Efficacy and Tolerance of Urea Compared with Vaptans for Long-Term Treatment of Patients with SIADH

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Summary

Background and objectives Vaptans (vasopressin V_2-receptor antagonists) are a new approach for the treatment of hyponatremia. However, their indications remain to be determined, and their benefit compared with that of the usual treatments for the syndrome of inappropriate antidiuretic hormone secretion (SIADH) have not been evaluated. This prospective, long-term study compared the efficacy, tolerability, and safety of two oral vaptans with those of oral urea in patients with SIADH.

Design, setting, participants, & measurements Patients with chronic SIADH of various origins were treated first with vaptans for 1 year. After an 8-day holiday period, they received oral urea for an additional 1-year follow-up. Serum sodium was measured every 2 months, and drug doses were adjusted accordingly.

Results Thirteen participants were initially included in the study (serum sodium, 125±3 mEq/L); 12 completed the 2-year treatment period. Treatment with vaptans (satavaptan, 5–50 mg/d, n=10; tolvaptan, 30–60 mg/day, n=2) increased natremia (serum sodium, 135±3 mEq/L) during the 1-year vaptan period without escape. Hyponatremia recurred in the 12 participants when vaptans were stopped (holiday period). Urea improved the natremia with the same efficacy (serum sodium, 135±2 mEq/L) as vaptans during the 1-year urea treatment period. One participant treated with tolvaptan withdrew from the study early because of excessive thirst. Another patient receiving urea developed hypernatremia without complications.

Conclusions Urea has efficacy similar to that of vaptans for treatment of chronic SIADH. Tolerance is generally good for both agents.

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Introduction

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) results from nonosmotic release of vasopressin from the pituitary gland or from ectopic secretion. Antidiuretic hormone secretion induces an excess of total body water due to a decrease in electrolyte free water excretion with relatively normal total-body sodium, resulting in euvolemic hyponatremia (1). The resulting hyponatremia can be transitory or become chronic depending on the initial cause of the SIADH. Many conditions can be associated with SIADH, but approximately one third of cases are of unknown origin (idiopathic), especially in the elderly (2,3).

Usual therapeutic options in hyponatremic patients with SIADH consist of fluid restriction, usually to less than 800–1200 ml/d (an intake difficult to maintain, particularly in patients with reset osmostat) (4,5); demeclocycline, which works in only 60%–70% of patients and can cause nephrotoxicity (5); furosemide with oral salt supplementation (6,7); and oral urea, an agent long used to treat hyponatremia of various origins (8–13).

The recent development of oral nonpeptide vasopressin V_2-receptor antagonists (vaptans) offers a new therapeutic approach that targets the mechanism of the disorder. Several vaptans have been studied in patients with SIADH, including satavaptan (selective V_2), tolvaptan (V_2), lixivaptan (V_2), and conivaptan (V_1/V_2) (14). Two of these are currently available on the market: In the United States, conivaptan is approved for intravenous use in euvolemic and hypervolemic hyponatremia (15,16), and oral tolvaptan is approved for euvolemic and hypervolemic hyponatremia (17,18). Tolvaptan is approved in the European Union only for SIADH.

However, none of the published studies compared the therapeutic effect of the V_2 antagonists with effects of any alternative available methods of correction in patients with SIADH on a long-term basis. We studied a series of patients with chronic SIADH of various origins by successively comparing the long-term (1-year) efficacy and tolerability of two different vaptans (satavaptan and tolvaptan) with those of oral urea (1 year).

Participants were first treated with different vaptans; when these drugs were no longer available, hyponatremia was then corrected with urea.

Materials and Methods

Patients

Between June 2007 and December 2009, 13 patients from our hospitals were included in different studies

to evaluate the efficacy and tolerability of vaptans in chronic hyponatremia related to SIADH. Results of these studies have been published for satavaptan (2) and tolvaptan (17,18). After 12 months, the vaptans were no longer provided by the companies. We then decided to treat hyponatremia with urea in those participants.

All the participants met the classic criteria for SIADH (hypo-osmolality, inappropriately concentrated urine with urine osmolality > 100 mOsm/kg H_2O hypertonic to serum and urine sodium concentration > 30 mEq/L with normal salt and water intake) (1). All patients had normal renal, adrenal, and thyroid function. Inclusion criteria were age older than 18 years, chronic (>72-hour) hyponatremia (serum sodium >115–132 mEq/L) due to SIADH (idiopathic or related to various secondary causes). Exclusion criteria were transient SIADH (*e.g.*, due to pneumonia), cardiac failure, symptomatic liver disease or serum aminotransferase or aspartate aminotransferase levels greater than twice the upper limit of normal, uncontrolled diabetes (blood glucose level > 200 mg/dl), and symptomatic gastric ulcer (for urea).

