Use of Oral Vasopressin V₂ Receptor Antagonist for Hyponatremia in Acute Brain Injury

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Dear Sir,

Hyponatremia, defined as an excess of water in relation to sodium in the extracellular fluid, is the most common electrolyte abnormality after brain injury [1, 2]. Excessive release of arginine vasopressin (AVP) following brain injury causes renal water reabsorption, which leads to dilutional hyponatremia, i.e. the syndrome of inappropriate release of antidiuretic hormone (SIADH) [2, 3]. In the injured brain, this hypo-osmotic state produces an osmotic gradient that shifts water from the extracellular to the intracellular compartment. As a result, headache, nausea, vomiting, lethargy, restlessness, disorientation and depressed reflexes can be observed [4]. Severe hyponatremia, especially when the condition develops rapidly as seen in acute brain injury, can manifest as seizures, coma, decerebrate posture, respiratory arrest and death [1]. Therefore, it is important to detect and reverse hyponatremia promptly in acutely brain-injured patients.

Until recently, pathophysiology-targeted therapy for SIADH had not been available and conventional treatments were frequently suboptimal [2, 5, 6]. AVP receptor antagonistic agents have been developed to promote urinary excretion of water, i.e. aquaresis and the increase in serum sodium concentration. Although a nonselec-

tive AVP receptor antagonist, conivaptan has shown an effective increase in serum sodium levels in a limited number of brain-injured patients [7–10], and the need for a dedicated intravenous line and its potential side effects due to actions on the AVP V_{1A} receptor limit its use [11–13]. Tolvaptan is an oral AVP V₂ receptor antagonist, having a 1.8 times greater affinity for the V₂ receptor compared with AVP and a 29-fold greater selectivity for the V₂ receptor than the V_{1A} receptor [14]. Binding of AVP to the V₂ receptor in the basolateral membrane of renal collecting duct cells results in the phosphorylation of aquaporin-2 channels, which allows reabsorption of free water from the collecting duct [6, 15]. V₂ receptor blockers interfere with water reabsorption and therefore mediate aquaresis. This drug has been shown to be effective in correcting hyponatremia from various diseases such as heart failure and cirrhosis [13]. However, clinical studies to date have only included patients without neurological disorders [5, 16].

In this study, we evaluated the efficacy of tolvaptan administration for the correction of hyponatremia in patients with acute brain injury. In selected patients, we explored the effects of tolvaptan on intracranial pressure (ICP) and other physiological variables.

Patients and Methods

Patients

This study considered all patients admitted to the Neurological Intensive Care Unit at Columbia University Medical Center from October 1, 2010, to October 30, 2011, where tolvaptan was prescribed at the discretion of an attending neurointensivist for the correction of hypervolemic or euvolemic hyponatremia. We included patients who (1) were 18 years of age or older; (2) had acute brain injury, and (3) received tolvaptan (Samsca®; Otsuka, Tokyo, Japan) while admitted to the neurological intensive care unit. We excluded patients whose serum sodium concentrations were not measured daily from 24 h before to 48 h after tolvaptan administration. Tolvaptan was given to symptomatic or asymptomatic patients with euvolemic or hypervolemic hyponatremia resistant to traditional therapies, including hypertonic saline, and fluid restriction.

Data Acquisition

We queried the hospital pharmacy database for all patients who received tolvaptan while in the neurological intensive care unit and met inclusion criteria for this study. Detailed patient information was retrieved from hospital medical records.

