COMMUNICATIONS

INTRAVENOUS UREA THERAPY IN GLAUCOMA*

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THE use of intravenous urea as a therapeutic agent is a recent development in the medical treatment of glaucoma and this paper reports a clinical evaluation of the drug in 43 cases.

The first account of urea being given intravenously would seem to be that of Tanner (1852) in a paper on the use of oral urea as a diuretic, where he mentioned that "half a drachm" of urea, prepared from urine, had been given into the vein of a dog. This resulted in "an excessive secretion of urine, so that the place where the animal was kept was literally flooded in an hour or two by the frequency and quantity of his micturition". The use of intravenous urea lay dormant until Hertel (1914) studied the effect on the intra-ocular pressure of giving various substances intravenously, including sucrose and urea. Duke-Elder (1926) revived interest in this form of therapy by showing that hypertonic solutions were effective in reducing the intra-ocular pressure whilst isosmotic solutions produced little change. Working with animals and using 50 per cent. urea intraperitoneally, Fremont-Smith and Forbes (1927) compared the fall in intra-ocular pressure with cerebrospinal fluid pressure and noted that the ocular tension fell less. However, the modern development of the use of urea in osmotic therapy in acute glaucoma stems from the work of Javid and his collaborators (Javid and Settlage, 1956; Javid, Settlage, and Monfore, 1957; Javid, 1958; Javid and Anderson, 1959) who established the safe combination of 30 per cent. lyophilized urea in 10 per cent. invert sugar and actually used this agent in a few cases of glaucoma. Advantage of this work was taken by Galin, Aizawa, and McLean (1959, 1960), who published the first account of the clinical use of this drug in acute glaucoma.

Methods and Selection of Cases

Over a 9-month period, cases of acute closed-angle glaucoma with a tension greater than 50 mm. Hg were treated as a primary measure with intravenous urea. In six cases, after a combination of miotics and intramuscular Diamox had failed, urea was also given. The arbitrary figure of 50 mm. Hg was chosen, as it was felt that eyes with lower tensions responded to miotics and Diamox, and that higher tensions would be a more exacting test for the intravenous urea. The selection of cases of acute closed-angle glaucoma was further restricted by rejecting any patients in whom the pupil was mobile and reacting to light since they were likely to respond to miotics. In the cases treated primarily with intravenous urea, no sedatives or

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analgesics were prescribed. Other cases (Table I) in which the intra-ocular pressure was sufficiently raised were also treated, provided that the indications were such that intravenous urea therapy would be advantageous.

Apart from the usual history of ocular symptoms inquiry was made as to liver or renal disease and, particularly in males, to any difficulty with micturition.

The type of glaucoma was classified and a special note was made of the degree of corneal oedema, the ease with which the anterior and posterior segments could be examined, and the pupil size. A general examination was made and, in patients where prostatic hypertrophy was suspected, a rectal examination was performed. The urine was tested for the presence of albumin and the blood urea was estimated, an upper level of normal being taken as 45 mg. per cent. A fluid balance chart was recorded for 24 hrs.

Intravenous urea was administered using the commercial preparation "Urevert" (Baxter Laboratories Ltd.), which has the advantage of providing both the 10 per cent. invert sugar for mixing with lyophilized urea and a disposable polythene giving-set. The dose was 1 g./kg. body weight and the infusion was given over a period of approximately 30 min. at a rate of 60 drops per minute into a forearm vein. Care was taken to ensure the needle was in the lumen of the vein to prevent extravasation of urea, and note was taken of any symptoms or untoward effects occurring during the infusion.

Tensions were taken by the same person at regular intervals during and after the infusion, and subjective improvement in pain and vision was recorded. The occurrence of corneal clearing followed by slit-lamp examination of the anterior segment (including pupil size, iris atrophy, and lens changes) was noted; gonioscopy was performed where possible, usually shortly after the infusion; and the discs and retinal vascular state were assessed.

When a normal tension had been achieved by intravenous urea alone, it was maintained at this level by miotics. In those cases where subsequently the tension rose above 35 mm. Hg, intramuscular Diamox was given.

The subsequent course was left to the individual surgeon concerned.

