THE USE OF HYPERTONIC UREA SOLUTIONS IN HYPOTHERMIA

AN EXPERIMENTAL STUDY*

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(Received for publication June 22, 1960)

HYPERTONIC urea solutions are used primarily for the reduction of brain volume and intracranial pressure, while hypothermia is used basically to reduce cerebral metabolism to allow temporary circulatory arrest. It is not unreasonable, therefore, to use these two techniques concomitantly, and in order to do this to the best advantage, detailed knowledge is required about the effects of hypothermia upon the use of hypertonic urea solutions. This paper presents a study of hypertonic urea given intravenously to dogs at various body temperatures from 38°C. to 23°C.

METHODS AND MATERIALS

Male mongrel dogs weighing about 15 kg. were used as the experimental animals. They were anesthetized for the experiment with a mechanically regulated intravenous infusion of pentobarbital which provided a steady level of anesthesia. Hypothermia was produced by shaving the dogs, covering them with cloths soaked in iced alcohol and blowing cold air on them. Thorazine was used to control shivering. During the experiments, recordings were made of arterial blood pressure, superior longitudinal sinus pressure, the electrocardiogram and the electroencephalogram. Either the intracranial pressure was recorded throughout the experiment or serial samples of cerebrospinal fluid were taken for chemical analysis, depending upon the experiment. Chemical analyses on serum and cerebrospinal fluid for Na, K, Cl, protein and total osmotic pressure were made by standard methods. The solution of urea used was approximately a 30 per cent solution of sterile, lyophilized urea in 5 or 10 per cent dextrose. The urinary bladder was catheterized for measurement of urinary flow.

Before injection of urea, samples of arterial blood and cerebrospinal fluid were taken, urinary flow was measured and the collection bottle was changed. The solution of urea, in the amount of 1½ gm. urea per kg. of body weight, was then injected intravenously in one single rapid injection, the midpoint of injection taken as T-O. Observations were recorded for 5 to 6 hours with samples of blood, urine and cerebrospinal fluid taken at appropriate intervals during this time. Temperatures were recorded from thermistors in the rectum, the esophagus, the region of the kidney

* Presented at the meeting of the Harvey Cushing Society, San Francisco, California, April 14, 1960.

This project was supported by Grant #B-1175 of the National Institute of Neurological Diseases and Blindness, National Institutes of Health, United States Public Health Service, Bethesda, Maryland.
and, in some cases, the fore limb. When the animals were studied at other than normal body temperature, they were allowed to equilibrate at the experimental temperatures for an hour before the injection of urea was made.

In considering the results of the disappearance of urea from the blood, the original level of blood-urea nitrogen was subtracted from the observed levels and these values, plotted against time on semilogarithmic paper, gave a straight line after about 15 min. (Fig. 1). The slope of this line was considered a measure of the rate of elimination of urea, and the time for the concentration of urea to fall by one half, called the blood-urea half-time, was used to compare the results at one tempera-

![Fig. 1. Disappearance of urea from the blood stream of dog following an intravenous injection of 1.5 gm. urea per kg. of body weight in a 30 per cent solution.](image)

ture with those at another. The same treatment was applied to the fall of the osmotic pressure, here called the osmotic pressure half-time.

The results of all experiments at any one temperature have been averaged and the mean has been taken for comparison. Changes in intracranial pressure were recorded as the percentage change from the original intracranial pressure recorded.

RESULTS

Forty-one experiments were carried out at temperatures ranging from 38°C to 29°C. These have been grouped according to temperature as follows: 36°C–38°C, 34°C, 30°C–32°C, 26°C–28°C, 23°C–25°C. and the mean value for each group was used in considering the results. The pertinent data are summarized in Table 1.