Table 1. Patient characteristics

No.	Age	Sex	Diagnosis	Days to 1st dose ^a	Hours to 2nd dose ^b	Baseline sodium ^c	Maximum sodium ^d	Hours to maximum ^e	Δ sodium over 24 h ^f	Δ sodium over 48 h ^g	GCS admission	GCS discharge ^h
1	69	M	CNS infection	2	–	133	143	33	9	10	14	14
2	32	M	brain tumor	2	–	128	138	12	7	4	15	15
3	78	M	CNS infection	3	–	130	137	19	7	7	15	15
4	44	F	SAH	1	–	130	139	9	7	4	4	14
5	68	M	SAH	3	–	132	146	37	9	8	6	13
6	72	M	brain tumor	5	–	133	141	21	8	5	12	15
7	60	F	encephalopathy	7	–	133	144	25	11	10	7	11
8	80	F	brain tumor	1	19	121	133	28	12	10	14	15
9	89	M	ischemic stroke	2	27	128	137	38	4	9	10	9
10	69	F	SAH	8	24	126	145	12	17	16	10	12
11	49	F	SAH	1	31	123	141	50	11	18	15	15
12	79	F	ICH, IVH	2	29	129	137	20	8	8	9	10
13	66	F	SAH	3	23	130	137	40	4	7	11	15
14	57	M	CNS infection	1	18	126	150	26	24	18	15	14
15	28	M	seizure	7	20	132	138	60	5	6	3	3
16	64	F	SAH	2	24	130	140	36	7	7	15	14
17	63	F	seizure	1	48	132	140	56	2	5	5	3

CNS = Central nervous system; SAH = subarachnoid hemorrhage; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage.

^a Duration of hyponatremia (serum sodium <135 mEq/l) until administration of 1st dose of tolvaptan.

^b Time interval from 1st to 2nd dose when tolvaptan was administered twice.

^c All values were obtained within 24 h before the 1st dose of tolvaptan, and the results of latest measurements are shown (mEq/l).

^d Maximum levels of serum sodium within 96 h after the last dose (mEq/l).

^e Time interval from 1st dose of tolvaptan to maximum levels of serum sodium.

^f Increase in serum sodium levels over 24 h since tolvaptan administration.

^g Increase in serum sodium levels over 48 h since tolvaptan administration.

^h GCS discharge from the neurointensive care unit.

Extracted data included patient demographics, neurological diagnosis, the dose and frequency of tolvaptan, administration route (per oral vs. tube), concurrent use of hypertonic saline, mannitol, diuretics, mineralocorticoids, demeclocycline, lithium chloride and urea, serum concentrations of sodium, potassium and creatinine, calculated serum osmolality ($2 \times \text{sodium} + \text{glucose}/18 + \text{urea nitrogen}/2.8$), urine output, net fluid balance (total intake minus total output) and Glasgow Coma Scale (GCS) from 24 h prior to the first dose to 96 h after the last dose of tolvaptan. ICP as well as cerebral perfusion pressure (CPP) and mean arterial pressure (MAP) were also reviewed when available. This retrospective study was approved by the institutional review board of our center.

Data Analysis

A baseline sodium level was defined as the last sodium level before the first dose

of tolvaptan was administered. The maximum sodium level was defined as the highest level within 96 h after the last dose. Study day (from day 0 to day 4) was defined as each 24-hour epoch after tolvaptan administration. Multiple measurements of laboratory tests, urine output, net fluid balance, GCS, ICP, CPP and MAP were averaged over study days. For example, if a patient's sodium level was 132 mEq/l, and a follow-up test 8 h later revealed a sodium level of 128 mEq/l, and tolvaptan was given 2 h later, his or her baseline sodium level was 128 mEq/l and averaged sodium level on day 0 was 130 mEq/l. The change in the average daily area under the curve was also calculated from baseline to day 4: the area under the curve for each patient, divided by the observation period (4 days), minus the baseline sodium value [5].

To assess daily changes in laboratory test results, urine output, net fluid balance and GCS, averaged daily values were compared with those of baseline or day 0 using

the Wilcoxon signed-rank test. All statistical comparisons were performed according to the frequencies of tolvaptan administration: single, double, and any (single or double) doses. A two-tailed *p* value of <0.05 was considered to indicate a significant difference. SPSS for Windows, version 17.0 (SPSS, Inc., Chicago, Ill., USA) was used for all statistical analyses.

