EFFECTS OF PREDNISOLONE EYE DROPS*

A TRIAL OF THE EFFECTS OF PREDNISOLONE PHOSPHATE EYE DROPS ON THE INTRA-OCULAR PRESSURE OF NORMAL VOLUNTEERS

BY

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There is now no doubt that topical treatment with soluble corticosteroids is a causative factor in the elevation of intra-ocular pressure. Some early workers who suggested this were Stern (1953), François (1954), and Covell (1958). More recently Armaly (1963), Becker and Mills (1963), and Nicholas (1964) have shown that if 0·1 per cent. dexamethasone or betamethasone drops are instilled into the eyes of normal volunteers, in some of these eyes a significant rise in intra-ocular pressure results.

Becker and Mills (1963) found that, in eyes receiving 0·1 per cent. betamethasone drops four times daily, an increase in pressure and decrease in outflow facility occurred after a minimum of 3 weeks' treatment. In 33 per cent. of their volunteers the pressure rose to 21 mm. Hg (applanation tonometer) after using betamethasone for up to 2 months. In those over 40 years of age, 44 per cent. had pressure rises to over 21 mm. Hg. Rises of up to 24 mm. Hg or more occurred in 17 per cent. of the series, and in 25 per cent. of those volunteers over 40 years of age.

Nicol's (1964) found, in ten normal volunteers aged 19 to 35 years (mean 24·3 yrs) after 28 to 65 days treatment with 0·1 per cent. dexamethasone drops applied four times daily, an average rise in intra-ocular pressure of 6·6 mg. Hg. He also found a decrease in outflow facility of 0·06 (average of ten volunteers).

Armaly (1966) took eighty volunteers drawn from the general population, and instilled dexamethasone drops (0·1 per cent.) three times daily into one eye. All the experimental eyes showed a significant rise in intra-ocular pressure, but Armaly found it impossible to fit all the subjects into one distribution and had therefore to accept three groups. It is possible that these three groups may fit the hypothesis of Becker and Hahn (1964), who suggest that glaucoma simplex is a homozygous recessive condition (gg) with an approximate 4 per cent. incidence in the population. The heterozygous state (Ng) and the homozygous dominant (NN) represent clinically normal eyes. The presence of a recessive gene, as in the homozygous recessive or the heterozygous condition, might then produce the abnormal steroid response. Paterson (1966) further studied the significance of these groups among the relatives of glaucoma patients.

Both Becker and Mills (1963) and Becker and Hahn (1964) suggest that other

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steroids (except desoxytocicosterone) produce a similar hypertensive effect in normal eyes. Neither of these papers contains numerical data for other steroids, but Becker and Hahn (1964) suggest that 0·1 per cent. prednisolone instilled four times daily produces about the same effect as dexamethasone or betamethasone in similar concentrations administered once a day.

Before 1957 the corticosteroids available in Great Britain were confined to the sparingly water-soluble compounds of cortisone and hydrocortisone. It was not until prednisolone-21-phosphate was introduced in 1958 that it was possible to use a stable, freely water-soluble compound in the formulation of eye drops; compounds with similar properties which have since come into use include dexamethasone and betamethasone.

A 1 per cent. aqueous suspension of cortisone acetate was a typical formulation of the pre-1957 era. As the solubility of cortisone acetate in water is of the order of 1 in 50,000 (0·00002 per cent.), the actual quantity of the corticosteroid to which a clinical effect might be attributed would be, apart from that which is lipid-soluble, the small amount dissolved in the saturated solution; the bulk of the insoluble solid suspended in it would be clinically unavailable.

It is known that the small amount of “available” (or dissolved) cortisone acetate has a beneficial clinical effect; it might therefore be expected that the water-soluble corticosteroids could be used in concentrations substantially less than 1 per cent. and might even be effective in concentrations similar to that of a saturated solution of cortisone acetate. In the past the water-soluble compounds were introduced in eye drops containing relatively high concentrations, such as 0·5 per cent. in the case of prednisolone eye drops. There would be no objection to this if such concentrations were free of undesirable side effects.

As it now appears that increased intra-ocular tension may occur with the use of the 0·1 per cent. solutions of the freely water-soluble corticosteroids, dexamethasone and betamethasone, it is relevant to discover whether this side-effect is attributable to these particular corticosteroids or to the strength of the solutions used.

The present work was done in order to assess the effects of 0·5 per cent. prednisolone phosphate drops on the intra-ocular pressure of normal eyes. The effect of diluting the commercial preparation of the drops by 10 and by 100 (i.e. to concentrations of 0·05 per cent. and 0·005 per cent. of prednisolone-21-phosphate) was also investigated. The statistical design of the trial also enabled the changes, if any, produced by the vehicle in which the drug is dissolved to be assessed.

Material and Methods

Twenty normal volunteers (four men and sixteen women) took part in the trial; their ages ranged from 18 to 58 years. None had any history of eye disease and there was no family history of glaucoma.

