Intravenous conivaptan for the treatment of hyponatraemia caused by the syndrome of inappropriate secretion of antidiuretic hormone in hospitalized patients: a single-centre experience

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Abstract

Background. Intravenous conivaptan is a novel therapeu-
tic agent indicated for the treatment of euvoalaemic and hy-
pervolaemic hyponatraemia. However, there is paucity of re-
ported clinical experience using conivaptan for the treat-
ment of the syndrome of inappropriate secretion of anti-

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diuretic hormone (SIADH). Moreover, while there is reasonable concern for overcorrection, no pre-treatment variables are known to be helpful to identify patients at risk for rapid correction.

**Methods.** We searched our records for hospitalized patients treated with intravenous conivaptan for moderate to severe hyponatraemia due to SIADH, with a starting serum sodium <130 mmol/L, between 2006 and 2009 (n = 18), to examine its efficacy as aquaretic, and to search for pre-treatment variables that could predict degree of response.

**Results.** Twenty-four hours after initiation of therapy, all patients had at least a 3-mmol/L increase in serum sodium, with 66.7% (12/18) of the patients having an absolute increase ≥4 mmol/L, and a median increase in serum sodium of 7 mmol/L (range: 3–16 mmol/L). Concomitantly, urine osmolality decreased in all patients with a mean reduction of 45.9 ± 28.8% from baseline. Lower serum sodium, lower blood urea nitrogen and higher estimated glomerular filtration rate at baseline had a significant correlation with the magnitude of the absolute increase in serum sodium 24 hours after initiation of therapy.

**Conclusions.** We conclude that intravenous conivaptan is an effective aquaretic to treat hyponatraemia caused by SIADH, as evidenced by a simultaneous increase in serum sodium and decrease in urine osmolality. Baseline values of serum sodium, blood urea nitrogen and estimated glomerular filtration rate may help predicting the magnitude of response to therapy.

**Keywords:** ADH; conivaptan; hyponatraemia; SIADH; vasopressin receptor antagonist

**Introduction**

Hyponatraemia is the most common electrolyte disorder in hospitalized patients [1–3]. Euvolaemic hyponatraemia caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) accounts for as many as 15–45% of cases [2,4–7]. Ominous clinical consequences can result from severe hyponatraemia, such as cerebral oedema [8], irreversible neurological damage [9] and non-cardiogenic pulmonary oedema [10]. Moreover, hyponatraemia is associated with significant economic burden in healthcare [11]. The traditional approach to the treatment of SIADH involves restriction of free water intake [12], use of loop diuretics [13], oral salt tablets [12], demeclocycline [14], urea [15] or intravenous administration of normal or hypertonic saline [16]. The non-selective V₁A/V₂ vasopressin receptor antagonist conivaptan is now available in its intravenous form as an alternative [17]. However, the published experience with the use of this drug in current clinical practice and in patients not enrolled in clinical trials remains limited. Many nephrologists remain unfamiliar with the use of conivaptan. Furthermore, clinical factors which can predict the magnitude or rapidity of response are unknown. Therefore, our aim was to examine and report our institutional experience with the use of intravenous conivaptan in order to assess its effectiveness in the treatment of SIADH, and to explore possible pre-treatment variables that could predict the response to therapy.

**Subjects and methods**

After obtaining approval from the Institutional Board Review, we conducted a retrospective review of our medical records with the purpose of identifying patients treated at Medical University of South Carolina Hospital with intravenous conivaptan, between the date the drug was incorporated in our inpatient pharmacy formulary in June 2006, and July of 2009. Data were collected using a log created from inpatient pharmacy charges. The following inclusion criteria were used: (i) hospitalized patients treated with at least one intravenous injection of Conivaptan; (ii) diagnosis of clinically significant hyponatraemia caused by SIADH, defined as euvolaemic hypoosmolar hyponatraemia (serum sodium <130 mmol/L and serum osmolality <280 mOsm/kg) with inappropriate urinary concentration (urine osmolality >100 mOsm/kg and urine sodium >20 mmol/L) [18]; (iii) documented failure to correct hyponatraemia despite at least 24 hours of free water restriction (<1 litre); (iv) age >18, and (v) lack of concomitant treatment with hypertonic saline or demeclocycline.

