Treatment of the Polydipsia-Hyponatremia Syndrome With Urea

Anne Verhoeven, M.D.; Wim Musch, M.D.; and Guy Decaux, M.D., Ph.D.

Objective: The polydipsia-hyponatremia syndrome is difficult to control in patients with severe mental illness, and there is no established effective therapeutic approach. We investigate the effect of oral daily intake of large amounts of urea to prevent hyponatremic episodes.

Method: Seven patients were treated during 4 to 18 months with urea (0.3–0.9 g/kg/day). Five of these patients had schizophrenia. Body weight variation between morning and evening was determined before and during the course of therapy in 5 patients. The dose of urea was increased if morning serum sodium level (SNa) was lower than 132 mmol/L.

Results: Urea therapy increased mean ± SD morning SNa (from 127.5 ± 3.4 mmol/L before initiation of urea treatment to 136.5 ± 2.4 mmol/L during the second month of urea treatment; $p < .01$) and mean ± SD urine osmolality (from 86 ± 39 mOsm/kg H_2O to 159 ± 58 mOsm/kg H_2O; $p < .05$), probably without changes in water intake or urine volume excretion as attested by the level of urinary creatinine concentration. Mean ± SD body weight variation decreased from 4.5% ± 1.0% before initiation of urea treatment to 2.8% ± 1.0% during the second month of urea treatment ($p < .05$). Two patients stopped urea treatment after 1 year and subsequently developed symptomatic hyponatremia.

Conclusion: These preliminary data show that urea appears to be an effective therapeutic approach for the polydipsia-hyponatremia syndrome.

(J Clin Psychiatry 2005;66:1372–1375)

Received Nov. 16, 2004; accepted May 2, 2005. From the Department of Psychiatry, Titeca Hospital (Dr. Verhoeven); the Department of Internal Medicine, Iris South Hospitals, Bracops Site Hospital (Dr. Musch); and the Department of General Internal Medicine, Erasme University Hospital (Dr. Decaux), Brussels, Belgium.

Supported by a grant from the Fonds National de la Recherche Scientifique, convention N3-45 09-03.

Drs. Verhoeven, Musch, and Decaux report no other financial affiliation relevant to the subject of this article.

Part of this study was presented at the 36th annual meeting of the American Society of Nephrology, November 16, 2003, San Diego, Calif.

Corresponding author and reprints: Guy Decaux, M.D., Ph.D., F.A.C.P.Hon., Department of General Internal Medicine, Erasme University Hospital, 808 Route de Lennik, 1070 Brussels, Belgium (e-mail: guy.decaux@skynet.be).

High water intake, particularly if combined with kidney dilution deficit, can induce hyponatremia. Hyponatremia is particularly frequent in schizophrenic patients and is associated with a high morbidity and mortality.[1,2] Water restriction is the cornerstone of treatment in these patients. Unfortunately, its use is limited by the poor compliance related to this approach. Increase in salt intake has also been proposed, but is not effective on a long-term basis.[3,4] Some physicians have tried demeclocycline, which induces reversible tubular antidiuretic hormone (ADH) resistance; however, this agent has generally not been effective.[5] Some observations suggest that the novel antipsychotic agent clozapine may be beneficial in some patients.[6] However, its efficacy remains to be proved in a larger number of cases.[4,7,8]

Urea therapy has been proposed to treat hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[9] In patients with SIADH, urea induces an osmotic diuresis, allowing mostly a normal water intake. In the polydipsia-hyponatremia syndrome (PHS), patients also frequently present with some impairment in urinary dilutional capacity, a defect that increases the risk of water intoxication. This perturbation in water excretion ability is related to various origins (nicotine, use of psychotropic drugs, nausea associated with massive water intake, psychosis itself, enhanced sensitivity to ADH, "reset osmostat").[10] This preliminary study reports the effective role of urea therapy in preventing water intoxication in severely polydipsic patients.

