INHIBITION OF CARBONIC ANHYDRASE IN THE TREATMENT OF GLAUCOMA

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In his Proctor Award Lecture on the formation of the intra-ocular fluid, Friedenwald expressed the view that more effort might profitably be directed toward a reduction in the formation of aqueous in addition to the present approach which concerns itself largely with an effort to increase the outflow from the eye. His work has inspired a useful advance in the therapy of glaucoma.

In the pre-war years our ideas on the formation of the aqueous were dominated by Leber and Starling’s views of the importance of osmotic and diffusional forces in the transfer of water and solutes across the capillary wall. Studies of the relative chemical composition of the aqueous and the blood plasma led Duke-Elder, at first, to the conclusion that the composition of the aqueous resembled that of a dialysate of the blood plasma.

The use of more refined techniques showed that this view could no longer be maintained and it seemed probable that electrolytes were transferred into the eye by a secretory process. The secretory organ appeared to be the ciliary body. Friedenwald’s work led him to postulate that the main product of this ‘gland’ would be a slightly hypertonic fluid whose chief electrolyte was bicarbonate. The reaction by which this is effected is

\[ \text{OH}^- + \text{CO}_2 \rightarrow \text{HCO}_3^- \]

Kinsey showed that there is, in fact, a considerable excess of bicarbonate in the aqueous of the rabbit’s eye as compared with the blood, and he ascribed to it a pilot role in the formation of the intra-ocular fluid. In a later paper, Kinsey demonstrated that the concentration of the bicarbonate in the posterior chamber exceeded that in the anterior chamber in the proportion of 100 : 81. This supported the idea that the bicarbonate was formed by the ciliary body.

The conversion of water and carbon dioxide into carbonic acid is known to be catalyzed by the enzyme carbonic anhydrase. It was therefore of some interest to determine whether this enzyme was present in the ciliary region of the eye. Wistrand was able to prove that carbonic anhydrase is present in the ciliary processes and iris of the rabbit.

From the foregoing it seemed likely that the enzyme carbonic anhydrase played an important part in the formation of the aqueous. As a corollary, it was logical to enquire whether inhibition of this catalyst would reduce the formation of aqueous. An inhibitor of carbonic anhydrase in the form of the heterocyclic sulphonamide acetazoleamide (Diamox) had been known for some time and was thought to have a low toxicity. Preliminary trials with rabbits by Grant and Trotter showed that the intravenous injection of Diamox produced a definite lowering of the intra-ocular pressure.

The idea of using Diamox in glaucoma seems to have occurred at about the same time to a number of American ophthalmologists. The pioneer publication on the subject was that of Becker. He found Diamox a useful agent in lowering the intra-ocular pressure in man. Becker used single oral doses of 500-1,000 mgms. Grant and Trotter considered Diamox to be a safe and helpful drug in the treatment of certain types of glaucoma. They published a chart showing the fall in intra-ocular pressure produced by Diamox in a series of 45 human eyes. The decrease in tension observed may best be described by the boxing maxim that the higher they come the harder they fall.

The present writers have had the opportunity of observing the effects of Diamox in a number of cases of glaucoma. In those reported below Diamox proved helpful where miotic therapy alone was ineffective in reducing the intra-ocular pressure.

CASE REPORTS

Case 1. Mr. M.D., aged 77, developed glaucoma in the left eye after needling of an after-cataract on 8 April 1954. The raised tension was not sufficiently lowered by eserine or by cortisone used.
locally. On 6 August the tension in mm. Hg (Schiotz) was as follows: right eye 32, left eye 60. The patient was given 125 mg. of Diamox t.d.s. He discontinued the exercise on his own initiative because it was beginning to irritate his eye. On 13 August the tension was: right 27, left 30. He was now put on pilocarpine 1½ % and the Diamox in the same dosage. On 27 August he complained that the tablets were causing gastric discomfort. The ocular tension was now right 25, left 28. On the same treatment his ocular tension was maintained at the same level for another fortnight. The Diamox was then discontinued. On 24 September the tension was right 19, left 25, and the corrected visual acuity in the left eye was 6/12 part, where it had been 6/36 at the commencement of treatment.

Case 3. Mrs. E.V.A., aged 54. Thrombosis of central vein in left eye, April 1953. The eye was blind. When seen on 20 August 1954 the tension of the left eye was 60 (Schiotz). She was put on Diamox, 125 mg. t.d.s. On 27 August the tension in this eye was 15. No miotics were used.

Case 4. A male patient with Marfan's syndrome developed acute glaucoma following upon the dislocation of a hypermature cataract. D.F.P. used for 4 days failed to reduce the tension below 70. She was then given 500 mg. of Diamox 6-hourly for 3 days, followed by 125 mg. 6-hourly for 3 days more. The tension was reduced to 30 and the eye was then operated on. This patient complained of paraesthesia in the course of Diamox therapy.

The exhibition of carbonic anhydrase inhibitor (Diamox) proved useful in the cases of glaucoma described. The only toxic symptoms noted were paraesthesias in one case and gastric discomfort in another. Acetazolamide would appear to be safe when given for short periods, but in view of the wide distribution of the enzyme carbonic anhydrase in the human body one would be hesitant about using it in large doses for long periods in the chronic forms of glaucoma. Tonographic studies by Becker and by Grant and Trotter show that there is no improvement in the facility of outflow of aqueous when Diamox is used. This seems to indicate that the drug acts by reducing the rate of formation of the aqueous. Further confirmation of this possibility is found in the suppression of the water provocative test in glaucoma by Diamox. The diuretic effect of the drug does not appear to be of importance in glaucoma. Diuretics, as such, have not proved of value in glaucoma therapy.

SUMMARY

The authors describe 4 cases of glaucoma in which Diamox proved of value. They believe it to be a useful adjunct to existing methods of therapy in glaucoma.

Thanks are due to Dr. M. Franks and the Superintendent of the Johannesburg Hospital for permission to publish details of cases 1 and 2 and to Dr. E. Miller for details of case 4.

REFERENCES


CONGRESS RESOLUTIONS

The Secretary of the Association has received the following letter dated 1 February 1955 from the private secretary of the Minister of Health.

Dear Sir,

With further reference to your letter dated 20 September 1954 I am directed by the Honourable the Minister of Health to reply as follows to the two resolutions adopted at the 39th S.A. Medical Congress:

1. Notification of Cancer

Representations have previously been made to Dr. van Rhijn, former Minister of Health, to the effect that cancer should be declared a notifiable disease in terms of the Public Health Act, 1919, as amended. This matter is at present being investigated by the Department of Health.

2. Milk and its Products

The Department has already done much in the direction advocated by the Congress as the following indicate:

Milk powders form part of the enriching mixtures used for the enrichment of both bread and mealie meal. In the latter case the scheme is still in its infant stage and is conducted largely as an experiment.

Under the State-aided Milk Scheme fresh milk, or full-cream powdered milk, when fresh milk is not available, is supplied free of charge, through pre-school milk clubs usually controlled by Welfare Organisations, to European, Coloured and Asiatic children of pre-school age. The scheme is limited to children of this age-group only, as children of school-going age participate in the National School-Feeding Scheme, which is administered by the various Provincial Administrations.

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Yours faithfully,

(Signed) H. J. Dreyer,
Private Secretary.