PHYSIOLOGICAL ALTERATIONS AND CLINICAL EFFECTS OF UREA-INDUCED DIURESIS*

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The management of increased intracranial pressure remains a challenge to the neurosurgeon. Surgical decompression, cerebrospinal-fluid shunts and numerous diuretics have been in vogue at different times. Every diuretic available has been evaluated and used with some degree of success; however, most are too slow-acting and therefore of limited value when a prompt reduction of intracranial pressure is essential. Some diuretics produce disturbances of electrolytes and are thus not suitable for long-term use. Hypertonic solutions of glucose, sucrose and Sorbitol have been employed and found somewhat unsatisfactory because of limited effectiveness in reducing intracranial pressure, rebound effect with a subsequent increase in intracranial pressure, renal tubular-cell changes or toxicity.

In 1927, Fremont-Smith and Forbes injected hypertonic solutions of urea intraperitoneally in animals and recorded decreases in both intracranial and intraocular pressure. They suggested at that time that hypertonic urea might have clinical usefulness. Further work was completed in 1936 by Fremont-Smith et al. but was not published until 1960. In 1950, Smythe et al. reported on the efficacy of intravenous solutions of hypertonic urea for the reduction of intracranial and intraocular pressure in monkeys. The first clinical evaluation of hypertonic urea was carried out by Javid and Settlage in 1956. A more recent summary of the clinical significance of urea has been presented by Javid.

There have been several reports regarding the effectiveness of hypertonic solutions of urea for the reduction of intracranial pressure and also the reduction of intraocular pressure. Most of the authors agree that urea is the most effective diuretic to date. However, Marsh and Anderson reported a limited degree of success, stating that only 3 of 19 patients who were given urea showed an observable reduction of brain volume at the time of surgery.

The mechanism of reduction of intracranial and intraocular pressure by infusion of urea has been discussed by several authors and is felt to be ascribable to differences in osmolarity between blood, cerebrospinal fluid and aqueous humor. In addition, Javid stated that diuresis is not essential for the reduction of intracranial pressure or brain volume.

Our initial experience with intravenous urea was in April, 1958, and to date we have administered urea to 175 patients on the neurological and neurosurgical services at Good Samaritan Hospital. Urea was given to the majority of patients at the time of surgery. After observing the profound diuresis following the infusion of urea (Urevert†) intravenously, the question arose of various physiological changes occurring with the diuresis. We were concerned with the quantity of electrolytes lost in the urine and if there were any subsequent changes of serum electrolytes. We also considered what solution might be most appropriate to use for replacement of fluid following diuresis. In addition to possible alterations of electro-

† The urea for the initial part of this study was generously supplied by Travenol Laboratories, Inc., Morton Grove, Illinois, for clinical investigation.
lytes we felt that changes in the blood-coagulating mechanism would occur since it is known that defects in coagulation occur in patients with various degrees of azotemia and uremia. Lastly, we felt that the diuresis caused by urea would have an effect upon the circulating blood volume since this occurs with dehydration of any etiology. Therefore this study was undertaken and data were obtained to help clarify these points.

**URINE ELECTROLYTES**

To determine accurately the output of urine, specific gravity and loss of electrolytes, studies were carried out on 50 patients who were catheterized prior to and for 5 days following the infusion of urea. Table 1 shows the average volume and specific gravity of urine both before and after diuresis. The average diuresis from 90 gm. of urea given intravenously was approximately 2500 cc. There is a marked decrease in output of urine during the second postdiuresis day since patients were given only 1500 cc. of fluids per day for the first few postoperative days; this was then gradually increased to 2000 cc. per day. The average prediuresis specific gravity of urine was 1.021; this decreased to 1.014 with the diuresis and then returned to 1.020. The specific gravity of the urine during the first 24 hours of diuresis was higher than one would expect considering the amount of electrolytes lost in the urine. The relatively high specific gravity is produced by the urea in the urine, which varies from 70–75 gm. during the 24-hour period following a 90-gm. infusion.

Quantitative determinations of sodium, potassium and chloride in the urine were carried out. Ten nonsurgical patients were used as controls to determine the effect of the electrolyte losses associated with the urea diuresis alone, without the superimposed effect of stress caused by trauma or surgery. Forty surgical patients were divided into three groups: first, 25 patients with intracranial neoplasms undergoing craniotomy without hypothermia or steroids; second, 5 patients with intracranial aneurysms undergoing craniotomy under hypothermia; and third, 10 patients operated upon in the pituitary area who received large doses of steroids pre- and postoperatively.

