NEPTAZANE IN GLAUCOMA*
A PRELIMINARY CLINICAL REPORT
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Neptazane (methazolamide) is a sulphonamide derivative closely resembling Diamox (acetazolamide) chemically. Both drugs are carbonic anhydrase inhibitors, but Neptazane is active in smaller and less frequent doses. To ascertain its value in the treatment of various types of glaucoma, a short-term study was made of fourteen patients admitted to Moorfields Eye Hospital (High Holborn). In every case the Neptazane was administered orally in the form of 50-mg. tablets, the doses being varied where possible for comparison of the effects. A Schiötz X-tonometer was used to estimate the ocular tension, and all other treatment was suspended during the trial unless specifically mentioned. The case histories therefore give no guide to the clinical treatment of various types of glaucoma, but merely reflect the patients' reactions to Neptazane.

Fig. 1 illustrates a typical response to a single oral dose of 125 mg. Neptazane in a normal adult; 4 hours after its administration there was a fall in ocular tension of 3 to 4 mm. Hg (Schiötz); this was maintained for a further 12 hours and then rose again to the original level approximately 18 hours after the Neptazane was given. In subjects who were given 250 mg., the fall in tension lasted about 24 hours.

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Case Reports

Case 1, a woman aged 78 years, had simple glaucoma which had been successfully controlled by miotics for several years. After her admission to hospital all treatment was stopped for several days, during which time the tension in each eye rose to 40–45 mm Hg; 125 mg. Neptazane were then given, and the tension was recorded hourly. Several days later the trial was repeated using 250 mg. Neptazane at a comparable time of day. Fig. 2 is a composite graph comparing the two results. In each case the ocular tension was reduced in 4 hours, but a slightly greater fall followed the higher dose. In both instances the tension remained controlled on the following morning at a time when it was normally high. This shows that the Neptazane was still having some effect 19 hours after administration.

![Graph showing ocular tension reduction](image)

FIG. 2.—Simple glaucoma (Case 1).

Case 2, a woman aged 48 years, had simple glaucoma, which was well controlled by miotics but without treatment fluctuated between 30 and 45 mm Hg. Treatment was suspended for 48 hours and a single dose of 250 mg. Neptazane was then given. In 5 hours the tension had fallen to 28 mm Hg, where it remained for about 14 hours, and then rose irregularly during the next 24 hours and regained the original level of 40 mm Hg (Fig. 3). The patient suffered nausea about 6 hours after taking the Neptazane; she later vomited several times, and the next day still felt ill enough to stay in bed.

![Graph showing ocular tension changes](image)

FIG. 3.—Simple glaucoma (Case 2).
A week later, a further dose of 250 mg. was followed by a similar reaction, and there seemed to be no doubt that the Neptazane was responsible for the vomiting.

**Case 3, a man aged 63 years**, had sub-acute narrow-angle glaucoma which was well controlled on miotics, but without treatment the tension rose to 40 mm. Hg. Fig. 4 is a composite graph showing the response to 125 and 250 mg., each given as a single dose at the same time on different days. In both instances the Neptazane had no significant effect for several hours. Although the tension was reduced to normal for about 24 hours, the larger dose had a more rapid effect and produced a greater fall in tension. It was not possible to assess the duration of action of the Neptazane tonometrically, because of the normal daily fluctuations in tension. In fact, after a subsequent dose of 125 mg. Neptazane the tension remained normal for 3 days before rising above 30 mm. Hg. At no time during this trial did the anterior chamber show any alteration in depth.

