# INTRAVENOUS UREA (UREVERT)

## A REVIEW

JAN A. PRETORIUS, B.A., M.B., CH.B., M.MED. (ANAESTH.), *Department of Anaesthetics, Groote Schuur Hospital, Observatory, Cape*

During the last 5 years the use of intravenous hypertonic urea solution for the reduction of raised intracranial pressure has gained particular prominence in America and the UK.[5,11,19] More recently its use in the field of ophthalmological surgery for glaucoma and retinal detachment has become fashionable.[1,7,12,14] As the anaesthetist is intimately concerned, in both these branches of surgery, with creating conditions of minimal tension in the cranial cavity and the orbital fossa, it is opportune to review briefly the clinical, technical and physiological aspects of the use of this new tool in the struggle against intraocular catastrophe, brain herniation, and retractor ischaemia.

The ever-increasing refinements of technique in neurosurgical and ophthalmological anaesthesia over the last 2 decades clearly indicate the need for absolute attention to minute detail in the anaesthetic management of the cases mentioned above, and any additions to the existing therapeutic equipment are exceedingly welcome. It is assumed that we will use this drug with a thorough understanding of the degree of physiological trespass entailed.

The concept of intravenous hypertonic solutions for the reduction of raised intracranial pressure is not a new one. In the past a wide range of substances have been used for this purpose; sodium chloride, sodium sulphate, sodium bicarbonate, magnesium sulphate, sodium arabinate, sucrose, and dextrose all reduce raised intracranial pressure, but have in turn been discarded because of undesirable side-effects:[11]

**(*a*) Sodium chloride produces a hypotension followed by an overshoot-pressure rise on recovery. This secondary rebound rise in intracranial pressure may then aggravate the existing pathology.**
**(*b*) 50% dextrose similarly effects a rebound pressure rise.**
**(*c*) 50% sucrose produces little or no secondary pressure rise, but causes injury to the renal tubules.**

### *Urea as a Diuretic and its Excretion*

Urea has been used as a diuretic for many years, a dose of 20 G. being taken 2 - 5 times daily. It is a non-metabolized, non-electrolyte diuretic which maintains its potency after prolonged administration, unlike the acid-producing salts. As such it has been prescribed in: (1) cardiac oedema of long standing, (2) nephrosis, and (3) the nephrotic stage of glomerulonephritis.[6]

On an average normal diet approximately 30 G. of urea is excreted daily. The fairly diffusible molecule is filtered rapidly through the glomerulus. A proportion of the filtered urea, approximately 40 - 50%, is reabsorbed in the proximal tubule, probably by a process of passive back diffusion.[2a] The remainder is excreted rapidly, and there is an obligatory loss of large volumes of water caused by the osmotic effect of this unabsorbed amount of urea.

*Non-diuretic Category*

Here we find LaLonde and Gardner[13] combining urea administration with sulphonamides in the treatment of meningitis. 180 G. was given daily for 15 days. It was suggested that the urea enhanced the effect of the sulphonamides by increasing their solubility, by being mildly bactericidal, by inhibiting antisulphonamide substances, and by being a proteolytic agent. These workers did not list the relief of raised intracranial pressure as one of the therapeutic actions of the drug.

*Reduction of Intracranial Pressure*

Such then was the place of urea in therapeutics in 1927 when Fremont-Smith[5] injected a 30% urea solution into the peritoneal cavity of 3 cats and remarked on the reduction of intracranial pressure he observed. He suggested that this effect may find a place in clinical therapeutics. It was a singularly non-impact-making suggestion which lay fallow for 30 years. Not until 1956 do we find a revival of this effect when Javid and Settlage[11] published their report on the effect of urea on CSF pressures in human subjects. They had conducted searching experiments in rhesus monkeys and dogs and showed beyond doubt that it was a substance well tolerated.

