Low serum urea level in dehydrated patients with central diabetes insipidus

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Dehydrated patients usually present with an elevated serum urea level, owing in part to increased renal reabsorption of urea mediated by antidiuretic hormone (ADH). We carried out a study to examine whether, during dehydration, the variations in the serum urea level could discriminate patients with central diabetes insipidus (CDI) from those with dehydration not due to CDI. We studied retrospectively 27 episodes of dehydration in 23 patients with CDI and 14 episodes in 14 patients without CDI. The mean serum urea level was 2.9 mmol/L in the CDI group and 15.4 mmol/L in the patients without CDI ($p < 0.001$); the mean serum sodium level was 155 mmol/L in both groups. All the patients with CDI had a sodium/urea ratio greater than 24.2, whereas the ratio was less than 21.7 in all the patients without CDI. In the patients with CDI a positive correlation was found between the magnitude of diuresis and the percentage decrease in the serum urea level compared with the level before dehydration ($p < 0.001$). In the patients with CDI the serum urea level returned to the level before dehydration after the administration of vasopressin; a striking increase in the clearance of urea, which exceeded the creatinine clearance, was observed during dehydration in the three patients in whom clearance studies were done. The results suggest that serum urea values can be used to distinguish patients dehydrated because of CDI from those with hypertonic dehydration but without ADH deficiency and that during dehydration the net reabsorption of urea is dependent on the renal action of ADH.

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Le malade déshydraté présente habituellement une augmentation de l'urée sanguine, du fait notamment de la stimulation de la réabsorption de celle-ci par l'hormone antidiurétique (HAD). Notre propos est de savoir si, dans le cours d'une déshydratation, l'étude des variations de l'urée sanguine permettra de distinguer les sujets atteints de diabète insipide central (DIC) de ceux qui sont déshydratés pour d'autres raisons. Nous étudions rétrospectivement 27 épisodes de déshydratation chez 23 porteurs de DIC et 14 épisodes chez 14 non porteurs de DIC. La concentration moyenne de l'urée sanguine est de 2,9 mmol/L chez les premiers et 15,4 mmol/L chez les seconds ($p < 0,001$); la natrémie moyenne est de 155 mmol/L dans les deux groupes. Le rapport sodium/urée dépasse 24,2 chez tous les porteurs de DIC mais reste inférieur à 21,7 chez tous les non porteurs. Chez les premiers on observe une corrélation positive entre la diurèse et le pourcentage d'abaissement de l'urée sanguine relativement à son chiffre antérieur à l'épisode de déshydratation ($p < 0,001$); ils retrouvent ce chiffre grâce à l'administration de vasopressine. Chez les trois malades où il a été suivi, le coefficient d'épuration de l'urée avait augmenté de façon remarquable pendant la déshydratation et dépassé celui de la créatinine. Nos résultats font penser que les chiffres de l'urée sanguine permettent de départager les sujets déshydratés par DIC et ceux qui sont en déshydratation hypertonique sans carence en HAD et qu'en cours de déshydratation la réabsorption nette de l'urée est régie par l'action de l'HAD sur le rein.

Dehydrated patients usually excrete a low volume of concentrated urine and have high serum urea levels. These phenomena result from net reabsorption of water and urea along the nephron, owing at least in part to the

action of antidiuretic hormone (ADH).[1] We noted that the serum urea level in patients with central diabetes insipidus (CDI) remained low, despite severe dehydration. To examine the possibility that urea levels could be used to monitor the action of ADH on the nephron, we studied retrospectively the changes in the serum urea concentration during episodes of dehydration in patients with and without CDI. As well, we studied prospectively the effect of CDI on urea and creatinine clearance in patients investigated before and after the onset of CDI and after pharmacologic replacement of ADH.

