UREA IN INTRACRANIAL SURGERY
A NEW METHOD*

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(Received for publication January 4, 1960)

THE neurosurgeon is often confronted with the difficult problem of increased intracranial pressure. During intracranial operations this tension may be so high that it may cause disruption of the cerebral cortex on opening the dura mater, often in spite of a ventricular puncture. Cerebrospinal fluid drainage by the lumbar route is contraindicated when intracranial pressure is high. Experience with the administration of urea to 700 patients (Table 1) and to more than 150 animals under various experimental conditions has proved that this is a valuable agent for reduction of brain volume, cerebrospinal fluid pressure and intraocular pressure.

The main purpose of this paper is to give a detailed description of the method that has proved most effective. 2

TABLE 1
Classification of 700 patients who received urea

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial neoplasms</td>
<td>267</td>
</tr>
<tr>
<td>Cranioencephal injuries</td>
<td>108</td>
</tr>
<tr>
<td>Cerebrovascular lesions</td>
<td>62</td>
</tr>
<tr>
<td>Glaucoma, ocular and orbital surgery</td>
<td>50</td>
</tr>
<tr>
<td>Brain abscesses and other infections of CNS</td>
<td>40</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>36</td>
</tr>
<tr>
<td>Trigeminal rhizotomies</td>
<td>25</td>
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<td>Migraine</td>
<td>25</td>
</tr>
<tr>
<td>Hypophysectomies</td>
<td>15</td>
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<tr>
<td>Ménière's syndrome</td>
<td>10</td>
</tr>
<tr>
<td>&quot;Pseudotumor cerebri&quot;</td>
<td>7</td>
</tr>
<tr>
<td>Encephalopathies</td>
<td>6</td>
</tr>
<tr>
<td>Status epileptic</td>
<td>5</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>26</td>
</tr>
</tbody>
</table>

Since this paper was submitted for publication, urea has been administered to 300 additional patients with similar results.

DOSAGE AND METHOD
Sterile lyophilized urea is dissolved in 10 per cent invert sugar in water4 to make a 30 per cent weight-volume solution (90 gm. urea plus 210 cc. of 10 per cent invert sugar in water yields 270 cc. of 30 per cent urea). A dose of 1 gm. urea per kg. of body weight is used routinely in adults and children when it is desirable to gain good visualization without the trauma that may be caused by retraction of the brain, as in pituitary operations or in cases of intracranial aneurysms. There is no need for lumbar drainage of cerebrospinal fluid in these cases since this amount of urea is adequate to cause considerable shrinkage of brain. Larger doses are unnecessary because of excessive reduction of brain volume. On the other hand, when dealing with space-occupying masses within the cranial cavity with shift of the ventricular system, marked brain swelling caused by severe head injury, or raised cerebrospinal fluid pressure caused by a ruptured intracranial aneurysm, 1.5 gm. urea per kg. of body weight is the dose recommended during surgery. Urea is given as the sole solution through a #16 or #18 needle, except in children, when blood is administered through another needle simultaneously with urea, or in adults who require transfusion. Other solutions may be administered at the same time whenever necessary, preferably at a very slow rate. Administration of urea is begun at the start of the craniotomy incision.

