Original Article

Experience with Tolvaptan for Euvolemic and Hypervolemic Hyponatremia in the Acute Care Setting

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ABSTRACT

Background: Hyponatremia is a common electrolyte disorder and is associated with multiple comorbidities. Management strategies are varied and etiology-dependent. The use of tolvaptan, a vasopressin antagonist, outside of clinical trials has not been well characterized.

Objectives: To quantify tolvaptan compliance with institutional guidelines and make recommendations concerning reasonable expectations for its role in hyponatremia management.

Methods: This was a retrospective observational study in a 125-bed community hospital. Patients admitted in 2013 who received at least one dose of tolvaptan were included.

Results: Thirty-seven patient encounters were evaluated. Tolvaptan was prescribed with 83.7% adherence to the institutional order set. Mean age was 71 ± 16.4 years with 20 (54%) females. Hyponatremia was a contributory cause of admission in 15 (40.5%) patients and offending medications were discontinued in 7 (19%). Causes of hyponatremia included syndrome of inappropriate antidiuretic hormone (SIADH), heart failure, and cirrhosis in 78.3%, 8.2%, and 13.5% of participants, respectively. Management included fluid restriction in 19 (51%) and furosemide in 5 (13.5%), with tolvaptan administration on average 3.2 days after admission. Most patients (78.4%) required ≤ 2 doses. Sodium concentration was elevated 8 mEq/L by the end of hospitalization. Discharge to palliative care or death occurred in 8 (21.6%). Postdischarge review revealed 3 (8%) maintained sodium concentration ≥ 130 mEq/dL.

Conclusion: Tolvaptan was initiated after other interventions and with limited duration per institutional guidelines. This cohort had complicating underlying chronic diseases. These results will be used to refine recommendations with pharmacist input for risk/benefit stratification based on reasonable expectations.

Key Words—hyponatremia, tolvaptan, SIADH

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Hyponatremia is an electrolyte disturbance where there is a relative or actual excess of body water compared to total body sodium. Low sodium is the most common electrolyte disorder in hospitalized patients, and it has been cited as a component of up to 20% of hospital admissions.¹ Prevalence of hyponatremia in the United States

has been estimated at 1.72%, and the condition is a potential predictor of mortality.² Chronic asymptomatic hyponatremia has been associated with increased hospital admissions for falls.³ Symptoms of hyponatremia include confusion, lethargy, muscle weakness, and cramps. The severity of hyponatremia in a given patient is based on not only serum sodium

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concentration but also the duration and speed of sodium depletion and patient symptoms.⁴ With more severe sodium depletion, patients could experience falls or seizures. Excessive endogenous vasopressin (antidiuretic hormone) is thought to be a contributing cause in many circumstances. Treatment strategies center on the correction of the underlying cause, if possible, and the patient's blood volume status. Management may involve administration of sodium-containing fluids or fluid restriction. Removal of drugs that can cause excessive endogenous vasopressin is also essential. Because hyponatremia is associated with many conditions, there has been variation in management approaches with very little published consensus.⁴

In 2009, the US Food and Drug Administration (FDA) approved tolvaptan, an oral agent indicated for the treatment of clinically significant hyponatremia in symptomatic patients who have been resistant to other methods of sodium correction.⁵ Its boxed warning emphasizes the need to initiate therapy in the hospital with close serum sodium monitoring.⁵ Tolvaptan works as a selective vasopressin V₂-receptor antagonist.⁵ Its approval was based on efficacy findings from placebo-controlled clinical trials in patients with hyponatremia. Use of tolvaptan compared with placebo led to improvements in mild or marked hyponatremia; however hyponatremia recurred when tolvaptan was discontinued.⁶ Tolvaptan, when evaluated in a randomized, double-blind, placebo-controlled study in patients hospitalized for heart failure, did not demonstrate reductions in heart failure rehospitalization rate or all-cause or cardiovascular mortality.⁷ Tolvaptan has an average wholesale price of \$375 for a single 15 mg or 30 mg tablet.⁸

Since the availability of tolvaptan, very little has been published about its use outside of clinical trial settings. Hyponatremia results from many conditions and is managed by hospitalists with varied backgrounds.⁴ Although tolvaptan has been proven effective to increase sodium levels, the conducted studies were short-term and very little is known about patient hospital experience or follow-up. We retrospectively reviewed our clinical experience with tolvaptan to evaluate adherence to institutional recommendations and help define reasonable expectations for its role in hyponatremia management.