Methods

We reviewed 138 patient records at Notre-Dame Hospital, Montreal, coded with the diagnosis of "hypertonic dehydration" because of CDI (in 36 cases) or other causes (in 102). All 138 patients had been seen between 1979 and 1985. Records were selected for study if the serum sodium concentration had been 147 mmol/L or greater, the measured or calculated plasma osmolality greater than 295 mOsm/kg of water and renal function normal during normal hydration. In addition, we retained a record for study only if a serum urea determination had been done on the specimen used for the sodium measurement and if a measured or calculated urine osmolality value for the same period was available.

Levels of sodium, urea and creatinine in serum and urine had been measured by means of conventional autoanalyser techniques. Plasma and urine osmolality had been measured with a standard cryoscopic procedure. When not measured, urine osmolality was estimated by dividing the urine specific gravity increment by 0.000263,[2] and plasma osmolality was calculated with the formula (2 × sodium level) + glucose level + urea level (expressed in mmol/L).

CDI was diagnosed if the plasma osmolality exceeded 295 mOsm/kg of water and if the urine osmolality was less than 200 mOsm/kg of water and rose by more than 9% when vasopressin tannate in oil (5 units given intramuscularly) was administered.[3] Subjects dehydrated from causes other than ADH deficiency or renal resistance to ADH had a urine osmolality greater than 300 mOsm/kg of water. The serum cortisol level was normal in all the patients studied, and no patient had nephrogenic diabetes insipidus.[4] No patient had evidence of abnormal urea production (e.g., severe malnutrition, hepatic failure, bleeding in the gastrointestinal tract, severe proteolysis or parenteral nutrition).

We measured the urea and creatinine clearance in three other, well-nourished patients with permanent CDI since neurosurgery. The measurements were obtained before surgery (with a 24-hour urine collection), during the dehydration episode (with a 2-hour urine collection) and after administration of vasopressin (with a 24-hour urine collection); the urine specimens were obtained by spontaneous voiding. Blood samples were taken after each period of urine collection.

We performed statistical analyses using paired and unpaired *t*-tests. Linear regression analyses were done and correlation coefficients determined by means of the least-squares method.

Results

Of the 138 records 37 were retained for study. The clinical characteristics of the 37 patients are shown in Table I. There were 27 episodes of dehydration in 23 patients with CDI and 14 episodes in 14 patients without CDI. CDI occurred after neurosurgery in 18 patients, was idiopathic in 3, occurred after skull fracture in 1 and was associated with Hand-Schüller-Christian disease in 1. The diagnoses in the patients without CDI were severe infection (in four), stroke (in three), advanced cancer (in three) and, in one patient each, hyperosmolar coma, intestinal obstruction, adipsia and hip fracture.

The serum creatinine and urea levels measured during normal hydration were similar in the two groups (Table I). As expected, the patients with hypernatremia not due to CDI were older than those with CDI. Dehydration led to a similar degree of hypernatremia in the two groups. However, during episodes of dehydration all the pa-

Table I — Clinical characteristics of patients with and without central diabetes insipidus (CDI) selected because of "hypertonic dehydration"

Characteristic	Patients with CDI (n = 23)	Patients without CDI (n = 14)	p*
Mean age (and standard deviation [SD]), yr	37 (17.3)	61 (15.3)	< 0.001
Sex, no. of patients			
Male	11	10	
Female	12	4	
No. of episodes of dehydration	27	14	
Renal function indices during normal hydration			
Mean serum urea level (and SD), mmol/L	4.6 (1.5)	5.4 (2.0)	NS
Mean serum creatinine level (and SD), μmol/L	86 (17)	95 (19)	NS

*NS = not statistically significant.

tients with CDI had low serum urea levels and a high sodium/urea ratio; as well, the urine osmolality was low and increased significantly after administration of vasopressin ($p < 0.001$) (Table II). In contrast, the patients without CDI had a high serum urea level, a low sodium/urea ratio and a high urine osmolality.

All the patients with CDI had a serum urea level less than 4.6 mmol/L, except one patient, whose level was 6.0 mmol/L. In contrast, all the patients without CDI had a serum urea level greater than 7.0 mmol/L. All the patients with CDI had a sodium/urea ratio greater than 24.2, whereas the ratio was less than 21.7 in all the patients without CDI.