PATIENTS AND METHOD

We prospectively studied 7 (consecutive) polydypsic patients (mean ± SD age = 49 ± 11 years) with hyponatremia and normal solute intake (normal diet) (Table 1). All of these patients had been hospitalized in the previous year for at least 1 episode of symptomatic hyponatremia (e.g., acute confusion, seizure). Five patients suffered from chronic schizophrenia (4 men and 1 woman), of whom 4 were residents at a state mental hospital. Two patients were not schizophrenic. The first patient was a 70-year-old man who developed polydipsia due to chronic dry mouth after oral surgery and radiotherapy for mouth cancer. The second patient was a 30-year-old

© COPYRIGHT 2005 PHYSICIANS POSTGRADUATE PRESS, INC

Table 1. Demographic, Biochemical, and Treatment Data for 7 Patients With Polydipsia Related to Hyponatremia Who Received Treatment With Urea, 0.3–0.9 g/kg/day

Variable	Patient 1	2	3	4	5	6	7
Baseline value							
Age, y	42	40	70	50	51	32	48
Sex	F	F	M	M	M	M	M
Schizophrenia	Yes	No	No	Yes	Yes	Yes	Yes
Morning body weight, kg	104	40	96	111	63	73	55
Morning-to-evening body weight variation	NA	NA	+	+	+	+	+
Morning SNa, mmol/L[a]	127	124	129	124	132	127	132
Urine osmolality, mOsm/kg H_2O[a]	96	132	122	42	39	92	68
Daily oral urea dose, g, needed to maintain SNa > 132 mmol/L	15 bid	15	30	30 tid	30 bid	30	30
Duration of treatment, mo	16	6	18	14	4	4	4

[a]The reported values of SNa and urine osmolality are those obtained the morning immediately before initiation of urea therapy.
Abbreviations: NA = not available, SNa = serum sodium level.
Symbol: + = variation was determined.

Table 2. Body Weight and Biochemical Parameters in 7 Patients With Hyponatremia Related to Polydipsia Who Were Treated With Urea, 0.3 to 0.9 g/kg/day[a]

Parameter	Before Urea Therapy[b]	During Urea Therapy[c]
Body weight, kg	78.1 ± 26	77 ± 25*
Normalized weight gain, %[d]	4.5 ± 1.0	2.8 ± 1.0*
SNa, mEq/L	127.5 ± 3.4	136.5 ± 2.4**
Serum urea level, mg/dL[e]	17 ± 7.5	37 ± 19*
Urine creatinine concentration, mg/dL	14 ± 5.8	16 ± 3
Urine osmolality, mOsm/kg H_2O	86 ± 39	159 ± 58*

[a]All values shown as mean ± SD
[b]For each patient, the mean value of 2 measurements determined at a 1-week interval was used.
[c]For each patient, the mean value of 4 consecutive measurements, made at 1-week intervals during the second month of urea therapy, was used.
[d]Data available for 5 patients.
[e]To convert value to BUN (blood urea nitrogen), divide by 2.14.
*$p < .05$; **$p < .01$.

Table 3. Effect of 1 Week of Treatment With Oral Urea (15 g b.i.d.) on Clinical and Biochemical Parameters in a 42-Year-Old Woman With Schizophrenia

Parameter	Before Urea Therapy	Treatment With Urea
Morning body weight, kg	104	102
Serum sodium level, mmol/L	127	140
Serum urea level, mg/dL	25	69[a]
Creatinine concentration, mg/dL	0.9	1.0
Uric acid concentration, mg/dL	3.5	3.8
24-h urine volume, L	10.0	10.2
Sodium excretion, mmol/24 h	130	144
Potassium excretion, mmol/24 h	91	85
Urea excretion, mmol/24 h	505	950
Urine osmolality, mOsm/kg H_2O	96	153
Osmotic excretion, mmol/24 h	960	1560[b]

[a]Urea was measured 1 hour after oral intake of 15 g (to convert value to BUN [blood urea nitrogen], divide by 2.14).
[b]24-Hour osmotic excretion was calculated by multiplying the daily urine volume (10.2 L) by the urine osmolality (153 mOsm/kg H_2O).

woman with chronic polydipsia without clear-cut psychiatric problems.

