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Effects of Intravenously Administered Hypertonic Urea Solution*

By

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With 3 Figures

Introduction

In the past 30 years, neurological and neurosurgical clinics have made frequent use of intravenously administered hypertonic urea solutions to lower intracranial pressure. Many papers have been published on this subject (e. g. *Javid* and *Settlage*, 1956; *Javid*, 1958[1,2], 1961; *Stubbs* and *Pennybacker*, 1960; *Langfitt*, 1961; *Beks* and *v. d. Kuy*, 1962; *Nemetschek-Gansler*, *Loew* and *Plogsties*, 1964). Administration of such solutions is believed to increase the osmolarity in the blood, thus dehydrating the tissues, and particularly the brain. It is believed that the brain in particular is dehydrated as a result of the activity of the blood-brain barrier. Also, urea is believed to diffuse more slowly to the central nervous system than other intravenously injected hypertonic solutions, e. g. sodium chloride, glucose, mannitol and sorbitol.

Some effects of intravenously administered hypertonic urea solutions were studied in 12 patients with increased intracranial pressure caused by an expanding process, who during a craniotomy received a hypertonic urea solution of the following composition:

urea "pro analyse"	300 g
sterile invert sugar solution (50 g/100 ml)	200 ml
sterile propylene glycol with, per 100 ml: 6,5 g methylparaben, 3,5 g propylparaben	7 ml
NaOH 4 N up to p_H 7,0	
sterile pyrogen-free water up to 1000 ml.	

The solution was prepared without heating lest the urea should be decomposed. After dissolving, the p_H of the fluid was adjusted to 7 with

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the aid of NaOH. The solution was then submitted to aseptic bacterial filtration (Seitz bacterial filter). The paraben mixture was added as preservative (*v. d. Kuy* and *Huizinga*, 1961). The patients received 1 g urea per kg body weigth.

Method and Material

In this group of 12 patients, the following preoperative *serum* values were determined: K, Na, Cl, urea, Ca, PO_4, glucose, total protein, haemoglobin, haematocrit and osmolarity. Four of these patients, moreover, were submitted to determinations of Ca, glucose, urea, total protein and osmolarity in the *cerebrospinal fluid* (C. S. F.).

After opening the cranium, the surgeon obtained biopsy specimens from the temporal muscle and from the cerebral cortex in the vicinity of the pathological tissue, for tissue analysis. The urea solution was then administered intravenously, evenly distributed over 20 minutes (1 g/kg body weight). After this the abovementioned substances in the serum and the C. S. F. were again determined; the urine production over this period was measured, and the quantity of urea excreted in the urine during this period was determined.

Muscle and cerebral tissue specimens were again excised and analysed. The entire procedure was repeated before the dura mater was closed, about 3 hours after starting the operation. After another 3 hours (i. e. 6 hours after starting the operation), the abovementioned determinations in serum and C. S. F. were repeated.

Sodium and potassium determinations were made with the aid of a flame photometer; the chloride was determined coulometrically; the urea by the method of Chaney and Marbach; the calcium titrimetrically with complexon; the phosphate according to Taussky and Shorr; the glucose according to Hagedorn and Jensen; the total protein by the biuret method; the Hb value by the Hi-CN method; and the osmolarity by the freezing-point lowering method.

Results

Like *Mason* and *Raaf* (1961) and *Gilboe* and *Javid* (1963) we found that administration of urea solution is not followed by any distinct changes in serum Na, K and Cl values (Table 1).