Written informed consent was obtained for each patient, and the study protocol was approved by the local ethics committee.

Protocol

Table 1 lists the characteristics and treatments for the study patients. In the first part of the study (12 months), all the participants were treated with open-label vaptans (V_2 selective receptor antagonists).

Ten participants received oral satavaptan (Sanofi-Synthélabo) at an adjusted dosage of 5–25 mg/d; three others received oral tolvaptan (Samsca, Otsuka), 30–60 mg/d. The drug was administered in the morning under fasting conditions for each vaptan. The dose was adjusted to obtain a serum sodium level between 135 and 145 mEq/L.

After the first 12-month period of treatment, vaptans were discontinued. An 8-day holiday period followed to ensure the recurrence of hyponatremia (serum sodium < 132 mEq/L) in all participants. Patients in whom hyponatremia did not recur were withdrawn from the study.

In the second part of the protocol (additional 12 months), all participants who met the inclusion criteria were then treated with oral urea at adjusted dosages of 15–30 g/d after meal (in one or two doses). Urea powder (medicinal urea, Certa, Braine-L'Alleud, Belgium) was mixed with orange juice or syrup. The target serum sodium level was similar to that used with vaptan treatment (serum sodium level > 135 mEq/L).

During the entire study, a total fluid intake limited to 1500–2000 ml/d was recommended to all participants but was not measured. The efficacy and safety of both treatments were assessed during the 24-month follow-up. Blood samples for serum sodium, serum urea, and serum creatinine measurements were collected every 2 months during the entire study period.

Safety was assessed at all visits for the 2-year study duration for each participant by recording adverse events, vital signs, and physical examination findings based on symptoms and diagnosis.

Statistical Analyses

Data are provided as the mean ± SD. All statistical tests were two sided at a 5% significance level. Data were compared between treatment groups using ANOVA for continuous data and Tukey-Kramer multiple-comparison tests (Statsdirect Software; Statsdirect Ltd.).

Results

Twelve participants (six women and six men), with a mean age of 73±17 years (range, 28–89 years), completed the 2-year follow-up study. SIADH was considered idiopathic in nine patients and was associated with central nervous system disorders in the other three patients (Table 1). At baseline, all patients presented moderate hyponatremia (mean serum sodium level, 125±3 mEq/L [range, 120–131 mEq/L]). The mean serum urea level was 26±7 mg/dl (range, 18–41 mg/dl), and the mean serum uric acid level was 3.3±1.2 mg/dl (range, 1.2–5.3 mg/dl). Mean urinary osmolality was 487±162 mOsm/kg H_2O (range, 264–800 mOsm/kg H_2O).

Table 1. Clinical characteristics and treatment in patients with syndrome of inappropriate antidiuretic hormone secretion

Patient No.	Sex	Age (yr)	Origin of SIADH	Vaptan Dose (mg)	Urea Dose (g)
1	F	86	Idiopathic	Satavaptan, 25	30
2	M	88	Idiopathic	Satavaptan, 12.5	30
3	F	89	Idiopathic	Satavaptan, 5	15
4	M	70	Idiopathic	Satavaptan, 5	15
5	M	76	Idiopathic	Satavaptan, 25	30
6	M	84	Idiopathic	Satavaptan, 12.5	30
7	M	56	Idiopathic	Satavaptan, 10	30
8	F	85	Idiopathic	Satavaptan, 5	15
9	F	70	CNS hemorrhage	Satavaptan, 25	15
10	F	70	Neurolupus	Tolvaptan, 60	30
11	M	59	Idiopathic	Satavaptan, 50	15–30
12	F	28	Olfactive neuroblastoma	Tolvaptan, 30	30
13	M	70	Idiopathic	Tolvaptan, 30	NA

SIADH, syndrome of inappropriate antidiuretic hormone secretion; F, female; M, male; CNS, central nervous system; NA, not applicable.

Vaptan Course (12 Months)

The evolution of serum sodium levels throughout the first year of treatment with vaptans is shown in Table 2 and Figure 1. Serum sodium levels increased significantly in the 12 patients during the 1-year vaptan follow-up (mean, 135±3 mEq/L at 12 months versus 125±3 mEq/L at baseline; $P<0.001$; Table 2). The mean serum sodium values at each consecutive measurement were >135 mEq/L (Figure 1). Nevertheless, the serum sodium level was <135 mEq/L (range, 125–134 mEq/L) in 28% of the values measured during the 1-year period, distributed among 6 of the 12 participants, with no difference between patients receiving satavaptan and those receiving tolvaptan.