![Graph showing ocular tension response to 125 and 250 mg. Neptazane (Case 3).](image)

**Fig. 4.—Sub-acute narrow-angle glaucoma (Case 3).**

**Case 4, a man aged 75 years**, had developed an attack of acute closed-angle glaucoma one evening when watching an exciting film. When he was admitted to the ward the next morning, the ocular tension was 70 mm. Hg. Nothing but 125 mg. Neptazane was given, and Schiötz readings were taken hourly. After 8 hours the tension was tending to rise rather than to fall, and intensive eserine drops and an injection of 500 mg. Diamox were given (Fig. 5). A rapid fall in tension followed and a drainage operation was performed. This case was one of uncomplicated narrow-angle glaucoma with a history of only one previous mild attack of sub-acute glaucoma a week before admission. It is there-
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fore significant that Neptazane alone completely failed to reduce the tension in a case which responded rapidly to the standard treatment. The reason for this was that the aqueous outflow was completely blocked at the angle. Decreasing the formation of aqueous with Neptazane had no effect on the primary cause of the raised ocular tension, but eserine, by constricting the pupil, opened the chamber angle and allowed normal drainage to be resumed.

Case 5, a man aged 63 years, had been suffering for 2 weeks with an acute attack of closed-angle glaucoma. When he was admitted to hospital the tension in the left eye was over 80 mm. Hg, and the visual acuity was reduced to perception of hand movements. For these reasons a trial of Neptazane was thought to be justified and a dose of 250 mg. was given immediately. There was a dramatic fall in tension to normal in about 6 hours and it remained low for a further 14 hours before rapidly rising again to 68 mm. Hg; 250 mg. Neptazane were then given twice daily for several days, but the original dramatic response was not repeated, the tension fluctuating between 40 and 50 mm. Hg (Fig. 6). The Neptazane was therefore stopped and next day intensive eserine drops were given. This produced a rapid fall in tension to normal and a drainage operation was performed. Gonioscopy revealed that the chamber angle was almost completely closed by anterior synechiae.

Case 6, a woman aged 24 years, had glaucoma due to mal-development of the angles which were partially blocked by mesodermal tissue. The ocular tension was controlled by guttae pilocarpine 2 per cent. four times daily, but without drops it rose to 45 mm. Hg in each eye and corneal oedema ensued. After treatment had been suspended for 24 hours, 250 mg. Neptazane were given and the tension was recorded hourly. After 4 hours there was a rapid fall to 30 mm. Hg and the tension remained within normal limits for a further 16 hours. Next morning, 20 hours after administration, the tension was 22 mm. Hg; over the next 4 hours it rose to 50 mm. Hg, corneal oedema appeared, and the patient complained of the rapid onset of misty vision (Fig. 7). Drainage operations have since been performed.
Case 7, a woman aged 83 years, had had symptoms for 2 days of acute glaucoma associated with a hypermature cataract in the left eye. The right eye had an immature cataract and normal tension. After the corneal oedema had been cleared with glycerine, the slit lamp revealed a faint flare and a deep anterior chamber in which were floating a number of shimmering polychromatic particles. The posterior corneal surface was peppered with tiny aggregations of debris, but there were no keratic precipitates. This was thought to be a case of phacolytic glaucoma, but the Pathology Department did not confirm this after a subsequent examination of the lens and aqueous.

250 mg. Neptazane were given on admission, but the tablets were vomited. A further dose of 250 mg. was therefore given together with intensive eserine drops, and the tension fell to normal overnight and remained so for 36 hours without treatment. Within the next few hours, however, the tension began to rise steeply and a further dose of 250 mg. Neptazane was given, but no miotics. This arrested the upward trend but did not lower the tension very much (Fig. 8).
The dose was therefore increased to 500 mg. Neptazane daily in divided doses, but the tension was never satisfactorily controlled by it. After 3 days on this dosage the Neptazane was stopped. Gutt. eserine 0·5 per cent. and Diamox 250 mg. four times daily were substituted and the tension fell to normal limits, where it remained until the lens was extracted. It is clear that Neptazane alone did not control the tension adequately.

Case 8, a man aged 71 years, had aphakic glaucoma due to anterior synechiae. He complained of blurred vision and was found to have an ocular tension of 54 mm. Hg and a cupped disc.