METHODS

This retrospective study was carried out at a 125-bed community hospital that provides health services including maternity, surgery, cardiovascular, cancer

care, and intensive care. General medical patients are cared for by inpatient care specialists (hospitalists). Local institutional review board exemption was obtained. All patients who received tolvaptan during the 12 months of 2013 were identified by charge data. Any patient who received at least one dose was included in the analysis. No further eligibility data were applied. Data were collected using electronic and paper medical records.

Collected information included age, gender, admission diagnoses, associated co-morbidities, serum sodium at baseline, quantity of tolvaptan, and length of stay. Additionally, charts were reviewed to determine that the baseline serum sodium levels were obtained according to the hospital's clinical standard procedures and that subsequent levels were obtained as needed. Initial therapies such as fluid restriction or administration of sodium-containing fluids and discontinuation of any medications contributing to hyponatremia were documented. Discharge summaries were read to determine whether continuation of tolvaptan therapy outpatient was indicated. A review of readmission data, when available, provided evidence of longer term outcomes including maintained serum sodium levels.

Our institution utilizes an order set for vasopressin antagonist therapy including tolvaptan (**Figure 1**). With initiation of the order set, therapy is restricted to euvolemic or hypervolemic hyponatremia when serum sodium level is less than 125 mEq/L or in patients with less severe hyponatremia with resistance to other therapies. Degree of prescriber compliance with utilizing the order set was also noted.

RESULTS

During the study period, tolvaptan was administered to 32 patients during 37 hospital admissions. In the majority of cases, it was prescribed by hospitalists. Patient demographics and comorbidities are outlined in **Table 1**. Mean age of the participants was 71 ± 16.6 years, and 20 (54%) were female. Causes of admission were varied and included pneumonia, respiratory failure, weakness, and cancer; however, hyponatremia was identified as a primary contributor to admission in 40.5% of patients. Potentially offending medications including hydrochlorothiazide, citalopram, metaxalone, fluoxetine, and olanzapine were discontinued in 7 (19%) patients. Elevated N-terminal pro-brain natriuretic peptide (NT-proBNP > 100 pg/mL) was noted in 15 patients. Serum creatinine was in an optimal range (≤1.0 mg/dL) in 89.1% of encounters; tolvaptan was withheld

Tolvaptan Hyponatremia Acute Care

Reminders for prescriber

- ▶ *Restricted to EUVOLEMIC or HYPERVOLEMIC hyponatremia when serum sodium level is LESS THAN 125 mEq/L. May also be used in patients with less severe hyponatremia (serum sodium level greater than or equal to 125 mEq/L) who demonstrate signs/symptoms of hyponatremia resistant to other therapies.*
- ▶ **WARNING:** Rate of correction of hyponatremia: Osmotic demyelination may occur if the rate of sodium correction exceeds 10 mEq/L in the first 24 hours, or 18 mEq/L in the first 48 hours.
- ▶ When initiating or titrating dose, suggest that fluid intake NOT be restricted for the first 24 hours of therapy

Medications

Information for prescriber and pharmacist:

- ☒ Use of the vasopressin antagonist order set is MANDATORY to order initiation and titration doses of conivaptan or tolvaptan. Conivaptan (Vaprisol) must be re-ordered daily and a new order set must be used with each dose of conivaptan. Handwritten orders will NOT be accepted in pharmacy.
- ☒ Conivaptan use is not allowed on all patient care units in all facilities; refer to the Medications Restricted by Location Tables for more information (RRMC and Greater Charlotte Market only)
- ☒ Drug interactions: Concurrent use with potent CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, ritonavir, indinavir, nelfinavir, saquinavir, clarithromycin, nefazodone) is CONTRAINDICATED. NOTE: Medication list is not all-inclusive.
- ☒ If drug interaction noted, pharmacist to call physician for instruction

conivaptan (Vaprisol): Must be re-ordered daily using new order set; maximum duration is 96 hours

- ☐ CrCl > 60 ml/min and NO liver disease: 20 milligrams IV piggyback x1 as bolus, give over 30 minutes. Then start 20 milligram IV infusion over 24 hours x 1 dose
- ☐ CrCl 30 - 60 ml/min and NO liver disease: 10 milligrams IV piggyback x1 as bolus, give over 30 minutes. Then start 10 milligram IV infusion over 24 hours x 1 dose
- ☐ Liver disease: 10 milligrams IV piggyback x1 as bolus, give over 30 minutes. Then start 10 milligram IV infusion over 24 hours x1 dose
- ☐ _____ milligrams IV piggyback x1 as bolus, give over 30 minutes
- ☐ _____ milligrams IV infusion over 24 hours x1 dose

tolvaptan (Samsca)