To examine whether the difference in age between the patients with CDI and those without CDI could be responsible for the difference in the change in the serum urea level after dehydration, we compared the data for a subgroup of seven patients with CDI who were older than 50 years (mean age 59 years) and who had had 10 episodes of dehydration with the data for the patients without CDI. The mean serum urea level of the patients with CDI (3.4 mmol/L) was significantly lower than that of the patients without CDI (15.4 mmol/L) ($p < 0.005$), in spite of a similar degree of hypernatremia (mean serum sodium levels 157 and 155 mmol/L respectively) and comparable renal function during normal hydration (mean serum creatinine levels 85 and 98 μmol/L respectively).

The urine flow rate was reliably measured in 22 of the 27 dehydration episodes due to CDI. For the 22 episodes there was a significant correlation between diuresis and the magnitude of the decrease in the serum urea level during the 24 hours before the administration of vasopressin ($r = 0.70$, $p < 0.001$) (Fig. 1). Furthermore, a negative correlation was found between the plasma sodium and urea levels during dehydration ($r = -0.407$, $p < 0.03$).

Fig. 2 shows the effect 24 hours later on the serum sodium and urea levels of treatment with vasopressin and hypotonic fluids in the 23 episodes of dehydration due to CDI for which these data were available. The mean serum sodium level was 140 mmol/L before the onset of CDI and rose to 154 mmol/L during dehydration ($p < 0.001$); it decreased to 143 mmol/L after treatment, significantly higher than the level before the onset of CDI ($p < 0.05$). The corresponding values for the mean serum urea level were 4.0, 2.9 ($p < 0.001$) and 4.0 mmol/L.

The results of studies of urea and creatinine clearance in the three patients studied prospectively are shown in Table III. During the dehydration episode each patient showed a striking increase in

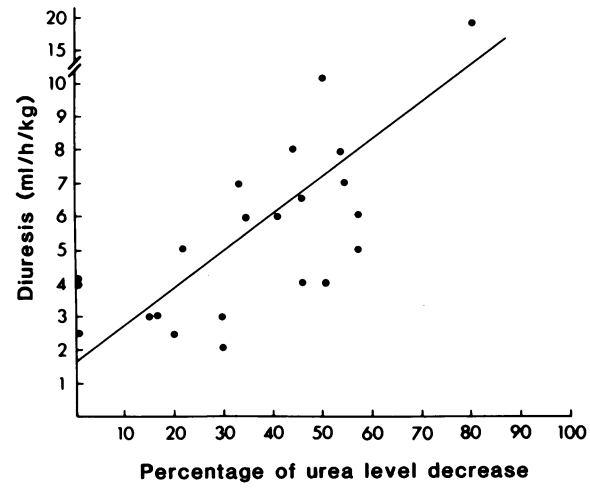


Fig. 1 — Relation between diuresis and percentage decrease in serum urea level compared with level before onset of central diabetes insipidus (CDI) in 22 episodes of dehydration due to CDI.

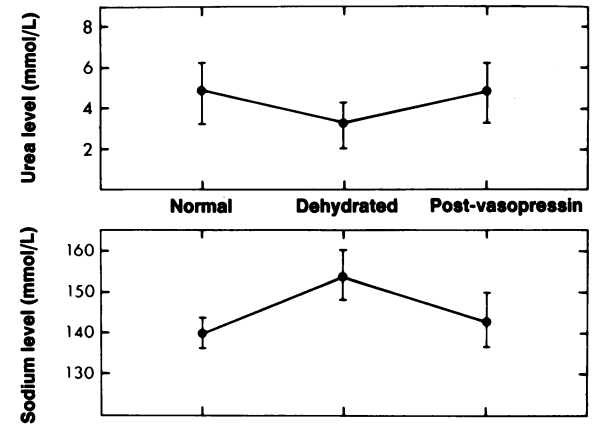


Fig. 2 — Mean serum levels of sodium and urea before onset of CDI, during dehydration and after administration of vasopressin in 23 episodes of dehydration. Vertical bars represent standard deviation.