* Presented at the meeting of the Harvey Cushing Society, New Orleans, Louisiana, May 1, 1959.
† Kindly supplied under the trade name "Urevert" by Travenol Laboratories, Morton Grove, Illinois.
or after the first burr hole is made. In cases of large meningiomas of the convexity, or in parasagittal craniotomies it is preferable to start urea after the burr holes are connected with a Gigli saw. This will prevent additional loss of epidural blood which may occur from a slack dura mater prior to elevation of the bone flap. The rate of administration depends on the time urea is started and the speed of the operation. The rate should be controlled by the neurosurgeon. That is to say, when urea is started at the time of the skin incision it may be given from 20–60 drops per min. and increased to as high as 150 drops per min. as seems indicated. When it is given after connecting the burr holes it may be started at a rate of 80–100 drops per min. and increased to full speed. It is desirable to give two-thirds of the total dose before opening the dura mater. It is essential that at least half of the urea be given before the dura mater is opened. After opening the dura mater the remainder of the urea solution may be given slowly and followed by blood or other solutions as indicated. This method of prophylactic use of urea is essential in order to obtain optimum brain shrinkage. On the other hand, there is no point in administering all of the urea before diagnostic procedures or craniotomy unless this is done as a life-saving procedure on a temporary basis until neurosurgery can be carried out, i.e., in patients with development of decerebrate rigidity and paralysis of the 3rd nerve caused by tentorial pressure cone, respiratory embarrassment or apnea from compression of the medulla oblongata by a cerebellar pressure cone. In such cases, the use of urea has often reversed these herniations and afforded the opportunity to proceed with emergency craniotomy. Under these circumstances, it should be emphasized that when urea is given a few hours prior to the exposure of the dura mater one should not expect the maximum degree of brain reduction which is observed during the hour following completion of administration of urea. When the cerebrospinal fluid pressure is markedly elevated, with dosages of 1 to 1½ gm. per kg. of body weight, the pressure returns to pre-injection levels after a period ranging from 3–10 hours.2

Tabulation of anesthetic charts of more than 200 patients who received urea during craniotomy under general anesthesia revealed an elevation of blood pressure with an average of 26 mm. of mercury shortly after the start of urea.3 The degree of this elevation seemed to correspond with the rapidity of infusion of urea. Excessive loss of blood during this period may be masked temporarily by urea. This may become an important factor in a small percentage of cases in which massive bleeding occurs in a short period of time during craniotomy. Replacement of blood is essential in these cases whether the patients have or have not received urea, except that in the cases in which urea was given blood should be administered before there is a significant drop in blood pressure.

Administration of fluid during and after craniotomy is similar to that carried out in cases in which urea has not been given. In the majority of procedures blood or fluids are continued in the same fashion, but in case of excessive urinary output or sweating, additional fluid may be necessary. In our cases, after completion of craniotomy we do not remove the intravenous needle for at least 12–24 hours and some solution, usually 5 per cent dextrose in water, is given.

An indwelling urinary catheter is inserted at the time of craniotomy and urinary output is measured carefully. This may be removed after surgery as soon as the patient is awake and able to void.

Urea should be repeated postoperatively when necessary on the basis of 1 gm. urea per kg. of body weight in a 24-hour period. This may be given intravenously or orally. These patients should be kept under careful observation with special attention to accurate measurement of fluid intake, urinary output, as well as daily serum-electrolyte studies and adequate replacement of water.4

Experimental Neurosurgery. We have observed shrinkage of brain in monkeys, cats, and dogs following the use of urea. This agent is useful in various experimental pro-
FIG. 1. Case 690. (Left) Right carotid arteriogram. Lateral view shows aneurysm of internal carotid artery at junction of posterior communicating artery. (Right) Photograph during right frontotemporal craniotomy. Reduction of brain volume is to a degree that exposure of right anterior cranial fossa, optic foramen and nerve, internal carotid artery, and aneurysm is maintained without the aid of a brain retractor. Note silk suture placed around neck of the aneurysm prior to ligation. At the time of this photograph 850 mg. urea/kg of body weight had been administered and a small amount of fluid had been suctioned from chiasmatic cistern.

cedures when reduction of brain volume is desirable, especially when it is important to gain access to deeper structures of brain, e.g., removal of mammillary bodies by direct subtentorial approach. Larger doses in the order of 1.5 to 2 gm. urea per kg. of body weight are recommended for neurosurgery on experimental animals.