- ☐ Initial dose: 15 milligrams orally x1 dose
- ☐ Initial dose: 15 milligrams orally daily
- ▶ *Titration MUST be done by the prescriber. If patient has received tolvaptan for greater than or equal to 24 hours AND serum sodium remains less than 130 mEq/L AND increase from baseline is less than 5 mEq/L, the prescriber may select one of the doses below:*
- ☐ Titration dose: 30 milligrams orally daily
- ☐ Titration dose: 60 milligrams orally daily

Laboratory

- ☒ BMP as baseline, unless done this AM
- ▶ *Prescriber MUST check one of the following BMP options below*
- ☐ BMP every 6 hours x 24 hours, then once a day while on therapy
- ☐ BMP every 12 hours x 24 hours, then once a day while on therapy
- ☐ BMP once a day while on therapy
- ☐ Digoxin level once in am (vasopressin antagonists may increase digoxin levels)

Nursing Orders

- ☒ Dedicated IV access is required: PICC or central line preferred or large vein (avoid hand) #20 gauge or larger (conivaptan only)
- ☒ Monitor conivaptan infusion site for erythema and pain and change site if present
- ☒ Change conivaptan infusion site every 24 hours if IV is peripheral and signs of injection site reactions
- ☒ Blood pressure checks every 30 minutes x2 after start of conivaptan infusion; then every 4 hours x24 hours, then per Unit protocol
- ☒ Flush conivaptan IV line with Dextrose 5% ONLY
- ☒ Strict intake and output (hourly). Call MD if output is greater than _____ or less than _____ over 2 hours
- Hold conivaptan / tolvaptan and notify physician if:
 - ☒ SBP less than 90 mm Hg
 - ☒ Serum sodium level above 132 mEq/L
 - ☒ If serum sodium increases by more than 10 mEq/L in the first 24 hours OR increases by more than 18 mEq/L in the first 48 hours of therapy

Figure 1. Institutional vaptan order set.

Table 1. Characteristics of the patient population

Characteristics	<i>n</i> (%) or mean (<i>SD</i>)
Assessable patient encounters	37 (100%)
Female	29 (54%)
Age, years	71 (16.6)
Comorbidity contributing to hyponatremia	
Heart failure	3 (8.2%)
Cirrhosis	5 (13.5%)
SIADH and other	29 (78.3%)
Urine osmolality, mOsm/kg	380.6 (148.2)
Urine sodium, mmol/L	49.9 (30.7)
Thyroid stimulating hormone, mU/mL	2.9 (1.9)

Note: SIADH = syndrome of inappropriate antidiuretic hormone secretion.

with creatinine clearance less than 10 mL/min. Documented causes of hyponatremia were noted to include syndrome of inappropriate antidiuretic hormone secretion (SIADH) or other, heart failure, and cirrhosis in 78.3%, 8.2%, and 13.5% of participants, respectively.

Details including hospital course, length of stay, number of tolvaptan doses, serum sodium levels, and follow-up data are given in **Table 2**. The average length of stay was 8.5 days. Prior management strategies included fluid restriction in 19 patients (51%) and furosemide in 5 patients (13.5%), with tolvaptan administration on average 3.2 days after administration. The tolvaptan order set was completed in 83.7% of instances; in some cases, it was completed by a nurse or pharmacist after the initial physician written order. Prior to tolvaptan initiation, the majority of patients (73%) had serum sodium less than 125 mEq/L, which has been defined as severe or profound hyponatremia, with the rest of the patients having moderate hyponatremia (serum sodium concentration, 125-129 mEq/L).⁴ The majority of patients (78.4%) required 2 or fewer tolvaptan doses. From the initiation of tolvaptan until the end of the hospital stay, serum sodium was elevated, on average, 8 mEq/L. The impact of tolvaptan during the course of the hospitalization is shown in **Figure 2**. Upon discharge from the hospital, mild hyponatremia (serum sodium concentration, 130-135 mEq/L) was observed in 40.5% of patients, and sodium concentration greater than 135 mEq/L was noted in 10.8%. Discharge to palliative care or death occurred in 8 patients (21.6%).

Table 2. Hospital course and impact of tolvaptan (*N* = 37)

Hospital course and impact	<i>n</i> (%) or mean (<i>SD</i>)
Length of stay, days	8.5 (6.2)
Prior management strategies	
Fluid restriction	19 (51.4%)
Loop diuretics	5 (13.5%)
Medical service prescribing tolvaptan	
Hospitalist	31 (83.7%)
Nephrology	5 (13.5%)
Oncology	1 (2.8%)
No. of days in hospital prior to receiving tolvaptan	3.2 (3.1)
Completion of order form	31 (83.7%)
Doses of tolvaptan	
Less than 2	29 (78.4%)
3 or more	8 (21.6%)
Serum sodium, mEq/L	
Prior to tolvaptan	122 (4.3)
End of hospital stay	130 (4.8)
Follow-up information	
None available	17 (45.9%)
Evidence of sodium ≥ 130	3 (8.1%)
Expired within 30 days	3 (8.1%)
Expired within 3 months	1 (2.7%)
Palliative care/hospice	4 (10.8%)
Readmitted (received tolvaptan again)	4 (10.8%)
Readmitted (other)	5 (13.5%)

Postdischarge review of readmission data (when available) revealed 3 patients (8%) maintained serum sodium level at 130 mEq/L or higher.