In the satavaptan group, the following doses were used: 5 mg (n=3), 10 mg (n=1), 12.5 mg (n=2), 25 mg (n=3), and 50 mg (n=1) (Table 1). The tolvaptan doses were 30 mg (n=1) and 60 mg (n=1). No drug escape effect occurred during the study period. One tolvaptan recipient (30 mg) not included in the 12 reported cases withdrew from the study because of excessive thirst after only 2 weeks of treatment; this is considered a drug-related adverse event. In the other participants, vaptans were well tolerated.

Holiday Period (8 Days)

After 1 year of vaptan treatment, the drug was stopped and participants were maintained for 8 days in a treatment-free period. Hyponatremia (serum sodium level < 135 mEq/L) recurred in all patients (mean serum sodium level, 126±5 mEq/L [range, 116–133 mEq/L; n=12). One patient treated with satavaptan fell during the treatment-free period (serum sodium level, 123 mEq/L) and broke her wrist.

Urea Course (12 Months)

After the 8-day holiday period, treatment was reintroduced in the 12 participants. They received oral urea for 12 additional months. Evolution of the serum sodium level during urea treatment is shown in Figure 1 and Table 2. The serum sodium level increased significantly in the 12 participants during the 1-year urea follow-up (mean, 135±2 mEq/L after 1 year versus 126±5 mEq/L during the holiday period; $P<0.001$ [Table 2]). Mean serum sodium values at each of six consecutive measurements were >135 mEq/L (Figure 1). Serum sodium levels were <135 mEq/L (range, 130–134 mEq/L) in 32% of all measured values and were recorded in 7 of the 12 patients. Six of these patients were the same as those who also exhibited low values during vaptan use (see section on vaptans course). The urea dosages used to correct serum sodium ranged from 15 g/d (n=5 of 12) to 30 g/d (n=7 of 12) (Table 1).

The level of serum sodium correction did not differ between the vaptan period and the urea period in the 12 participants. The serum urea level was, as expected, significantly higher during the urea period (mean, 61±25 mg/dl [range, 25–106 mg/dl]) compared with the basal level (26±7 mg/dl; $P<0.001$) and the level during the vaptan period (37±13 mg/dl; $P<0.01$). The greatest variability in serum urea observed in the urea-treated participants is related to the difference in the time of urea intake between them.

Urea was generally well tolerated in the participants during the overall exposure. Only one patient, an 89-year-old man, was admitted to the hospital (for bacterial pneumonia) during urea treatment. At admission, he was hypernatremic (155 mEq/L) because of fever and decreased thirst combined with urea use. He completely recovered without neurologic sequelae and restarted urea without further complications.

Discussion

Our results demonstrate that patients with chronic moderate hyponatremia related to SIADH could be treated with the same efficacy, safety, and tolerance with oral vaptans or oral urea over a long-term period (1 year for

Table 2. Evolution of serum sodium during 2-year follow-up treatment period

Patient No.	Basal		Vaptans (1 yr)		Sodium during Drug Holiday (8 d) (mEq/L)	Urea (1 yr)	
	Sodium (mEq/L) [a]	Urea (mg/dl)	Sodium (mEq/L)[b]	urea (mg/dl)[b]		Sodium (mEq/L)[b]	urea (mg/dl)[b]
1	124	41	131±3	52±5	123	133±4	106±35
2	122	23	136±0.4	29±2	120	138±2	93±15
3	125	23	133±1.8	48±5	131	134±2	52±9
4	121	25	139±1.5	34±2	130	135±1	41±9
5	120	23	134±2	40±8	116	131±1	101±25
6	131	41	136±1	63±2	126	137±1	56±6
7	123	18	134±1	22±4	125	131±6	42±3
8	129	28	137±1	52±4	130	138±2	74±5
9	130	28	140±2	36±6	132	134±4	49±6
10	128	21	141±1	24±1	133	137±2	44±17
11	125	25	129±0.8	31±1	131	133±2	48±6
12	124	19	141±1	23±4	124	135±4	35±2
Overall means	125±3	26±7	135±3	37±13	126±5	135±2	61±25

Values expressed with a plus/minus sign are mean ± SD.
[a]Basal values: n=2.
[b]Mean value of six levels measured over 1-year follow-up.