Results

Table I shows the analysis of eyes treated. The subdivision of the cases of acute glaucoma is that used in the glaucoma clinic of the Birmingham and Midland Eye Hospital (Martin Walker, 1960).

TABLE I
ANALYSIS OF EYES TREATED

Total Number of Eyes (43 cases)	50
Acute closed-angle glaucoma	26
Acute open-angle glaucoma	2
Compound glaucoma	1
Mydriatic-induced glaucoma	2
Malignant glaucoma	2
Absolute glaucoma	6
Lens induced { intumescent cataract	4
{ phacolytic glaucoma	5
Dislocated lens	1
Haemorrhagic glaucoma	1

Acute Closed-angle Glaucoma.—The results of therapy in 26 eyes are illustrated in Fig. 1. It will be apparent that the overall response is very satisfactory, a significant reduction in intra-ocular pressure being achieved by the end of infusion, and that a rapid fall was maintained for the next half hour. (The initial sharp drop in tension was accomplished by intravenous urea alone and in the cases where miotic therapy was used this was not commenced till at least half an hour after the end of the infusion.) As can be seen from Table II, 84·6 per cent. responded to intravenous urea alone, 7·7 per cent. to intravenous urea followed by miotics, and 7·7 per cent. to urea followed by the combination of Diamox and miotics.

TABLE II
RESPONSE IN 26 EYES WITH ACUTE CLOSED-ANGLE GLAUCOMA

Therapy	Normal Tension Achieved	
	Number	Per cent.
Intravenous urea	22	84·6
Intravenous urea followed by miotics	2	7·7
Intravenous urea followed by miotics and Diamox	2	7·7

Six eyes are included in which Diamox and miotics had failed to reduce the tension, but treatment with intravenous urea was successful (Fig. 2).

In the majority of eyes the cornea had cleared sufficiently by the end of the infusion to allow more accurate examination of the anterior segment, gonioscopy (where there was doubt as to the exact state of the angle), and inspection of the ocular media and fundus. It was noted that, though in some cases the central part of the cornea showed a cloudy appearance, often associated with folds in Descemet's membrane, the periphery had cleared sufficiently to allow gonioscopy.

In four cases the pupil began reacting normally to light during the intravenous urea infusion. In those eyes with irregular fixed pupils, the region of maximum dilatation was often related to an area of localized iris atrophy, and in these eyes the pupils did not subsequently contract on miotic therapy. Two of the latter cases showed anterior lens opacities which conformed to the picture of cataracta disseminata subepithelialis glaucomatosa acuta described by Vogt (1930, 1931) and further elaborated by Jones (1959).

The anterior chamber was visible in the majority of cases on completion of the infusion and, apart from a flare and circulating cells often being noted, there was found in one case, on the anterior lens capsule and on an exactly

corresponding area on the corneal endothelium, a deposit similar to that found in exfoliation of the lens capsule. This material subsequently disappeared and when the eye was further examined after iridencleisis, there was no evidence of true or pseudo-exfoliation. The fellow eye was normal at all times.

Out of a total number of 43 cases, in which 26 eyes with acute closed-angle glaucoma were treated, four were resistant to intravenous urea therapy. Poor response was considered to have occurred in those cases in which normal tension was not achieved one hour after the infusion was completed.

Case 1, a female aged 69 years, with a 2-day history of pain in the right eye, presented with an initial tension greater than 90 mm. Hg. The urea was given over a period of 55 minutes producing a drop in tension to 49.9 mm. Hg, and remained unchanged for the following half hour. Intensive eserine was then commenced and this reduced the tension to 17.3 mm. Hg one and a half hours later.

It would seem reasonable to assume that the prolonged duration of infusion moderated the osmotic effect of the urea. However, it should be noted that there was almost a 50 per cent. fall in the tension before miotics were started.

Case 2, a male aged 54 years, with a one-day history of haloes and pain in the left eye, declined admission on first attending the Out-patient Department, but reappeared 2 weeks later (having been married in the interim) with severe pain in the same eye. On the day of admission he had consumed "6 pints of brown ale and a drop of rum". An initial tension of 70.7 mm. Hg reduced only to 61 mm. Hg after intravenous urea, and fell to 40 mm. Hg after one hour. Thereupon miotics were commenced and produced a gradual fall to 27.4 mm. Hg. It may be that this patient's intake of alcohol before the infusion had modified the response.