Table II — Renal function during dehydration in the two groups

Renal function indices	Mean (and SD) Patients with CDI	Patients without CDI	p
Serum sodium level, mmol/L	155 (4.3)	155 (4.6)	NS
Serum urea level, mmol/L	2.9 (1.2)	15.4 (10.3)	< 0.001
Serum sodium/urea ratio	67 (42.8)	14 (5.9)	< 0.001
Urine osmolality, mOsm/kg of water			
During dehydration	66 (47)	956 (228)	< 0.001
After administration of antidiuretic hormone	568 (241)	–	–

the clearance of urea, but the value returned to the normal range after replacement of ADH.

Discussion

Our results show that during dehydration, patients with CDI can be distinguished from those without CDI by their lower serum urea values. Furthermore, our patients with CDI had lower serum urea values during dehydration than before dehydration. The reverse was observed in our patients without CDI. The opposite changes in the serum urea level during dehydration in the two groups may be explained by the groups' different ADH and diuretic status. Indeed, in our patients with CDI who were polyuric the urea clearance significantly increased and even exceeded the creatinine clearance. The reverse is known to occur in dehydrated patients without CDI.[5] In our patients with CDI the increase in the serum urea values with vasopressin therapy provides strong evidence that polyuria and ADH deficiency were indeed the cause of the low serum urea levels.

In healthy people the clearance of urea is around 60% of that of inulin (or creatinine), so that there is a net reabsorption of urea.[6,7] It is usually accepted that urea reabsorption occurs mainly in the proximal tubules, at a relatively fixed level.[6] Furthermore, urea is reabsorbed in the distal nephron in a manner related to urine flow.[1,6] During dehydration the increment in the urine/plasma urea ratio due to reabsorption of water as well as the ADH-induced increase in permeability of the distal nephron to urea synergistically favour net urea reabsorption.[8,9] Consequently, under conditions of net water reabsorption and low urine flow the clearance of urea falls below 40% of the inulin clearance.[5] This phenomenon results in an increase in the serum urea level, as seen in our patients without CDI during dehydration.

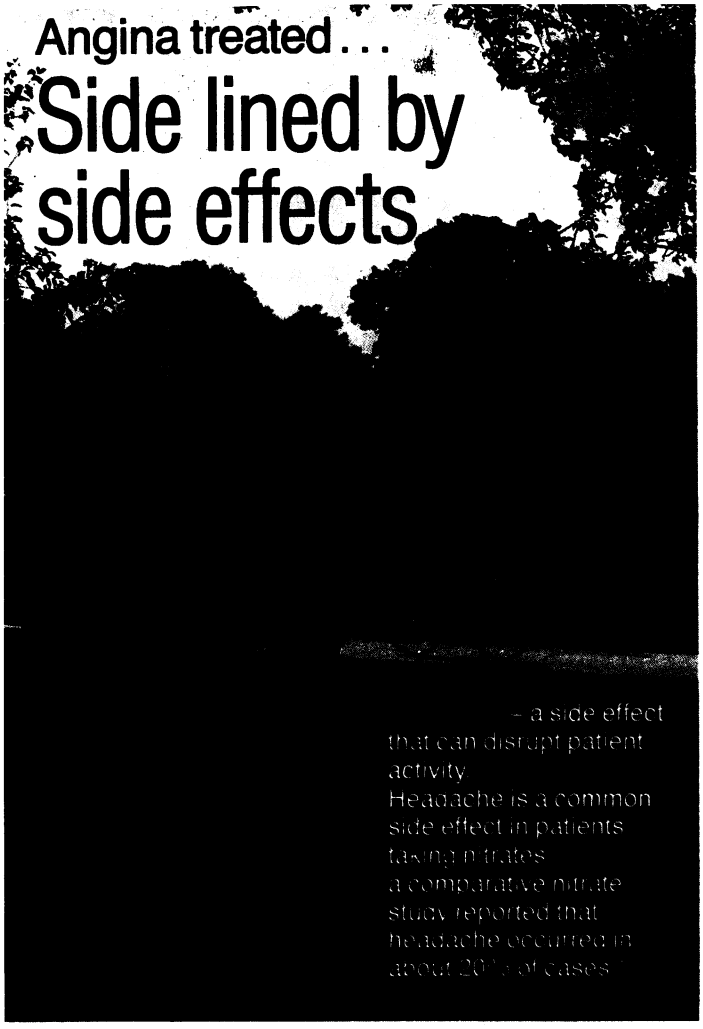
During maximal water diuresis the urea clearance usually rises to 65% to 70% of the creatinine clearance.[6] If this situation is prolonged a modest fall in the serum urea level is expected to occur. In our patients with dehydration due to CDI the mean decrease in the serum urea level was relatively large (40%), and a decrease as large as 60% to 80% was observed in patients with severe CDI and a high urine flow rate. These observations challenge the conventional view and suggest that in dehydrated people urea reabsorption occurs mostly in distal ADH-sensitive segments of the nephron and is greatly influenced by the presence or absence of ADH.