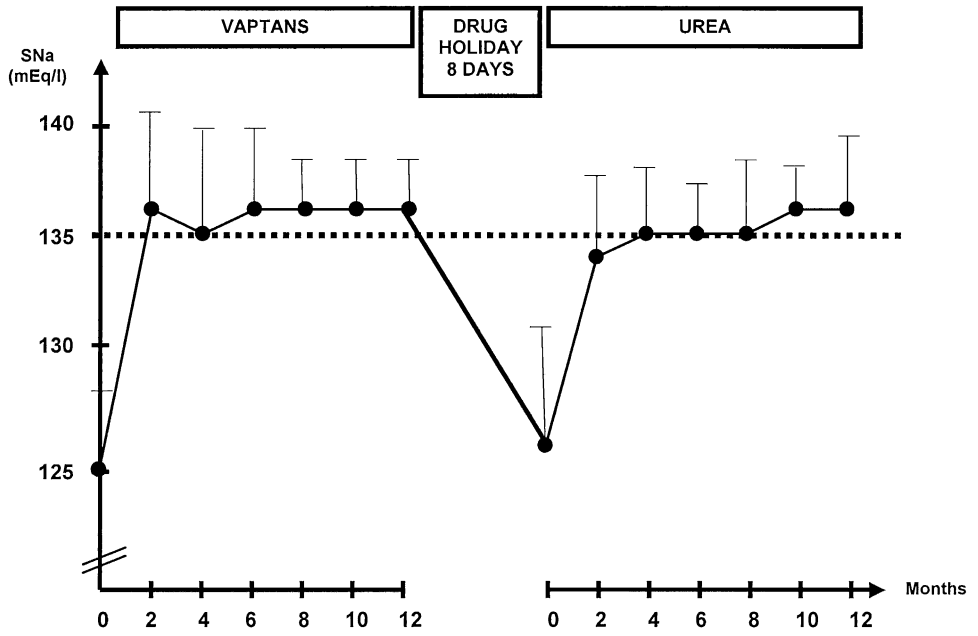

Figure 1. | Serum sodium (SNa) values during treatment with vaptans and urea. Each point is the mean value of serum sodium for the 12 patients (mean ± SD).

each component). To our knowledge, this is the first study to compare the vaptans with another current therapeutic option in SIADH.

In the first period of the study, administration of satavaptan (n=10) or tolvaptan (n=2) allowed good control of the natremia (mean serum sodium level, 135±3 mEq/L) for the 1-year follow-up. The return to hyponatremia within 8 days after vaptan discontinuation in the 12 participants confirmed that all presented irreversible defects in water excretion and that all theoretically required treatment. After the holiday period, each patient then received urea, with similar efficacy (mean serum sodium level, 135±2 mEq/L). Approximately 70% of the recorded values of serum sodium returned to normal (serum sodium level > 135 mEq/L) with both vaptan and urea treatments. Indeed, intermittent mild (130–134 mEq/L with urea) to moderate (125–134 mEq/L with vaptans) hyponatremia was observed despite optimal doses of vaptans and urea in some participants. This could be partly explained by the uncontrolled relative fluid restriction recommended to participants during the entire treatment period.

Usually, the reported response to vaptans in SIADH is approximately 70%–80% with tolvaptan (19) and satavaptan (2), and the same level of response is observed with oral urea (13). The response to treatment was maintained during the entire administration period for each drug. Serum urea levels were logically significantly higher with urea than with vaptans at an oral daily dose of 15–30 g.

Some participants had a serum urea concentration > 100 mg/dl, and this was not associated with any discomfort. Urea intake shortly before serum sodium measurement in some patients could explain their higher recorded values.

Tolerability was generally good for vaptans and urea; however, one participant stopped taking tolvaptan because of excessive thirst as a consequence of drug use. This case probably presented reset osmostat. In addition, hypernatremia developed incidentally in another patient treated with urea. He was hospitalized for pneumonia, and hypernatremia was induced by fever, altered general status, and decreased fluid intake at home combined with urea use. He completely recovered without neurologic complications, and urea was reintroduced at hospital discharge.

Change in serum sodium from baseline obtained with vaptans is generally around 3–6 mEq/L during the first 24 hours of correction depending on the degree of water restriction (2,16,20). Incidence of hypernatremia was not significantly increased.

Overly rapid correction (change in serum sodium level > 12 mEq/L per 24 hours) occurs in approximately 6% (18) to 10% (2) of patients receiving vaptans. A similar gradient of correction is obtained after treatment of mild to moderate hyponatremia with urea (approximately4 mEq/L in the first 24 hours of correction) (13).

