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# Urea treatment in fluid restriction-refractory hyponatraemia

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## Summary

**Objective:** Hyponatraemia in hospitalized patients is common and associated with increased mortality. International guidelines give conflicting advice regarding the role of urea in the treatment of SIADH. We hypothesized that urea is a safe, effective treatment for fluid restriction-refractory hyponatraemia.

**Design:** Review of urea for the treatment of hyponatraemia in patients admitted to a tertiary hospital during 2016-2017. Primary end-point: proportion of patients achieving a serum sodium ≥130 mmol/L at 72 hours.

**Patients:** Urea was used on 78 occasions in 69 patients. The median age was 67 (IQR 52-76), 41% were female. Seventy (89.7%) had hyponatraemia due to SIADH—CNS pathology (64.3%) was the most common cause. The duration was acute in 32 (41%), chronic in 35 (44.9%) and unknown in the rest.

**Results:** The median nadir serum sodium was 122 mmol/L (IQR 118-126). Fluid restriction was first-line treatment in 65.4%. Urea was used first line in 21.8% and second line in 78.2%. Fifty treatment episodes (64.1%) resulted in serum sodium ≥130 mmol/L at 72 hours. In 56 patients who received other prior treatment, the mean sodium change at 72 hours (6.9 ± 4.8 mmol/L) was greater than with the preceding treatments (−1.0 ± 4.7 mmol/L; $P < 0.001$). Seventeen patients (22.7%) had side effects (principally distaste), none were severe. No patients developed hypernatraemia, overcorrection (>10 mmol/L in 24 hours or >18 mmol/L in 48 hours), or died.

**Conclusions:** Urea is safe and effective in fluid restriction-refractory hyponatraemia. We recommend urea with a starting dose of ≥30 g/d, in patients with SIADH and moderate to profound hyponatraemia who are unable to undergo, or have failed fluid restriction.

KEYWORDS

fluid restriction, hyponatraemia, inappropriate ADH syndrome, sodium, urea

## 1 | INTRODUCTION

Hyponatraemia, defined as a serum sodium <135 mmol/L, is the most frequent electrolyte abnormality amongst hospital inpatients and is associated with increased morbidity and mortality.[1,2] An improvement in hyponatraemia is associated with a reduced risk of mortality.[3] The most common cause of hyponatraemia in inpatients is the syndrome of inappropriate antidiuretic hormone (SIADH).[4] Antidiuretic hormone (ADH) secreted from the posterior pituitary regulates free water excretion in the nephric collecting ducts. Nonosmotic elevation of ADH (or lack of suppression) in SIADH leads to excess water accumulation and subsequent dilutional hyponatraemia.[5] The diagnosis of the syndrome typically requires hyponatraemia in the setting of reduced serum osmolality,

  

inappropriately concentrated urine with normal sodium excretion levels, and the absence of interfering medications, hypothyroidism and adrenal insufficiency.[6]

Treatment of SIADH is traditionally determined by acuity of onset (within the last 48 hours), presence/absence of symptoms, and biochemical severity of hyponatraemia. The European Clinical Practice Guidelines use the terminology "profound" hyponatraemia to denote a serum sodium <125 mmol/L and "severe" to describe the symptomatology.[6] Unless hypertonic saline is indicated for acute onset profound hyponatraemia and/or with severe symptoms, the mainstay of management has traditionally been fluid restriction, a treatment often difficult to implement practically and effective in less than 50% of patients.[4] Recent European and American guidelines differ in their approach to second-line management.[6,7] Urea has been used for the treatment of SIADH since the 1980s[8] and case reports/series have demonstrated it is an effective adjunct where fluid restriction is impractical or ineffective.[8,9] Urea is readily absorbed from the gut and freely filtered at the glomerulus; in a patient with normal renal function, the entirety of a 15 g dose is excreted within 12 hours of ingestion.[13] Administration of urea in the setting of hyponatraemia induces an osmotic diuresis, a reduction in natriuresis, and net free water excretion.[8] Studies in animal models suggest that urea may additionally protect from osmotic demyelination, a rare complication of overly rapid correction of serum sodium.[14] Despite this, it is infrequently used as shown in a multinational hyponatraemia registry of 3087 patients, where only 10 were treated with urea.[4]

In a recent audit of the investigation and management of hyponatraemia at our institution, it was noted in a small number of patients that urea was a safe and effective second-line treatment.[15] This in turn led to a departmental change in policy, such that urea was used routinely in cases of SIADH where fluid restriction either had resulted in no or minimal change in serum sodium or was not feasible for other reasons. We hypothesized that urea is a safe, effective treatment for hyponatraemia due to SIADH in fluid restriction-refractory patients, or those unable to be restricted.