Our definition of SIADH was taken from published literature [6,18–21]. Although urinary sodium excretion is usually expected to be >30 mmol/L in SIADH [6,21], natriuresis depends on sodium intake. All patients were treated with at least 24 hours of free water restriction prior to receiving conivaptan. It is conceivable that unintended salt repletion occurred during that process. Therefore, we opted to use a more liberal definition of SIADH and included patients with urine sodium >20 mmol/L. Such cutoff has been used elsewhere [18]. Four patients (22.2%) were diagnosed with SIADH with a urine sodium <30 mmol/L in this series. Interestingly, those four patients had a pulmonary cause of SIADH. Low urine sodium in the setting of SIADH has been previously described in pulmonary diseases, presumably because of activation of volume receptors led by decreased pulmonary venous return [22,23].

SIADH is a diagnosis of exclusion and requires normal renal function for the diagnosis. However, we included three cases in which the treating nephrologists had compelling clinical evidence for diagnosing SIADH superimposed over underlying chronic kidney disease. One case was of a subject with a renal allograft and chronic allograft nephropathy with stable renal function who presented with acute respiratory insufficiency caused by pulmonary nocardiosis and de novo hyponatraemia; one case of a subject with mild chronic decrease in glomerular filtration rate (GFR) who was diagnosed with maxillary sinus carcinoma and subsequently developed hyponatraemia; and one case of a subject with chronic unexplained euvolaemic hyponatraemia in the setting of stable chronic kidney disease and dementia. Since this study is intended to reflect real clinical practice, we considered it important to include those patients in the analysis. However, it is possible that the mechanisms of generation of hyponatraemia in those patients were more complex than those caused by SIADH alone.

The standard protocol recommended by the manufacturer and approved by the Food and Drug Administration (FDA) indicates intravenous administration of a 20-mg loading dose followed by 20 mg as continuous infusion daily for up to 4 days. However, because of lack of previous first-hand experience using the drug, treating physicians did not strictly follow the recommended protocol in all cases and rather made decisions about how to dose the drug in an individual basis.

All patients were kept on free water restriction (<1 litre) during treatment. We collected data from the chart at baseline and from the time of administration of intravenous conivaptan until 72 hours thereafter. Data included age, gender and race, presumed etiology of SIADH, comorbid conditions, duration of hyponatraemia prior to treatment, vital signs, urine output, serum and urine sodium and serum and urine osmolality at initiation of treatment and every 6 hours for the first 24 hours, and daily for the ensuing 48 hours. Additional laboratory data included serum creatinine, blood urea nitrogen (BUN), serum uric acid and serum potassium. Our clinical laboratory converted to the use of Integrated Database Management System calibrated creatinine standards in December of 2007, so there may be small differences in values measured before that time. Renal function was estimated using the abbreviated form of the Modification of
Diet in Renal Disease (MDRD) study equation [24]. Because that method of GFR estimation has not been validated in individuals with normal renal function, we also estimated renal function using creatinine clearance (CrCl) calculated by the Cockcroft-Gault equation [25]. Knowing that SIADH is associated with increased GFR, we defined hyperfiltration as GFR >125 ml/min, as estimated by both MDRD and Cockcroft-Gault equations.

Endpoints

The primary endpoint was the efficacy of conivaptan in correcting hypoponatraemia, defined as the proportion of patients with an absolute increase in serum sodium ≥4 mmol/L over baseline. This endpoint was selected in order to be consistent with previous publications in which similar treatment interventions were examined [26–28]. Secondary endpoints included absolute increase in serum sodium, proportion of subjects who reached the primary endpoint within the first 12 hours, relative and absolute decrease in urine osmolality and proportion of subjects with >15% relative reduction in urine osmolality. Free water clearance (FWC) was estimated from an established equation using urine volume and urine and serum osmolality [27,29]. Electrolyte-free water clearance was not calculated because urine potassium was not measured.

