a means to examine the differences in IOP among these three conditions.

**Results**

Figure 1 shows the plasma-free glucocorticoid activity as measured by radioreceptor assay for one of
As described in Methods, frequent intraocular pressure measurements were performed on all patients. These are plotted above the plasma-free glucocorticoid levels for the patient shown in Figure 1. Since diurnal changes in IOP were observed in the patients, it was important to compare similar time periods on experimental and control days to evaluate the effects of dexamethasone on IOP. As an example, the time periods from 4:00 PM to 8:00 PM are indicated by shading on the different days of observation (Fig. 1). IOP values appear higher during this time period (4–8 hr after the first dexamethasone dose) on the day of steroid administration compared with control days.

The IOPs for control and experimental days are presented in detail for all four patients in Table 1; these represent the mean (±SD) of duplicate readings obtained three or four times during each 4-hr period. Mean values of all patients are shown in Figure 2. As is evident from this figure, the mean IOP decreased on both control days from 8–12 AM. However, as indicated in Table 1, this was not always observed, eg, patient 2, right eye on control day 1. Also, the mean IOPs on the second control day were lower than on control day 1. These findings are in accordance with the general clinical impression that the IOP tends to fall with hospitalization.

In contrast to the drop observed for the control days, there was an increase in IOP on the experimental day (dexamethasone day), with a blunting of the drop in IOP observed on the control days for 4 hr after administration of the steroid. The IOP then increased and peaked by the period four to 8 hr after the first dose (Table 1, Fig. 2). Compared with controls, the increase was also evident in the period 12–4 AM, 4–8 hr after the second dose of dexamethasone.

The change in IOP due to steroid treatment was evaluated by subtracting the mean IOP obtained during the 4-hr period prior to dexamethasone administration (8 AM–12 PM) from the afternoon (12–4 PM) and evening (4–8 PM) IOPs on each day. Table 2 presents IOP changes from individual eyes for the different patients; however, since each eye is not considered to be an independent variable, we averaged IOPs obtained from the left and right eyes at each time point for statistical evaluations. The mean changes in IOP are presented at the bottom of Table 2. The changes in IOP during the afternoon (12–4 PM) and evening (1600–2000) appeared quite similar on both control days. Compared to control days, the IOP on the experimental day was approximately 2 mmHg higher during the first 4-hr period and approximately 5.5 mmHg higher during the second 4-hr period following the first dose of dexamethasone.
The IOP data for this 4–8-hr period then were analyzed using a Scheffe multiple range test. The mean IOP change for the dexamethasone condition was shown to be significantly different from the mean IOP changes observed for the two control conditions, and the control conditions were shown not to differ from one another (P < 0.006). The Scheffe test provided a direct means of comparing differences among three experimental conditions and therefore was preferred over a paired t-test with pairwise comparisons. Use of a paired t-test also demonstrated a significant increase in IOP following dexamethasone compared with controls (P < 0.010, P < 0.022; for comparisons between the dexamethasone day and control days 1 and 2 in the 4–8-hr period following the first dose of dexamethasone, respectively). However, this test does not represent the analysis of choice for our experimental design.

Thus, these data demonstrate that dexamethasone significantly influences IOP, and that this effect be-
comes statistically significant during the 4–8 hr period following steroid administration.

**Discussion**

These data support the concept that glucocorticoids can increase rapidly the intraocular pressure in patients with primary open-angle glaucoma. Although these findings are in substantial agreement with those of Linner and Kimura and Maekawa, our studies represent the first detailed evaluation of steroid effects on IOP performed in a rigorously controlled and masked fashion. The fact that we performed comparisons of IOP changes on control days with those obtained on the day of steroid administration is an important aspect of our experimental design. It is possible that Spaeth and Weitzman et al did not observe a rapid steroid effect on IOP because their studies did not include the use of similar controls.

The finding that dexamethasone causes a transient increase in the IOP with a short lag period provides support to the concept that diurnal variations of IOP may be related to diurnal changes in cortisol production. This possibility is consistent with the reports of Boyd and McLeod, who found a 4-hr difference between the maximum IOP and plasma cortisol concentrations in glaucoma patients when a 4-hr sampling interval was used. These workers also administered intravenous metyrapone, an inhibitor of adrenal 11-hydroxylase, to glaucoma patients to block adrenal cortisol synthesis. This resulted in the interruption of the ascending phase of the IOP, again suggesting that the elevated IOP is dependent on systemic cortisol levels. Investigations by Weitzman et al confirmed the temporal relationship between IOP and plasma cortisol found in these earlier studies. Based on hourly IOP measurements, they determined that the lag period between the changes in the IOP and plasma cortisol was about 3 hr. More recently, Levi and Schwartz have confirmed the earlier work of Boyd and McLeod on the effect of metyrapone on IOP. In a double-masked cross-over trial using metyrapone or a placebo, they noted a general decrease of IOP during a 7-hr period following me-