Their first major problem was in the preparation of the hypertonic solution. Even with careful preparation of crystals and solution in 5% dextrose-water earlier patients occasionally developed haemoglobinuria. It was only after diligent research that Javid and Anderson[10] finally found 10% invert sugar to be the only vehicle that consistently did not produce haemoglobinuria. Since then to the present time the combination of 30 G. of urea with 70 ml. of 10% invert sugar solution has been used as a routine at their unit and elsewhere.

*Dosage.* The average standard dose is 1,000 - 1,500 mg. per kg. body weight.

The rate of administration by the intravenous route has varied between 6 and 20 ml. per minute. From the work of Javid *et al.*[8,11] and the more recent publication of Stubbs and Pennybacker[19] it appears acceptable to administer the average adult dose of 90 G. (i.e. 210 ml. of 30% solution) over a period of 15 - 20 minutes. The effects on intracranial pressure supervene within 15 - 20 minutes of starting the infusion, and adequate pressure reduction lasts for 4 - 8 hours.

Clinical effects were clearly noticeable on doses as small as 100 mg. per kg., but the effect on intracranial pressure was more pronounced and sustained on the larger doses.[8] Repeated administration of urea did not prove to be harmful, and several of Javid's patients received daily doses for periods of days to weeks by infusion, and continued for months on oral therapy.[8]

*Intragastric route.* This has a place only in prolonged slow administration. Large doses given by this route have a purgative effect which creates disturbing nursing problems in comatose patients.[8,15]

*Clinical Effects of Intravenous Hypertonic Urea Solution*

The main clinical effects noted by leading workers in this field can be stated briefly as follows:

**1. A definite reduction of intracranial pressure occurred in every patient with a dose range of 100 - 1,000 mg./kg. of 30% urea.[8]**

**2. Shrinkage of brain volume is in the order of 3·5 - 4·5 cm. when measured at the craniotomy site.[8]**

**3. Secondary rises in CSF pressure, such as occurred in the rebound phenomena with hypertonic saline and dextrose, did not occur with urea.[11]**

**4. With high initial pressure the intracranial hypotensive effects are relatively greater.**

**5. In the presence of rapidly expanding lesions the reduction is less well sustained than when the intracranial pathological condition is quiescent.**

**6. Urea injection has no significant effect on blood pressure.[1,11,20]**

**7. Bleeding at the operation site is increased in the early stages of the operation.[19]**

**8. Blood urea-nitrogen levels did not rise above the 90 - 120 mg. per 100 ml. level in the reported series.[11,16]**

*Theories of Action of Urea*

On infusion the urea concentration in the blood reaches an immediate peak. The CSF peak of urea concentration is not reached until 2 - 4 hours later. Urinary levels of urea nitrogen correspond with urinary output, and this in turn has an inverse relation to CSF pressure changes.[8] One can predict the CSF pressure changes following urea infusion from the urinary excretion curve. It seemed at first that the diuretic effect of urea was the important factor in the reduction of CSF pressure. Two observations showed, however, that diuresis was not essential, particularly in the early phase of reduction of CSF pressure:

(*a*) Brain volume reduction occurred at operation before there was an increase in urinary output.

(*b*) A drop in CSF pressure follows intragastric urea before there is a diuresis.

Furthermore, Javid and Anderson[9] found that urea infusion into bilaterally nephrectomized monkeys produced a more pronounced and sustained CSF pressure drop than in the normal controls. They suggested therefore that urea acts primarily on the basis of osmotic-pressure differential between blood and CSF.

