MECHANISM OF ACTION OF A UREA PREPARATION ON THE CEREBROSPINAL FLUID PRESSURE IN MAN

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In recent years an intravenous infusion of a hypertonic solution of urea has found use in clinical practice for lowering the intercranial pressure [1, 2, 6, 7]. A number of studies carried out on animals have been devoted to the mechanism of this effect [5, 8, et al.]. Taking into account the possibility of species differences of the blood-brain barrier, we consider clinico-physiological investigations carried out on patients to be of particular importance.

According to the presently widespread hypothesis, dehydration of the brain and a drop of intracranial hypertension under the effect of a urea preparation are explained by the increase of the osmotic concentration of the blood [3, 4, 9]. Apparently the action of urea is based not only on the change of the osmotic concentration of the blood properties. Only osmotically free water can pass over the osmotic gradient from the brain to the blood. Since in the intercellular substance and in the cells the water is bound with electrolytes, then with an increase of the osmotic concentration of the blood the loss of tissue water should have led to an increase in the concentration of electrolytes in the tissue.

In the present investigation we made a physiological analysis of the mechanism of action of a urea preparation on lowering of the cerebrospinal fluid pressure.

METHOD

We observed 22 patients with brain tumors in whom we injected the Soviet preparation of lyophilized urea "urogluc" for therapeutic purposes [2]. In all we made 25 intravenous infusions of a 30% solution of the preparation on a 10% solution of glucose in doses from 0.25 to 1.5 g/kg of body weight. To study the dynamics of the blood composition we sampled the blood from a vein after the introduction of various quantities of the preparation. To evaluate the clinical effect we measured the pressure of the cerebrospinal pressure and investigated its composition. For the characteristics of renal function we investigated the urine formed during the time of the infusion of the preparation. Urea was determined by Conway's method, Na and K by the flame photometric method, osmolar concentration by the cryoscopic method, the erythrocyte-plasma relationship by the hematocrit reading, and the serum proteins level by the refractometric method.

RESULTS

After infusion of urea in a dose of 1 g/kg of body weight the cerebrospinal fluid pressure dropped on the average by a factor of 2 (see table). The table gives data on the composition of the blood, cerebrospinal fluid, and urine after 14 infusions of the urea preparation. The concentration of urea in the blood increased in proportion to the quantity of the injected preparation. After infusion of the first 15 g of urea the content of osmotically active substances in the serum changed. At the same time evident hydremia occurred which was indicated by the drop of the serum protein concentration. Hydremia was also confirmed by investigations carried out on four patients in which a decrease of the refractometric index, hematocrit, and dry weight of the plasma was noted after the infusion of 15 g

Changes of the Composition of the Blood, Cerebrospinal Fluid, and Urine Upon an Intravenous Infusion of a Hypertonic Solution of a Urea Preparation

Quantity of injected urea (in g)	Blood serum				
	urea (in mg %)	osmolar concentration (in mosm/liter)	Na (in m-eqv/liter)	JK (in m-eqv/liter)	protein (in %)
0	26 ± 2.7	291 ± 2.5	143 ± 1.35	4.5 ± 1.52	6.46 ± 0.15
15	49 ± 2.4	289 ± 5.9	140 ± 1.19	4.2 ± 1.39	5.84 ± 0.1
30	84 ± 11.6	301 ± 4.6	139 ± 1.85	4.4 ± 1.67	5.6 ± 0.14
45	117 ± 7.5	309 ± 5.0	140 ± 1.68	4.4 ± 1.36	6.0 ± 0.13
60	144 ± 8.8	312 ± 7.5	141 ± 1.28	4.5 ± 1.69	6.12 ± 0.14
1 h after end of infusion	121 ± 7.7	302 ± 3.6	141 ± 1.61	4.3 ± 2.15	6.17 ± 0.16

Quantity of injected urea (in g)	Cerebrospinal fluid				
	urea (in mg %)	osmolar concentration (in mosm/liter)	Na (in m-eqv/liter)	(in m-eqv/liter)	cerebrospinal fluid pressure (in mm H_2O)
0	23 ± 2.3	285 ± 3.5	145 ± 1.3	3.3 ± 1.8	227 ± 12.8
60	32 ± 2.2	287 ± 2.7	145 ± 1.5	3.2 ± 1.7	111 ± 9.9