Table 1. *Serumconcentrations at different times (before and after a hypertonic ureasolution had been given intravenously)*

		osmolarity m osm	urea mg/100 ml	total protein g/100 ml	Ca mg/100 ml	PO_4 mg/100 ml	K mEq/l	Na mEq/l	Cl mEq/l	creatinine mg/100 ml
pat.	1 before urea infusion	292	23.3	7.1	10.0	3.3	4.1	141	97.0	—
	at the end of urea infusion	324	111.7	5.9	9.3	4.4	4.2	141	94.0	—
	3 hours after the end of urea infusion	308	80.3	6.5	11.1	5.7	4.1	141	93.0	—

	osmolarity m osm	urea mg/100 ml	total protein g/100 ml	Ca mg/100 ml	PO_4 mg/100 ml	K mEq/l	Na mEq/l	Cl mEq/l	creatinine mg/100 ml
pat. 2 before urea infusion	292	16.2	7.1	9.3	3.4	4.9	131	88.3	0.83
at the end of urea infusion	384	175.9	5.7	8.4	3.9	4.7	140	91.6	0.97
3 hours after the end of urea infusion	326	117.3	6.2	10.6	4.6	4.0	140	94.0	0.85
pat. 4 before urea infusion	—	27.4	6.5	8.9	4.6	4.9	—	—	—
at the end of urea infusion	—	182.8	5.0	7.6	4.5	4.9	—	—	—
3 hours after the end of urea infusion	—	140.8	6.4	9.9	5.1	4.1	—	—	—
pat. 5 before urea infusion	313	35.8	8.3	10.1	4.8	5.2	136	—	—
at the end of urea infusion	358	103.0	5.9	9.5	4.2	5.2	132	—	—
3 hours after the end of urea infusion	330	—	7.5	10.8	5.2	4.7	136	—	—
pat. 7 before urea infusion	—	62.2	7.5	—	4.3	4.2	145	109.2	1.24
at the end of urea infusion	—	231.8	5.4	—	4.4	3.9	142	109.4	1.36
3 hours after the end of urea infusion	—	210.0	6.8	10.3	4.8	4.1	152	114.5	—
pat. 8 before urea infusion	303	35.9	7.5	8.9	3.8	4.0	136	99.0	0.80
at the end of urea infusion	351	231.8	5.4	7.7	4.1	4.3	124	92.0	0.83
6 hours after the beginning urea infusion	318	130.3	6.7	10.0	2.9	4.7	135	93.0	0.80
pat. 10 before urea infusion	310	34.8	7.6	—	4.2	4.3	144	101.0	—
at the end of urea infusion	346	132.3	5.6	—	5.3	4.1	137	103.0	—
6 hours after the beginning urea infusion	324	107.1	7.3	—	3.4	4.2	146	102.0	—
pat. 11 before urea infusion	300	57.5	6.5	9.6	5.6	5.4	139	103.0	—
at the end of urea infusion	351	206.3	5.1	8.3	5.6	4.9	135	100.0	—
3 hours after the end of urea infusion	331	170.7	6.6	8.9	6.0	4.6	140	101.0	—
pat. 12 before urea infusion	308	31.7	—	10.2	3.4	4.4	139	104.0	—
at the end of urea infusion	341	164.0	—	8.2	2.8	4.4	135	97.0	—
3 hours after the end of urea infusion	327	126.7	—	10.2	2.9	4.3	148	95.0	—
6 hours after the beginning urea infusion	319	105.9	—	10.4	3.4	5.8	141	96.0	—

There was a slight decrease in these values during the infusion, but return to the initial values took place after about 3 hours. The decrease in Ca considerably exceeded that in K, Na and Cl. The total protein value of the serum also showed a pronounced decrease (Fig. 1).

