CUMBERLAND® PHARMACEUTICALS

WEBINAR TRANSCRIPT

Hyponatremia in the Critically ill Patient with Dr. Biff Palmer

This transcript is a written reproduction of Dr. Biff Palmer's audio presentation of "Hyponatremia in the Critically ill Patient with Dr. Biff Palmer," a Cumberland Pharmaceuticals Inc. approved webinar. The transcript should be viewed in tandem with the Audio and Visual content of the webinar, available On-Demand at www.vaprisol.com/webinar-landing-page/.

Introduction

"Welcome! Thank you for participating in this on-demand webinar. Our speaker, Dr. Biff Palmer, will be examining hyponatremia in critically ill patients. He will discuss the three types of hyponatremia, as well as the current treatment options available.

Dr. Biff Palmer is a professor of internal medicine at UT Southwestern Medical Center in Dallas, Texas. He is board-certified in internal medicine and nephrology and serves as editor for the Southwestern Internal Medicine Conference in the American Journal of Medical Sciences and an associate editor for the American Journal of Nephrology. Dr. Palmer is a leading expert on hyponatremia, a condition that results when serum sodium levels drop below 135 milliequivalents.

Thank you for viewing this webinar, and now Dr. Palmer will begin his presentation, 'Hyponatremia in Critically Ill Patients.'"

Presentation

"Well thank you very much, and what we're going to do today is review a slide set involving hyponatremia in critically ill patient.

Recent studies have shown that over 30% of patients admitted to the intensive care unit already have true hyponatremia. Additionally, another 18% of patients entering the ICU without hyponatremia will develop the condition while in the intensive care unit. Overall, almost 50% of neurological and critically ill patients have, or will develop, hyponatremia while in the hospital.[1,2]

The treatment course of hyponatremia is dependent upon the type of hyponatremia. Hypovolemic hyponatremia is a decrease in total body water followed by a larger decrease in serum sodium. Euvolemic hponatremia is caused by normal sodium levels but an increase in total body water. Hypervolemic hyponatremia involves an increase in serum sodium followed by a larger increase of total body water. All three types of hyponatremia involve too little sodium for the amount of total body water. Because the cause of each type of hyponatremia is different, treatments must be selected that will be applicable to the particular type.

Hyponatremia commonly increases mortality rates and length of hospital stays. An observational, cross-sectional study by Mahmoud et al. showed that hyponatremia increased mortality and length of stay for critically ill patients. Of 600 patients, 132 or 22% acquired a dysnatremia, 111 patients or 18.5% acquired hyponatremia, while only 21 patients, 3.5%, acquired hypernatremia. The risk of developing hyponatremia increased with increasing age more than 50 years (RR 2), presence of fever (RR 2.7), administration of hypotonic fluid therapy (RR 2.4), use of diuretics (RR 4.8), presence of renal impairment (RR 2.9), and advanced liver disease (RR 2.3). Compared with normonatremic patients, hyponatremia was associated with ICU mortality (RR 2.52) and with increased ICU length of stay (RR 1.8). The risk of mortality associated with dysnatremias has remained unchanged over a 21-year-period. In a study of over 80,000 ICU patients between the beginning of 1992 and the end of 2012, mortality rates ranged between 13 and 16 percent for

dysnatremic patients.[2,3]

More critically ill patients are diagnosed with hyponatremia than hypernatremia; therefore, severe outcomes are more often seen with hyponatremic patients. In an observational, prospective 12-month study by Pahdi et al., patients with hyponatremia spent a longer time in the ICU ($P = 0.02$), have longer mechanical ventilators days ($P = 0.03$), and an increased mortality rate (19.5%); ($P = 0.01$), than patients in the normal serum sodium group (16.5%).[1]

To examine the economic impact of hyponatremia upon admission, a retrospective cohort study was undertaken by identifying all inpatient admissions of adults with a serum sodium less than 134 mEq/L at a university hospital from January 2004 through May 2005. Extrapolating the increased cost from a single center study to a 2003 national inpatient admission and a hospital charge data set, it was estimated that patients with hyponatremia incur 1.4 million additional bed days and have additional costs of $1.1 billion per year, which were primarily born by the hospitals themselves as reimbursement methods usually are unable to bill patients or payers. Investigators concluded that hyponatremia upon admission was associated with longer length of stay, more frequent ICU admissions, and higher total medical care costs.[4,5]