**Blood-Serum Composition.** The blood-urea concentration rose to a maxi-
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### TABLE 1

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<tr>
<td>36-38</td>
<td>4 60</td>
<td>13 179</td>
<td>2 108</td>
<td>12 204</td>
<td>5 84</td>
<td>6 22</td>
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<tr>
<td>36-38</td>
<td>1 62</td>
<td>4 203</td>
<td>1 145</td>
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<tr>
<td>30-32</td>
<td>3 250</td>
<td>4 562</td>
<td>3 107</td>
<td>3 200</td>
<td>4 70</td>
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<td>25-29</td>
<td>3 59</td>
<td>4 570</td>
<td>4 210</td>
<td>4 292</td>
<td>5 60</td>
<td>2 60</td>
<td>2 57</td>
<td>6 38</td>
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</table>

The serum sodium showed a sharp temporary drop at 10 min. but by 20 min. it had returned to near normal. It then showed a slow decrease over a longer period of time. These same general changes were seen at all temperatures, but there were not sufficient data to determine a quantitative effect of temperature.

The serum potassium showed a sharp increase at the time of the sodium drop and then returned to normal levels where it remained. This was seen at all temperatures.

The chloride followed a pattern similar to the sodium with first a sharp decrease followed by a return to nearly normal levels, occurring within 20 min., and then a slow fall (Fig. 2).

**Cerebrospinal-Fluid Composition.** The urea concentration of cerebrospinal fluid, originally equal to that of the blood, rose gradually until it was equal to or slightly greater than that of the blood and then fell with the blood urea. This equilibrium took about 120 min. at 37°C., 140 min. at 34°C., and 240 min. at 25°C.

The total osmotic pressure of the cerebrospinal fluid increased rapidly to
that of the blood and continued to levels considerably higher before beginning to fall again to a value equal to that of the blood. The osmotic pressures of the cerebrospinal fluid and serum became equal in about 20 min. at normal temperatures, 40 min. at 30°C, and in about 60 min. at 25°C, a much shorter time than for the equilibrium of urea to take place.

The cerebrospinal-fluid sodium showed a sharp temporary initial rise of about 5 per cent, then a slow increase, and finally a fall as the osmotic pressure began to come down. These general changes occurred at all temperatures, but the fall was not as pronounced at lower temperatures. The data were insufficient for detailed quantitative studies.

The cerebrospinal-fluid potassium showed a very slight initial rise about equal to that of the sodium (5 per cent), but quickly returned to its initial level and did not change subsequently.

The cerebrospinal-fluid protein rose in all experiments to a much higher degree than did the sodium and chloride. This was without any evidence of bleeding, and it did not seem closely related to other events observed. Only at normal temperatures did it tend to return to normal levels with sodium and chloride (Fig. 2).

Urinary Output. The urinary output was decreased by hypothermia in all experiments. However, the injection of urea always caused a diuresis and continued increase in urinary flow during the entire experimental period, although the maximum rates of urinary flow were always greater in the warmer animals. Hematuria was observed in some of the hypothermic animals with body temperatures below 28°C. (Fig. 3).

Intracranial Pressure. Hypothermia caused a decrease in intracranial
pressure, but the hypertonic urea always caused an additional decrease. The relative maximum decrease in pressure at 36°–38°C. was 31 per cent of the original pressure, occurring in 22 min. after the injection of urea; at 30°–32°C. there was a 49 per cent drop occurring 48 min. after injection of urea; and at 28°–25°C. there was a 57 per cent drop reached 60 min. after injection (Fig. 4).

The changes in intracranial pressure at all temperatures seemed to be dependent upon the osmotic pressure gradient between the serum and cerebrospinal fluid. As long as the osmotic pressure of the serum was greater than that of the cerebrospinal fluid, the intracranial pressure fell, but as the serum and cerebrospinal fluid came into osmotic equilibrium, the pressure fall stopped. When the osmotic pressure of the cerebrospinal fluid became greater than that of the blood the intracranial pressure began to rise and usually continued to above the initial levels except in the hypothermic animals in which the observations were stopped before this occurred (Fig. 5).