Results

During the study period, 19 patients received tolvaptan in the neurological intensive care unit. Two patients were excluded from the analysis because serum sodium concentrations were not measured after tolvaptan was given: 1 patient was transferred to another hospital the day after tolvaptan administration and the other patient was transitioned to hospice care on the day of tolvaptan administration. The remaining 17 patients were included in the

Table 2. Sodium response sorted by doses of tolvaptan

	Single dose (n = 7) ^a	Double dose (n = 10) ^b	p value ^c	Any dose (n = 17)
Serum sodium, mEq/l				
Day 0	130.6±2.4	127.7±3.0	0.026	128.9±3.1
Day 1	137.0±2.5	133.0±4.5	0.034	134.7±4.3
Day 2	138.7±3.5	137.6±4.1	0.434	138.1±3.8
Day 3	134.3±2.9	136.1±3.8	0.416	135.4±3.5
Day 4	134.7±3.8	135.2±3.3	0.883	135.0±3.4
Day 5	–	134.7±4.7	–	134.9±4.6
Maximum levels during follow-up	141.1±3.3	139.8±4.8	0.364	140.4±4.2
Maximum changes from baseline levels	9.9±2.3	12.1±6.1	0.887	11.2±4.9
Hours from baseline to maximum levels	22.3±10.3	36.6±15.6	0.043	30.7±15.1
Hours from first to second doses	–	26.3±8.7	–	–

Values were averaged daily, except for baseline and maximum values. ^a Observed until 96 h after first doses. ^b Observed until 96 h after second doses. ^c Comparison between single-dose users and double-dose users.

final analysis: their median age was 66 years [interquartile range (IQR) 53–75 years], and 8 (47%) were male. Serum sodium concentrations were measured 5.4 ± 1.7 times in the first 2 days and 9.0 ± 3.4 times over 4 days after tolvaptan administration. In 4 patients (Nos. 2, 5, 12 and 16 in table 1), ICP was monitored using ventriculostomy catheter (Ventriclear™; Medtronic, Inc., Minneapolis, Minn., USA) during the study period.

Table 1 shows characteristics of 17 patients. The median time interval from admission to the administration of tolvaptan was 10 days (IQR 3–14.5 days). The median time interval from the detection of hyponatremia to the first administration of tolvaptan was 2 days (IQR 1–4 days). Single dosage of tolvaptan was 15 mg in all cases. Tolvaptan was given once to 7 patients (single-dose users) and twice to 10 patients (double-dose users): a median time interval from the first to the second dose was 24.0 h (IQR 19.8–29.5 h). No patients were given tolvaptan more than twice during the study period. The degree of hyponatremia was milder ($p = 0.026$) and the time intervals to maximum sodium levels were shorter ($p = 0.043$) in single-dose users although the maximum sodium levels were not significantly different in both groups (table 2). Doses were given orally in 8 patients, by nasoduodenal tubes in 8 patients, and by gastrostomy tube in 1 patient. In all cases, hypertonic saline, mannitol, diuretics, mineralocorticoids,

demeclocycline, lithium chloride and urea were not administered after tolvaptan. Serum concentrations of sodium, potassium, creatinine and serum osmolality were measured daily on days 0–2 in all patients and on days 3–4 in 15 patients. Urine output, net fluid balance and GCS were documented on days 0–4 in all patients. ICP and CPP concurrently with MAP were measured in 4 patients (2 single-dose users and 2 double-dose users).

Correction of Hyponatremia

All patients had hyponatremia, defined as a serum sodium concentration <135 mEq/l [17], at the time of tolvaptan administration. Mean $\pm$ SD baseline serum sodium was 131.3 ± 2.0 mEq/l in single-dose users and 127.7 ± 3.7 mEq/l in double-dose users. First follow-up measurements were performed 7.2 ± 4.0 h (median 8.0, IQR 4–10 h) after administration of tolvaptan and showed an increase in sodium levels by 4.1 ± 4.6 mEq/l ($p < 0.001$). Serum sodium on day 0 was 130.6 ± 2.4 mEq/l in single-dose users and 127.7 ± 3.0 mEq/l in double-dose users. Serum sodium concentrations increased in all cases after tolvaptan was given. Serum sodium levels increased by an average of 5.7 ± 2.1 mEq/l in single-dose users and 5.3 ± 5.0 mEq/l in double-dose users by day 1, and increased by an average of 7.4 ± 2.2 mEq/l in single-dose users and 9.9 ± 5.5 mEq/l in double-dose users by day 2. The change in the average daily area under the curve for the serum sodium con-

