of the syndrome. Clinicians need to be aware of atypical presentations of NMS because they may obscure diagnosing a potentially fatal condition and delay life-saving treatment.

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Oral Urea Treatment for Polydipsia-Hyponatremia Syndrome in Patients With Schizophrenia

To the Editors:

At least 20% of hospitalized schizophrenic patients demonstrate polydipsia and polyuria; more than 25% polydipsic patients may eventually develop hyponatremia, which is called polydipsia-hyponatremia syndrome (PHS).[1] An acute and severe hyponatremia due to polydipsia can lead to a serious clinical condition called water intoxication, which may cause loss of consciousness, seizures, or even death.[1,2] Several pharmacologic approaches have been tested to treat polydipsia in schizophrenic patients; however, none of them has been proven to be effective, thus far.[3] Clozapine, a prototype of so-called atypical antipsychotic drugs, may reduce polydipsia in schizophrenic patients.[4] Unfortunately, it has serious adverse effects and may not be prescribed for all the patients with PHS; clozapine is not yet approved for clinical use in Japan.

Another pharmacologic approach for the management of PHS would be to increase renal capacity to excrete water. Patients with PHS have reduced free water clearance rate, which has generally been linked to a syndrome of inappropriate secretion of antidiuretic hormone.[5] Several researchers have examined the effect of a vasopressin receptor antagonist, demeclocycline, on patients with PHS; however, a carefully performed double blind placebo-controlled trial failed to show any significant benefit.[6] More recently, specific vasopressin V_2 receptor antagonist, tolvaptan, has been shown to elevate serum sodium levels in schizophrenic patients with chronic hyponatremia.[7] The result seems to be promising, although efficacy and safety of this drug should be confirmed in a longer-term study.

Verhoeven et al[8] reported that orally administered urea elevated serum sodium levels in 7 patients with mental illness including 5 schizophrenic patients with PHS. Urea is one of the main components responsible for urine osmolarity. When administered orally, urea is quickly absorbed and excreted in urine, efficiently producing osmotic diuresis.[9] In Japan, urea has previously been used to reduce edema in chronic heart failure or ascites in liver cirrhosis.[9] Urea has been reported to reduce water retention efficiently and safely in patients with syndrome of inappropriate secretion of antidiuretic hormone.[10] If disturbed free water clearance is a key factor for the development of hyponatremia, it is likely that urea will reduce water retention and prevent severe hyponatremia in PHS. Therefore, we conducted a clinical trial to confirm the effect of oral urea treatment on PHS in schizophrenic patients.

Inclusion criteria for selecting subjects were as follows: (1) patients with a condition diagnosed as schizophrenia

TABLE 1. Mean ± SD Changes in Serum and Urine Data and NDWG After Oral Urea Treatment (n = 7)

	Dosage of Urea, g/d			
	Baseline	**30**	**45**	**67.5**
Serum analysis at 4 PM				
Na^+, mEq/L	127.6 ± 3.0	128.9 ± 3.5	131.7 ± 3.9*†	133.5 ± 3.0‡§
K^+, mEq/L	3.75 ± 0.53	3.87 ± 0.47	4.02 ± 0.60‖	3.99 ± 0.35‖
Cl^-, mEq/L	90.0 ± 4.5	91.0 ± 4.2	93.0 ± 5.3‖	94.4 ± 3.6*
Blood urea nitrogen level, mg/dL	7.7 ± 4.3	20.1 ± 11.6‖	26.5 ± 14.0‡	48.8 ± 20.0‡§
Cre, mg/dL	0.84 ± 0.26	0.81 ± 0.28	0.83 ± 0.26	0.84 ± 0.28
Urine analysis at 4 PM				
Osmolarity, mOsm	92.0 ± 36.0	132.8 ± 63.4	171.1 ± 67.8*	231.2 ± 94.0‡¶
Na^+, mEq/L	23.6 ± 7.3	21.9 ± 8.4	21.4 ± 9.8	18.6 ± 5.0
Cre, mg/dL	15.2 ± 8.4	14.9 ± 9.6	14.0 ± 7.2	14.3 ± 5.8
Serum and urine analyses at 6 AM				
Serum Na^+, mEq/L	131.1 ± 4.3	132.0 ± 3.3	135.0 ± 4.4‖	136.3 ± 2.6*†
Urine Cre, mg/dL	17.4 ± 4.6	22.4 ± 10.2	26.6 ± 9.8	37.6 ± 14.1*†
NDWG, %	5.7 ± 1.4	6.0 ± 1.9	6.2 ± 1.7	6.2 ± 1.3