250 mg. Neptazane reduced the tension to 22 mm. Hg overnight, and next day the rise was controlled by a further dose of 250 mg. Neptazane. It is interesting to note that the tension then remained normal for 3 days without treatment, before suddenly rising to 45 mm. Hg. For comparison, guttae eserine 0·5 per cent. three times daily were then substituted, and the tension became normal the next day (Fig. 9). A drainage operation has since been performed.

Case 9, a woman aged 58 years, had bilateral aphakic glaucoma and a vitreous haemorrhage in the left eye. Diamox (250 mg. four times daily) controlled the tension in the right eye, but the tension in the left eye had been raised to between 40 and 50 mm. Hg for several months. All treatment was stopped for 24 hours before the trial began, and the ocular tension rose to 80 mm. Hg in the left eye and 45 mm. Hg in the right eye (Fig. 10, overleaf).

250 mg. Neptazane were given daily for 5 days. In the left eye there was a maximum fall in tension to about 45 mm. Hg in 10 hours each day, and the tension remained at this level for about 8 hours before rising. The dose was then increased to 350 mg. daily in divided doses at 12-hrly intervals and, although the fluctuations were eliminated, there was no further fall in tension. The effects of a dose of 500 mg. daily were then tried in divided doses of 300 mg. at 6 a.m. and 200 mg. at 6 p.m. (Fig. 10). A marked fall in tension occurred in both eyes, but because of the onset of tingling in the extremities and
the complaint of a peculiar light-headed feeling, the dose was reduced to 350 mg. daily divided into four doses, and potassium bicarbonate 1 g. three times daily was introduced. The symptoms stopped, but despite the even spacing of the doses of Neptazane, the pressure fluctuated by at least 20 mm. Hg in the course of each day.

It is interesting to note that the fluctuations of tension in the right eye ran parallel to those in the left, but at a correspondingly lower level throughout.

Bilateral cyclodiathermy operations have since reduced the tension in both eyes.

**Case 10, a man aged 46 years,** had bilateral posterior uveitis and secondary glaucoma; treatment for 3 months had not altered the clinical picture and the tension in each eye remained at about 40 mm. Hg. He was therefore admitted for a trial of Neptazane, 20 mg. oral prednisolone daily being continued throughout the investigation.

500 mg. Neptazane daily did not alter the tension; 750 mg. produced a fall of 5 to 10 mm. Hg in each eye, but the tension still remained above 30 mm. Hg and the patient complained of an unpleasant light-headed feeling. The dose was therefore reduced to 250 mg. twice daily; the side-effects disappeared but the tension rose again to 40 mm. Hg. Potassium bicarbonate 1 g. three times daily was subsequently introduced without effect. In this case there was little difference in the effectiveness of Diamox and Neptazane in controlling the tension, but bilateral cyclodiathermy has since kept the tension down to normal.

**Case 11, a man aged 68 years,** was suffering from aphakic glaucoma due to extensive peripheral anterior synechiae. In 1957 he had had an extra-capsular cataract extraction in an otherwise normal eye, followed by abscission of an iris prolapse. Over the succeeding weeks the tension had slowly risen to 50 mm. Hg and cyclodiathermy had failed to control it. Guttae eserine 0-5 per cent. together with potassium bicarbonate 1 g. three times daily and 250 mg. Diamox four times daily had also failed to reduce the pressure below 40 mm. Hg.

He was therefore admitted for a trial of Neptazane, guttae eserine 0-5 per cent. three times daily being continued throughout. 250 mg. Neptazane twice daily for 3 days
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failed to lower the tension significantly. On the fourth day, 750 mg. were administered, 250 mg. at 6 a.m. and 500 mg. at 6 p.m. This produced a fall in tension of 10 mm. Hg overnight, but because of moderate nausea, vomiting, and paraesthesiae, the Neptazane was suspended. Diamox and potassium bicarbonate were again given in the same doses as before and the tension again rose to between 40 and 50 mm. Hg. The tension is now normal after a further cyclodiathermy operation.