Inclusion criteria were morning serum sodium level (SNa) < 133 mmol/L with urine osmolality lower than 150 mOsm/kg H_2O, determined twice at a 1-week interval (Table 2).

In most of these patients, a 24-hour urine collection was not possible because of lack of cooperation (except in 1 patient, for whom data are presented in Table 3). In 5 patients (4 schizophrenic), body weight determination was performed at 8:00 a.m. and 6:00 p.m. at least twice a week before and during urea therapy. Morning SNa was measured at least once a week, with a concurrent spot urine collection for measurement of urine osmolality and urine creatinine concentration. Urea is available as a powder, which is dissolved in water (usually 100 mL) and taken orally during or after meals. To avoid gastric upset, urea can be taken with an antacid.

During the first month of treatment, the dose of urea was progressively increased if morning SNa was lower than 132 mmol/L, usually by escalating the dose by 30 g. The data reported in Table 2 represent the mean values of 2 measurements determined at a 1-week interval before initiation of urea therapy and 4 consecutive measurements, made at 1-week intervals, during the second month of therapy in the 7 patients. The patients were at that time on a fixed dose of urea (15–90 g/day), and the morning SNa was higher than 133 mmol/L for all patients. During treatment with urea, fluid intake was free and no changes were made to regimens of oral medications.

The local ethics committee approved urea therapy for PHS, and informed consent was obtained from the patients. The Mann-Whitney test was used for statistical analysis. The data are presented as mean ± SD.

RESULTS

Urea significantly increased morning SNa (see Table 2). One patient needed only 15 g/day (a nonschizophrenic woman with an initial morning body weight of 40 kg). Hyponatremia in 4 patients was controlled with 30 g/day; 1 patient needed 60 g/day (30 g with breakfast and 30 g with lunch), and 1 needed 90 g/day to maintain a morning SNa higher than 132 mmol/L (Table 1). Table 2 shows that urinary flow was probably not increased by urea, as indirectly reflected by the stable urine creatinine concentration, while urine osmolality increased in each patient.

During urea therapy, morning body weight was lower and diurnal weight gain decreased (from a mean of 4.5% to a mean of 2.8%). In the 2 patients requiring higher urea doses, urea was increased after 1 month of therapy to 60 g in 1 patient and to 90 g in the other. During the study,

2 patients experienced a recurrence of symptomatic hyponatremia after stopping urea treatment (after 1 year). One of these patients, a female outpatient with schizophrenia, was rehospitalized for seizure secondary to hyponatremia (SNa = 120 mmol/L). She was treated at the emergency department with urea, 30 g orally, and water restriction; 24 hours later, her SNa returned to within normal limits. In the other patient (who was taking 90 g of urea daily), acute confusion in conjunction with an 8% increase in evening body weight was observed; this patient refused all blood analysis but agreed to take urea again. In both of these patients, oral urea was reintroduced and led to rapid neurologic recovery.

Table 3 presents the data for a female outpatient with schizophrenia who took 15 g urea in the morning and 15 g in the evening. This patient agreed to collect urine for a 24-hour period before and after 1 week of urea therapy. It is interesting to note that the 24-hour urine volume did not differ between the 2 time points. As expected, the increase in the daily osmole excretion was mainly accounted for by urea.

In all of the patients social behavior improved during urea therapy (e.g., better collaboration with the nurses, no episodes of confusion). No side effects were reported even with high doses (60 and 90 g during more than 1 year in 2 patients).