*$P < 0.01$ versus baseline.
†$P < 0.05$ versus 30 g of urea; by 1-way analysis of variance with repeated measures followed by Tukey test.
‡$P < 0.001$ versus baseline.
§$P < 0.001$ versus 30 g of urea; by 1-way analysis of variance with repeated measures followed by Tukey test.
‖$P < 0.05$ versus baseline.
¶$P < 0.01$ versus 30 g of urea; by 1-way analysis of variance with repeated measures followed by Tukey test.

(*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria) and hospitalized in our facility; (2) polydipsia of the patients had to be identified by (*a*) staff observations, (*b*) constant hyposthenuria, and (*c*) marked diurnal weight gain (DWG, >5%); (3) patients had to show hyponatremia (<135 mEq/L) in routine blood analysis at least once in the last 6 months; and (4) patients had to have at least one clear episode of water intoxication during their hospitalization period. Patients with a history of renal disease, heart disease, or diabetes mellitus were excluded. Seven male schizophrenic patients met the criteria and provided written informed consent to the study. Mean age of the subjects was 53.3 ± 5.9 years (range, 44–63 years). Means of durations of illness and hospitalization periods were 31.3 ± 7.0 (range, 21–42) and 20.1 ± 8.9 (range, 5–32) years, respectively. Subjects were basically allowed free access to water throughout the study period except for several hours of involuntary water-restriction period occasionally imposed according to a target-weight procedure.[1,2] The water restriction has not been done on the day of blood and urine analyses. Subjects were not allowed to take any diuretics and/or lithium during the study. The study protocol was approved by the ethical committees of both the Tsukuba University Hospital and Mitsukaido-Kosei Hospital.

The ultrafine grade of urea (purity, >99.0%) was purchased from the Takasugi Pharmaceutical Co, Ltd (Fukuoka, Japan). A starting dosage of urea, 30 g/d, was decided according to the previous report[8]; the dosage was increased subsequently as described later on. Because the urea tasted so bitter and salty, we dissolved it in orange juice and added artificial sweetener containing aspartame (Palsweet; Ajinomoto, Tokyo, Japan). The urea/orange juice cocktail was divided into 2 or 3 portions depending on the urea dosage and served twice or thrice a day.

The blood and urine analyses were carried out twice every month on the first and the third Friday. Verhoeven et al[8] reported the elevated morning serum sodium levels in their subjects after the urea treatment. However, the serum sodium levels of the typical patients with PHS decrease in the afternoon even if those in the morning are normal.[2] Thus, we decided to collect the blood and urine samples in the afternoon at 4 PM; serum sodium, potassium, chloride, creatinine, and blood urea nitrogen levels were determined. In addition, morning (at 6 AM) blood samples were analyzed once with a given urea dosage; serum electrolytes, blood cell counts, liver enzymes, fasting blood glucose, total cholesterol, and triglyceride levels were determined. Urine samples were taken twice every month at 4 PM on the same day of the afternoon blood analysis. Urine specific gravity, osmolarity, and sodium and creatinine concentrations were determined. Morning urine samples were also collected at 6 AM on the same day; urine creatinine concentrations were determined. Normalized diurnal body weight gain (NDWG) was calculated every day for each subject as previously described.[11] The blood and urine examinations were performed for 3 months before the beginning of urea treatment; means of the 3-month data were regarded as baseline for each subject. Changes of the data after oral urea treatment were monitored and statistically analyzed using 1-way analysis of variance with repeated measures followed by Tukey multiple comparison test.