On the other hand, McKibben[22] had suggested in 1919 that hypertonic agents act by reducing principally the brain bulk rather than the CSF volume and that the reduction is due to water loss. As long as the concentration of the agent in the blood is higher than in the brain, there is an osmotic-pressure gradient favouring the passage of water from brain to blood. The less readily a substance passes from blood to brain the longer will such an osmotic-pressure gradient be maintained and the greater will be the transfer of water. If a substance enters the brain much less readily than it enters the other soft tissues, i.e. the blood/brain barrier effect, then, when given in intravenous hypertonic solution, it will selectively dehydrate the brain. Stubbs and Pennybacker[19] feel that such a blood/brain barrier effect, rather than Javid's blood/CSF barrier hypothesis,[8] best explains their clinical observations, and suggest the following in favour of the McKibben hypothesis:

**(*a*) Urea is less effective in patients with much hydrocephalus in whom there is relatively more CSF and a smaller brain volume than normal.**

**(*b*) Urea effectively reduces brain bulk at craniotomy in patients with diffuse severe cerebral swelling owing to trauma. At the time of giving urea very little intracranial CSF could have been available for reabsorption.**

**(*c*) If urea is given to patients in whom continuous ventricular drainage has first been established, then the volume of the intracranial contents is reduced very much further still. In practice the need for lumbar or ventricular CSF drainage in fact falls away when the use of intravenous urea is contemplated for craniotomy.[8]**

*Physiological Alterations*

From the clinical observations on the effects of intravenous hypertonic urea, 3 questions arise about physiological alterations:[15]

1. What is the electrolyte loss to which a patient is subjected?

2. What changes occur in the blood-coagulating mechanism, since it is known that defects in coagulation supervene in patients with various degrees of azotaemia and uraemia?

3. What is the effect of diuresis on the circulating blood volume, since this parameter is affected by dehydration from any aetiology?

*Electrolyte loss.* The average diuresis after 90 G. of urea is 2,500 ml.[15] Investigations by Mason and Raaf[15] in surgical and non-surgical subjects subjected to intravenous urea showed that patients in normal hydration have no significant deviation of serum electrolytes following a single diuresis.

The data show, however, that if a patient is maintained in negative water balance over a prolonged period because of repeated diuresis, a hyperosmolarity with increase in serum electrolytes will result. Thus, too large a loss of water will significantly alter serum electrolytes in patients who are in a state of excess water, with dilution of serum electrolytes — the changes being from abnormal towards normal values. Therefore, with increased intracranial pressure caused by water retention in the eclamptic state, a urea diuresis of, say, 3,000 - 5,000 ml. will not only decrease the intracranial pressure, but also increase the concentration of serum electrolytes towards normal values.[23]

Because of the absence of significant electrolyte losses 5% dextrose-water appears to be the fluid of choice for replacement in the postdiuresis period[15] — the total volume depending on the state of hydration and the degree of postoperative oedema anticipated. To the average neurosurgical patient 1,500 ml. per day for the first 2 or 3 postoperative days is suggested as adequate.

As stated before, the post-urea infusion blood-urea level rarely rises above 90 - 120 mg. per 100 ml. and usually returns to the pre-diuresis level within 24 - 36 hours of the infusion.

Persistently high levels of 60 - 80 mg. per 100 ml. for up to 72 hours may occur in patients who had poor urine output because of impaired renal function, or in patients with good function but with persistent hypotension during and after surgery.[15]

*Blood coagulation.* 1. Stubbs and Pennybacker[19] in their report comment that they found no upset in preliminary studies of the coagulation mechanism. Mason and Raaf[15] observed coagulation times in surgical and non-surgical patients and found one abnormal value among 28 patients studied.

2. Clot retraction was evaluated at 24 hours and revealed one abnormal value in 16 patients.[15]

3. O'Grady[16] studied clotting times in various containers, prothrombin index, platelet counts, thromboplastin regeneration, clot retraction and capillary fragility in patients with blood-urea levels above 50 mg. per 100 ml. of whom some were in uraemia. No conclusive results were obtained except that more of the tests gave abnormal results at the higher levels of uraemia. These workers suggest that the bleeding tendency may be due to a qualitative defect in the platelets.