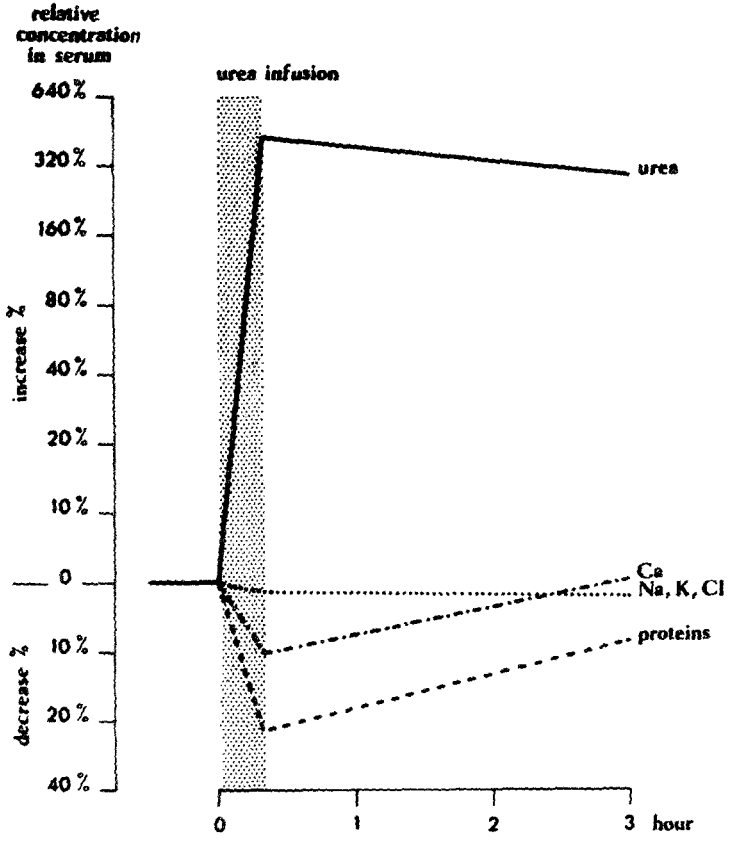

Fig. 1. Relative concentrations of urea, Na, K, Cl, Ca, and proteins in *serum* before and after urea infusion. Determinations at 0, 1/3, and 3 hour

Prior to the urea infusion the urea concentrations in the muscle and in the brain, expressed per unit of weight, was found to exceed the urea concentrations in C. S. F. and serum; the C. S. F. concentration practically corresponded with the serum concentration (Fig. 2). In two patients the urea excretion was measured during 24 hours a ter urea administration; the patients received 75 and 80 g urea, respectively. Table 2 shows that about 70% of the urea administered was excreted within those 24 hours.

Discussion

For the sake of convenience we assume that the "average" patient has a body weight of 60 kg. The extracellular fluid in such a patient constitutes 15% of the body weight, i. e. 9 l. The total quantity of body fluid is 36 l (i. e. 62% of the body weight) (*Gorter* and *de Graaff*, 1955). These values are

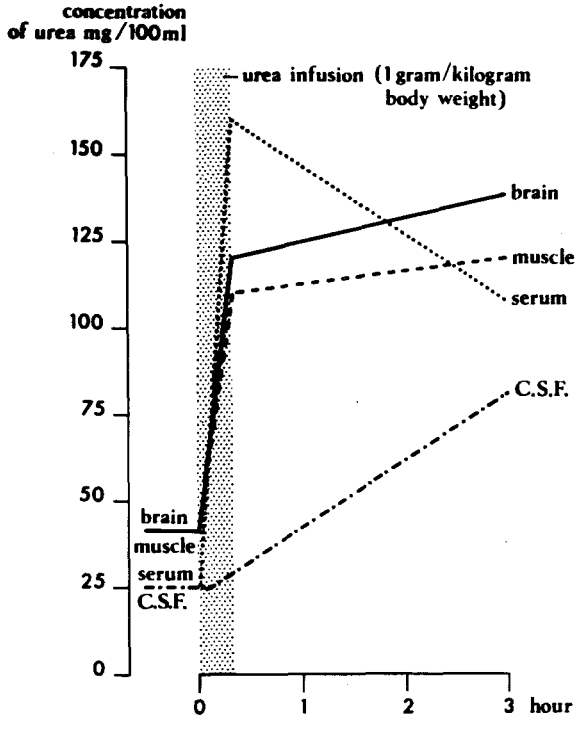

Fig. 2. Concentrations of urea in serum, brain tissue, muscle, and C. S. F. before and after urea infusion. Determinations at 0, 1/3, and 3 hour

of course not absolute but variable; moreover, they depend on the patient's fat distribution and state of hydration.