There are many factors associated with the development of hyponatremia in critically ill patients. In the Padhi et al. study, Syndrome of Inappropriate Antidiuretic Hormone (SIADH) criteria was met in 91 patients (36.25%); pneumonia being the leading cause of SIADH. Patients with severe sepsis, elective surgery patients, renal failure and heart failure, cirrhosis of liver and subarachnoid hemorrhage were other likely etiologic causes ($P < 0.05$).[1]

One of the difficulties in diagnosing hyponatremia is that many patients can appear asymptomatic. Although a patient may appear asymptomatic, it may only be a situational finding. Renneboog et al. performed a case-control study of 122 elderly patients with chronic "asymptomatic" hyponatremia (mean serum sodium of 126 mEq/L). This study suggested that asymptomatic patients, particularly neuro patients, may in fact show symptoms such as gait disturbances that would otherwise be undetectable if a patient was left in bed. Neuropsychiatric testing revealed subtle abnormalities in these asymptomatic patients showing instability in dynamic tests such as gait and attention impairments in sensitivity tests that were successfully treated by raising serum sodium levels. This slide shows an example of a gait disturbance in an "asymptomatic" patient with hyponatremia. This individual does not have a normal gait due to neurological impairments associated with the sodium disturbance when serum sodium is 130 mEq/L. However, after treatment for hyponatremia resulting in a serum sodium increase to 139 mEq/L, the patient resumes a more normal gait pattern.[6]

When Renneboog compared 244 age-match controls to the 122 hyponatremic patients, 26 hyponatremic patients (21.3%)of 122 were admitted for falls, compared with only 5.3% of the control patients (adjusted odds ratio: 67; 95% confidence: 7.5-607; $P < 0.001$). The frequency of falls was the same regardless of the level of hyponatremia.[6]

Current commonly used treatments for hyponatremia include hypertonic saline, salt tablets, fluid restriction, isotonic saline, and the aquaretic vaptans. Hypertonic saline was the gold standard treatment for many years and is still a commonly utilized protocol for acute hyponatremia. Salt tablets may seem to be an intuitive treatment but are rarely useful in patients who can't take an oral medication, or for certain types of hyponatremia where the issue is total body water and not salt content. Fluid restriction is still utilized in some areas, though has largely fallen out of favor

for critically ill patients. Isotonic saline is used to treat acute hypovolemic hyponatremia but may result in overly rapid correction, particularly in elderly patients. Vaptans are an aquaretic class of agent that remove free water while not disturbing electrolytes. A consideration for treatment of any hyponatremic patient is the method of delivery. As hyponatremia is very common in the ICU patients, providers must consider delivery as a treatment variable for patients who are on a ventilator, who are NPO, or otherwise not able to swallow medications. These conditions limit treatment options to fluid restriction or agents given by IV, such as hypertonic saline, diuretics, or vaptans. [7–9]

During hyponatremia, extracellular and intracellular fluid shifts have the ability to cause severe damage, particularly to the neurological system. In the initial stages of hyponatremia, extracellular fluid becomes hypotonic, causing fluid to shift into the cell. This intracellular fluid uptake leads to cellular dysfunction, particularly in neurons, and may lead to cerebral edema. When hyponatremia is corrected properly, fluid shifts back out of the cells into the extracellular space and normal cellular function returns.[10]

Overly rapid correction of hyponatremia can lead to further neurological complications such as osmotic demyelination syndrome. Overly rapid correction occurs when extracellular fluid becomes hypertonic to the intracellular space and fluid shifts out of the cell. When this shift occurs and if it's sustained for too long, it can damage the myelin sheaths protecting axons of neurons in the central and peripheral nervous systems.[10]

Many healthcare professionals are wary of treating hyponatremic patients too rapidly to avoid the development of osmotic demyelination syndrome or other iatrogenic brain damage. First described as extrapontine myelinolysis, osmotic demyelination is the result of rapid correction of hyponatremia. Brain damage associated with rapid correction of chronic hyponatremia presents clinically 1 to 7 days after treatment and includes pseudobulbar palsy and quadriparesis, as well as development of movement disorders, behavioral disturbances, and seizures.[11]

The V2 receptor in kidney tubules is largely responsible for holding water that causes hyponatremia. The mechanism of action of vaptans includes acting as a V2 receptor antagonist, leading to aquaresis, or elimination of free water without a loss of sodium.

