Dexamethasone testing in prison inmates

Allan E. Kolker, Robert M. Stewart, Ellen Alton, and Linda LeMon

Topical dexamethasone responsiveness was determined in a group of 56 volunteer prison inmates. Drops were administered to each volunteer four times daily, thus eliminating the factor of patient reliability in use of the medication. The findings fit closely a prevalence of 0.25 for the steroid responder gene in the general population. An increased prevalence of nontasters to phenylthiocarbamide was found in those more highly responsive to topical dexamethasone. Thyroid function, as measured by protein-bound iodine (PBI) determination, did not correlate with the topical corticosteroid response, probably because of high dietary iodide intake. Plasma cortisol suppression testing also failed to correlate with corticosteroid response. This was felt to be the result of concomitant diphenylhydantoin administration.

Key words: topical dexamethasone, steroid-responsive gene, phenylthiocarbamide taste test, plasma cortisol suppression, corticosteroid response, diphenylhydantoin.

The ability to respond to topically applied corticosteroids with elevation of intraocular pressure is a genetically determined characteristic. When volunteer populations are tested with 0.1 per cent dexamethasone applied four times daily for six weeks, three categories of steroid responsiveness can be identified. The degree of pressure response depends upon the presence of a responder gene (g), and the homozygous high-responsive state (gg) is closely related to primary open-angle glaucoma. The gene appears to have a prevalence of about 0.20 to 0.25 among outpatient volunteers.

The use of outpatient volunteers in determining drug response requires the investigator to depend upon patient reliability in using the medication. In the case of topical corticosteroid testing, volunteers must use drops in one eye four times daily for six weeks. It seems obvious that patient reliability, or lack of it, can affect the estimate of the prevalence of the steroid-responsive gene. Because of this, topical corticosteroid responsiveness was tested in a group of volunteer prison inmates to whom the medication could be reliably administered. Other genetic markers relating to primary open-angle glaucoma (phenylthiocarbamide [PTC] taste testing, thyroid function, diabetes mellitus, and plasma cortisol suppression) were also evaluated.

Method

Patient selection. Inmates of the Missouri State Penitentiary assigned to the prison hospital were asked to volunteer for the study. Laboratory technicians, orderlies, operating room personnel, and a few hospital patients comprised the study population. All were ambulatory, and those with significant previous ocular disease, including one on
medication for glaucoma, were excluded. The purpose of the study was explained briefly. Each volunteer received a complete baseline eye examination, including visual acuity, slit lamp examination, ophthalmoscopy, gonioscopy, and applanation tonometry. Volunteers completing the study were paid ten dollars each. Sixty inmates volunteered and 56 of these completed the study. The age distribution of the study population is shown in Fig. 1. All were men, 43 (77 per cent) were Caucasian, and 13 were Negroes.

**Topical corticosteroid testing.** Following completion of the baseline examination, a 0.1 per cent dexamethasone* ophthalmic solution was instilled into the right eye of each volunteer four times daily for six weeks. The drops were administered by three inmates, all of whom assisted the hospital physician and were recommended by him as reliable. These three inmates were given special instructions in administering the eye drops. Intraocular pressures were measured at two week intervals by applanation tonometry, and repeated one month after the completion of the study on all patients who showed a significant pressure response. All examinations and intraocular pressure measurements were performed by the authors.

**Phenylthiocarbamide (PTC) taste testing.** Solutions of PTC were prepared in the manner described by Harris and Kalmus, and administered as described by Becker and Morton. Patients who failed to taste a solution of 8 mg. % were considered nontasters.

**Thyroid function.** Thyroid function was estimated by means of the protein-bound iodine (PBI) determination.

**Glucose tolerance test.** Fasting blood for glucose was obtained on all patients. A 75 Gm. load of glucose was administered orally and a repeat glucose determination made on a two-hour blood specimen.

**Plasma cortisol suppression.** Fasting blood was drawn at 8:00 A.M. for baseline plasma cortisol determination. At 11:00 P.M. of the same day, dexamethasone (1 mg.) was given orally, and fasting blood obtained at 8:00 A.M. the following morning for plasma cortisol levels. Plasma cortisol was measured by the method of Mattingly.

### Results

**Intraocular pressure response to topical dexamethasone.** The intraocular pressure in control eyes presented a normal distribution curve prior to and following topical dexamethasone testing in the opposite eye (Fig. 2). Intraocular pressures in the experimental eyes were normally distributed prior to testing, but appeared to present more than one population after six weeks of topical dexamethasone (Figs. 3 and 4). Previous studies have shown three levels of steroid responsiveness, identified on the basis of intraocular pressure levels after dexamethasone testing: poor responders (nn) with pressures less than 20 mm. Hg, intermediate responders (ng) with pressure rises to 20 to 31 mm. Hg, and high responders (gg) with pressures over 31 mm. Hg after six weeks of topical dexamethasone. Using these criteria, there were 31 (55 per cent) poor responders, 22 (39 per
Fig. 3 and 4. (Fig. 3, left) Experimental eyes. Intraocular pressure before and after six weeks of topical 0.1 per cent dexamethasone four times daily. (Fig. 4, right) Cumulative frequency plot of intraocular pressure in experimental eyes before and after six weeks of topical 0.1 per cent dexamethasone four times daily. Note single population before steroids and break into more than one population after six weeks.

cent) intermediate responders, and 3 (5 per cent) high responders. As illustrated in Table I, these findings fit a gene prevalence value of 0.25 for the responder gene closely.