**TABLE 1**

<table>
<thead>
<tr>
<th>Time</th>
<th>Pre-Diuresis</th>
<th>Diuresis 2nd day</th>
<th>3rd day</th>
<th>4th day</th>
<th>5th day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sp. Gr.</td>
<td>1.021</td>
<td>1.014</td>
<td>1.024</td>
<td>1.022</td>
<td>1.016</td>
</tr>
<tr>
<td>Vol. cc.</td>
<td>2480</td>
<td>975</td>
<td>1430</td>
<td>1250</td>
<td>1470</td>
</tr>
</tbody>
</table>

Fig. 1A shows the urine sodium concentrations in mEq./l. The prediuresis sodium concentration varies between 60–120
mEq./l for all groups. With the diuresis, the nonsurgical controls show a decrease in urine sodium concentration to a level of 40 mEq./l, followed by a gradual increase towards the prediuresis concentration. All three groups of patients undergoing surgery show slightly greater decrease in urine sodium concentrations with levels between 15–30 mEq./l during the period of diuresis. Subsequently, the group undergoing craniotomy without hypothermia or steroids show a gradual increase in urine sodium concentration after the third postoperative day. The patients undergoing craniotomy with hypothermia exhibit a similar curve to the normothermic group, but show a greater degree of sodium concentration varying between 10–25 mEq./l during the first 4 postoperative days. The urine sodium then approaches the concentration of the normothermic group of surgical patients. The patients receiving steroids pre- and postoperatively show the similar early postoperative retention with outputs varying between 25–35 mEq./l during the first 4 postoperative days, but exhibit greater retention with lower urine sodium concentration during the late postoperative period because of continued steroid therapy.

The total sodium output of the average surgical patient in milliequivalents per 24 hours is shown in Fig. 1B. Since the average diuresis is over 2 liters of urine during the first 24 hours after administration of urea, the total sodium excreted is higher than on the days following, during which time the output was slightly less than 1 liter per day. The average neurosurgical patient will lose between 10–50 milliequivalents of sodium per day during the first 5 postoperative days.

The urine chloride concentration is shown in Fig. 2A and the outputs are noted to be nearly identical to those of sodium. The control patients again show a decrease in urine chloride concentration during diuresis with a prompt increase toward the prediuresis outputs following this. The patients undergoing craniotomy without hypothermia or steroids show chloride retention followed by a gradual increase in urine chloride concentration. The hypothermia patients show the most profound retention during the immediate postoperative period and the patients receiving steroids show the greatest late retention of chloride. The quantitative daily loss of urine chlorides is shown in Fig. 2B, and is similar to the daily quantitative sodium outputs. Fig. 3A represents the urine potassium concentrations. Here a different pattern is noted with all four groups exhibiting a slight decrease in urine potassium concentration during the period of diuresis only, and by the second day have returned to
these findings, Bering\textsuperscript{1} feels that patients operated upon under hypothermia who were given urea should lose a greater quantity of sodium than the normothermic patients. While this may be true under conditions of hypothermia alone, when the stress of a neurosurgical procedure is superimposed upon hypothermia the quantity of sodium and chloride excreted is less than when a similar procedure is done under normothermic conditions. The group of hypothermia patients actually lost the smallest quantity of sodium and chloride of all four groups evaluated, as shown in Figs. 1 and 2. This retention of sodium and chloride with the slightly greater loss of potassium exhibited by the patients undergoing surgery is consistent with the metabolic response to stress. Our data would indicate that both surgical and nonsurgical patients do not lose a significant quantity of electrolytes with the urea-induced diuresis, even though over 2 liters of fluid are lost.

**SERUM ELECTROLYTES**

In addition to the studies of electrolytes in the urine, an evaluation of the electrolytes in the serum, pre- and postdiuresis, was carried out. The serum sodium, potassium, chloride and alkali reserve were determined in 15 surgical and 5 nonsurgical patients prior to and following diuresis with urea. The data are summarized in Fig. 4, representing the average values for each group. The serum

From the amounts of electrolytes lost in the urine as shown, it is apparent that the average neurosurgical patient having received 90 gm. of intravenous urea will excrete from 35–55 mEq. of sodium, 50–70 mEq. of chloride, and 40–70 mEq. of potassium at the time of diuresis and will later lose 10–50 mEq. of sodium, 15–50 mEq. of chloride, and 40–70 mEq. of potassium per day during the following 4 postdiuresis days. In contrast to

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**Fig. 3.** Urinary potassium output with urea diuresis.