The return or “rebound” of the intracranial pressure above the initial level seen in some experiments at all temperatures above 25°C. was probably the result of the continued elevation of the osmotic pressure of the cerebrospinal fluid above that of the serum, as the intracranial pressure

Fig. 3. Urinary output of the dog after intravenous injection of 30 per cent solution of urea in the amount of 1.5 gm. urea per kg. of body weight. A diuresis occurs at both normothermic and hypothermic levels, but the flow is always greater at normal temperatures.

Fig. 4. Changes in intracranial pressure at three body temperatures following intravenous injection of 1.5 gm. urea per kg. of body weight in a 30 per cent solution. Preinjection pressure considered 100 per cent at all temperatures.
always would rise when this occurred. This was not prevented by giving the urea slowly (Table 2).

The Electrocardiogram. There were marked effects of the injection of urea upon the electrocardiogram seen at all temperatures. These consisted of increased conduction time, an elevation of the ST segment, inversion of the T wave and a distortion of the QRS complex with a split R wave in some cases. These changes occurred during injection and remained for 5–10 min. after the injection was finished, when the electrocardiogram returned to normal. These effects were seen at all temperatures (Fig. 6) when urea was injected, but not when a large volume of isotonic saline was injected at the same rate.

Electroencephalogram. There were no changes of any consequence noted in the electroencephalogram during or after the injection of the urea.

Arterial Blood Pressure. There were no significant changes in the arterial blood pressure during or after the injection of the urea.

Longitudinal Sinus Pressure. The injection of the hypertonic solution usually caused a decrease in the longitudinal sinus pressure which remained down for an indefinite period. It usually returned to normal levels as the cerebrospinal fluid pressure increased.

**DISCUSSION**

The urea was given very rapidly in these experiments so that a good point of time could be obtained for the measurement of the elimination of urea. It was recognized that this is not done in clinical practice,4–6 but this does not make these observations any less useful in planning the clinical use of urea.

The augmented effect of the hypertonic solution upon the intracranial pressure in the hypothermic state seemed to be secondary to the slow elimination of urea and the slow distribution of the urea throughout the body. Particularly important was the slow distribution of the urea throughout the body which resulted in a longer period of time with the serum osmotic pressure elevated above the cerebrospinal fluid osmotic pressure. This osmotic pressure gradient appeared to be the controlling factor in changes in intra-
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Table 2

<table>
<thead>
<tr>
<th>Injection of Urea</th>
<th>Maximum Decrease in Pressure</th>
<th>Time for Pressure to Return to Initial Value</th>
<th>Maximum Increase in Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate ml./kg./min.</td>
<td>Duration Min.</td>
<td>% Initial Pressure</td>
</tr>
<tr>
<td>*</td>
<td>1.0</td>
<td>5</td>
<td>-31</td>
</tr>
<tr>
<td>Start 1.0</td>
<td>Then 0.17</td>
<td>70</td>
<td>-9</td>
</tr>
<tr>
<td>Start 1.0</td>
<td>Then 0.1</td>
<td>55</td>
<td>-25</td>
</tr>
<tr>
<td>Start 1.0</td>
<td>Then 0.07</td>
<td>60</td>
<td>-12</td>
</tr>
<tr>
<td>Start 0.08</td>
<td>Then 0.04</td>
<td>55</td>
<td>-31</td>
</tr>
<tr>
<td>Start 0.09</td>
<td>Then 0.025</td>
<td>75</td>
<td>-36</td>
</tr>
<tr>
<td>0.08</td>
<td>75</td>
<td>-58</td>
<td>60</td>
</tr>
<tr>
<td>0.08</td>
<td>57</td>
<td>-31</td>
<td>30</td>
</tr>
<tr>
<td>0.7</td>
<td>75</td>
<td>-33</td>
<td>22</td>
</tr>
</tbody>
</table>

* Mean of 6 experiments with a single rapid injection.

cranial pressure so that by prolonging it a greater relative decrease in pressure was obtained.