The V_2 receptor antagonists act specifically at the vasopressin kidney target site, preventing activation of Aquaporin-2 channel and thus normalizing the natremia by increasing solute-free aquaresis (14). Data on long-term (>6 months) effects of oral vaptans in patients with chronic SIADH are limited to two studies. The first one involved patients treated with satavaptan for 1 year (2), and the other included both SIADH patients and a population of patients with hyponatremia of various causes treated with tolvaptan for 2 years (17,18). An analysis limited to the subset of patients (n=52) with SIADH treated with tolvaptan had only 30-day follow-up (19). With both components (satavaptan and tolvaptan), moderate hyponatremia was corrected successfully with minimal side effects (increased thirst, dry mouth, nausea, and polyuria).

To our knowledge, osmotic demyelination syndrome associated with vaptans or urea use in humans has not been

reported. However, the studies that used vasopressin antagonists excluded patients with severe hyponatremia (serum sodium level < 115 mEq/L), and we know that most of the described patients with myelinolysis had an initial serum sodium level < 115 mEq/L (21). Experimental data also show that inappropriate correction of chronic hyponatremia with vaptans (conivaptan and satavaptan) also leads to brain damage (osmotic demyelination syndrome) (22).

Urea normalizes natremia by inducing osmotic diuresis similar to that achieved with other osmotic agents (23,24) but without the risk for volume overload, decreased serum sodium (as observed with mannitol), or hypokalemia. Urea also ameliorates hyponatremia in SIADH by a more specific effect, diminishing the natriuresis in association with increased inner medullary urea content (25). These data are consistent with the concept that solute excretion is a determinant of free water excretion (26).

The first demonstration of efficacy of oral urea was published 30 years ago in a series of patients with SIADH (8). Since then, urea has been given in a large population of euvolemic hyponatremia in adults (12,13) or children (27,28) and in short-term (13) or long-term (years) (12,29–31) use. Oral urea has also been used for other indications, such as Ménière disease (32), glaucoma, and brain edema (33). Urea is also available for intravenous delivery (Ureaphil, Abbott) and can be administered in the intensive care unit *via* gastric tube (13). In patients with nephrogenic syndrome of inappropriate antidiuresis and those with gain-of-function $AVPR_2$ mutations (29), vaptans are not effective but urea can be used to correct the hyponatremia (27).

An unpleasant taste is a largely overstated problem with oral urea; in our experience, only about 15% of patients discontinue treatment for this reason. No participants reported unpleasant taste of urea during our long-term study.

Although urea has been used for decades in many patients, even those with severe hyponatremia, we are not aware of any cases of osmotic demyelination syndrome among urea-treated patients in our practice, and no cases have been reported in the literature. It is now well demonstrated that urea protects the brain against myelinolysis caused by inappropriate correction of chronic hyponatremia (12,34–37).

Growing evidence suggests that a patient with chronic hyponatremia, even mild (128–134 mEq/L), should not be left untreated. Indeed, even if mild to moderate chronic hyponatremia is generally considered "asymptomatic," the symptoms are often subtle and sometimes difficult to detect but are not without consequences (38). A decreased serum sodium level is associated with attention and posture deficits, gait instability, and increased falls (mainly in the elderly) (39). The risk for bone fracture is also increased, and hyponatremia is responsible for the development of osteoporosis (40–43).

Chronic hyponatremia could also increase oxidative stress, thereby increasing manifestations of senescence in animals (44). Nevertheless, no studies have shown the benefit of treating mild to moderate hyponatremia (whether symptomatic or not) in terms of quality of life, morbidity, and mortality in SIADH. Whether mortality in patients with hyponatremia is related to the electrolyte disorder itself or to the underlying illness is also controversial (45).

In patients with congestive heart failure (with or without hyponatremia), analysis of mortality is inconclusive (46); thus, the indications for vaptans in the short- and long-term treatment of mild to moderate chronic hyponatremia remain to be determined.

Although data on cost-effectiveness and clinical benefit for the available alternative treatments (water restriction, furosemide and salt, urea) are also lacking (47,48), it seems logical to give priority to those "classic" approaches. Vaptans are more expensive than urea, and this study has shown that their efficacy and tolerability are similar to those of urea; thus, urea appears to be the easier and appropriate choice in this setting. Prospective trials comparing both drugs on the different aspects of treatment, efficacy, quality of life, morbidity, and mortality are needed (47).

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Disclosures

G.D. has participated in clinical trials sponsored by Sanofi, Wyeth, Cardiokine, and Otsuka. A.S. has participated in clinical trials sponsored by Sanofi and Cardiokine.

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