Case 12, a man aged 69 years, had untreated simple glaucoma, the tension in the left eye fluctuating between 30 and 45 mm. Hg. He was admitted to hospital and given 125 mg. Neptazane daily, but no miotics. This reduced the tension to normal, apart from a transient rise on the sixth day (Fig. 11).

After the ninth day, the tension again began to fluctuate and rose to the original high level, but it has since been controlled by a drainage operation.

Case 13, a man aged 67 years, had simple glaucoma which was not controlled by guttæ pilocarpine 2 per cent. four times daily. As the tension was found to fluctuate between 35 and 45 mm. Hg., miotics were continued throughout the trial in which 250 mg. Neptazane were given daily for 12 days. The tension fell considerably until the fifth day, after which it slowly increased to the original level (Fig. 12). Wide fluctuations of tension then
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occurred, indicating that the glaucoma was out of control. On the seventh day, potassium bicarbonate 1 g. three times daily was introduced but had no significant effect.

Case 14, a woman aged 62 years, had simple glaucoma in which the tension fluctuated between 30 and 40 mm. Hg during treatment with guttae pilocarpine 2 per cent. three times daily. Miotics were stopped and 125 mg. Neptazane twice daily were substituted. Within 12 hours the tension fell to between 20 and 30 mm. Hg, and it remained within these limits for a further 5 days, but then slowly rose again to 35 mm. Hg by the eighth day.

The patient had no complaints until the sixth day, when paraesthesiae developed and mild nausea and anorexia began to make her feel miserable. On the eighth day the trial was stopped, because she had developed shortness of breath and palpitations on exertion, so that walking the length of the ward and back doubled the respiratory and pulse rates. After the Neptazane had been discontinued these side-effects disappeared in 48 hours. Even before the onset of these symptoms, it was becoming apparent that the tension was ceasing to be controlled by Neptazane.

Discussion

As Neptazane is excreted more slowly than Diamox, it maintains a useful concentration in the plasma for a longer period. Because it also penetrates into the aqueous humour more readily than Diamox, smaller and less frequent doses are required (Lederle Laboratories, Neptazane). Throughout the trial, 125 to 250 mg. Neptazane once daily reduced the ocular tension in most cases, although doses of up to 750 mg. daily were tried. Within these limits, the larger doses produced a greater effect on the tension, and no maximum dose was found.

After administration, Neptazane is absorbed more slowly than Diamox from the alimentary canal, and it was found that the latent period in most patients lasted from 3 to 5 hours. In some cases it appeared to be shorter, but this was probably because the Neptazane happened to be given at a time when the tension was falling for other reasons. When the drug did not take effect in 6 hours, no subsequent decrease in tension occurred with that particular dose. Animal experiments (Langham, 1958) indicate that Neptazane by injection acts very rapidly, but we have not yet had the opportunity of testing human subjects in this way.

The fall in ocular tension which followed a single dose generally lasted about 16 to 18 hours. This effect was relatively easy to assess in normal subjects and in some patients with glaucoma, but in others the large fluctuations in tension made it difficult to say when the drug was no longer taking effect. In some instances, the fall in tension following a single dose of Neptazane lasted for several days, but because the average duration of action was slightly less than 24 hours the proper spacing of repeated doses was difficult to assess. Single daily doses did not always keep the tension constantly normal, and when the Neptazane was given more frequently in amounts necessary to keep the pressure down all the time, some of the patients suffered from the cumulative effects of the drug. When single
doses were administered, the tension fell rapidly once the Neptazane began to take effect, but a correspondingly rapid rise usually occurred as the effect of the drug passed off.

With repeated doses, it was found that Neptazane began to lose its effect after several days, even when the original response had been good. This occurred not only in narrow-angle glaucoma but also in simple glaucoma treated by Neptazane alone or in combination with miotics.

Potassium salts are now often used in combination with Diamox in the hope of enhancing its action in long-term therapy, but in this trial, when it was given to patients in whom the tension was poorly controlled by Neptazane, no significant fall in tension followed.