4. Prothrombin index: Normal pre-diuresis values were compared with estimations 24 - 48 hours after infusion. Out of 37 patients 24 became abnormal, showing a fall of 40 - 60% below the pre-diuresis values.[15] To assess the effects of surgery and anaesthesia in this reduction, 3 groups of patients were compared:[15]

| | *Number* | *Normal* | *Abnormal* |
|---|---|---|---|
| (*i*) **Surgery without urea** | **30** | **24 (80%)** | **6 (20%)** |
| (*ii*) **Surgery with urea** | **30** | **10 (33%)** | **20 (67%)** |
| (*iii*) **Surgery with urea + intravenous vit. $K_1$, 50 mg., on pre-operative and operation days respectively.** | **15** | **10 (67%)** | **5 (33%)** |

It appears advisable to prepare patients in whom the use of hypertonic urea is anticipated with vitamin $K_1$ pre-operatively.

*Blood volume.* Using radio-iodinated serum albumin for blood-volume estimations in 6 surgical and 4 non-surgical patients subjected to urea infusion, Mason and Raaf[15] found a 100 - 1,200 ml. decrease in 9 out of the 10. They comment that this decrease in blood volume plus the surgical blood loss could lead to a hypotensive state. In dog experimental studies Bounons *et al.*[2] noted a transient fall in blood pressure after infusion of urea; this lasted for approximately 10 minutes. The blood volume, however, showed a slow rise to reach a level 30% above normal by the end of 100 minutes.[2] As pointed out earlier, most investigators comment on the absence of blood-pressure changes after urea infusion. In our own unit at the Groote Schuur Hospital it is our experience that there is a steady rise in the blood pressure during the first hour after commencing the infusion. This observation would agree with the findings of Bounons *et al.* in their experiments.

*Intravenous Urea and the Hypothermic State*

In our attempts to create ideal operating conditions within the cranium there may arise the need for using urea in conjunction with hypothermia. The experimental dog studies of Bering and Avman[1] have revealed findings of which we must take particular note:

1. *Blood-urea concentrations* **rose to a maximum immediately following infusion and then fell steadily at varying rates depending on the body temperature. With the fall in body temperature the blood urea half time (i.e. the time required for the urea concentration to fall by half) steadily increased, e.g.:**

**at 37°C. blood urea half time = 179 minutes**
**,, 30°C. ,, ,, ,, ,, = 250 ,,**
**,, 25°C. ,, ,, ,, ,, = 570 ,,**

2. *The osmotic pressure of the serum* **also rose rapidly to a maximum and then fell gradually to normal. The osmotic pressure half time (i.e. the time required for the osmotic pressure to drop by half) did not increase with the fall in body temperature as was the case with the blood-urea concentration.**

3. *The serum sodium and chloride* **showed a transient sharp drop for 10 minutes after infusion, then returned to normal and gradually decreased over a long period.**

4. *The serum potassium* **showed a sharp rise during the initial serum sodium and chloride fall, and then returned to normal and remained there for the duration of the experiment.**

5. *The ECG.* **Marked effects were noted during the infusion of urea, and for 5 - 10 minutes afterwards. The changes, which occurred at all temperature levels, were: (*a*) Increased conduction time, (*b*) elevation of ST segment, (*c*) T-wave inversion, and (*d*) distortion of the QRS complex.**

6. *The amount of urea* **required to obtain an adequate reduction of intracranial pressure is considerably less at low body temperatures. The dose at 28°C. can probably be reduced by one third of that used at normal body temperature.**

COMMENT

As shown above, the return of serum osmotic pressure to normal levels is not affected much by hypothermia, and occurs considerably faster than the elimination of urea at comparative temperatures. It means, therefore, that solutes other than urea must be lost — presumably sodium and chloride. At normal temperatures sodium is reabsorbed, but with the reduction of renal metabolism in hypothermia it is not adequately reabsorbed and is therefore washed out with the diuresis. When using hypertonic urea in the presence of hypothermia, consideration must be given to this fact or hyponatraemia might easily result — another reason for reducing the dose of urea in the presence of hypothermia.