Iatrogenic volume expansion or osmotic diuresis (due to rapid intravenous infusion of 5% dextrose in water) may have contributed to the increased urea clearance in our patients with the highest urea clearances and the lowest serum urea values. However, we did not document any glycosuria in our patients, and with the use of vasopressin vigorous intravenous rehydration was never necessary. The negative correlation found between the serum sodium and urea levels also argues against the possibility of volume overexpansion. Furthermore, in our clearance study urea clearance rose to very high levels during dehydration. Since the clearance studies during dehydration were done after the first 24 hours of CDI, it seems unlikely that excretion of urea out of the renal medulla played an important role in the increase of the urea clearance above that of creatinine.

Although the serum urea and creatinine levels were similar in the patients with CDI and those without CDI after rehydration, there may have been a difference in the degree of dehydration and in renal function between the two groups, since the patients without CDI were significantly older than those with CDI. Indeed, even though the serum creatinine level was similar in the two groups before dehydration, the patients with CDI probably had a larger muscle mass and greater creatinine clearance than those without CDI. It is unlikely, however, that this factor played a significant role in the fall in the serum urea level during dehydration episodes. On the contrary, it would only lead

Table III — Results of clearance studies before the onset of CDI, during dehydration and after administration of vasopressin in three patients with CDI after neurosurgery

Patient no.; time	Weight, kg	Serum sodium level, mmol/L	Serum urea level, mmol/L	Serum creatinine level, μmol/L	Urea clearance × 100 ÷ creatinine clearance % (ml/s)	
1						
Before surgery	57.0	141	3.2	62	47	(0.8/1.7)
During dehydration	55.1	148	0.4	62	165	(3.3/2.0)
After rehydration	56.5	138	1.8	62	50	(0.9/1.8)
2						
Before surgery	62.0	141	3.2	88	60	(0.6/1.0)
During dehydration	60.5	147	1.4	97	110	(1.1/1.0)
After rehydration	61.8	139	3.2	88	60	(0.6/1.0)
3						
Before surgery	61.2	139	4.3	71	56	(0.9/1.6)
During dehydration	58.9	147	3.2	71	128	(3.2/2.5)
After rehydration	61.0	138	4.3	62	66	(1.2/1.8)



to a greater increase in the serum urea level during dehydration due to CDI. It is also unlikely that differences in protein intake or urea production rate were responsible for our findings,[10] since the serum urea level decreased rapidly with CDI and was fully corrected by replacement of ADH, reaching values within the normal range in both groups. Furthermore, 18 of the patients with CDI were well-nourished neurosurgical patients, and their CDI had begun less than 24 hours after surgery. In contrast, the patients without CDI may have had a lower protein intake for longer before and during the dehydration episode. On the basis of diet they may therefore have had a lesser degree of serum urea elevation than patients with CDI.

We conclude that during dehydration the serum urea level can be considered a reliable indicator of the renal action of ADH. Serum urea determination may also be useful in all situations in which estimation of the effects of ADH on kidney function is required.

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