Should the values for the "average" human be taken as a starting point, we might make the following calculation. If urea were administered at a dosage 1 g/kg body weight, and if this would be confined to the extracellular

Table 2. *Amounts of urea in grams, excreted in successive intervals*

Patient	0 min until 20 min	20 min until 3 h	3 h until 6 h	6 h until 24 h	cumulated excretion
5	2.2	7.7	9.0	36.4	55.3
10	0.15	18.3	12.0	25.9	56.3

fluid, then this would result in a rise of the urea concentration in this compartment of $\frac{60 \times 1}{9}$, or 667 mg/100 ml. Should the urea administered be distributed throughout the total body fluid, the rise in concentration would be $\frac{60 \times 1}{36}$, or 167 mg/100 ml.

The values which we obtained (Table 1) show that the urea administered is localized in both the intracellular and the extracellular fluid even after only 20 minutes. During and after the urea infusion the total protein value of the serum diminishes. The diminution amounts to 17–29% (Table 1).

Table 3

	alterations of the serumosmolarity (milli-osmol/l), calculated according to the changes in the serumconcentrations of K, Na and Cl				difference between measured serumosmolarity and osmolarity, calculated from the changes in serumconcentrations of urea and glucose			
	pat. 1	pat. 8	pat. 10	pat. 12	pat. 1	pat. 8	pat. 10	pat. 12
during administration of urea	— 3	— 19	— 5	— 11	+ 20	+ 8	+ 13	+ 6
3 hours after administration of urea	- 1				— 7.8			
6 hours after administration of urea		+ 12	+ 8	+ 6		— 12	— 14	— 8

If the diminution of the total protein value of the serum can be considered a yardstick of the increase in extracellular fluid as a result of urea administration, then the above means that the extracellular fluid in a patient of 60 kg increases by 1.5 to 2.6 l. This quantity of fluid is withdrawn from 60 kg — 9 kg (extracellular fluid) = 51 kg. This means that 30–50 ml fluid per kg has been withdrawn from the intracellular volume.

The average brain weight is 1250–1400 g and 40–70 ml fluid has consequently been withdrawn from the brain. Comparing the serum osmolarity measured with the osmolarity calculated on the basis of changes in the serum urea and serum glucose concentrations, we find that during urea infusion the osmolarity measured exceeds that calculated from the rise in urea and glucose concentrations (Table 3). Normal values and our measurements scatter far too much to warrant any definite conclusions. They might bear a possible indication that, under the influence of urea infusion, particles are dissolved which make the serum osmolarity higher than it would be according to the rise resulting from the quantity of urea and glucose administered. These low-molecular particles do not belong to the Na, K and Cl. After urea infusion, more "particles" again disappear from the extracellular fluid than would be explained by the decrease in urea and glucose concentrations.

This could be based on displacement of organic substances from the intracellular to the extracellular localization.

The decrease in electrolytes (if any) is considerably less pronounced than the decrease in total protein value of the serum. This indicates that the electrolytes in the extracellular fluid increase during urea infusion. This must probably be explained by a displacement from intracellular to extracellular. This view is supported by the fact that during urea infusion the urea invades the cells and thus disturbs the intracellular osmolarity relations. The fact that the decrease in serum Ca considerably exceeds the decrease in serum Na, K and Cl values, could possibly be dependent on a less rapid mobilization of the Ca.

Table 4

Patient	amounts of urea in grams, excreted from 0 until 20 min	volumes of urine in ml from 0 until 20 min
2	3.66	362
3	6.60	230
4	2.40	32
5	2.22	152
6	4.36	194
7	1.77	60
9	2.90	180
10	0.15	12
11	2.68	100

During urea infusion, the serum urea concentration rises, and so does the osmolarity. This serum hypertonia persists until the serum urea concentration and the urea concentration in the brain tissue are equalized. The brain cell continues to dehydrate until that time, and the urea concentration in the brain tissue consequently rises.