DISCUSSION

Psychogenic polydipsia is a clinical disorder characterized by excessive water drinking in the absence of a physiologic stimulus to drink. The excessive water drinking is well tolerated unless hyponatremia supervenes, which can induce high morbidity and mortality. Classically, this disorder has been described in individuals with schizophrenia. In the setting of normal renal function, hyponatremia secondary to pure water intake is rare because the normal kidney can excrete 15 to 20 L of urine with osmolality around 50 mOsm/kg H_2O. However, most patients with PHS have some degree of deficit in urinary dilutional capacity, a defect that increases the risk of water intoxication.[10] Like patients with SIADH, they frequently have hypouricemia, low blood urea levels, and increases in body weight due to water retention.[11] Urea is a well-established treatment in SIADH and is particularly effective in patients with relatively low urine osmolality (< 500 mOsm/kg H_2O).[12] Urea is a solute that must be excreted by the kidneys, and high doses will induce an increase in the urine volume. Oral supplements of urea are usually eliminated in the urine in 12 to 24 hours.[13] If the daily solute excretion is, for example, 700 mmol (half of the solute is represented by electrolytes and half by urea), and the patient can dilute urine to 100 mOsm/kg H_2O, the patient should be able to eliminate 7 L of urine daily. If, additionally, the patient takes 30 g (or 500 mmol) of urea, then he or she should be able to eliminate 12 L/day (7 L baseline and an extra 5 L due to the addition of urea). Urea is operationally osmotically active in the urine. Therefore, it takes water with it in lieu of sodium taking water with it. Because urea removes water instead of allowing sodium to take the water with it, serum sodium level increases and the patient is less likely to suffer from the complications of water intoxication (delirium, seizures, coma, death).

Urea was well tolerated in all of our patients when taken after a meal (at a usual dose of 0.5 g/kg/day), and it can be administrated on a long-term basis without major adverse effects.[14] In addition, Vieweg and colleagues[15] have reported the value of the combination of lithium and phenytoin in normalization of baseline serum sodium level in 6 patients with psychosis, intermittent hyponatremia, and polydipsia. This normalization of baseline serum sodium levels protects the patients against complications, including hyponatremic seizures and coma. Urea has the advantage of acting very rapidly. During our study, we allowed the nurse to adapt the amount of urea relative to body weight changes. A supplement of 30 g (or 0.5 g/kg) of urea was given if body weight increased by more than 4% to 5% (a total dose of 120 g was used occasionally in 1 patient). Oral urea, when administered at a dose of 0.5 to 1 g/kg body weight, produces a rapid osmotic gradient of 15 to 30 mOsm/kg H_2O with striking reduction in intracranial pressure even before any significant increase in natremia occurs.[16]

Oral urea is rapidly reabsorbed and diffuses rapidly in most tissues in less than 1 hour, but it penetrates brain tissue more slowly (4–10 hours), explaining why urea is used to decrease brain edema (e.g., during neurosurgery).[17] Diuresis will progressively increase during the subsequent hours and contribute to the increase in serum sodium level. When the patient is unable to take it orally, urea can easily be given by the intravenous route.[13,17] In the 2 patients who stopped urea treatment, its reintroduction greatly improved their neurologic status within a few hours.[17]

It is interesting to note that all patients had increased urine osmolality (mean urine osmolality about 160 mOsm/kg H_2O) concomitant to the increase in SNa and without a reduction (or increase) in urine volume (indirectly estimated by the urine creatinine concentration). Thus, urine osmolality appears to be adapted to the water intake and the solute load. It must be noted that mean body weight in the morning was only 1.1 kg lower during urea therapy, despite a large increase in SNa (from 127.5 to 136.5 mmol/L).[18]

We did not compare urea therapy with treatment by salt supplementation, but comparable solute load in the form of salt tablets will induce gastric intolerance on a long-term basis. Vasopressin V_2 receptor antagonists are in development, but it is also unlikely that in patients with urine osmolality as low as 40 mOsm/kg H_2O, as in some

© Copyright 2005 Physicians Postgraduate Press, Inc.

of our patients, these new medications would be effective.[19] The approach we suggest seems to be effective, but, as expected, no medication could prevent water intoxication if fluid intake largely overwhelms water excretion capacity. In these patients, control of water access is the only possibility. There are actually no efficient drugs acting on the thirst center. Comparison of clozapine with urea therapy should be done. In some patients, combined treatment could be needed. Urea will decrease the risk of hyponatremia, but urea therapy will not decrease the risk of developing anatomical complications, such as hydronephrosis.[20]

These preliminary data show that urea therapy is particularly useful in the long-term management of polydipsic patients with recurrent symptomatic hyponatremia.