As a safety endpoint, we examined the rate correction of hypoponatraemia. We defined rapid correction as any increase in serum sodium ≥12 mmol/L after 24 hours of therapy or a rate of correction ≥20.5 mmol/L/hour at any point during the observation period [21]. All patients with rapid correction underwent complete neurological examination prior to treatment, during treatment (daily for 7 days), at the time of discharge (between 1 and 12 weeks after therapy) and during subsequent hospitalizations. To account for delayed onset of osmotic demyelination, neurological examinations were performed at least 30 days after therapy in all but three cases. In two subjects, a telephone conversation was conducted to verify the patients’ neurological status. One patient expired due to fungalaemia and shock in the context of metastatic disease 2 weeks after therapy. We also searched for adverse reactions resulting from conivaptan infusion such as injection site reactions, haemodynamic compromise and effects on serum potassium and renal function. We defined a significant rise in serum creatinine as any increment >25% over baseline, and a significant episode of azotaemia as any increment in BUN >30% over baseline; in both cases after 24 hours of conivaptan therapy.

Statistical analysis

Comparison between continuous variables was done using the Student’s t-test. Association between pre-treatment variables and treatment effects were analysed by linear correlation. A two-tailed P-value <0.05 was considered significant.

Results

A total of 38 patients treated with conivaptan within the study period were identified. Of those, 14 patients had hypervolaemic hypoponatraemia in the setting of congestive heart failure. Six patients had a baseline serum sodium ≥130 mmol/L at the time of treatment. One patient was treated twice with conivaptan during two separate hospitalizations; however, in one instance, the patient also received demeclocycline. Therefore, we included only the treatment during which demeclocycline was not given. As a result, 18 patients were included in the analysis. Table 1 displays the key baseline demographic, clinical and laboratory characteristics. The majority of them had a pulmonary cause of SIADH: five subjects had lung cancer, two had large pleural effusions, two had lobar pneumonia, one had cavity nocardiosis, one had bronchiectasis and one had chronic obstructive pulmonary disease. The remainder of the cases was attributed to miscellaneous causes (one meningioma, one maxillary sinus carcinoma, one post-operative pain, one post-operative nausea, one carbamazepine and one idiopathic). The median duration of hypoponatraemia prior to treatment was 10 days (range: 1–75 days). Seven patients had a prior episode of hypoponatraemia, whereas the remaining 11 were newly diagnosed.

Administration of conivaptan

All but one patient received a 20-mg loading dose of Conivaptan. Twelve patients (66.7%), including one who did not receive a loading dose, were treated with a subsequent partial or full dose of a continuous infusion of 20 mg per 24 hours of conivaptan which lasted between 4 and 72 hours, depending on whether the infusion was interrupted or not. The cause for interruption of the infusion was rapid correction in four cases, and reaching a serum sodium ≥130 mmol/L in one case. One patient received a 40-mg dose for the continuous infusion during the first day. The median total dose of conivaptan was 30 mg (range: 20–80) over a median time of 13 hours (range: 1–60).