Table 4 demonstrates that a certain degree of osmodiuresis occurs during urea infusion, although *Javid* and *Anderson* (1959) deny this. In 6 of our patients the urea excretion and production of urine were found to be 5–10 times as high as normal values of 20–30 ml per 20 min. In 2 patients (No. 4 and No. 7), there was only a slight increase in diuresis.

One patient (No. 10) showed markedly lower diuresis and excretion than the others.

The dehydrating effect of intravenously administered hypertonic urea solutions is, apart from this osmodiuresis, brought about by the direct osmotic action of the high urea concentration of the blood upon the brain (and other) tissues.

It has been established that the increase in urea concentration in the muscles and in the brain following urea infusion are of the same order of magnitude and have a similar time course (Fig. 2). This would seem to warrant the conclusion that the blood-brain barrier does not have an important role in the mechanism by which urea dehydrates the brain

tissue. Contrastingly, such an influence may be brought about by the other barriers, *viz.* the blood-C. S. F. and brain-C. S. F. barriers, as the rise in the osmolarity and in the urea concentration of the C. S. F. occurs considerably later than in the serum (Fig. 3).

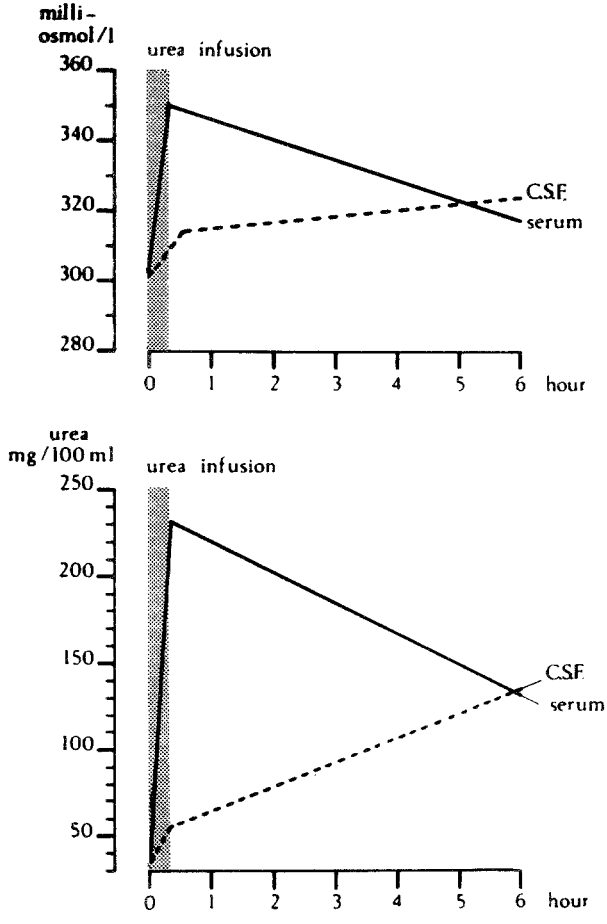

Fig. 3. Alterations in the osmolarity and the concentrations of urea in serum and C. S. F. Determinations at 0, 1/3, 1, 4½, and 6 hour

Summary and Conclusions

In 12 patients with increased intracranial pressure, caused by an expanding process, a hypertonic urea solution was intravenously administered during a craniotomy. At different times before, during and after the operation, the electrolytes, urea, glucose and total protein values were determined in various body fluids and tissues.

This study disclosed that the urea administered was distributed through both the intracellular and the extracellular space after 20 minutes. The values of the electrolytes, except the calcium, in the extracellular fluid remained constant after administration of the urea solution; the total protein value, however, showed a considerable decrease.

It was established that the blood-brain barrier plays no appreciable role in the mechanism of action of hypertonic urea solutions in dehydrating the brain tissue; the blood-C. S. F. and brain-C. S. F. barriers may do.

Zusammenfassung

Bei 12 Patienten mit intrakranieller Drucksteigerung infolge eines raumbeengenden Prozesses wurde Harnstofflösung intravenös während der Schädeleröffnung gegeben. Zu verschiedenen Zeitpunkten vor, während und nach der Operation wurden Elektrolyte, Harnstoff, Glukose und Gesamteiweiß quantitativ bestimmt und zwar sowohl in verschiedenen Körperflüssigkeiten wie auch in Geweben.