**Table 2.** Intraocular pressure changes between the period from 0800–1200 and the periods corresponding to 0–4 hr (1200–1600), 4–8 hr (1600–2000) after the first dose of dexamethasone (Dex) and 4–8 hr after the second dose of dexamethasone (2400–0400)

<table>
<thead>
<tr>
<th>Patient</th>
<th></th>
<th></th>
<th>0-4 hr after first dex dose</th>
<th></th>
<th></th>
<th>4-8 hr after first dex dose</th>
<th></th>
<th></th>
<th>4-8 hr after second dex dose</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td></td>
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<td></td>
<td>Control</td>
</tr>
<tr>
<td>Eye</td>
<td>1</td>
<td>2</td>
<td>Dex</td>
<td>1</td>
<td>2</td>
<td>Dex</td>
<td>1</td>
<td>2</td>
<td>Dex</td>
</tr>
<tr>
<td>1 OD</td>
<td>-2.7</td>
<td>-0.3</td>
<td>0</td>
<td>-2.4</td>
<td>0</td>
<td>+3.2</td>
<td>-4.2</td>
<td>+0.3</td>
<td>0.9</td>
</tr>
<tr>
<td>1 OS†</td>
<td>-0.2</td>
<td>-1.5</td>
<td>-1.3</td>
<td>-0.4</td>
<td>-0.2</td>
<td>+2.5</td>
<td>-5.2</td>
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<td>-2.3</td>
</tr>
<tr>
<td>2 OD</td>
<td>-0.8</td>
<td>0</td>
<td>-2.0</td>
<td>+0.5</td>
<td>-2.0</td>
<td>+3.0</td>
<td>+3.0</td>
<td>-7.5</td>
<td>+4.0</td>
</tr>
<tr>
<td>2 OS</td>
<td>-1.5</td>
<td>-1.0</td>
<td>+0.7</td>
<td>-3.5</td>
<td>-3.0</td>
<td>+2.5</td>
<td>+7.2</td>
<td>-9.0</td>
<td>+9.0</td>
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<tr>
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<td>-1.0</td>
<td>-1.3</td>
<td>+5.0</td>
<td>-6.0</td>
<td>+0.2</td>
<td>+1.3</td>
<td>-6.7</td>
<td>+1.5</td>
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<tr>
<td>3 OS</td>
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<td>-3.5</td>
<td>0</td>
<td>-2.8</td>
<td>-4.7</td>
<td>+3.3</td>
<td>-11.3</td>
<td>-3.2</td>
<td>-7.3</td>
</tr>
<tr>
<td>4 OD</td>
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<td>-3.0</td>
<td>-1.1</td>
<td>-4.3</td>
<td>-4.5</td>
<td>+3.5</td>
<td>-8.7</td>
<td>-5.3</td>
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<tr>
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<td>-3.5</td>
<td>+1.1</td>
<td>-4.0</td>
<td>-4.5</td>
<td>+5.0</td>
<td>-6.7</td>
<td>-6.3</td>
<td>-0.9</td>
</tr>
<tr>
<td>Mean</td>
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<td>+0.3</td>
<td>-2.9</td>
<td>-2.3</td>
<td>+3.0</td>
<td>-4.1</td>
<td>-4.1</td>
<td>0</td>
</tr>
</tbody>
</table>

† OD = right eye.
‡ OS = left eye.
tyramine administration in a group of ocular hypertensive and glaucoma subjects.\textsuperscript{19} Schwartz\textsuperscript{20} also has reported that there may be significantly higher plasma cortisol levels in patients with elevated IOP compared with those whose IOP is normal, although this hypothesis requires further investigation.

In our investigation, the IOP tended to increase following the rise in plasma cortisol; however, the experimental design of this study does not allow a definitive determination of the temporal relationships between plasma cortisol levels and IOP. In addition, the peak plasma-free glucocorticoid activity achieved after the administration of 3 mg dexamethasone was two- to threefold greater than the observed diurnal peak on control days. For these reasons, our observation cannot be extended necessarily to the normal effects of diurnal variations of endogenous cortisol on IOP. However, continued investigation of glaucoma patients, using the approach employed in our study and experimental techniques such as fluorophotometry, may provide an explanation for the effects of dexamethasone. If it is confirmed that glucocorticoids play an important role in the regulation of IOP, then therapeutic manipulations to block steroid action, such as the use of local glucocorticoid antagonists, might prove beneficial for glaucoma therapy.

**Key words:** glucocorticoid, dexamethasone, intraocular pressure, diurnal rhythm

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**References**