VAPRISOL® (conivaptan hydrochloride) injection is indicated to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia. VAPRISOL has not been shown to be effective for the treatment of the signs and symptoms of heart failure and is not approved for this indication. It has not been established that raising serum sodium with VAPRISOL provides a symptomatic benefit to patients.[12]

Vasopressin receptor antagonist or "vaptans" are the only approved pharmacologic therapy for hyponatremia. Conivaptan hydrochloride, or VAPRISOL, is indicated for the treatment of euvolemic and hypervolemic hyponatremia. This agent antagonizes the V1A and V2 receptor of vasopressin causing an increase in urine volume and a decrease in urine osmolality.[12]

Overly rapid correction of serum sodium levels for trials comparing vasopressin antagonists with placebo or no treatment in patients with hypervolemic of euvolemic hyponatremia. Relative risks are pooled using the random effects model and shown on a scale of 0.05 to 20.[13]

In a double-blind, placebo-controlled, randomized, multicenter study, 69% of patients given 40 mg of VAPRISOL demonstrated a confirmed greater than 6 mEq/L increase in serum sodium concentration or reached a normal serum sodium concentration or greater than 135 mEq/L, compared with 21% of those given placebo ($P \leq 0.001$). In these patients, effective water clearance (EWC), an indicator of the aquaretic effect of VAPRISOL, was calculated by subtracting electrolyte clearance from urine volume in patients under a 2-liter fluid restriction. VAPRISOL, administered at 40 mg per day, produced an aquaretic response as shown in the change in EWC. The aquaretic effect of VAPRISOL was evident on the first day of treatment. By the end of day 4, VAPRISOL produced a baseline-corrected cumulative increase in effective water clearance of more than 3.8 liters, compared with approximately 1.3 liters with placebo.[12]

In a subgroup of the previous controlled study, 56 euvolemic patients, under a 2-liter fluid restriction with a serum sodium concentration of 115 to less than 130 mmol/L, received conivaptan, 40 mg per day, or placebo via continuous intravenous infusion for 4 days. A 20-mg loading dose was administered intravenously over 30 minutes in the conivaptan groups; the placebo group received a placebo loading dose. Although 80 mg per day was also studied, it was not significantly more effective than 40 mg per day and was associated with a higher incidence of infusion site reactions and a higher rate of discontinuations for adverse events. Change in the serum sodium concentration, measured by the baseline-adjusted area under the serum sodium concentration time curve (AUC), was the primary efficacy parameter. Secondary efficacy measures included the time from the first dose to a confirmed value greater than or equal to 4 mmol/L increase in serum sodium concentration, total time with serum sodium concentration greater than or equal to 4 mmol/L above baseline, change in serum sodium concentration from baseline, and number of patients with a confirmed increase greater than or equal to 6 mmol/liter increase in serum sodium concentration or normal sodium concentration. Safety assessments included adverse events, incidence of overly rapid correction of serum sodium concentration, and changes in vital signs and electrocardiographic in clinical laboratory parameters. During the first 2 days of treatment and over the entire 4-day treatment period, both conivaptan doses significantly increased the serum sodium concentration more than the placebo using a least-squares mean change analysis.[14]

In the same subgroup of 56 patients with euvolemic hyponatremia, conivaptan significantly increased the mean serum sodium concentration more than the placebo. Conivaptan also significantly improved all secondary efficacy measures including total time with serum sodium concentration greater than 4 mmol/L above baseline, change in serum sodium concentration from baseline, and number of patients with confirmed increases of greater than 6 mmol/L in the serum sodium concentration or normal sodium concentration. Conivaptan was generally well tolerated with infusion site reaction being the most common adverse event. In this study of hospitalized patients with euvolemic hyponatremia, intravenous conivaptan significantly increased serum sodium concentration promptly and was well tolerated.[14]

A separate VAPRISOL trial, an open-label study of 251 patients with euvolemic or hypervolemic hyponatremia, examined efficacy of VAPRISOL, 20 mg and 40 mg. The increase in serum sodium concentration demonstrated after 4 days of therapy with VAPRISOL continued through follow-up day 11 and day 34. The most frequent cause of hyponatremia was SIADH. Among patients given VAPRISOL 20 mg per day, mean serum sodium concentration increased from 122.5 mEq/L at baseline to 131.8 mEq/L at the end of treatment, with a mean change of 9.4 mEq/L. When measured at day 11 and day 34, mean serum sodium concentrations were 129.9 and 134.3 mEq/L respectively. Among patients given VAPRISOL at 40 mg/day, mean serum sodium concentration increased from 123.8 mEq/L at baseline to 132.5 mEq/L at the end of treatment, for a mean change from baseline of 8.8 mEq/L. When measured at

day 11 and day 34, mean serum sodium concentration levels were 131.8 and 134.3 mEq/L, respectively.[15]

Over the next several slides we will now review safety information with regards to VAPRISOL.