The evaluation of the changes in pressure was made on a relative basis and it must be pointed out that the absolute changes in pressure were not as markedly increased by the depression of the body temperature. No attempt was made to determine whether or not brain shrinkage was greater at lowered temperatures.

The fluctuation of the venous pressure of the sagittal sinus certainly caused some of the changes in intracranial pressure, but it was not always possible to determine cause and effect. Variations in cerebral venous pressure have been seen following injections of many substances in hypertonic solutions and it did not seem to be specific for urea.

The amount of urea required to
achieve an adequate increase in intracranial space for surgical procedures is considerably less at low temperatures than at normal temperatures. The dose of urea for a patient at 25°C can probably be reduced to about one third or one fourth the dose used at normal temperatures.

The return of serum osmotic pressure to normal levels not being affected much by hypothermia and being considerably faster than the elimination of urea at the lower body temperatures was an observation of considerable importance. This meant that solutes other than urea were being lost, presumably sodium and chloride. Such a loss of sodium and chloride is perfectly reasonable in the light of known alterations of renal physiology in the hypothermic state. Sodium is reabsorbed at normal temperatures while urea passes freely out of the kidney, but with the reduction of renal metabolism, sodium is not reabsorbed and is washed out by the diuresis. When using hypertonic solutions of urea in patients with lowered body temperature consideration must be given this or hyponatremia might easily result. It is another indication for considerably reducing the dosage of urea in the hypothermic state.

The electrocardiographic changes seen were of considerable importance. The changes in the serum electrolytes, the potassium elevated and the sodium decreased, probably account for the electrocardiographic changes, rather than an increase in the volume of blood resulting from a shift of water to the hypertonic blood. These early electrolyte changes and electrocardiographic changes have been confirmed in unpublished work of Giordano, Blum and Merrill of the Kidney Laboratory of the Peter Bent Brigham Hospital. It is their opinion that the change is caused by a poisoning of the sodium pump, allowing intracellular potassium to escape. This effect upon the heart makes slow injection mandatory, regardless of the effects of pressure. This is particularly important in hypothermia as in one experiment ventricular fibrillation was precipitated by the injection of urea.

The fact that no changes in the electroencephalographic tracings were seen probably is a reflection of the manner in which they were recorded. These recordings were made from scalp electrodes, as contrasted with the intracerebral electrodes used by Stevenson in recording the changes that they found.

The initial changes in composition of cerebrospinal fluid—5 per cent concentration of sodium and potassium—probably represent a shift of water alone. The later changes are a combination of sodium, chloride and urea entering the cerebrospinal fluid. The very constant level of potassium is remarkable, and is evidence of considerable metabolic effort to keep the level constant in the face of other violent changes.

No explanation of the very marked rise of protein has been found. It has been seen with the other hypertonic agents and is not a special effect of urea.

**SUMMARY**

1. The effects of intravenous injections of 25–30 per cent solutions of
urea in the amount of 1.5 gm. urea per kg. of body weight have been studied in dogs at temperatures from 38°–23°C.

2. The elimination of urea was reduced markedly by the hypothermia, but the return of the total osmotic pressure of serum to normal was much less affected. This suggested an increased loss of electrolytes in the diuresis produced by the urea in the hypothermic state.

3. The relative effects on intracranial pressure were greater in the hypothermic state than at normal temperatures. Because of this and the loss of electrolytes, the amount of urea used in the hypothermic state should be reduced considerably.

4. The changes in intracranial pressure were dependent upon the osmotic pressure gradient between the serum and the cerebrospinal fluid. As long as that of the serum was higher than that of the cerebrospinal fluid, the pressure fell, but when this gradient was reversed the intracranial pressure began to rise and continued to do so to levels higher than the initial intracranial pressure.

5. The rapid injection of urea caused severe changes in electrolytes in the serum which were of sufficient degree to cause marked changes in the electrocardiogram. In the hypothermic state this was enough to cause ventricular fibrillation. This finding is a strong contraindication for large rapid injections of solutions of urea at any temperature.