Case 3, a female aged 62 years, had a one-day history of pain in the left eye, the fellow eye being blind with absolute glaucoma. The initial tension in the left eye was 80 mm. Hg, and urea was given over a period of 45 minutes, by which time the tension had fallen to 49.9 mm. Hg. Intensive eserine was then commenced and reduced the tension only to 42.9 mm. Hg in 2½ hours. The combination of Diamox and miotics resulted in a slow fall to 27.4 mm. Hg in 7 hours and to 17.3 mm. Hg in 11 hours. The slow rate of infusion could have modified the effective fall in tension, but Diamox and miotics were only able to produce a further reduction over 7 hours.

Case 4, a male aged 66 years, complained of pain in the right eye of 12 hours' duration. Intravenous urea administered over 25 minutes had caused no reduction in an initial tension of 81.7 mm. Hg + by the end of the infusion, but the tension fell over the subsequent hour to 53.4 mm. Hg. Intensive eserine failed to reduce the tension over the next 2 hours but when Diamox was given the tension fell to 12.4 mm. Hg in a further 3 hours. The reason for this failure is obscure.

Hill, Whitney, and Trotter (1961) also reported three refractory cases.

Lens-induced Glaucoma.—The phacolytic group all showed a very satisfactory response within half an hour of the end of the infusion, whereas the

FIG. 3.—Lens-induced glaucoma.

intumescent cataracts showed a good response in two cases, fair in one (infusion over $\frac{3}{4}$ hour), and poor in one (infusion over 1 hour) (Fig. 3). The poor response may be related to the duration of the infusion. Extraction of the lens was performed in all cases soon after the infusion and thus by the provision of a clearer cornea facilitated surgical manoeuvres as well as obviating the dangers of operating on a hard eye. No particular operative hazards (such as haemorrhage) or post-operative complications occurred.

Other Cases.—Four cases of absolute glaucoma (three chronic closed-angle, one thrombotic) showed a fall of approximately 50 per cent. in the intra-ocular pressure, resulting in considerable clearing of the cornea in one case, allowing gonioscopy and full examination of the fundus which revealed evidence of old venous occlusion, cupping of the disc, and macular degeneration.

The response in the remainder of the cases treated is indicated in Table III.

TABLE III
RESPONSE OF MISCELLANEOUS GROUP OF CASES

Type of Glaucoma	No. of Eyes	Response (percentage reduction in tension)
Acute open-angle	2	55 and 79
Compound	1	71 after miotics
Mydriatic-induced	2	55 and 25
Malignant	2	55 and 61
Dislocated lens	1	30
Haemorrhagic	1	75

Complications

The complications of intravenous urea therapy can be divided into immediate and late. The immediate side-effects occurred commonly during the infusion and were disturbing to the patients but caused no lasting harm. They consisted of frontal and occipital headache, which was associated with a curious shock-like

state in which the patient's skin had a cyanotic pallor and showed beads of sweat. This was often accompanied by nausea and vomiting. The severity of the headache was directly related to the speed of the infusion. These symptoms lasted about 15 to 20 minutes and were probably due to the osmotic effect of the urea as the intracellular fluid was being mobilized. The headache and vomiting have been noted by other observers (Stubbs and Pennybacker, 1960), but the pallor has not been described previously.

We observed eight cases (18.6 per cent.) of phlebitis localized to the site of the infusion. This was not associated with extravasation which at all times was carefully watched for in view of the report of Small (1960) in which sloughing necessitated skin grafting. (A similar case has recently been observed by Davis, Duehr, and Javid, 1961). The phlebitis was localized to superficial veins at the site of infusion and resolved in about 2 weeks, but in one case the phlebitis extended from a forearm vein to involve all the superficial veins proximal to it in the upper limb. This was treated with anti-coagulants and rest, the symptoms resolving in a week.