Die Untersuchungen ergaben, daß der verabfolgte Harnstoff in 20 Minuten sich sowohl auf den intrazellulären, wie den extrazellulären Raum verteilt hat. Die Elektrolytwerte, mit Ausnahme von Kalzium, blieben nach der Harnstoffinfusion in den extrazellulären Flüssigkeiten unverändert, der Gesamteiweißwert nahm dagegen beträchtlich ab.

Es wurde festgestellt, daß die Bluthirnschranke keine wesentliche Rolle für die entwässernde Wirkung des Harnstoffes auf das Hirngewebe spielt, während die Blut-Liquor-Schranke und die Hirn-Liquor-Schranke vielleicht von Bedeutung sind.

Résumé

Lors d'une craniotomie, une solution d'urée hypertonique fut administrée par voie intraveineuse chez 12 patients présentant une pression intracrânienne grandissante causée par une expansion de l'apophyse. De temps en temps, avant, pendant et après l'opération, les valeurs des électrolytes, de l'urée, du glucose et de la protéïne totale étaient déterminées dans les différents liquides et tissus du corps.

Cette étude démontra que l'urée administrée était distribuée à travers l'espace intra et extracellulaire au bout de 20 minutes. Les valeurs des électrolytes, excepté le calcium, demeurèrent constantes dans le liquide extracellulaire après l'administration de la solution d'urée ; la valeur de la protéïne totale, pourtant, montrait une baisse considérable.

Il fut établi que la barrière hémato-encéphalique ne joue aucun rôle appréciable dans le mécanisme d'action des solutions d'urée hypertonique dans la déshydratation du tissu cérébral ; les barrières sang-liquide céphalo-rachidien et cerveau-liquide céphalo-rachidien, peut-être.

Riassunto

In 12 pazienti con ipertensione endocranica, causata da un processo espansivo, è stata somministrata durante la craniotomia dell'urea in soluzione ipertonica per via venosa. A diversi tempi prima, durante e dopo l'intervento, sono stati dosati gli elettroliti, l'urea, il glucosio e le proteine totali in vari fluidi e tessuti corporei. Queste ricerche hanno evidenziato che l'urea viene distribuita tra spazio intracellulare ed extracellulare in 20 minuti. I livelli

degli elettroliti, eccetto il calcio, rimangono costanti nel liquido extracellulare dopo la somministrazione di urea, i valori della proteinemia totali invece mostrano una notevole diminuizione.

E' stato stabilito che la barriera emato-cerebrale non gioca alcun ruolo apprezzabile nel meccanismo d'azione dell'urea ipertonica nel disidratare il tessuto cerebrale; un ruolo importante potrebbe essere invece giocato dalla barriera emato-liquorale e tra liquor e sistema nervoso.

Resumen

Después de una craniectomía se administró una solución de urea hipertónica por vía intravenosa a 12 pacientes que presentaban una presión intracraneal creciente a causa de una exposición de la hipófisis. Periódicamente, antes, durante y después de la operación se determinaron los valores de los electrolitos, de la urea, de la glucosa y de las proteinas totales en los diferentes líquidos y tejidos del organismo.

Este estudio demostró que la urea administrada se distribuia a través del espacio intra y extracelular al cabo de 20 minutos. Los valores de los electrolitos, excepto el calcio, permanecieron constantes en el líquido extracelular después de la administración de la solución de urea; el valor de las proteinas totales, sin embargo, mostró un descenso considerable.

Se concluyó que la barrera hemato-encefálica no juega ningún papel apreciable en los mecanismos de acción de las soluciones de urea hipertónica en la deshidratación del tejido cerebral; tal vez lo juegue en las barreras sangre-líquido cefalo-raquídeo y cerebro-líquido cefalo-raquídeo.

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