PTC taste test. Of the 43 Caucasian inmates, 14 (33 per cent) were nontasters of PTC. This is similar to values reported previously for Caucasian populations. When the volunteers are classified according to their topical corticosteroid response, the prevalence of nontasters is higher in the gg group than in the nn and ng responders (Table II). These findings are quite similar to those noted in previous studies.5

Thyroid function. Only one individual had a relatively low PBI value of 4.6 µg per cent. Several volunteers had markedly elevated values in the range of 10 to 12 µg per cent. None were clinically hyperthyroid or had suspected thyrotoxicosis. Investigation by the hospital physician and dietician indicated that the hospital food had a high iodide content, and this was felt to be the explanation for the unusually high PBI values. In addition, most of the inmates took vitamins which were found to have a significant iodide content. Because of this, correlations between topical steroid pressure response and thyroid function were not possible.

Glucose tolerance. A plasma glucose level greater than 160 mg per cent two hours after 75 Gm. of oral glucose was considered diagnostic of diabetes mellitus. On this basis, one individual was considered to have diabetes. He was 80 years old and in the ng responder group.

Plasma cortisol suppression. A surprisingly high number (9/56, 16 per cent) of the volunteers failed to show at least a 35 per cent suppression of their plasma cortisol level following oral dexamethasone (1 mg.). Furthermore, none of the non-suppressors were in the gg steroid category, as had been anticipated from previous studies (Table III).7 Four of the inmates knew that they were taking diphenylhydantoin (DPH, Dilantin), a drug which blocks the dexamethasone suppression test. Three others were taking "nerve pills." Even when the results from inmates known to be taking DPH were excluded, the prevalence of nonsuppressors was still rather high and failed to demonstrate an association between high responders and non-suppressors.
Table I. Topical corticosteroid response

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<thead>
<tr>
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<th>Applanation pressure after steroids</th>
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<tr>
<td></td>
<td>No. (&lt;30 (nn) (%) 20-31 (ng) (%) &gt;31 (gg) (%))</td>
</tr>
<tr>
<td>Prison inmates</td>
<td>56 55 39 5</td>
</tr>
<tr>
<td>Predicted*</td>
<td>56 38 6</td>
</tr>
<tr>
<td>Outpatient volunteers</td>
<td>100 62 32 6</td>
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</table>

*Based on a gene prevalence of 0.25.

Table II. PTC taste test

<table>
<thead>
<tr>
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<th>% Nontasters*</th>
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<tr>
<td></td>
<td>nn  ng  gg</td>
</tr>
<tr>
<td>Prison inmates</td>
<td>43 28 43 50</td>
</tr>
<tr>
<td>Volunteers</td>
<td>290 25 33 52</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>250 — — 53</td>
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*Caucasian men.

Discussion

The present study indicates a prevalence of 0.25 for the corticosteroid responder gene (g) in the general population, a finding in close agreement with results obtained in outpatient volunteers. More important, it indicates that patient reliability in the outpatient volunteer studies is sufficient to draw reasonably accurate conclusions. It also means that about 45 per cent of normal individuals will develop pressure elevation to 20 mm. Hg or higher when treated with topical dexamethasone for six weeks. In approximately 6 per cent of cases the pressure response will be to levels in excess of 31 mm. Hg.

The inability to taste PTC represents a genetic marker which relates to primary open-angle glaucoma.5 The prevalence of nontasters in the Caucasian population is approximately 30 per cent. In patients with proven open-angle glaucoma, 53 per cent are nontasters (Table II). When individuals are classified according to their topical corticosteroid response, 52 per cent of gg responders are nontasters, while the other steroid groups resemble the general population more closely. The findings in the present series of prison inmates confirm these observations. Nontasters are less frequent among the Negro subjects, but similar correlations exist between steroid responsiveness, glaucoma, and PTC nontasting.

Thyroid function, as measured by PBI, also correlates with open-angle glaucoma and the topical corticosteroid response.6 Patients with open-angle glaucoma and high steroid responders (gg) have an increased prevalence of low PBI values when compared to the general population and the other steroid groups. The prison inmates in the present study had remarkably high PBI values and failed to demonstrate any correlation with topical corticosteroid response. An unusually high dietary intake of iodide probably accounts for these findings, and invalidates the PBI as an accurate measure of thyroid function.

The relationship between diabetes mellitus, open-angle glaucoma, and topical corticosteroid responsiveness has recently been studied extensively.9 Primary open-angle glaucoma and high steroid responsiveness are found more often in patients with diabetes. Furthermore, the frequency of diabetes is greater among glaucoma patients and high steroid responders than in the general population. The relative absence of positive glucose tolerance tests in the prison volunteers may be due to the age distribution of the inmates, with a preponderance of young males (Fig. 1).
The comparatively low-carbohydrate prison diet is another consideration.

Over 20 per cent of high responders (gg) to topical corticosteroids failed to suppress their plasma cortisol levels by at least 35 per cent when given oral dexamethasone (1 mg.). This lack of suppression is seen only rarely in the other steroid categories and in patients with primary open-angle glaucoma. The absence of non-suppressors in the gg inmates is not surprising, as this group comprises only three individuals. The high prevalence of non-suppressors in the entire study, however, is an unexpected finding. Recent studies indicate that DPH blocks the cortisol suppression test in most normal individuals. Interestingly, the effect is much reduced in patients with open-angle glaucoma and in about half of patients in the gg steroid category. As noted, an unusually large number of the prison inmate volunteers were under treatment with DPH. It is likely that this medication effectively blocked the cortisol suppression test, accounting for the findings in the present study.

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REFERENCES