**Fig. 4.** Alterations of serum sodium, potassium, chloride and alkali reserve with urea diuresis. (\(D = \text{period of diuresis}\).)
EFFECTS OF UREA-INDUCED DIRESIS

Sodium varied between 136–141 mEq./l. following diuresis, the potassium from 3.6–4.5 mEq./l., the chloride from 100–107 mEq./l. and the alkali reserve between 20–26 mEq./l. Usually the patient in normal state of hydration shows no significant deviation of serum electrolytes following a single diuresis. However, significant changes in serum electrolytes may be observed in some patients receiving urea. It is evident from the data on urine electrolytes that even though urea primarily is a water diuretic producing little loss of electrolytes, if a patient is maintained in a negative water balance over a prolonged period because of repeated diuresis, a hyperosmolarity with increase in serum electrolytes will result. We have observed this on several occasions in our series of patients and this aspect has been the subject of a report by Wise. In contrast to the situation of hyperconcentration of serum electrolytes, a large loss of water will also significantly alter the serum electrolytes in patients who are in a state of excess of water with dilution of serum electrolytes; the change here is from abnormal values of electrolytes towards normal levels. The following brief history illustrates this latter situation:

A 27-year-old patient had development of post-partum hypertension with a blood pressure of 220/130 and peripheral, facial and orbital edema. Papilledema, exudates and retinal hemorrhages were noted on fundoscopy. She became confused, had a generalized seizure and fell from bed. Following this she had only decerebrate-like movements to painful stimuli. It was thought that she had increased intracranial pressure secondary to retention of water and hypertension. A lumbar puncture was done and the opening pressure was 29 cm. of water.

The values for her serum electrolytes, urine electrolytes and specific gravity of urine are shown in Table 2. Following the administration of 90 gm. of urea, 200 cc. of 5 per cent saline were given intravenously because of the degree of dilution of serum electrolytes. The output of urine during the next 24 hours was 3760 cc. Serum electrolytes were drawn the following morning, and the concentrations of electrolytes in the serum and urine after administration of urea are summarized in Table 2. There was a definite improvement in the patient’s level of responsiveness and within 48 hours she was able to respond to verbal stimuli.

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
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<tbody>
<tr>
<td><strong>Serum and urine electrolytes before and after urea diuresis</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Serum Na</td>
</tr>
<tr>
<td>K</td>
</tr>
<tr>
<td>Cl</td>
</tr>
<tr>
<td>CO₂</td>
</tr>
<tr>
<td>BUN</td>
</tr>
<tr>
<td>Urine Na</td>
</tr>
<tr>
<td>K</td>
</tr>
<tr>
<td>Cl</td>
</tr>
<tr>
<td>Sp. gr.</td>
</tr>
<tr>
<td>Vol.</td>
</tr>
</tbody>
</table>

She progressed to an uneventful recovery.

With increased intracranial pressure caused by retention of water, as in the eclamptic state, diuresis of 3000–5000 cc. will not only decrease the intracranial pressure, but will also increase the concentration of serum electrolytes towards normal levels. At times the concentration of serum electrolytes may be so low initially that it is necessary to give hypertonic saline simultaneously. This was true in the case cited, though we have had several patients in whom the concentration of serum electrolytes was increased to normal levels from various states of dilution simply by diuresis with no associated administration of hypertonic saline.

Because of the lack of significant losses of electrolytes, dextrose in water would appear to be the fluid of choice for parenteral replacement in the postdiuresis period. The total volume given would depend upon the state of hydration and upon the degree of postoperative edema anticipated. To the average neurosurgical patient we usually give 1500 cc. of dextrose in water per day for the first 2 or 3 postoperative days and then increase it gradually depending upon the patient’s clinical condition. When urea is used to gain surgical exposure and when there is no postoperative elevation of intracranial pressure, the limitation of fluid need not be so great.

The blood urea nitrogen varied from 90–120 mg. per cent following infusion of urea.
and usually returned to the pre-diuresis level within 24–36 hours after administration. There were several exceptions to this noted and, in these, the blood urea nitrogen remained elevated between 60–80 mg. per cent for 24–72 hours. The persistent elevation occurred in patients who had a poor output of urine because of impaired renal function, or, in a few instances, in patients with normal renal function but whose output of urine was limited because of persistent hypotension during and after surgery. In each of the latter cases the blood urea nitrogen returned to normal following a delayed diuresis.