DISCUSSION

Urea has been administered to 275 patients during craniotomy under general anesthesia. Even though great reduction of brain volume has occurred, no rupture of bridging veins has been observed regardless of the position of the patient on the operating table. Urea facilitates intracranial operations in both supratentorial and infratentorial procedures. Its routine use in such operations as removal of pituitary tumors, hypophysectomies, ligation of intracranial aneurysms (Fig. 1), and orbital decompressions produces significant shrinkage of brain to a degree that cannot be achieved by lumbar drainage of cerebrospinal fluid. When dealing with intracranial neoplasms, such as meningiomas, the removal of tumor may be carried out with minimum sacrifice of normal cerebral tissue and trauma to the brain by forceful retraction. This is particularly important when operating on the dominant hemisphere (Fig. 2). Furthermore, in cases of large neoplasms the need for ventricular puncture is obviated (Fig. 3). In fact, this degree of brain reduction cannot be achieved by ventricular puncture. When sudden hemorrhage has occurred into a neoplasm, one may still notice some bulging of the brain after administration of urea. Even in these instances, the tension of the brain has been reduced sufficiently to prevent rupture of the cortex. Urea is also valuable in posterior fossa operations with patients in sitting or prone position (Fig. 4). With its use in cases of acoustic neuroma there is no need for ventricular puncture or removing the lateral third of the cerebellum. Urea is also of value in trigeminal rhizotomies by the subtentorial approach. Its use facilitates the procedure not only by improving visualization, but also minimizes the discomfort of holding the retractor in an awkward position and forceful retraction of the temporal lobe (Fig. 5).

Head Injuries. It should be emphasized that administration of urea should be based on sound neurosurgical principles.

In many instances this agent has been of value in the following situations:
Fig. 2. Case 293. Photograph of left frontotemporal osteoplastic craniotomy for parasagittal tumor. Widening of gyrus is indicated by (X) overlying subcortical neoplasm (oligodendroglioma); shrinkage of brain volume is illustrated after 1.5 gm. urea/kg. of body weight.

A = Anterior  P = Posterior  L = Lateral  M = Midline

1. As a temporary lifesaving measure to reduce intracranial pressure in patients who were in critical condition until trephination could be carried out.

2. In the acute stage, when increased intracranial pressure was verified by brain swelling observed at the time of exploratory trephinations and hematoma was ruled out.

3. In cases of depressed fractures of the skull with marked contusion and laceration

Fig. 3. Case 526. (Left) Drill pneumoventriculogram. Anteroposterior view shows marked elevation of temporal horn on right (arrow), indicating a mass in temporal lobe as well as shift of ventricular system to the opposite side. (Right) Photograph during right temporal osteoplastic craniotomy (metastatic carcinoma). Shrinkage of brain is illustrated following a dose of 1.6 gm. urea/kg. of body weight. Exposure of lateral aspect of middle fossa is maintained without the aid of a retractor.

A = Anterior  P = Posterior  L = Lateral  M = Medial
of brain, for débridement of severe cerebral injuries. It has diminished or eliminated further trauma to an already injured brain. Urea was beneficial in cases of depressed fractures over the dominant hemisphere. With closed depressed fractures of the anterior frontal region, elevation of depressed fragments could be carried out through a smaller cranial opening and this improved the cosmetic result which is important over the forehead.

4. Cranioplasty, when brain was bulging and insertion of a plate was not possible without causing pressure over the cerebral cortex.²

5. In cases of acute subdural hematoma administration of urea has reduced the accompanying cerebral edema to a degree that subdural blood could be removed through one or two burr holes.


7. In a few cases, when lumbar puncture showed marked elevation of cerebrospinal fluid pressure and hematoma was ruled out by trephination or carotid arteriography.

8. In some unconscious patients with severe head injury and no evidence of hematoma.

9. Patients with severe headache on whom hematoma had been ruled out.

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**Fig. 4. Case 314.** Photograph of left suboccipital craniectomy with patient in semiprone position. Rhizotomy V, IX, and partial X cranial nerves for intractable pain caused by metastatic carcinoma. Note marked shrinkage of cerebellum following a dose of 1.2 gm. urea/kg. of body weight. Exposure of internal acoustic meatus, jugular foramen, and the nerves is maintained without the aid of a brain retractor.

L = Lateral  M = Medial

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**Fig. 5. Case 301.** Right temporal craniectomy (retrogasserian rhizotomy). Exposure of foramen rotundum (maxillary nerve), foramen ovale (mandibular nerve) and Gasserian ganglion (arrow) is maintained without the aid of a lighted retractor, following a dose of 1 gm. urea/kg. of body weight.

A = Anterior  DM = Dura mater over inferior aspect of right temporal lobe.
10. Occasionally when trephination did not seem indicated urea was used and the patient was kept under careful observation so that burr holes could be made whenever necessary.