Efficacy endpoints

Twelve (66.7%) patients met the criterion for successful response, defined as an absolute increase in serum sodium ≥4 mmol/L over baseline, as measured 24 hours post-initiation of conivaptan administration (Table 2). Among those 12 ‘responders’, complete measurements of serum sodium at 6-hour intervals were available in nine patients. In that group, it was observed that four (44.4%) patients achieved an increase of serum sodium ≥4 mmol/L within the initial six hours; three (33.3%) reached the endpoint after 12 hours, and the remaining two (22.2%) reached the endpoint only after 24 hours of therapy. Overall, 100% of the patients had at least a 3-mmol/L increment in serum sodium at 24 hours (Figure 1). Mean baseline serum sodium of 121.7 ± 3.3 mmol/L (range: 117–127 mmol/L) increased to 129.2 ± 2.6 mmol/L (range: 123–135 mmol/L) at 24 hours after initiation of therapy (P < 0.001). Increase in serum sodium was sustained at 48 and 72 hours post-initiation of therapy (129.6 ± 2.4 and 130.5 ± 2.5 mmol/L, respectively; P < 0.001) (Figure 1). In addition, the mean absolute increment in serum sodium at 24 hours was +7.44 ± 4.3 mmol/L [median: +7 mmol/L (range: 3–16)] (Table 2).

Post-treatment urine osmolality was recorded in 15 of the 18 patients. Mean baseline urine osmolality was 476.8 ± 132.2 mOsm/kg (range: 197–679 mOsm/kg), and it decreased in all patients to a mean of 243.2 ± 151.8 mOsm/kg (range: 48–523 mOsm/kg) 24 hours post-initiation of treatment (Figure 2). Eleven patients (73.3%) had at least 15% reduction in urine osmolality over baseline. The average percentage decrease in urine osmolality from baseline levels was 45.9 ± 28.8% (range: 6.6–85.4%) after 24 hours. Mean values of urine output and FWC significantly increased post-treatment (1504.2 ± 289 to 2722.6 ± 508 and −973.7 ± 237 to 525.2 ± 636 ml, for urine output and FWC, respectively; Figure 3), as expected.
Table 1. Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Cause of SIADH</th>
<th>n (%)</th>
</tr>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>66.7 (12/18)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>27.8 (5/18)</td>
</tr>
<tr>
<td>Non-malignant</td>
<td>38.9 (7/18)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>5.5 (1/18)</td>
</tr>
<tr>
<td>Post-operative</td>
<td>11.1 (2/18)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>5.5 (1/18)</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>5.5 (1/18)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>5.5 (1/18)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>5.5 (1/18)</td>
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</tbody>
</table>

Baseline laboratory data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>121 (117–128)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.7 (0.3–2.6)</td>
</tr>
<tr>
<td>Estimated GFR (ml/min)</td>
<td>110 (26–252)</td>
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<tr>
<td>Estimated creatinine clearance (ml/min)</td>
<td>96 (31–230)</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dL)</td>
<td>11 (1–41)</td>
</tr>
<tr>
<td>Urine osmolality (mOsm/kg)</td>
<td>465 (197–679)</td>
</tr>
<tr>
<td>Urine sodium (mmol/L)</td>
<td>74 (21–126)</td>
</tr>
</tbody>
</table>

SIADH = syndrome of inappropriate secretion of antidiuretic hormone.
GFR = glomerular filtration rate estimated by the Modification of Diet in Renal Disease study equation.

Magnitude of response and predictive variables

Although all treated patients had at least a 3-mmol/L increase in serum sodium, there was noticeable variability in the magnitude of the response. Therefore, we searched for variables that could correlate with the magnitude of the response to conivaptan. Baseline serum sodium level was the serological value with the strongest correlation with the magnitude of response to therapy (Figure 4). In addition, baseline BUN, baseline GFR estimated by the abbreviated MDRD equation and baseline CrCl estimated by the Cockcroft–Gault equation also had a statistically significant correlation with the absolute increase in serum sodium at 24 hours (Figure 4). Five patients (27.8%) fulfilled the criteria for hyperfiltration at baseline. The mean absolute increase in serum sodium at 24 hours among those subjects was significantly higher than that of those without hyperfiltration (12.4 ± 2.0 versus 5.5 ± 3.3 mmol/L, respectively; P < 0.001). On the other hand, no correlation was found between the magnitude of response to treatment and either baseline urine osmolality, baseline serum sodium, demographics or the duration of documented hyponatraemia prior to treatment. Furthermore, the total dose of conivaptan failed to correlate with the magnitude of response to conivaptan (R² = 0.0096, P = 0.7).