The most interesting observation was the occurrence in two cases of central retinal vein obstruction:

Case 5, a female aged 79 years, presented with subacute symptoms of a fortnight's duration culminating in continuous pain for one day. The patient had bilateral varicose ulcers. Intravenous urea was given and, when the cornea cleared 4 days later, distension of the central retinal vein was seen with some haemorrhages and early neovascularization near the disc, together with minimal disc oedema. Gonioscopy revealed narrow angles on both sides and no neovascularization. Surgery was not performed and when the patient was seen a month later, the haemorrhages had all absorbed and the optic disc was normal.

Case 6, a female aged 57 years, attended with a history of subacute attacks in the right eye for 3 weeks and an acute attack of 3 days' duration. The left eye was blind following old glaucoma and examination of this eye showed a hypermature cataract and hyphaema. The day after intravenous urea therapy the right disc was observed to be swollen with fullness of the veins and haemorrhages, the latter being confined to the disc. The condition remained unchanged in the right eye for the following week but a fresh hyphaema occurred in the left. A right iridencleisis was performed one week after the infusion without complication, and the disc returned to normal 2 weeks after operation.

The reason for the appearance of the discs and vessels in the above two cases must remain obscure, since the condition of the anterior segment precluded examination of the fundi before infusion. The rapid subsidence of the abnormal signs and the localization of the haemorrhages solely to the disc would suggest that this is not primarily a central retinal vein obstruction but may be due to rapid hypotony. However, Duke-Elder (1940) states that the optic disc, when it can be seen during an attack of acute glaucoma, is oedematous and hyperaemic, but he makes no mention of the presence of haemorrhages.

Advantages

There can be no doubt from our own results and those of other workers (Galin, Aizura, and McLean, 1959, 1960; Klöti, 1960) that intravenous

urea is a most efficient agent in the reduction of intra-ocular pressure in glaucoma of any aetiology. This fall is achieved rapidly and allows more detailed examination of the eye in cases of doubtful aetiology, such as in secondary glaucoma or acute closed-angle glaucoma occurring in active uveitis. The rapid fall in intra-ocular pressure also reduces the risk of permanent damage to the eye which is directly related to the duration of the attack (Miller, 1953).

By obtaining a better response to medical treatment, surgery of election is possible, thus allowing operation on a decongested soft eye with better results (Haas, 1959; Graham and Stevens, 1960). It is also apparent that intravenous urea is most effective in producing a soft eye in lens-induced glaucoma before the extraction of the lens (*vide supra*).

Disadvantages

The most obvious handicap to urea therapy is that to be effective the method of administration must be intravenous. This is minimized by the provision of a sterile disposable polythene giving-set of easy manipulation, which is particularly valuable in specialized units. Phlebitis as an immediate complication is encountered rather frequently (*vide supra*) and is directly related to the rate of infusion (60 drops per minute) which is required to produce a satisfactory fall in intra-ocular pressure. Such a rate of infusion is likely to be attended by a considerable incidence of side-effects, *e.g.* headache, nausea, and vomiting, but these are of short duration and may be offset by the relief of ocular pain.

It has been assumed that chronic renal insufficiency is a contraindication, but this may not apply to slight degrees of impaired renal function.

Haemorrhage as an operative complication has been observed in intracranial surgery during the infusion of urea (Stubbs and Pennybacker, 1960), but is likely to occur in ocular surgery only if the operation is performed while the urea is being administered.

Conclusions

It is our opinion that intravenous urea is best reserved for use in acute closed-angle glaucoma when classical therapy (intensive miotics and intramuscular Diamox) has failed, thus allowing surgery on a decongested eye at a later date. If considered desirable, its use as a primary procedure should be confined to cases with a very high initial tension.

In lens-induced glaucoma with markedly raised tension, the reduction of intra-ocular pressure is most efficiently achieved by intravenous urea and this would seem to be the most desirable method before extraction of the lens. This also applies to anterior dislocation of the lens.

Secondary glaucoma of doubtful aetiology and malignant glaucoma may be taken as indications for primary treatment with intravenous urea.

There is a direct correlation between the rate of infusion and the resultant fall in intra-ocular pressure. This would appear to be more critical than previously suspected.

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