For those who routinely prefer to operate with local anesthesia in order to minimize rise of intracranial pressure or increase of cerebral hernia resulting from general anesthesia, proper use of urea in combination with general anesthesia will prevent this and will facilitate surgery, especially on a very restless and uncooperative patient.

In general, urea is not of significant value in cases of massive brain injuries.

**Vascular Lesions.** Urea is indicated for craniotomy in cases of intracranial aneurysms and arteriovenous malformations. Easier access to the lesion may obviate the need for hypothermia in some instances. Also, the degree of brain reduction obtained with hypothermia is not comparable to the rapid shrinkage of brain that urea produces, e.g. as described in the following case.

*Case #414.* A 19-year-old male had a ruptured aneurysm of the left internal carotid artery with a history of three subarachnoid hemorrhages. His cerebrospinal fluid pressure prior to craniotomy was 600 mm. of water.

He underwent craniotomy during induced hypothermia with lowest temperature being 28.5°C. Urea was withheld in order to determine the effect of hypothermia on the volume of the brain. The dura mater was bulging markedly. It was extremely tense, and to such a degree that it was felt that if it were opened the cerebral cortex would rupture even with a ventricular tap. Urea was given, 1.5 gm. per kg. of body weight, following which the dura mater became slack and then it was opened. There was a marked shrinkage of brain. Excellent exposure of the roof of the orbit, the falx cerebri, and the anterior part of the middle fossa was obtained. The reduction was to such a degree that following the exposure of the aneurysm, the exposure of the left optic nerve and chiasm, left carotid, left anterior cerebral and left middle cerebral arteries, as well as the aneurysm, could be maintained after the brain retractor was removed.

**Brain Abscesses.** Preoperatively, in a few cases, we have used urea daily during the stage of "cerebritis" and formation of the capsule of the abscess and have found it helpful. Postoperatively, urea was found useful in combating cerebral edema, especially in cases in which, because of its location, only aspiration of the abscess or open surgical drainage without removal of the capsule could be carried out. During surgery in these patients routine use of urea will minimize the amount of brain to be sacrificed.

**CONTRAINDICATIONS**

In cases of severe renal damage, urea should be used only if absolutely necessary as a lifesaving agent. Urea should not be repeated if diuresis does not occur within 5 to 10 hours after administration of urea. This agent should not be employed in patients who have active intracranial bleeding except during craniotomy. It is evident that urea should not be used in cases of chronic subdural hematoma before or during surgery. In cases of marked dehydration urea is contraindicated unless one can safely rehydrate the patient prior to the use of urea.

**SIDE EFFECTS**

Side effects of intravenous urea are minimal and insignificant statistically. Often times there is pain at the site of injection which can easily be remedied by injecting 1–2 cc. of 1 per cent procaine through the rubber tubing of the same needle. Local phlebitis is observed occasionally with 30 per cent urea. In 3 of our patients there has been thrombosis of the superficial and deep veins of the leg. It is important that one does not use veins of the lower extremity for intravenous administration in older patients or patients who are arteriosclerotic. Patients whose intracranial pressure is normal may experience headache of varying degree, but usually more severe than headache following a lumbar puncture, when urea is administered. This is because of the profound intracranial hypotensive effect of this agent. The patient should remain in bed without elevation of the head for the period of administration of urea and the subsequent 3-4 hours. It is extremely important, as with use of any hypertonic solution, to keep the needle within the lumen of the vein securely so that 30
per cent urea does not extravasate into subcutaneous tissue. Whereas, extravasation of small amounts occasionally has caused little blebs of the skin, in larger amounts sloughing of surrounding skin occurred in 3 cases.

CONCLUSION

Significant shrinkage and protection of brain has been achieved with urea in 275 patients who underwent craniotomy under general anesthesia in supratentorial and infratentorial procedures. It has obviated the need for lumbar drainage of cerebrospinal fluid or ventricular tap during craniotomy. In order to obtain maximum benefits as far as reduction of brain volume is concerned, strict adherence to this prophylactic method by administering about two-thirds of urea before opening the dura mater is essential.

The results from the use of urea are, of course, influenced by administering it before irreversible damage to the brain has occurred.

REFERENCES

1. Akert, K. Personal communication.