The short-term duration of the effect of conivaptan was assessed by comparing the changes in serum sodium concentration at 24 and 72 hours post-initiation of therapy. A significant correlation was observed between the initial rise in serum sodium after 24 hours and the subsequent fall in serum sodium 48 hours later (R² = 0.5124, P < 0.01).

Three patients (16.7%) experienced rapid correction of hyponatraemia at 24 hours. A total of five patients (27.7%) had a rapid rate of correction at any point during the observation period (Table 2). In all those instances, Conivaptan therapy was terminated. One patient was started on intravenous 5% dextrose water solution at a rate of 50 ml/hour. The infusion was interrupted 3 hours later after subsequent serum sodium revealed that the rate of correction was no longer ≥0.5 mmol/L/hour. Nine patients (50%) had a rise in serum sodium ≥8 mmol/L at 24 hours. All events were asymptomatic.

Adverse reactions

One patient experienced transient symptomatic hypotension, with a fall in systolic blood pressure from 110 to 88 mmHg. The patient complained of dizziness. A bolus of 250 cm³ of normal saline was sufficient to restore his blood pressure. Median baseline blood pressure was 119/66 mmHg (range: 86/50–153/83 mmHg), which did not change significantly 24 hours post-therapy [median 114/62 mmHg (range: 97/56–141/76 mmHg); P = 0.2 and P = 0.6 for systolic and diastolic blood pressure, respectively]. In addition, two out of four patients that were treated through a peripheral venous line experienced mild injection site reactions. All of the remaining 14 patients received conivaptan through a central venous catheter and did not experience injection site reactions. Two patients met the crite-

Table 2. Outcomes at 24 hours after initiation of conivaptan therapy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
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<tr>
<td>≥4 mmol/L increase in serum sodium over baseline (%)</td>
<td>66.7 (12/18)</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
</tr>
<tr>
<td>Absolute increase in serum sodium over baseline (mmol/L)</td>
<td>7.44 ± 4.3</td>
</tr>
<tr>
<td>≥4 mmol/L increase in serum sodium over baseline achieved within first 12 hours (%)</td>
<td>50.0 (8/16)</td>
</tr>
<tr>
<td>Absolute decrease in urine osmolality over baseline (mOsm/kg)</td>
<td>222.1 ± 163.9</td>
</tr>
<tr>
<td>Relative decrease in urine osmolality over baseline (%)</td>
<td>45.9 ± 28.8</td>
</tr>
<tr>
<td>≥15 % decrease in urine osmolality over baseline (%)</td>
<td>73.3 (11/15)</td>
</tr>
<tr>
<td>≥12 mmol/L increase in serum sodium over baseline (%)</td>
<td>16.6 (3/18)</td>
</tr>
<tr>
<td>≥0.5 mmol/L/hour increase in serum sodium at any point during therapy (%)</td>
<td>27.8 (5/18)</td>
</tr>
</tbody>
</table>

*12-hour data point not available in two patients.
*Post-treatment urine osmolality not available in three patients. Values expressed as mean ± SD unless noted otherwise.
ria for a significant rise in serum creatinine. However, in both cases, the peak serum creatinine was <1.0 mg/dL (0.3 to 0.4 and 0.6 to 0.8 mg/dL), and was therefore considered clinically insignificant. One patient fulfilled the criteria for azotaemia (BUN rose from 22 to 40 mg/dL) but did not meet the criteria for a significant rise in serum creatinine. No other adverse events were documented.