The ECG changes probably occur on the basis of serum electrolyte changes indicated above during the early phase of infusion and immediately after infusion, i.e. the period coinciding with decreased serum sodium and increased serum potassium. Workers at the Peter Bent Brigham Hospital have confirmed these changes and suggest that they result from a poisoning of the sodium pump mechanism with consequent escape of intracellular potassium.[1]

These effects on the heart make slow injection of urea in the presence of hypothermia mandatory, particularly as ventricular fibrillation is already a concomitant danger in the hypothermic state *per se*.

*Indications for the Use of Intravenous Hypertonic Urea*

1. *Intracranial surgery.* On the basis of the present published experience it would seem that urea has an established place here with the aim of obtaining brain shrinkage, facilitating exposure, and reducing the risks of retractor ischaemia.[8,11,19,20] In particular we think of the difficult exposures for basilar artery aneurysms and some of the acoustic nerve tumours, to mention only a few of a long list.

2. In the preparation and *diagnosis of comatose patients*, urea may improve the state of unresponsiveness from concomitant cerebral oedema to the extent of making an adequate neurological examination and assessment possible.

3. As *temporary relief* and tiding over patients with raised intracranial pressure presenting with severe headache and vomiting until such time as definitive surgical treatment can be embarked upon.

4. In the treatment of *postoperative oedema* and the 'second-day slump' patients.[19] Not infrequently the latter group present with signs of drowsiness, aphasia or hemiplegia on the second postoperative day. If they are re-opened they reveal very little, if any, haematoma formation, with just diffuse brain swelling. Intravenous urea, given repeatedly if necessary, can tide these patients over to full recovery.

5. *Acute head injuries* with a tight brain after sizable clots have been excluded by multiple burrholes or craniotomy.

6. Owing to the increased bleeding tendency, Stubbs and Pennybacker[19] suggest that urea has no place in the treatment of acute subarachnoid and intracranial haemorrhage. It has however been used by some workers to facilitate adequate haematoma evacuation in *acute subdural haemorrhage.*[8,20]

7. As a *palliative measure* in patients with multiple neoplasms in the brain and in those patients with primary brain neoplasms where surgery is not indicated.

8. A definite place has been established for urea infusion in the pre-operative preparation of patients with glaucoma, during glaucoma surgery, retinal detachment surgery, and orbital tumours. The dangers of expulsive haemorrhage, iris prolapse and lens and vitreous expulsion are considerably decreased.[7,12,14,4] It has been shown that urea is more effective than the carbonic anhydrase inhibitors (e.g. 'diamox') and has proved to be successful in cases where diamox failed to reduce the raised intra-ocular pressure.[12] The risk of hypopotassaemia from disturbance of the ion-exchange mechanism in the distal renal tubule from carbonic anhydrase inhibition is thus immediately overcome.[2b]

9. To the above list can be added yet a considerable number of conditions; to mention only a few: (*a*) Tuberculous meningitis,[13,19] (*b*) eclampsia,[11] (*c*) hydrocephalus,[8] (*d*) hypertensive and lead encephalopathy,[11] (*e*) encephalitis,[11] (*f*) delirium tremens,[8] (*g*) status epilepticus,[8] and (*h*) Menière's disease.[8]

*Toxicity and Complications*

1. Stubbs and Pennybacker[19] report 5 cases of rigors during infusion in a series of 129 cases. They implicate too rapid infusion or decomposition of the solution through age or improper storage.

2. Change in tissue turgor, dry tongue, hypotension and tachycardia may present should there be excessive loss of fluid and electrolytes.[15,20]

3. Local venous complications varying from transient redness to superficial and deep-vein thrombosis have been reported in most series. Again stale solutions are implicated. It is emphasized that solutions deteriorate and decompose rapidly on heating, and under no circumstances must they be heated to body temperature before administration.[18]

4. Javid[8] reports skin blebs forming after subcutaneous leak of urea solution. These cleared up spontaneously. Mason and Raaf[15] relate a case of urea extravasation causing a 3 x 5 cm. slough which needed skin grafting.