DISCUSSION

Our review of tolvaptan use in the community hospital setting demonstrated over 80% compliance with institutional criteria. Immediately prior to tolvaptan administration, the majority of patients (73%) had serum sodium less than 125 mEq/L. The determination of urgency for intervention to correct serum sodium is typically based on the patient's neurologic status. In just under half of the patients in our cohort, hyponatremia was a contributing cause

Figure 2. Extent of biochemical hyponatremia prior to tolvaptan initiation and at the end of hospitalization.⁴ Severe hyponatremia = serum sodium concentration < 125 mEq/L; moderate hyponatremia = serum sodium concentration 125-129 mEq/L; mild hyponatremia = serum sodium concentration 130-135 mEq/L.

to hospitalization. Tolvaptan was initiated an average of 3.2 days after hospital admission, which in the majority of cases occurred after other interventions, including removal of potential contributory medications, administration of loop diuretics, and fluid restriction. This cohort had multiple complicating underlying chronic diseases and potential offending medications, which is consistent with the associated conditions in persons with hyponatremia.⁹ In our population, hyponatremia was attributed to SIADH in 78.3%.

In general, the management of hyponatremia is complicated by complex comorbidities of the presenting patient population, the lack of well-designed studies in the field, the varied backgrounds of clinicians, and the potential risks involved with treatments.^{4,10} The potential for neurologic damage exists with too rapid sodium correction or from the hyponatremia itself.¹⁰ Fluid restriction has been a supported strategy in the setting of SIADH-associated hyponatremia, although it is not a highly evidence-based strategy.⁴ Successful fluid restriction can raise serum sodium by 2 to 3 mEq/L and requires significant patient compliance. In this cohort of very ill patients with multiple comorbidities, and in some cases heading toward palliative care, fluid restriction may not be the most optimal management strategy. The vasopressin receptor

antagonism produced by tolvaptan theoretically directly addresses the pathophysiology of SIADH-associated hyponatremia. However the effects of the vaptans are short-term, and there is considerable drug cost involved.^{6,8,9} Individualized review of risk factors, development of methods to focus on risk reduction, and setting individualized sodium targets are strategies that can be undertaken by health systems to optimize patient care and reduce costs.⁹

Part of a comprehensive plan to optimize care would include defining reasonable expectations in terms of the impact of hyponatremia on the patients' health-related quality of life.⁹ Ultimate goals for patients may differ in respect to clinical goals such as improving gait and reducing fall risk, in addition to changes in absolute numbers of serum sodium. The goal serum sodium concentration may be individualized depending on patient risk factors. For example, a malnourished patient or a patient with alcohol dependency may have different sodium concentration goals than someone with chronic pulmonary disease. Reviewing and monitoring these factors is an important role for pharmacists.⁹

Education to providers and modifications to the institutional order set are anticipated outcomes of these findings. A multidisciplinary team-based approach, including pharmacist involvement, to

understanding the hyponatremia pathophysiology in a given patient and managing it accordingly is essential. Some modifications may include options for target ranges for sodium, such as indicating a range of 125-130 mEq/L with a maximum limit, and using performance-related goals such as improvements in gait.

There are several limitations to this study. The retrospective design was an impairment to data collection in terms of documentation related to insights behind some of the individual hyponatremia management strategies. It was not feasible to determine how rapidly the sodium was corrected. Outpatient follow-up data were limited to patients who utilized our health care system. Although this project focused on those patients receiving tolvaptan, it may have been valuable to comprehensively review how hyponatremia was managed in similar patients who did not receive tolvaptan. The small number of patients, although representative of a community hospital setting, may limit applicability in some contexts.

Prescribers at our hospital demonstrated adherence to institutional recommendations regarding tolvaptan use in the majority of circumstances. Tolvaptan increased serum sodium by an average of 8 mEq/L; upon discharge from the hospital, serum sodium remained improved from baseline. The acute care patient population with hyponatremia is a heterogeneous group with multiple comorbidities. Therefore an understanding of hyponatremia pathophysiology and an individualized patient assessment of risk and management by a multidisciplinary team can help to optimize patient care and reduce costs.

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