When 30 g/d of urea was given to the subjects for 2 months, their serum sodium levels did not seem to elevate. Therefore, we increased the dosage to 45 g/d and observed for additional 3 months. The mean serum sodium level of the subjects apparently elevated with this dosage; however, it still remained below the reference range (Table 1). We decide to increase the dosage to 67.5 g/d, and the observation continued for an additional 2 months. As shown in Table 1, the means of serum sodium concentrations at 4 PM were significantly higher than the baseline at daily doses of 45 and 67.5 g, although a difference

between 45 and 67.5 g was not significant. The means of morning serum sodium concentrations were also significantly higher than the baseline at doses of 45 and 67.5 g (Table 1). Mean concentrations of serum potassium and chloride at 4 PM were also significantly higher than the baseline at doses of 45 and 67.5 g (Table 1). None of these variables showed any significant differences between the 45- and 67.5-g doses. No particular adverse event was observed during the study.

The mean urine creatinine concentration at 6 AM was significantly elevated with 67.5-g dose of urea as compared with baseline, suggesting that the subjects became capable of reducing water retention by the morning. This may indicate that their renal capacity to excrete water has improved. On the other hand, the mean urine creatinine level at 4 PM of our subjects remained low despite the urea treatment (Table 1). Although Verhoeven et al[8] reported that NDWG of their subjects significantly decreased after the urea treatment, our subjects failed to show any reduction in NDWG (Table 1). It is suggested, therefore, that our subjects were still polydipsic and experiencing water retention in the afternoon. This was, however, somewhat puzzling because the serum sodium levels at 4 PM of our subjects significantly increased. A possible explanation for this discrepancy would be that the elevated serum sodium after the urea treatment was not entirely related to the reduction of water retention. Musch et al[12] suggested that a solute loss, as well as the water-retention, plays a major role in polydipsia-related hyponatremia. It may be the case that the oral urea treatment elevates serum sodium not only by reducing water retention but also by preventing sodium loss in the urine. This notion remains to be clarified in future studies.

This study has some limitations. The study was designed as an open naturalistic trial without a control group. The sample size was small. The mean of serum sodium concentration with highest dosage used (67.5 g/d) was still below reference range, suggesting that oral urea treatment would not be an entire solution for PHS. We could not find significant difference between mean serum sodium concentrations with 45- and 67.5-g doses. The optimal urea dosage should be determined in future studies. Nevertheless, increased serum sodium levels not only in the morning but also in the afternoon in schizophrenic patients with PHS support the notion that the oral urea treatment possibly reduces the risk of severe hyponatremia. Further studies with larger sample sizes and longer-term protocols are required to evaluate beneficial effects and safety of the oral urea treatment for schizophrenic patients with PHS.

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Clozapine Monotherapy for 66 Months in Treatment Resistant Bipolar Disorder
A Case Report

To the Editors:

In the last decade, there has been a rapid growth in treatment approaches for bipolar disorder. Most atypical antipsychotics are now licensed for maintenance therapy in bipolar disorder. However, despite the use of anticonvulsants, mood stabilizers and atypical antipsychotics, many patients are resistant to treatment.

Clozapine has been shown to be useful in the treatment of acute mania[1,2] and refractory psychotic mania.[3] Long-term studies of clozapine as add-on or monotherapy in treatment resistant bipolar disorder have shown significant improvement in manic symptoms, decrease in hospitalizations, and reduction in suicidality.[4–6] Two case reports and a case series have also highlighted the beneficial effect of clozapine add-on in treatment resistant bipolar disorder.[7–9]

I describe the case of a young man with treatment resistant bipolar disorder