REFERENCES


DISCUSSION

Dr. W. F. Collins: I think this is a most important study for one is struck by the discrepancy between the frequency with which hypothermia and/or urea is used and how little is known concerning their effects on the body. This is particularly true concerning their effect on the nervous system.

Although hypothermia is used as an aid in controlling cerebral edema, Barbour and his
co-workers have shown that in monkeys, in the temperature range used clinically, hypothermia causes a shift of water intracellularly. While hypothermia is useful in decreasing cellular metabolism, it also causes a decrease in oxygen available because of changes in oxygen-oxyhemoglobin dissociation. Eckstein et al. have demonstrated a marked increase in viscosity of blood, while Oppenheimer and McCravey have shown prolongation of circulation time and decreased cardiac output. Puchkov has demonstrated acceleration in clotting time. Thus intracellular shift of water, decrease of oxygen available, increased viscosity of blood, lowered cardiac output, increased circulation time and accelerated clotting are found in the hypothermic state. All these factors must be evaluated in assessing what we are trying to accomplish with hypothermia.

Add urea to hypothermia and the problems are compounded. With the infusion of urea, there is a rise in serum potassium. Under hypothermia the danger of cardiac fibrillation is always present and while there may be many causative factors, its production is facilitated by elevation of serum potassium. Would their combined use predispose to cardiac fibrillation?

Hypothermia has been shown in dogs to produce paroxysmal changes in cortical activity. In our laboratory, urea has been demonstrated to alter cortical excitability in cats with production of prolonged seizures. The blood levels of urea necessary to produce these cortical changes are higher and of longer duration than those found in clinical use but in a patient with predisposition to seizures, in which both hypothermia and urea are used, will this altered cortical excitability be important?

These are some of the problems. Only critical evaluation of our use of these agents in the clinic and careful laboratory investigation can give us the answers we require in order to use these techniques intelligently and effectively. The authors are to be congratulated on attacking this difficult problem.

May I close with two questions? The first deals with cardiac complications of hypothermia. Does Dr. Bering feel the safe levels of hypothermia, namely 29°C. to 30°C., should be raised when urea is used? The second is in regard to the use of urea. Would Dr. Bering care to state in numerical terms an approximate rate and amount of urea he feels should be used when the patient is hypothermic?

Dr. Edgar A. Bering, Jr. The problem of cardiac complications and hypothermia is not really within the scope of this paper. However, in order to get the maximum benefits of hypothermia for protection against anoxia, the body temperature should be below 30°C. (86°F.), so that raising this will not help much. I can not say with certainty whether or not urea will be important in causing more cardiac complications, but the possibility should not be overlooked.

As to the dose of urea in hypothermia, probably one-quarter the usual dose would be adequate, but our data at present are not complete on this point.

The cerebrospinal fluid pressure began to rise as soon as the total osmotic pressure of cerebrospinal fluid became greater than the total osmotic pressure of serum. When we have followed it long enough the cerebrospinal fluid pressure usually rose above the original level until the cerebrospinal fluid and serum were again in osmotic equilibrium.

Dr. James L. Poppen: Dr. Bering, while you are still up here, from just a practical standpoint as to the rapidity with which you give the urea, have you noticed any difference in the local reaction in the veins as to whether you give it rapidly or slowly?

Dr. Edgar A. Bering, Jr.: If you are giving it rapidly and you have any leakage, you get into pretty serious trouble. If you are giving it slowly, you don’t usually get into it, unless the leak is not noticed. It is certainly something you have to watch with great care to make certain you don’t get any extravascular leakage.

Dr. James L. Poppen: Does it make any difference as to what position the leg is in, whether it is in the sitting position or horizontal position?

Dr. Edgar A. Bering, Jr.: I don’t think it makes any difference as long as you are certain the drainage from the vein into which the urea is going is not obstructed.