Drug names: clozapine (FazaClo, Clozaril, and others), demeclocycline (Declomycin and others), lithium (Eskalith, Lithobid, and others), phenytoin (Dilantin, Phenytek, and others).

REFERENCES

1. Blum A, Tempey FW, Lynch W. Somatic findings in patients with psychogenic polydipsia. J Clin Psychiatry 1983;44:55–56
2. Hariprasad MK, Eisinger RP, Nadler IM, et al. Hyponatremia in psychogenic polydipsia. Arch Intern Med 1980;140:1639–1642
3. Goldman MB, Nash M, Blake L, et al. Do electrolyte-containing beverages improve water imbalance in hyponatremic schizophrenics? J Clin Psychiatry 1994;55:151–153
4. Reeves RR. Worsening of hyponatremia with electrolyte-containing beverage [letter]. Am J Psychiatry 2004;161:374–375
5. Alexander RC, Karp BI, Thompson S, et al. A double blind, placebo-controlled trial of demeclocycline treatment of polydipsia-hyponatremia in chronically psychotic patients. Biol Psychiatry 1991;30:417–420
6. Canuso CM, Goldman MB. Clozapine restores water balance in schizophrenic patients with polydipsia-hyponatremia syndrome. J Neuropsychiatry Clin Neurosci 1999;11:86–90
7. Quitkin FM, Garakani A, Kelly K. Electrolyte-balanced sport drink for polydipsia-hyponatremia in schizophrenia. Am J Psychiatry 2003;160:385–386
8. Spears NM, Leadbetter RA, Shutty MS Jr. Clozapine treatment in polydipsia in intermittent hyponatremia. J Clin Psychiatry 1996;57:123–128
9. Decaux G, Genette F. Urea for long-term treatment of syndrome of inappropriate secretion of antidiuretic hormone. Br Med J (Clin Res Ed) 1981;283:1081–1083
10. Sterns RH, Ocdol H, Schrier RW, et al. Hyponatremia: pathophysiology diagnosis and therapy. In: Narins RG, ed. Clinical Disorders of Fluids and Electrolyte Metabolism. 5th ed. New York, NY: McGraw-Hill; 1995:583–615
11. Decaux G, Schlesser M, Coffernils M, et al. Uric acid, anion gap and urea concentration in the diagnostic approach to hyponatremia. Clin Nephrol 1994;42:102–108
12. Decaux G. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by long loop diuretics. Nephron 1983;35:82–88
13. Decaux G, Unger J, Brimouille S, et al. Hyponatremia in the syndrome of inappropriate secretion of the antidiuretic hormone: rapid correction with urea, sodium chloride and water restriction. JAMA 1982;247:471–474
14. Decaux G, Prospert F, Penninckx R, et al. 5-year treatment of the chronic syndrome of inappropriate secretion of ADH with oral urea. Nephron 1993;63:468–470
15. Vieweg WV, Weiss NM, David JJ, et al. Treatment of psychosis, intermittent hyponatremia, and polydipsia (PIP syndrome) using lithium and phenytoin. Biol Psychiatry 1988;23:25–30
16. Soupart A, Decaux G. Therapeutic recommendations for management of severe hyponatremia: current concepts on pathogenesis and prevention of neurologic complication. Clin Nephrol 1996;46:149–169
17. Decaux G, Soupart A. Treatment of symptomatic hyponatremia. Am J Med Sci 2003;326:25–30
18. Musch W, Xhaet O, Decaux G. Solute loss plays a major role in polydipsia related hyponatremia of both water and beer drinkers. QJM 2003;96:421–426
19. Decaux G. Long term treatment of inappropriate secretion of ADH by the vasopressin receptor antagonist conivaptan, urea or furosemide. Am J Med 2001;110:582–584
20. Streitz JM Jr, Streitz JM. Polyuric urinary tract dilatation with renal damage. J Urol 1988;139:784–785