5. Conscious patients will complain of nausea with pain at the infusion site.

6. Urea in the presence of a normotensive CSF may cause low-pressure headache such as is seen after lumbar puncture.[5,7]

7. In the past year we encountered 3 patients at the Groote Schuur Hospital presenting with ischaemic changes in the infusion forearm.[17,21] The main feature was a gross, blue discolouration of the forearm skin during the immediate post-infusion period. A demarcation line presented at the level of the sphygmomanometer cuffs which were attached to the infusion limbs. The first patient has developed a Volkmann's ischaemic contracture; the second recovered spontaneously without residual defect, and the third, on whom a brachial-block sympathectomy was done, died a few days postoperatively from other causes, but with an apparently normal arm. We advise the removal of all constricting bandages or blood-pressure cuffs from the infusion limbs before commencing infusion of the urea solution. Chemical sympathectomy may play a part in limiting or preventing the residual anatomical damage caused by this complication.

## CONCLUSION

Thus, an old agent has returned in a new guise to take its place among the existing aids to anaesthesia in the management of patients receiving surgical treatment for neurological and ophthalmological conditions. Like the raised head, ventricular and lumbar CSF drainage, hypothermia, induced hypotension and controlled ventilation, it entails a certain degree of physiological trespass and the risk of systemic and local complications. That is the price we have to pay for progress. The art of anaesthesia, however, still lies in the hands of the administrator who understands both the scope and limitations of his equipment and can avoid turning it into a Frankenstein by blind devotion or physiological abuse.

## REFERENCES


1. Bering, E. A. and Avman, N. (1960): J. Neurosurg., **17,** 1073.
2. Bounons, G., Omnis, M. and Shumacker, H. B. (1960): Surg. Gynec. Obstet., **111,** 309.
3. (*a*) Campbell, E. J. M. and Dickinson, C. J. (1960): *Clinical Physiology*, 1st ed., p. 154. Oxford: Blackwell.
   (*b*) *Idem* (1960): *Ibid.*, p. 157.
4. Crews, S. J. and Davidson, S. I. (1961): Brit. J. Ophthal., **45,** 769.
5. Fremont-Smith, F. and Forbes, H. S. (1927): Arch. Neurol. Psychiat., **18,** 550.
6. Goodman, L. S. and Gilman, A. (1955): *The Pharmacological Basis of Therapeutics*, p. 843. New York: Macmillan.
7. Irvine, M. D. (1960): Amer. J. Ophthal., **49,** 164.
8. Javid, M. (1958): Surg. Clin. N. Amer., **38,** 907.
9. Javid, M. and Anderson, J. (1959): J. Lab. Clin. Med., **53,** 484.
10. *Idem* (1958): *Op. cit.*[8]
11. Javid, M. and Settlage, P. (1956): J. Amer. Med. Assoc., **160,** 943.
12. Keith, C. G. (1961): Brit. J. Ophthal., **45,** 307.
13. LaLonde, A. A. and Gardner, W. J. (1948): J. Amer. Med. Assoc., **138,** 406.
14. Annotation (1962): Lancet, **1,** 901.
15. Mason, M. S. and Raaf, J. (1961): J. Neurosurg., **18,** 645.
16. O'Grady, J. A. (1959): J. Amer. Med. Assoc., **169,** 1727.
17. Rossouw, G. J. (1962): Personal communication.
18. Streicher, M. H. (1928): Arch. Intern. Med., **42,** 835.
19. Stubbs, J. and Pennybacker, J. (1960): Lancet, **1,** 1094.
20. Taheri, Z. E. (1959): J. Int. Coll. Surg., **32,** 389.
21. Voss, T. J. V. (1962): Personal communication.
22. Weed, L. H. and McKibben, P. S. (1919): Amer. J. Physiol., **48,** 512.
23. Wise, B. L. (1960): Arch. Neurol. (Chic.), **2,** 160.