**BLOOD COAGULATION**

In addition to the changes in serum electrolytes, we thought that a transient elevation of the blood urea nitrogen might have an effect on the coagulation of blood since it is known that patients with uremia at times have abnormal bleeding tendencies. A correlation between hemorrhagic phenomena and abnormal blood urea nitrogen has been shown previously. Therefore, pre- and post-diuresis Lee-and-White coagulation times, clot retraction times and prothrombin times were determined in both surgical and nonsurgical patients. The results were considered only if the patient had normal values for these tests prior to the diuresis.

The normal value for the Lee-and-White coagulation time in our laboratory is 6–15 min. and those over 15 min. were considered abnormal times. The clots were evaluated at 24 hours and described as good, fair or poor. Values from 75 to 100 per cent were considered normal for the prothrombin time, thus any value below 75 per cent of normal was considered abnormal. The results in both surgical and nonsurgical patients are summarized in Table 3.

The Lee-and-White coagulation time was determined in 21 surgical and 7 nonsurgical patients with only 1 abnormal coagulation time noted in both groups. Clot retraction times were completed in 16 patients and only 1 abnormality was noted. Prothrombin times taken 24–48 hours following the infusion of urea were found abnormal in 24 out of 37 patients. The values were decreased from 40 to 60 per cent and then returned to normal. The majority of the patients with abnormal prothrombin times were undergoing surgery and it was felt that general anesthesia might temporarily decrease the prothrombin values. To evaluate this, prothrombin times were determined pre- and postoperatively in a series of patients undergoing a major neurosurgical procedure under endotracheal anesthesia, but receiving no urea for the procedure. The results are compared with the surgical group receiving urea and are shown in Table 4. Surgery and anesthesia alone resulted in abnormal prothrombin times in 20 per cent of the patients, while the addition of urea increased the number of patients with abnormal prothrombin times to 67 per cent.

The importance of the abnormal prothrombin values is that they occur in the early postoperative period when hematomas are most likely to form. Recently we have been giving 50 mg. of vitamin K1 intravenously on the day before and the day of operation in an attempt to prevent this transient decrease in the prothrombin time. In 15 patients (Table 4) normal prothrombin times have been noted in 10 and abnormal

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**Table 3**

Coagulogram of surgical and nonsurgical patients

<table>
<thead>
<tr>
<th>Test</th>
<th>Total Patients</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee-and-White coagulation time</td>
<td>28</td>
<td>27 (96%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Clot retraction time</td>
<td>16</td>
<td>15 (94%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>37</td>
<td>13 (35%)</td>
<td>24 (65%)</td>
</tr>
</tbody>
</table>

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**Table 4**

Prothrombin times in a series of neurosurgical cases

<table>
<thead>
<tr>
<th>Test</th>
<th>Total</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery without urea</td>
<td>30</td>
<td>24 (80%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Surgery with urea</td>
<td>30</td>
<td>10 (33%)</td>
<td>20 (67%)</td>
</tr>
<tr>
<td>Surgery with urea and vitamin K1</td>
<td>15</td>
<td>10 (67%)</td>
<td>5 (33%)</td>
</tr>
</tbody>
</table>
prothrombin times in 5. We are hoping that the use of vitamin K\textsubscript{1} will prove helpful.

**BLOOD VOLUME**

The effect of urea diuresis on the blood volume was then considered since it is known that diuresis of any etiology will effect a decrease in blood volume. Pre- and post-diuresis blood volumes were measured in 4 nonsurgical and 6 surgical patients with radio-iodinated serum albumin as described by Fields.\textsuperscript{4} Blood-volume determinations on the surgical patients were of course difficult to evaluate because of loss of blood which had to be estimated. We attempted to replace by transfusion the estimated amount lost. Nine of the 10 had a decrease in blood volume varying from 100–1400 cc. The decrease was directly proportional to both the volume of fluid lost, and the degree of replacement. In a nonsurgical patient following diuresis in whom fluids were withheld rigorously for 24 hours, there was a decrease in blood volume of 1400 cc. A recognition of this decrease is important during surgery and in the early postoperative period because this, coupled with loss of blood at surgery, can cause the development of a hypotensive state and tachycardia, a situation which we have encountered clinically on numerous occasions. In a surgical patient who was overtransfused and given 2500 cc. of fluids during the first 24 hours after surgery, the blood volume was actually greater than before surgery in spite of diuresis.