centration from baseline to day 4 was 5.2 ± 1.9 mEq/l in single-dose users and 7.8 ± 4.2 mEq/l in double-dose users. Sodium changes ≤ 12 mEq/l over 24 h were seen in 15 (88%) patients, and the changes ≤ 18 mEq/l over 48 h were seen in 17 (100%) patients. Sodium changes over 24 h were 12 mEq/l in 1 patient and the changes over 48 h were 18 mEq/l in 2 patients. All patients who were borderline or out of these ranges were double-dose users (Nos. 8, 10, 11 and 14 in table 1).

Maximum sodium concentrations were 141.0 ± 3.3 mEq/l in single-dose users and 139.8 ± 4.8 mEq/l in double-dose users, and maximum changes from baselines were 9.9 ± 2.3 mEq/l after 22.3 ± 10.3 h in single-dose users and 12.1 ± 6.1 mEq/l after 36.6 ± 15.6 h in double-dose users (table 2). Mean serum sodium levels were higher on days 1 and 2 compared with those on day 0 in single-dose users ($p = 0.001$) and on days 1 through 5 in double-dose users ($p = 0.001$) (fig. 1).

Other Laboratory and Physiological Changes

Serum osmolality significantly increased on days 1–2 in single-dose users (275.1 ± 2.2 mmol/l on day 0, 286.9 ± 5.1 mmol/l on day 1, and 287.0 ± 5.0 mmol/l on day 2) and on days 1–4 in double-dose users (266.0 ± 6.9 mmol/l on day 0, 278.9 ± 9.1 mmol/l on day 1, 288.3 ± 7.2 mmol/l on day 2, 282.9 ± 6.7 mmol/l on day 3, and 281.6 ± 6.8 mmol/l on day 4) ($p < 0.05$)

Fig. 1. Changes of serum sodium and osmolality after administration of tolvaptan. Triangles indicate 15 mg of tolvaptan. Error bars represent means and 95% CIs; * $p < 0.05$ compared with day 0.

(fig. 1). Serum creatinine concentrations did not show any significant changes, but potassium concentrations increased by 0.2 ± 0.2 mEq/l only on day 1 in single-dose users. Urine output increased by 2.3 ± 1.9 liters on day 1 in single-dose users ($p = 0.038$), but the increase by 0.8 ± 1.5 liters was not statistically significant in double-dose users. Net fluid balance did not show significant changes (fig. 2).

None of the patients showed a significant change in GCS associated with tolvaptan administration. In 4 patients with invasive neuromonitoring, ICP, CPP and MAP did not change significantly after administration of tolvaptan (fig. 3).

Newly developed hemodynamic instability, seizures or symptoms suggesting osmotic demyelination were not noted in any patients during the study period or during the hospitalization.

Discussion

The main finding of our study is that oral tolvaptan effectively corrected hyponatremia in nontraumatic brain-injured patients in the acute setting. Serum sodium concentrations increased approximately 5.5 mEq/l in 24 h and 7.5 mEq/l in 48 h after one dose of 15 mg tolvaptan. After a second dose on the next day, serum sodium concentrations increased approximately 10 mEq/l in 48 h. These results are comparable to the increases in serum sodium levels after tolvaptan in other populations [5, 18] and those by an intravenous nonselective AVP receptor antagonist in brain-injured patients [7–9]. Sodium changes over 24 and 48 h were mostly in accordance to current recommendations (correction of hyponatremia to <12 mEq/l in 24 h and to <18 mEq/l in 48 h) [19]. However, 2 patients were outside these ranges, both of them were double-dose users.