Discussion

Conivaptan was introduced to clinical use in 2006. A randomized clinical trial sponsored by the manufacturer demonstrated that conivaptan is superior to placebo for the correction of euvoletic or hypervolaemic hyponatraemia [27]. A subgroup analysis in patients with euvoletic hyponatraemia also found that conivaptan increased serum sodium promptly and safely [26]. Our study further demonstrates that conivaptan is effective at correcting euvoletic hyponatraemia caused by SIADH in day-to-day in-hospital clinical practice, beyond industry-sponsored trials. We used a fairly stringent serum sodium cutoff of 130 mmol/L for our analysis to avoid including patients for whom the clinical benefit of correction of hyponatraemia would be less clear.

The median value of baseline serum sodium in this study was lower than that of previous studies [26,30,31], indicating that our patients had more severe hyponatraemia. Importantly, the overall magnitude of the observed increment in serum sodium is in agreement with previous studies [26,28,30]. All patients raised their serum sodium at the end of the study period, with more than half of them achieving the primary endpoint of a 4-mmol/L increase within the first 12 hours of treatment. Similarly, as expected, urine osmolality decreased in all the patients. Together, these results constitute confirmatory evidence for the aquaretic efficacy of conivaptan in SIADH.

Because of the known risks of overcorrection of hyponatraemia, we searched for variables that may help predicting the degree of response to intravenous conivaptan and could be useful to guide therapy. Baseline serum sodium levels significantly correlated with the subsequent rise in serum sodium resulting from treatment. Although statistically significant, the clinical significance of this observation can be debatable since the analysed variables are not independent. The observed correlation could merely reflect the fact that subjects with higher baseline serum sodium have less room for improvement. Nevertheless, our findings resemble those reported by Metzger et al. who observed that ‘responders’ had a lower mean serum sodium compared to ‘non-responders’ [28].

Perhaps one of the most interesting findings of our study is the inverse correlation between the level of BUN at the time of initiation of treatment and the subsequent magnitude of the natraemic response to conivaptan. Hypouraemia is a known feature of SIADH [32]. Although the mechanism has not been fully elucidated, hypouraemia is thought to correspond to decreased proximal tubular reabsorption of urea and increased GFR resulting from expansion of body fluids and a high volemia state [33]. One could speculate that subjects with the lowest BUN levels carry the largest increase in whole body water content, greatest extracellular fluid expansion, highest GFR, lowest proximal tubular reabsorption and greatest distal delivery of substrate, thereby making them more responsive to water diuresis. Differences in compensatory activation of atrial natriuretic factor release may also account for differences in volemia [34]. In addition, vasopressin is known to stimulate the expression of urea transporters in the inner medullary collecting duct [35]. However, it seems difficult to reconcile the observed predictive value of low BUN and the reported link between vasopressin and urea transporters. Nevertheless, this finding suggests that BUN may serve as a useful pre-treatment marker of response in which patients with a very low BUN may have a larger response to conivaptan. Estimated renal function parameters, i.e. MDRD-estimated GFR and Cockcroft–Gault-calculated CrCl, also correlated with re-
sponse to therapy. Indeed, individuals with baseline hyperfiltration had the largest rise in serum sodium after therapy. Because increases in GFR parallel increases in renal plasma flow resulting from high volaemic state in SIADH [36,37], then increased delivery of conivaptan to the peritubular capillaries at the inner medullary collecting duct site may be partly responsible for such observation, since V₂ receptors are mainly localized at the basolateral membrane [38–40]. Although these correlations will need to be confirmed in future studies, patients with low BUN and high GFR may need to be watched closer for over rapid response.

Subjects with the most pronounced response to Conivaptan also displayed the largest ‘rebound’ reduction in serum sodium when checked 72 hours after initiation of therapy, in most instances, 24 or even 48 hours after the last dose of conivaptan. This observation is not explained by therapeutic interventions made as a result of the observed rapid correction since only one patient received intravenous free water to revert rapid correction and that patient was not included in this analysis. Since vasopressin levels were not measured, it is not known whether the ‘rebound’ reduction was a reflection of higher levels of plasma vasopressin and more dependency to vasopressin receptor antagonism.