Although the toxicity of Neptazane is greater than Diamox weight for weight, its side-effects tend to be milder because of the smaller and less frequent doses. Even so, these side-effects were quite pronounced in several instances, although not severe enough to limit its use clinically except in the last patient. In Case 14, shortness of breath and palpitations on exertion, together with nausea and anorexia, combined to make the patient feel very miserable for several days. Nausea and vomiting occurred in another patient (Case 2) after a single dose of 250 mg., and also in Case 11 when 750 mg. were given in one day. However, as high doses of the drug had been given for several days previously, some accumulation may have resulted. Mild paraesthesiae also occurred in three cases, and after several days' treatment with high doses, three patients complained spontaneously of an unpleasant light-headed sensation, as if they were not completely in touch with their surroundings. These mild side-effects all disappeared within 24 hours of discontinuing the Neptazane, but the severe symptoms took several days to resolve.

Apart from these side-effects, no contraindications to the use of Neptazane were found during the trial. Our findings in the various types of glaucoma may be summarized as follows:

Simple Glaucoma.—Since Neptazane may be given in smaller and less frequent doses than Diamox, one might conclude that it would find a wide application in the long-term treatment of simple glaucoma. The response to single doses was very encouraging, but as there were some doubts whether carbonic anhydrase inhibitors retain their effect on the intra-ocular pressure indefinitely, the last three cases are of special importance:

Case 12 was that of a man whose glaucoma had been recently discovered and who had not been using miotics. In Cases 13 and 14 the glaucoma was not controlled by miotics. In Case 13 the miotics were continued in combination with Neptazane, and in Case 14 they were stopped during the trial. In all three cases, Neptazane reduced the ocular tension to normal for a period of several days, but the tension then began to fluctuate and regained the original high level, and potassium bicarbonate had no significant effect.
This throws doubts on the value of Neptazane used either alone or in combination with miotics in the long-term treatment of this disease. We have not yet carried out any comparable tests with Diamox.

**Acute Narrow-Angle Glaucoma.**—In these cases the immediate aim in treatment is to reduce the tension to normal as rapidly as possible. Thus, because of its long latent period and also because of the possibility of the tablets being vomited oral Neptazane should not displace Diamox by injection as the drug of choice. The depth of the anterior chamber remained unaltered in all cases during the administration of Neptazane. Thus miotics must still be used to open the angle and facilitate the aqueous outflow (see Case 4).

In animals (Langham, 1958) the intra-ocular pressure falls rapidly after Neptazane is given by injection, but it is suggested that its administration by this route would still be contraindicated in acute congestive glaucoma because of the long duration of its action. Thus, in cases in which early operation is undertaken, the long-continued suppression of aqueous formation may delay the reformation of the anterior chamber long enough to allow anterior synechiae to form, and the advantages of early operation will thus be jeopardized. For these reasons, it is possible that the shorter acting Diamox is superior to Neptazane in the treatment of acute congestive glaucoma.

**Secondary Glaucoma.**—These cases showed a varied response and in general where Diamox had failed so also did Neptazane. However, because of the fewer side-effects, Neptazane may find a useful place in reducing the ocular tension in such cases until the primary cause can be dealt with.

**Summary**

1. Neptazane is a long-acting carbonic anhydrase inhibitor, clinically active in doses of a half or a quarter of the necessary dosage of Diamox.

2. Its effects were tested in fourteen cases of glaucoma admitted to hospital.

3. After a latent period of 3 to 5 hours, single doses of 125 and 250 mg. lowered the intra-ocular pressure for at least 16 hours.

4. It is doubtful whether repeated daily doses will continue to control the intra-ocular pressure for more than a few days.

5. The place of Neptazane in the control of glaucoma is discussed.

I should like to express my appreciation to Mr. S. J. H. Miller for encouraging me to undertake this study, and to Sir Stewart Duke-Elder for his advice. I am also indebted to the consultants of Moorfields Eye Hospital (High Holborn) who kindly allowed me to carry out these tests on their patients. The Neptazane was supplied by Lederle Laboratories, Ltd.

**REFERENCES**
