GLAUCOMA TREATED WITH DARANIDE*

A CLINICAL TRIAL

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THE use of Diamox (2-acetylamino-1,3,4-thiadiazole-5 sulphonamide) in the treatment of glaucoma followed the observation of Becker (1954) that the oral administration of this carbonic anhydrase inhibitor caused a reduction in ocular tension in many glaucomatous and normal eyes.

Although the drug is known to be a powerful inhibitor of carbonic anhydrase and therefore acts as a diuretic, its mode of action in the eye has not been fully elucidated. Systemic administration of Diamox has been shown to produce an increase in urinary volume and increased excretion of bicarbonate, sodium, and potassium (Campbell, Tonks, and Jones, 1956). According to Friedenwald (1955) the bicarbonate ion is secreted in the production of aqueous so that it has been suggested that the loss of bicarbonate from the blood is responsible for the suppression of aqueous secretion. However, Langham and Lee (1955, 1957), after studying the distribution of the ionic constituent of the aqueous humour after Diamox, concluded that the effect on the intra-ocular pressure was not the direct outcome of the inhibitory effect of the drug on carbonic anhydrase but was probably due to an alteration in the osmotic balance between the blood and aqueous humour, independent of its renal action. Duke-Elder, Perkins, and Langham (1956) suggested that it was due to a decrease in the base-binding capacity of the blood below normal, which in turn resulted in a slower rate of formation of intra-ocular fluid.

Recently a new carbonic anhydrase inhibitor, 1,3-disulfany-4,5-dichlorobenzene (Daranide or dichlorophenamide, Merck, Sharp and Dohme), has been evolved, which is more potent than Diamox and can be used in smaller dosage. It was therefore decided to conduct a clinical trial in the Glaucoma Clinic of St. Mary's Hospital, Western Ophthalmic Hospital, London, to compare its action and side-effects in the treatment of glaucoma with that of Diamox.

Material and Method

Fifteen cases were selected presenting 21 eyes in which the ocular hypertension was not controlled with miotics alone. There were eight cases of chronic simple

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glaucoma, three of closed-angle glaucoma, one aphakic, and three thrombotic glaucomas. Details of the cases are given in the Table.

TABLE
RESULTS IN FIFTEEN CASES
All patients on Pilocarpine 1 per cent. three times daily both eyes

Case No.	Age (yrs)	Sex	Side Not Controlled by Miotics	Diagnosis	Previous Operations
1	70	F	Right and left	Chronic simple glaucoma	Right: Iris inclusion Left: Trephine
2	71	F	Right	Aphakic glaucoma	—
3	60	F	Right and left	Thrombotic glaucoma	—
4	72	F	Left	Closed-angle glaucoma	—
5	79	F	Right	Chronic simple glaucoma	—
6	75	M	Right	Chronic simple glaucoma	Left: Iris inclusion
7	61	F	Right	Chronic simple glaucoma	Left: Iris inclusion
8	67	M	Left	Chronic simple glaucoma	Right and left: Iris inclusion
9	56	M	Right and left	Chronic closed-angle glaucoma	Right and left: Iris inclusion
10	69	F	Left	Chronic simple glaucoma	—
11	66	F	Right and left	Chronic simple glaucoma	Left: Iris inclusion
12	72	F	Right	Thrombotic glaucoma	—
13	69	F	Right and left	Chronic simple glaucoma	Right and left: Iris inclusion
14	68	M	Right	Thrombotic glaucoma	—
15	66	F	Right and left	Closed-angled glaucoma	Left: Iris inclusion

All the patients were given gutt. Pilocarpine 1 per cent. three times daily in both eyes, and they were then given successively a course of Diamox 250 mg. twice daily, Daranide 50 mg. twice daily, and ascorbic acid 100 mg. twice daily, the last being used as a control. Each drug was taken for one month, so that each trial lasted 3 months. Tablets were given to the patient by the sister in the casualty department so that only she knew which drug the patient was using. Patients were seen twice weekly. On each occasion the ocular tension was taken by the author, using the same X-tonometer each time. The patients were also questioned about side-effects.

The 21 eyes not controlled by miotics alone (where the ocular tension was greater than 25 mm. Hg Schiötz) were numbered from one to 21. Fig. 1 (opposite) shows the average tension with each drug plotted against the particular eye in which it was used.

Results

(a) *Control of Ocular Tension.*—The mean ocular tension is plotted against each eye tested, for one of the drugs used in treatment, the results for each drug being plotted simultaneously (Fig. 1).

FIG. 1.—Mean ocular tension for each drug used in treatment, plotted simultaneously. Each column represents the results for one eye.

The ocular tensions when using ascorbic acid were higher in all cases than when using Diamox or Daranide (as indeed might be expected). The two latter drugs produced similar results. The mean tension (including all the eyes in the series) when Daranide was used was 29.8 mm. Hg Schiötz, and when Diamox was used it was 29.1 mm. Hg Schiötz.

In eyes controlled by miotics and in non-glaucomatous eyes, both Daranide and Diamox caused a small fall in the ocular tension.

(b) *Side-Effects.*—There were no side-effects when ascorbic acid was being taken.

The side-effects noted in patients taking Diamox and Daranide are shown in Fig. 2. Apart from paraesthesiae, which were a common complaint with both drugs, there were very few side-effects when Diamox was used (one patient complained of depression, one of loss of appetite, and one of indigestion).

FIG. 2.—Incidence of side-effects. There were none at all when ascorbic acid was used.

With Daranide, however, almost every patient complained of one or more side-effects, some of them serious. Thus, in Case 12 (Table), the drug had to be abandoned, because the patient complained of drowsiness, headache, giddiness, and blurring of vision. One patient broke out in a petechial rash which disappeared as soon as the drug was stopped—the bleeding time and clotting time were normal. Depression was a fairly common complaint, which also disappeared as soon as the drug was stopped. The dosage of Daranide used was well within the limits suggested by the makers (50 mg. once to four times daily).

Conclusions

It appears from this trial that Daranide (dichlorphenamide) in a dose of 50 mg. twice daily is at least as effective as Diamox 250 mg. twice daily in controlling ocular hypertension when used by mouth in combination with a miotic. However, the side-effects with Daranide are more frequent and more severe than with Diamox. There does not appear to be any material advantage in the use of Daranide as opposed to Diamox in the treatment of established ocular hypertension.

Summary

A clinical trial of a new carbonic anhydrase inhibitor, Daranide (dichlorphenamide), is reported and the results are discussed.

My thanks are due to the surgeons of this hospital for allowing me to use in this trial patients under their care, and also to the surgeon-in-charge of the Glaucoma clinic, Mr. Redmond Smith, for encouraging me to do this work. I also wish to thank Messrs. Merck, Sharp, and Dohme for supplying the Daranide tablets. My thanks are also due to Sister Edwards, the casualty sister, for her help.

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