Quantity of injected urea (in g)	Urine				
	urea (in mg %)	osmolar concentration (in mosm/liter)	Na (in m-eqv/liter)	K (in m-eqv/liter)	Diuresis (in ml/min)
0	1801 ± 135	755 ± 13	140 ± 39.3	54.3 ± 9.78	0.58 ± 0.08
60	1873 ± 37	516 ± 61	91.6 ± 11.4	20.75 ± 2.7	2.2 ± 0.22

of the urea preparation. Hydremia ensued without a change of the osmolar concentration of the serum (see table) and, consequently, it was not caused by the osmotic effect of the urea on the tissue. It is evident that hydremia was caused not by the fluid infused but by the uptake of water from the tissues, since only 50 ml of the solution was injected into the vein during this time but the volume of blood increased on the average by 9.5 %. Despite the evident dilution of the blood, the Na concentration dropped only 2.5%.

During further infusion of urea, the concentration of Na and K in the serum was not substantially changed, and its osmolarity increased in proportion to the increase of the urea concentration increased on the average by 118 mg %. Since 6 mg % of urea increased the osmolar concentration of the solution by 1 mosm, then 118 mg % should have increased the concentration of osmotically active substances in the serum by almost 20 mosm and, actually, it increased 21 mosm (see table).

The urea was quickly and uniformly distributed in the liquid phases of the organism freely penetrating the intercellular fluid and cells; this was indicated by calculation which yielded unambiguous results in all investigations.

For example: for female patient K. during the infusion 10.25 g of the 60 g of injected urea was excreted with the urine. The water content in the organism was 70% of body weight, i.e., 42.6 liters at a body weight of 61 kg. Provided there is a uniform distribution of urea its end concentration should be 117 mg %. Actually, it was close to the calculated—110 mg %.

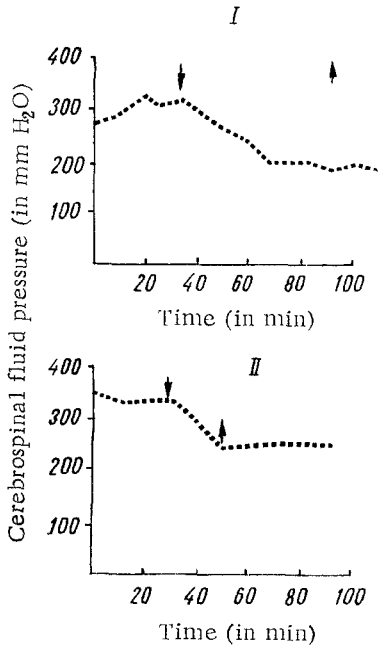
Unlike in the blood the urea content in the cerebrospinal fluid after infusion of the preparation increased by only 9 mg % and the concentration of Na, K, and osmotically active substances did not change (see table). The

difference in urea distribution between the blood and the cerebrospinal fluid was clearly elicited upon infusion of 60 g of the preparation at various rates. On injecting urea into 8 patients over the course of 145 ± 12 min the serum urea concentration 1 h after infusion increased to 121 ± 10.7 mg %, and with injection of the preparation into 6 patients during the course of 54 ± 3 min it increased to 127 ± 12.2 mg %. At the same time the increase in the urea content in the cerebrospinal fluid is a function of time: with rapid infusion of urea within 54 min its concentration in the fluid increased 6 mg % (124 % of the initial level), whereas with slow infusion it rose by 11 mg % (154 % of the initial level).

Thus urea is quickly distributed in the liquid phases of the body with the exception of the cerebrospinal fluid and, apparently, the brain tissues bounded by the blood-brain barrier. Hydremia was the most evident effect in the initial period of infusion of urea; at the end of infusing the total clinical dose of the preparation the osmotic gradient between the blood and the cerebrospinal fluid became the leading one.

The noted separation in time of the two effects of the urea preparation permitted us to elicit whether the cerebrospinal fluid pressure at the period of evident hydremia changed after the infusion of the first portions of urea or the development of an appreciable blood-fluid osmotic gradient was necessary for a drop of the cerebrospinal fluid pressure. To analyze this alternative we carried out additional investigations on seven patients with continuous recording of the cerebrospinal fluid pressure during the entire time of urea infusion. A polyethylene catheter was inserted subdurally into the patients through a special spinal needle, the needle was removed, and the catheter connected with a Waldmann manometer. The results showed that the cerebrospinal pressure began to drop from the first minutes after the start of infusion of the preparation. This process continued during the entire period of infusion of the preparation (see figure). The pressure of the cerebrospinal fluid dropped even after small quantities of urea were infused. Thus, the infusion of urea causes a drop of the cerebrospinal fluid pressure not only owing to the osmotic gradient between the fluid and the blood but also by another, nonosmotic mechanism.

