# UREA INDUCED SERUM HYPEROSMOLALITY AND THE CENTRAL NERVOUS SYSTEM

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Experimentally [1, 2] cerebrospinal fluid pressure can be lowered very rapidly by intravenous injections of hypertonic solutions of various substances. The physiological explanation lies in the change in the osmotic value of blood and the subsequent fluid readjustments within the body tissues including the brain.

Previous studies have demonstrated that urea infusions could be used to produce this effect in man.[3, 4] The lowered intracranial pressure induced by the urea hyperosmolality in blood has been shown to be a lifesaving procedure in patients with cerebral edema.[5]

However, documentation that urea acts chiefly through this osmolality effect in man has not yet been presented. Established ranges of response to urea injection in humans with normal and increased intracranial pressure are not known. Collected group observations over a sufficiently long period of time in man are not available. The purpose of this study is to elucidate this problem and investigate the mechanism of action of urea in man with normal intracranial pressure.

## Materials and Methods

Patients who had had spinal anesthesia and an operation and had normal intracranial pressures were studied. The physiological status of these patients was normal in all respects, except for their being postoperative and postspinal anesthesia. All patients were observed over a standardized three-hour period with blood and cerebrospinal fluid for chemical assays being drawn at the start, each one-half hour, and at the end of the study. Forty grams of urea (Ureaphil 4)* in 250 ml. of 5 per cent dextrose and water were administered rapidly intravenously immediately after the first control observation. Blood chemical determinations made at each period included urea nitrogen, osmolality, sodium, potassium, and chloride. Concomitant assays of cerebrospinal fluid, obtained through a catheter inserted into the lumbar subarachnoid space, were performed for sodium, chloride, potassium, urea nitrogen, and osmolality.

## Results

Ten patients given urea were studied. Two additional normal patients not given urea were used as controls. The mean chemical values in the 10 patients are summarized in table 1 and graphic comparisons are drawn from these values.

The time-dose relationship of blood and cerebrospinal fluid urea nitrogen is illustrated in figure 1. The blood urea concentration

TABLE 1

Mean Values in 10 Normal Patients Given Urea

| Hour | $Na^+$ (mEq./L.) | Cl (mEq./L.) | $K^+$ (mEq./L.) | Serum Urea Nitrogen (mg. %) | Milli-osmolals |
|---|---|---|---|---|---|
| **Blood** | | | | | |
| 0 | 145.8 | 100.8 | 4.9 | 12.7 | 286.3 |
| ½ | 141.3 | 100.1 | 4.8 | 74.5 | 272.3 |
| 1 | 141.5 | 99.0 | 4.8 | 65.5 | 267.2 |
| 1½ | 143.2 | 98.9 | 4.4 | 61.2 | 265.9 |
| 2 | 145.1 | 99.2 | 4.6 | 58.6 | 265.4 |
| 2½ | 146.9 | 99.4 | 4.6 | 57.6 | 267.6 |
| 3 | 148.9 | 99.4 | 4.6 | 56.1 | 268.5 |
| **Cerebrospinal Fluid** | | | | | |
| 0 | 143.5 | 128.1 | 2.9 | 10.8 | 288.3 |
| ½ | 144.0 | 130.0 | 3.0 | 18.8 | 291.1 |
| 1 | 146.2 | 121.1 | 2.8 | 25.8 | 293.1 |
| 1½ | 145.9 | 130.0 | 2.9 | 30.1 | 295.5 |
| 2 | 144.3 | 120.8 | 2.9 | 28.4 | 295.7 |
| 2½ | 145.0 | 120.4 | 3.0 | 30.0 | 295.9 |
| 3 | 146.1 | 118.3 | 3.0 | 32.0 | 294.5 |

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* Courtesy of Abbott Laboratories.

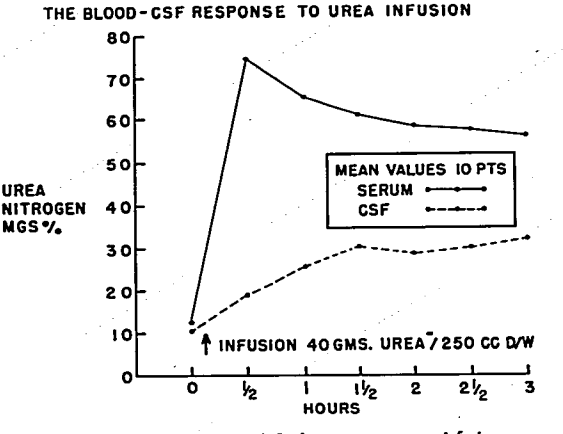


FIG. 1. The blood-cerebrospinal fluid response to urea infusion.

