PHYSIOLOGICAL ALTERATIONS AND CLINICAL EFFECTS OF UREA-INDUCED DIURESIS*

MICHAEL S. MASON, M.D., AND JOHN RAAF, M.D.
Department of Neurosurgery, Good Samaritan Hospital, Portland, Oregon

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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.

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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

**TABLE 1**

*Changes in specific gravity and volume of urine following administration of urea*

<table>
<thead>
<tr>
<th>Time</th>
<th>Pre-Diuresis</th>
<th>Diuresis</th>
<th>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>
<td>1.014</td>
</tr>
<tr>
<td>Vol. cc.</td>
<td>1480</td>
<td>975</td>
<td>1430</td>
<td>1450</td>
<td>1470</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1A shows the urine sodium concentrations in mEq./l. The prediuresis sodium concentration varies between 60-120