The increase of diuresis after the infusion of urea cannot explain the clinical action of the preparation, mainly because the drop of the cerebrospinal pressure occurred before the kidneys excreted any appreciable quantity of fluid. Excretion of urine increased according to an osmotic diuresis type.



Drop of cerebrospinal fluid pressure in female patient K. upon infusion of a 30% solution of the urea preparation. 1) Infusion of 20 g of urea; II) infusion of 60 g of urea. Arrows denote start and end of infusion of the preparation.

The characteristics of excretion of Na, K, and urea are shown in the table.

Our results confirm the data on the difference in distribution of urea between the blood and cerebrospinal fluid [3-6, 8, 9]; however, they do not help to explain the therapeutic effect of the preparation just by the increase of the osmotic concentration of the blood in comparison with that of the brain and cerebrospinal fluid. The physiological mechanism of the effect of urea on the aqueous phases of an organism apparently lies in the following: urea freely penetrates into the inter- and intracellular aqueous phase of various organs and tissues of the body except those bounded by barriers (e.g., blood-brain) which preserve the constancy of the chemical composition and concentration of the specialized internal environment. Urea, freely penetrating into the aqueous phase of the cells, does not become an osmotically active substance for them. The urea concentration inside and outside the cell is the same, an osmotic gradient is not created, and dehydration of the cell does not occur. The osmotic effect of urea extends only to the barrier-bounded tissues into which it does not penetrate.

Despite hydremia after the infusion of the first portions of the preparation, the concentration of Na and K in the serum dropped little in comparison with the hydremia observed. Consequently, dilution occurs not by water but by a salt solution close in composition to the plasma. Since in the intercellular fluid (in contrast to the cells) the dominating cation is Na, we assume that urea has an effect on the proteins and mucopolysaccharides of the intercellular substance. However, hydremia is in part caused by the uptake of water without sodium

salts into the blood. The osmolar concentration of the blood serum after infusion of 15 g of urea does not change, whereas the Na content drops 3 m-eqv/liter. These facts can be explained only by the uptake of osmotically free water into the blood. Nevertheless, this effect cannot be called osmotic since the osmolar concentration of the blood does not increase; the uptake of salt-free water into the blood is probably caused by the effect of urea on the tissue colloids.

The conclusion about the possibility of a nonosmotic effect of urea is also confirmed by the fact that the drop of cerebrospinal fluid pressure begins after the infusion of the first portions of urea when there has still been no substantial increase of the osmotic concentration of the blood exceeding the limits of normal physiological variations.

The presence of an osmotic gradient between the cerebrospinal fluid and the blood after the infusion of the total therapeutic dose of the preparation, of course, creates the conditions for the uptake into the blood of the osmotically free water from the fluid on the other side of the barrier with a lower osmotic pressure. The quantity of water which can enter the blood over the gradient is determined by the difference in the osmotic concentration of the cerebrospinal fluid (or of the brain) and blood; as soon as this water enters the blood the osmotic concentration of the cerebrospinal fluid rises to the osmotic concentration of the blood and movement of the water stops.

The hypothesis about the osmotic effect of urea on lowering intracranial hypertension as the only mechanism of its effect also meets theoretical objection. According to current notions edema is caused by primary retention of Na salts in the body tissues. The successful use of urea in edema and swelling of the brain should evidently be due to the fact that the preparation lowers the quantity of edematous fluid in the brain tissues, i.e., promotes excretion of Na and water. Only water and not salts can pass along the osmotic gradient through the semipermeable membrane. If urea enhances the excretion of both Na and water from the edematous tissue, the effect cannot be called osmotic.

Thus, the results obtained indicate that the effect of urea on intracranial hypertension is associated with its effect on the redistribution of the liquid phases of the body. Water and Na salts are taken up into the blood from the tissue under the effect of the preparation, which leads to hydremia. A drop of cerebrospinal fluid pressure ensues after the infusion of even the first portions of the preparation when the osmotic concentration of the blood has still not increased. Consequently, the decrease of the cerebrospinal fluid pressure and of the volume of the brain under the action of the urea preparation is caused both by its osmotic and nonosmotic effect.

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