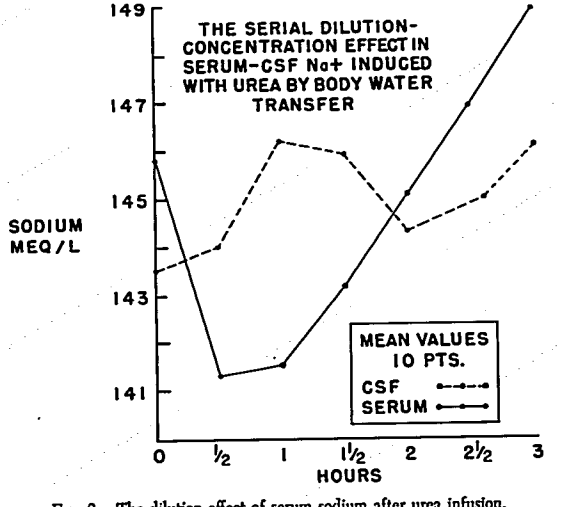


FIG. 2. The dilution effect of serum sodium after urea infusion.

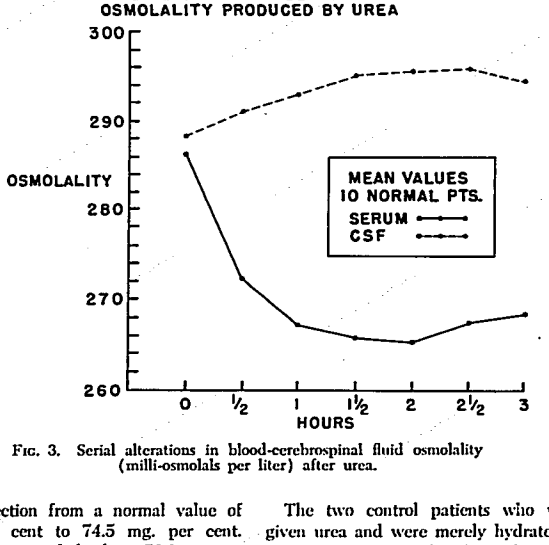


FIG. 3. Serial alterations in blood-cerebrospinal fluid osmolality (milli-osmolals per liter) after urea.

rose after injection from a normal value of 12.7 mg. per cent to 74.5 mg. per cent. Thereafter it decreased slowly to 56.1 mg. per cent at three hours. By contrast, the cerebrospinal fluid urea nitrogen content rose from a normal of 10.8 mg. per cent to 32.0 mg. per cent.

The effect of injected urea on the sodium content of serum and cerebrospinal fluid is demonstrated in figure 2. There is a rapid dilution of serum sodium from a normal of 145.8 mEq./l. to 141.8 mEq./l. at the end of the first half hour and then a continuous rise to 146.1 mEq./l. The concentration of sodium in cerebrospinal fluid on the other hand rose irregularly from 143.5 mEq./l. to 146.1 mEq./l.

Figure 3 illustrates the relationship of the blood cerebrospinal fluid osmolality after urea injection. Blood osmolality decreased from a normal of 286.3 milli-osmolals to a low of 265.4 after two hours and then rose slightly. Cerebrospinal fluid osmolality rose from a normal of 288.3 to 295.9 milli-osmolals after two and one-half hours and then decreased to 294.5 milli-osmolals.

The two control patients who were not given urea and were merely hydrated during the observation period, did not show a statistically significant alteration in the blood and cerebrospinal fluid assays performed.

## Discussion

The dilution of the extracellular serum sodium produced by the alteration of serum osmolality with secondary mobilization of body water is shown in figure 2. The concomitant relative increase in cerebrospinal fluid sodium produced by the presumed transfer of intracranial water into blood in response to the osmotic load is also shown in figure 2. A significant sodium blood-brain transfer is not suspected to occur within this three-hour period in the 10 urea-treated patients. Other radioactive and organic tracer studies confirm this statement.[6-9] However, the divergence of these blood-cerebrospinal fluid sodium values at the termination of the period may be secondary to some barrier transfer, or rate of exchange of water. That brain water, extra- and intracellular, is in free and rapid equilibrium with the water of the blood has been

shown by previous deuterium oxide studies.[10] This is believed to be the chief central nervous system constituent that is mobilized in response to a serum osmotic load of urea.