In terms of safety, few patients experienced rapid correction of hyponatraemia but no cases of central pontine myelinolysis [41] or severe neurological damage occurred. Interestingly, some patients achieved a clinically significant rise in serum sodium with only a single loading dose of Conivaptan and without a subsequent continuous infusion. From our experience, we consider that is advisable not to initiate a full protocol in all patients, but rather to individu-

![Fig. 3. Changes in urine output (light grey bars) and free water clearance (black bars) observed between baseline and 24 hours post-initiation of conivaptan therapy; *P < 0.05.](image)

![Fig. 4. Correlation between baseline serological or serum-based laboratory parameters and the magnitude of the increment in serum sodium 24 hours after initiation of conivaptan therapy.](image)
alize therapy based on clinical scenario, pre-treatment variables and serial measurements of serum sodium and urine osmolality during treatment. Nevertheless, our findings need to be interpreted in the context of the limitations of a retrospective study design and a small sample size. Larger prospective studies are necessary to confirm our observations related to predictive variables for response to therapy.

Although administration of hypertonic saline is effective correcting hyponatraemia in SIADH, it entails a salt load that may be undesirable in some scenarios. Intake of salt does not address the causative factor in SIADH, which is free water excess. Moreover, it is not known whether the potentially devastating consequences of rapid correction may be more likely to occur in patients treated with hypertonic saline compared to vasopressin receptor antagonists. Intravenous convivatan is an attractive option to treat SIADH, particularly in cases when the underlying cause of SIADH is time-limited or could be eradicated with appropriate treatment, such as post-operative states, pulmonary consolidation or other conditions where the stimulus for inappropriate release of vasopressin is expected to be transient. A different approach may be required for conditions such as malignancies when the duration of hyponatraemia is typically longer. Few of the patients in our series with lung cancer were discharged on oral demeclocycline as maintenance regimen.

Treatment of mild to moderate hyponatraemia in the absence of overt neurological symptoms has been a matter of controversy. However, emerging evidence indicates that asymptomatic hyponatraemia may be associated with gait impairment and increased risk for falls and bone fractures, suggesting that such individuals are not truly asymptomatic [7,42–44]. Thus, correcting hyponatraemia even in the absence of overt symptoms may be clinically beneficial. More studies are needed to better characterize the subclinical or inadvertent clinical consequences of hyponatraemia and its treatment.

In summary, intravenous convivatan is an effective aquaretic for the treatment of SIADH in hospitalized patients. Nephrologists and internists should incorporate its use in their practices, especially for individuals who fail to respond to free water restriction and other interventions, but must be aware that some patients may experience a rapid rise in serum sodium. Indeed, it might be necessary to infuse 5% dextrose in water in some cases for a few hours. Therefore, serum sodium should be closely monitored during therapy. Pre-treatment BUN and estimated renal function may be predictive of a more vigorous response. An oral selective V2 vasopressin receptor antagonist has been recently approved by the United States FDA to treat euvolaemic and hypervolaemic hyponatraemia [45] and other oral formulations of vasopressin receptor antagonists are currently under development [46,47]. The availability of both intravenous and oral forms of vasopressin receptor antagonists adds versatility to the treatment approach of SIADH-induced hyponatraemia that is unresponsive to traditional measures.

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Conflict of interest statement. J.C.V. is a member of the Astellas Pharma US Inc. Speaker Bureau. J.C.V. and J.M.A. have participated in clinical trials sponsored by Astellas Pharma US Inc.

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24. Levey AS, Bosch JP, Lewis JB et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new predic-
Using RIFLE criteria to evaluate acute kidney injury in brain-deceased kidney donors

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Abstract

Background. The limited supply of deceased donors for renal transplantation led to considering alternative strategies for making more organs available. One of these strategies is the use of donors with renal dysfunction, as this is usually a reversible condition. RIFLE (risk, injury, failure,