Eighteen of the twenty volunteers were arranged in nine pairs, both members of any pair being of similar age and of the same sex; the two remaining volunteers were not matched for age.

Five series of drops were prepared, viz:

- \( A = 0\cdot5 \text{ per cent. prednisolone phosphate (normal commercial strength)} \)
- \( B = 0\cdot05 \text{ per cent. prednisolone phosphate (i.e. } 10 \times \text{ dilution)} \)
- \( C = 0\cdot005 \text{ per cent. prednisolone phosphate (i.e. } 100 \times \text{ dilution)} \)
- \( S = \text{ Saline} \)
- \( V = \text{ Vehicle in which drug is dissolved (i.e. placebo)} \)
Each person received each of the three doses, these being given in a randomly-decided sequence during the three periods of 3 weeks each into which the trial was divided. In the first period one eye of each volunteer received prednisolone while the other eye received the placebo. In the next period the eye previously receiving the placebo was given prednisolone and the other eye was given the placebo. The third period reversed the procedure again. The placebos were randomly allocated, the same placebo being used for any one person throughout the trial. A split-plot design was used, the "whole unit treatments" being placebos and the "sub-unit treatments" being doses, the latter being arranged in Latin Squares (Cochran and Cox, 1957).

Random numbers were allocated to the (identical) bottles in which the drugs and placebos were made up, using a table of random permutations. For each person, eye, and period, a bottle was issued using a treatment allocation sheet on which only these numbers appeared. For convenience in making up the bottles, a list was compiled giving for each dose and for the placebos the numbers allocated to them. A sealed copy of this list was issued to the clinicians for use in emergency.

All measurements were taken at the same time each day by the same applanation tonometer (Gambs) and by the same observer. Before the trial commenced all the eyes were examined to establish normal visual function and three readings of normal intra-ocular pressure were obtained. Tonography was not performed.

Numbered bottles of drops were then issued and volunteers were asked to instil these into the relevant eye four times daily. Applanation tonometry was performed at weekly intervals. After 3 weeks the bottles were collected (to establish the amount used by each person and each eye) and two further bottles issued. This was repeated for a third period of 3 weeks. At the end of the trial the amount of fluid used from each bottle was measured (the bottles originally having identical volumes). No untoward effects were reported during the trial.

One person withdrew before the end of the trial. Results are therefore shown for nineteen volunteers.

**Results and Statistical Analysis**

Fig. 1 shows the distribution of intra-ocular pressure at the start of the trial. The values in this histogram are based on the means of three readings. In the graph the letters V, W, X, Y, and Z refer to five particular patients, who will be discussed later.

Fig. 2 (opposite) shows the difference between the intra-ocular pressure after 3 weeks on each of the three test drops and control values on placebos. Volunteers on 0·5 per cent. prednisolone, V (a 27-year-old male) and W (a 31-year-old female), showed rises in pressure of 12 and 10 mm. Hg respectively after 3 weeks' treatment. Three other volunteers, X, Y, and Z, showed smaller rises on similar treatment. All pressures returned to the normal range within one week of stopping treatment. The other two groups in Fig. 2 show that there was no such pressure rise after using the diluted preparations.

The mean values for the three doses were, for A, B, and C respectively, 19·3,
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Fig. 2.—Difference between intra-ocular pressure on last dose of placebo (in that eye) and that after 3 weeks' treatment with prednisolone drops (0·5, 0·05, or 0·005 per cent.).

17·4, and 18·2, compared with 17·3 and 17·5 for placebos S and V respectively and 17·3 for the initial pressures. The standard error for the difference between any two of the means for A, B, and C is 0·7.

Conclusions

Using twenty normal volunteers a trial was performed of the response of intra-ocular pressure to 0·5 per cent. prednisolone phosphate and to $\times 10$ and $\times 100$ dilutions, also to saline and to the vehicle in which the prednisolone was prepared. After using a commercial preparation of 0·5 per cent. prednisolone drops four times daily for 3 weeks, at least two and possibly five of the volunteers showed a rise in intra-ocular pressure. Use of the diluted preparations was not followed by a rise, nor was that of the saline or the vehicle. No age-effect response could be demonstrated. There was no family history of glaucoma in any of the subjects.

Although pressure returned to the initial range within one week of stopping treatment, we suggest that the use of 0·5 per cent. prednisolone eye drops may not be without hazards similar to those mentioned and well established, for 0·1 per cent.
dexamethasone and for 0.1 per cent. betamethasone. It is possible that the use of a weaker strength of commercial prednisolone phosphate may reduce this undesirable effect, although it remains to be seen whether such dilutions are still effective clinically in reducing inflammation.

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REFERENCES
Effects of prednisolone eye drops. A trial of the effects of prednisolone phosphate eye drops on the intra-ocular pressure of normal volunteers.
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