Previous work on glucose induced serum hyperosmolality has provided a physiological explanation of the urea effect as demonstrated in figure 3. It has been stated[11] that the unbalancing of the hydrostatic and osmotic equilibria across the walls of the craniospinal capillaries, by urea infusion, for example, causes the fluid shift which induced the observed depressor response in the cerebrospinal fluid and decrease in brain bulk.[12] It must be emphasized that these effects are chiefly between the brain itself and the blood vessels. The mechanism for equilibration is essentially the same at high and at normal pressures.[12]

Cerebrospinal fluid is an intermediate diluent in this process, reflecting these changes at a slower rate. Because of its availability, frequent assays of its chemical constituents were performed in these experiments. Obviously brain water is not readily available.

Some recorded values in the earlier literature were confirmed in this study. The cerebrospinal fluid-blood urea nitrogen fraction in normal untreated patients averaged 85 per cent.[13] The blood-cerebrospinal fluid sodium ratio normally averaged about one. The cerebrospinal fluid-serum potassium ratio averaged near 0.5 in normal untreated patients.[14] The equilibration between blood-cerebrospinal fluid nitrogen levels was reached in about two hours in the normal patients. This is slightly earlier than has been reported. Thus a rapid and continuing change in blood-brain osmolality was induced over a three-hour period in these normal patients given 40 Gm. of urea. During this observation time no untoward effects were noted.

The function of the urea-induced changes in the central nervous system was directly reflected in the alteration of blood-cerebrospinal fluid osmolality, and secondary transfer of body water in this group. The serial dilution of serum sodium with the simultaneous decrease in serum osmolality and the rise in cerebrospinal fluid osmolality reflect the rapid change of water between the brain and the blood. This is the prime mechanism of the urea effect. It is reasonable to recommend, on the basis of our results, that urea be employed early in all cases of cerebral hypoxia, both as a curative and preventive agent against acute brain swelling.

## Summary

Serial observations of 10 postoperative and postspinal anesthetic patients given 40 Gm. of urea have been made. Serial chemical analyses of blood and cerebrospinal fluid suggest that shifts of body water from brain into blood occur as the result of urea serum hyperosmolality. No adverse responses to the injection of urea were observed. On the basis of these data, the early use of urea in cerebral hypoxia is recommended.

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**STATUS ASTHMATICUS** All investigators of status asthmaticus have emphasized the predominant role of viscid mucus as the final cause of asphyxia in patients suffering from this malady. Up to this time, all forms of therapy have seemed inadequate. Apparently, a successful line of therapy in two otherwise hopeless cases of status asthmaticus is reported. Both patients, apparently preterminal, were anesthetized with thiopental and succinylcholine, their tracheas intubated, and treated by continuous intermittent positive pressure respiration under anesthesia with either ether and oxygen or nitrous oxide and continuous drip succinylcholine maintained for 18 to 24 hours. Both patients demonstrated striking improvement and were subsequently discharged from the hospital. Periodic tracheal aspiration was used on both patients, and endobronchial lavage with trypsin enabled aspirations, previously ineffective, to be performed satisfactorily. The rapidity with which the mucus was subsequently aspirated suggested that the effect of trypsin was not due to its digestive action. The method is worthy of further trial. (*Broom, B.: Intermittent Positive-Pressure Respiration and Therapeutic Bronchial Lavage in Intractable Status Asthmaticus, Lancet 1: 899 (April 23) 1960.*)

**INTRACRANIAL PRESSURE** The most likely mechanism of action of urea in reducing intracranial pressure is the presence of a blood-brain barrier to urea, thereby withdrawing fluid from cerebrospinal spaces. No major toxic effects arose in the patients studied. Local reactions were noted in the vein through which the injections were made, but these never progressed to thrombosis. The blood urea level rose and diuresis began shortly after the infusion was started. Urea should not be given to patients with impaired renal function. (*Stubbs, J., and Pennybacker, J.: Reduction of Intracranial Pressure with Hypertonic Urea, Lancet 1: 1094 (May 21) 1960.*)

**INTESTINAL OBSTRUCTION** Observations are needed to establish the claim that endotoxemia is a principal cause of fatal shock in acute intestinal obstruction. If this evidence is positive, the place for antibiotics as an adjuvant to surgery for obstruction becomes even stronger. The best protection, however, against bacterial toxins is not antibiotic therapy, but surgical treatment of the vascular lesion. By delaying surgery, the success of resection and anastomosis becomes increasingly doubtful. Some surgeons, as well as some internists and general practitioners, are dilatory in resorting to surgery because they are not sufficiently aware of the danger to these patients. (*Fine, J.: Cause of Death in Acute Intestinal Obstruction, Surg. Gynec. & Obstet. 110: 628 (May) 1960.*)