As opposed to other causes of chronic hyponatremia, the time course for correction of hyponatremia in brain injury needs to be considered. Hyponatremia in the acute brain-injury patients can lead to neurological deterioration, cerebral edema, increased ICP, and ultimately is associated with poor outcomes [2, 4]. Rapid correction increases the risk of osmotic demyelination [1, 2, 20]. With tolvaptan, we found a prompt correction of sodium levels on average 4.1 mEq at 8 h after enteral administration. With regard to a maximal change in sodium levels, an approximately 10-mEq increment was achieved at 22 h after single doses and a 12-mEq increment was achieved at 37 h after double doses. The effect lasted for 2 days in single-dose users and at least 4 days in double-dose users, consistent with the pharmacokinetics of tolvaptan (peak concentration in 2 h and elimination half-life of 9.4 h). It is unknown how multiple re-

Fig. 2. Urine output and net fluid balance after administration of tolvaptan. Triangles indicate 15 mg of tolvaptan. Error bars represent means and 95% CIs; * $p < 0.05$ for compared with day 0.

peated doses of tolvaptan will affect serum sodium levels.

Aquaresis may be an inappropriate, potentially harmful treatment for patients with hypovolemic, hypo-osmotic hyponatremia (cerebral salt wasting) and is a safety concern with the use of tolvaptan in the brain-injured population [20, 21]. We were careful to treat only patients who were euvolemic or hypervolemic, but the assessment of volume status is very challenging in the critically ill setting. As expected, we observed a transient increase in urine output over the first day, reflecting the mechanism of the drug. However, the daily fluid balance did not change significantly, suggesting that fluid intake was increased concomitantly. No detrimental clinical signs of hypovolemia, such as decreases in MAP, GCS or change in creatinine and osmotic demyelination, were noted. Preliminary reports suggest that conivaptan, an unselective V_{1A} and V_2 receptor antagonist, might

reduce cerebral edema and ICP [9, 10]. This ICP-lowering effect has been hypothesized to be mediated through the V_{1A} receptor and aquaporin-4 channel expressed by astrocytes in the brain [10, 22–26]. Although V_2 receptors are also expressed in the brain, animal studies are inconclusive regarding the role of V_2 receptor antagonists in the reduction of cerebral edema [3, 24, 26, 27]. V_2 receptor antagonists' ability to reduce cerebral edema in humans has not been studied.

Although tolvaptan's effect on sodium concentration was similar to that of conivaptan [7, 11], our results suggest that tolvaptan does not have any significant effects on ICP. Possible explanations include no physiologic effects of V_2 receptor antagonism on cerebral edema and ICP, lower baseline ICP in our patients compared with those in the previous study (13.7 ± 2.9 vs. 18.0 ± 10.4 mm Hg) [9], or the changes were too small and transient for our study

to detect them. Given the limitations in the current study, any conclusions regarding tolvaptan's effect on cerebral edema should be made cautiously. Larger prospective studies are necessary to investigate whether AVP receptor antagonists can reduce ICP and cerebral edema in acutely brain-injured patients.

In addition to the inherent limitations of a small retrospective design, this study has other limitations. First, our practice was to use tolvaptan only when we were confident that the patient was either hypervolemic or euvolemic. The causes of hyponatremia in our patients are believed to be SIADH, but differentiating SIADH from cerebral salt wasting is often challenging [28]. The possibility that other conditions, such as hypothyroidism, hypoadrenalism, hypovolemia, hypotension, positive-pressure ventilation, pain, stress, nausea and drugs, might have contributed to hyponatremia could not be completely excluded

Fig. 3. Changes of GCS, ICP, CPP and MAP after administration of tolcapitan. Triangles indicate 15 mg of tolcapitan. Error bars represent means and 95% CIs.

[2]. Second, in all the patients we first attempted conventional treatments to correct hyponatremia before giving tolcapitan. Conventional treatments have an unreliable time course of effects. It is possible that some of the conventional treatments, although discontinued with the addition of tolcapitan, might have influenced the rate

or degree of sodium changes after tolcapitan. Third, only a small number of patients had intracranial monitoring, making conclusions about effects on cerebral edema difficult.

In summary, this preliminary study showed that tolcapitan was effective for the correction of hyponatremia in hypervol-

emic or euvolemic acute nontraumatic brain-injured patients. Larger prospective studies are necessary to confirm our findings and to further evaluate the role of tolcapitan in the treatment of acute brain-injured patients, particularly for assessing its utility on cerebral edema and ICP.

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