**CLINICAL**

From April 1958 to December 1960, 175 patients on the neurological and neurosurgical services at Good Samaritan Hospital were given urea. In most instances, intravenous urea (Urevert) was used; in a few a 20 per cent solution was given by nasogastric tube. This latter method was found effective but was abandoned because of gastrointestinal irritability with occasional diarrhea. Several times prolonged diuresis was carried out on an outpatient basis, by having the patients take from 45–60 gm. of urea per day. We found the most palatable formula to be 15 gm. of commercial urea (Merck) in a glass of orange or grapefruit juice, with sugar added. We rarely carry out the latter program now, preferring other diuretics for long-term use.

Most of the patients who were given urea had increased intracranial pressure as a result of a neoplasm, trauma or infection. The infusion is started at the beginning of surgery and in most instances the brain volume decreased sufficiently to permit easy opening and closing of the dura mater. With a single diuresis at surgery and limited intake of fluid postoperatively, we have only occasionally had to repeat the administration of urea in the postoperative period.

As others have pointed out, we have found urea extremely valuable to gain surgical exposure about the sella turcica, cerebello-pontine angle and for intracranial aneurysms. We feel that continuous drainage of cerebrospinal fluid by the lumbar route in conjunction with urea is helpful in cases of difficult exposure. In spite of good diuresis we tap the ventricles in some to obtain adequate relaxation.

There was a marked difference in rate of onset of diuresis. In 1 patient diuresis of 1200 cc. occurred within 1 hour after the urea was started, while in others diuresis was not noted until 24–48 hours after the infusion. Older patients, those with varying degrees of renal disease and the hypotensive patients will have the lowest urinary output. It is essential to maintain adequate systolic pressure to produce a glomerular filtrate, thus the premedicated, anesthetized surgical patient, who is hypotensive, will not begin to have diuresis for many hours following the completion of the infusion of urea. In some patients with delayed diuresis, decrease in brain volume was observed, but in general the most marked retraction was noted in those patients with marked diuresis. Body fluids must be lost in order to maintain decreased volume of tissue. If no diuresis occurs, a temporary shift of fluid may result, but a state of equilibrium soon occurs and another infusion of urea may be required.

We do not believe moderate renal disease necessarily constitutes a contraindication to
the use of urea. We have given urea to several diabetic patients with extensive renal involvement and have noted no toxic effects. These patients were refractory to the usual diuretic programs and the resulting diuresis with urea was significantly greater but less than the average output of a patient with normal renal function. We do not feel that moderately elevated blood urea nitrogen is a contraindication to the use of urea in a patient with increased intracranial pressure.

Our most frequent complication has been excessive losses of fluid and electrolytes. This was manifested clinically by obvious changes in the turgor of the tissues, dry tongue, hypotension and tachycardia while a concentration of serum electrolytes, an increased hematocrit and a decreased blood volume can be demonstrated by laboratory tests. This situation was corrected by adequate replacement either orally or parenterally. Patients who are conscious and alert at the time of infusion will complain of nausea and burning of the arm at the site of administration.

A serious complication was a slough, 3×5 cm. in size, over the dorsal aspect of a foot secondary to the subcutaneous infiltration of 30 per cent urea. A skin graft was required at a later date. Since this incident we perform a venous cutdown or a percutaneous catheterization of the femoral vein if suitable veins of the extremities are not available. If an infiltration does occur, we now inject the area with one ampule of Wydase diluted in 10 cc. of water in order to facilitate mobilization of the hypertonic urea. We have recently encountered no sloughs.

SUMMARY

1. From April 1958 to December 1960, urea was administered to 175 patients on the neurosurgical and neurological services at Good Samaritan Hospital, and has proven to be valuable in the reduction of intracranial pressure and brain volume.

2. No significant changes in serum electrolytes occur with a single diuresis in a normally hydrated patient. Abnormalities of serum electrolytes may occur with repeated diuresis, however.

3. The losses of sodium, chloride and potassium in the urine are minimal with a single diuresis and in the early postoperative period. Dextrose in water is most suitable for replacement of parenteral fluid.

4. Abnormal prothrombin times occurred in two-thirds of the patients receiving urea, while the Lee-and-White coagulation time and the clot retraction time were not affected. Intravenous vitamin K appears to be helpful in reducing the incidence of abnormal prothrombin times with urea-induced diuresis.

5. A decrease in blood volume occurs following diuresis and may lead to hypotension and tachycardia.

6. Extravasation of urea will result in sloughing of overlying tissue, necessitating grafting. This may be prevented by immediate infiltration of the area of extravasation with Wydase.

REFERENCES