The coadministration of VAPRISOL with potent CYP3A inhibitors, such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated. In addition, for patients unable to make urine, no benefit can be expected. VAPRISOL is contraindicated in patients with hypovolemic hyponatremia. In hypervolemic hyponatremia associated with heart failure, safety data on the use of VAPRISOL in these patients is limited; consider other treatment options. In overly rapid correction of serum sodium, monitor serum sodium, volume and neurologic status, and if the patient develops an undesirably rapid rate of rise of sodium serum, VAPRISOL should be discontinued. Serious neurologic sequelae, including osmotic demyelination syndrome, can result from overly rapid correction of serum sodium. In susceptible patients, including those with severe malnutrition, alcoholism, or advanced liver disease, slower rates of correction should be utilized. Serious infusion site reactions have occurred. One should administer this drug through large veins and change the infusion site every 24 hours.[12]

Adverse reactions in greater than 10% reported cases occurred in clinical trials and included things like headache, hypokalemia, orthostatic hypotension, infusion site reactions (including pruritus), and pyrexia.[12]

Potent CYP3A inhibitors may increase the exposure of conivaptan and are contraindicated. Generally, one should avoid CYP3A substrates. Exposure to coadministered digoxin may be increased and digoxin levels should be monitored.[12]

Therapy should begin with a 20 mg dose of IV VAPRISOL administered over 30 minutes. Additional doses should be given to reach treatment goals. Days 2 to 4 should be a continuous IV infusion of VAPRISOL of 20 mg. If a patient has evidence of moderate to severe hepatic impairment, a dosage of 10 mg VAPRISOL administered IV should be used by infusing 50 mLs from the 100 mL premixed intravenous bag.[12]

In patients with moderate to severe hepatic impairment, one should infuse 10 mg VAPRISOL over 30 minutes, followed by 10 mg administered over 24 hours for 2 to a maximum of 4 days. If serum sodium is not rising at the desired rate, VAPRISOL may be titrated upwards to 20 mg over 24 hours. Dose adjustments are not needed for patients with mild hepatic impairment or mild to moderate renal impairment. VAPRISOL is not recommended for use in patients with severe renal impairment.[12]

Based on clinical experience in these studies that were conducted post-approval, VAPRISOL was administered as a 30-minute infusion with additional 30-minute infusion dosing based on monitored volume status and serum sodium levels.[16–20]

In studies conducted for approval of VAPRISOL, continuous infusion dosing was recommended at the 20, 40, and 10 mg dose. For patients requiring 20 mg of conivaptan injection per day, one should give 20 mg VAPRISOL administered over 30 minutes, followed by a 20 mg dose administered over 24 hours. For patients requiring, 40 mg of conivaptan per day, a 20 mg VAPRISOL 30-minute infusion should be given followed by 2 consecutive 20 mg doses over 24 hours. For patients requiring 10 mg of conivaptan injection per day, one should initiate therapy with a dose of 10 mg of VAPRISOL administered over 30 minutes, followed by 10 mg over 24 hours.[12]

For additional information please see FULL VAPRISOL PRESCRIBING INFORMATION. Cumberland Pharmaceuticals Inc. 2017

Patients on VAPRISOL should be monitored for serum sodium volume and neurologic status. Multiple studies have determined that in patients with chronic hyponatremia, serious neurologic sequelae, including osmotic demyelination syndrome, can result from over-rapid correction of serum sodium. In susceptible patients, including those with severe malnutrition, alcoholism, or advanced liver disease, slower rates of correction should be utilized. Sterns et al. and Verbalis et al. discussed the limits of serum sodium correction over time to prevent overly rapid correction that may lead to demyelination or other neurologic symptoms. The 24-hour limit for rate of rise is recommended at less than 10 mEq/L due to several cases in which individuals corrected to over 10 mEq/L were found to develop myelinolysis. The 48-hour limit comes from multiple studies suggesting that over half of the individuals corrected to over 18 mEq/L over two days developed neurologic symptoms. Based on these data, Sterns et al. also suggest a 72-hour limit of 20 mEq/L. The goal of therapy should be adequate to keep patients safe from serious complications of hyponatremia while staying well clear of correction rates that risk iatrogenic injury. Accordingly, Sterns et al. suggest a goal of 6-8 mmol/L in 24 hours, 12-14 mmol/L in 48 hours and 14-16 mmol/L in 72 hours based on multiple clinical studies.[11,21]

Hyponatremia is present in over 30% of patients admitted to the ICU and will develop in another 18% during their stay.[1,2] Hyponatremia increases: falls, length of stay, ventilator days, and mortality in critically ill patients.[1–3,6] As a result of increased health care needs, hyponatremia adds over 1 billion dollars per year in health care costs.[4,5] Vaptans are the only approved treatment for hyponatremia. VAPRISOL, which is conivaptan hydrochloride injection, is approved to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia.[12] VAPRISOL has a lower rate of overly rapid correction than other approved vaptans.[13,15] The most common adverse reactions (>10%) are headache, hypokalemia, orthostatic hypotension, pyrexia, and infusion site reactions. VAPRISOL enhances the clearance of free water and increases serum sodium in critically ill patients with effects lasting up to 35 days.[12]

I would like to thank everybody for taking the time to listen to this presentation, and thank you again very much."

Conclusion

"Thank you very much Dr. Palmer for your insights into hyponatremia and ways in which clinicians can tailor their treatment approach. And thank you to our audience for watching this on-demand webinar brought to you by Cumberland Pharmaceuticals, makers of VAPRISOL. This concludes our webinar. If you have questions for Dr. Palmer or would like to learn more about hyponatremia and VAPRISOL, please email vaprisol@cumberlandpharma.com."

IMPORTANT SAFETY INFORMATION AND IMPORTANT LIMITATIONS

Vaprisol (conivaptan hydrochloride) Injection

(1) Indication

(2) Important Safety Information

Indication: VAPRISOL is indicated to raise serum sodium in hospitalized patients with euvolemic and hypervolemic hyponatremia.

Important Limitations: VAPRISOL has not been shown to be effective for the treatment of the signs and symptoms of heart failure and is not approved for this indication. It has not been established that raising serum sodium with VAPRISOL provides a symptomatic benefit to patients.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

VAPRISOL is contraindicated in patients with hypovolemic hyponatremia. The coadministration of VAPRISOL with potent CYP3A inhibitors, such as ketoconazole, itraconazole, clarithromycin, ritonavir, and indinavir, is contraindicated. In addition, no benefit can be expected in patients unable to make urine.

WARNINGS & PRECAUTIONS

Hyponatremia associated with heart failure: Safety data on the use of VAPRISOL in these patients are limited. Consider other treatment options.

Overly rapid correction of serum sodium: Monitor serum sodium, volume and neurologic status and if the patient develops an undesirably rapid rate of rise of serum, VAPRISOL should be discontinued. If serum sodium concentration continues to rise, VAPRISOL should not be resumed. Serious neurologic sequelae, including osmotic demyelination syndrome, can result from over rapid correction of serum sodium. In susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction should be used.

Hypovolemia or Hypotension: For patients who develop hypovolemia or hypotension while receiving VAPRISOL, VAPRISOL should be discontinued, and volume status and vital signs should be monitored.

Infusion site reactions: Serious reactions have occurred. Administer through large veins and change infusion site every 24 hours.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥10%) are infusion site reactions (including phlebitis), pyrexia, hypokalemia, headache and orthostatic hypotension.

DRUG INTERACTIONS

Potent CYP3A inhibitors may increase the exposure of conivaptan and are contraindicated. Generally avoid CYP3A substrates. Exposure to coadministered digoxin may increase digoxin levels and should be monitored.

USE IN SPECIAL POPULATIONS

Use in Patients with Hepatic Impairment

In patients with moderate to severe hepatic impairment, initiate VAPRISOL with a loading dose of 10 mg over 30 minutes followed by 10 mg/day as a continuous infusion for 2 to 4 days. If no rise in serum sodium, VAPRISOL may be titrated upward to 20 mg/day.

For additional information please see FULL VAPRISOL PRESCRIBING INFORMATION. Cumberland Pharmaceuticals Inc. 2017

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