## 2 | METHODS

Inpatients with moderate hyponatraemia (serum sodium <130 mmol/L) between December 2015 and December 2017 were identified using the laboratory information system at the Princess Alexandra Hospital, a tertiary referral hospital in Brisbane, Australia. These data were cross-referenced with pharmacy dispensing records for urea to identify all those that were prescribed urea. Exclusion criteria were age <18 years, pregnancy, and pseudohyponatraemia due to hyperglycaemia or hyperlipidaemia. A small number of patients had hyponatraemia not due to SIADH, they were included in the data and statistical analyses except where stated. A further 51 contemporaneous patients with SIADH treated with fluid restriction alone were reviewed for comparison.

Medical records were retrospectively reviewed by one investigator (JL) to record demographic details, clinical and biochemical parameters and treatment details. Data collected were patient demographics, admission diagnoses, clinical volume status parameters and documented assessment (by treating team), serum and urinary electrolytes, medications, treatment and documentation of adverse events. Cause of hyponatraemia was adjudicated using criteria published by Spasovski et al at time of data collection,[6] regardless of treating team diagnosis. Labserv Urea Pronalys AR crystals (Thermo Fisher Scientific, Scoresby, Australia) were used in all patients who received urea. This was divided into doses of 15-45 g (based on total daily dose) and dissolved in fluid (orange juice where possible to increase palatability) to be taken orally. The primary outcome was the proportion of patients with serum sodium ≥130 mmol/L at 72 hours postinitiation of urea as a categorical variable. Secondary outcomes were change in serum sodium pre- and postinitiation of treatment as a continuous variable, overcorrection of hyponatraemia (defined as >10 mmol/L rise in serum sodium in 24 hours or >18 mmol/L rise in 48 hours) and frequency of adverse events from urea treatment.

Normality of continuous variables was assessed by the Shapiro-Wilk test. Nonnormally distributed data are displayed as median and interquartile range (IQR) and were compared using the Mann-Whitney U test; normally distributed data are displayed as mean and standard deviation (SD), and compared using *t* tests (unless otherwise stated). Categorical variables are displayed as number and percentage and compared using the chi-squared or Fisher's exact test where appropriate. Logistic regression was used to assess predictors of the primary outcome and one-way ANOVA was used for cumulative change in serum sodium. Data were analysed using SPSS Statistics version 25 (IBM, New York, NY) and Prism 7 (GraphPad Software, San Diego, CA). Two-sided *P*-values were used and <0.05 was deemed statistically significant.

The study was approved by the Metro South Human Research Ethics Committee (reference HREC/16/QPAH/490). All authors had full access to all data (including statistical reports and tables), and no funding was acquired to undertake this study.

## 3 | RESULTS

Urea was used in the treatment of hyponatraemia on 78 occasions in 69 patients. There were 6 patients who received multiple courses with intervening periods of normal serum sodium off treatment. The demographic information of the urea-treated patients is shown in Table 1. The most common cause of hyponatraemia receiving urea treatment was SIADH, of which the most frequent precipitant was central nervous system pathology (more common than in the comparison group not receiving urea). A number of patients had multifactorial causes for their hyponatraemia, including some patients who had a contribution of salt depletion or diuretic use. In such cases, correction of hypovolaemia/nonrenal salt depletion was undertaken prior to free water restriction or urea treatment. Other differences compared to the nonurea group include a lower proportion on antidepressants and pregabalin, and fewer with no cause found for the SIADH or unknown duration of hyponatraemia.

**TABLE 1** Demographics of patients treated with urea (n = 78) and fluid restriction alone (n = 51)

| Characteristic | Urea | FR | *P* |
|---|---|---|---|
| Age | 67 (52-76) | 68 (54-77) | 0.739 |
| Female | 32 (41.0%) | 23 (45.1%) | 0.717 |
| Admission diagnosis | | | |
| Hyponatraemia | 16 (20.5%) | 10 (19.6%) | 0.900 |
| Infection | 9 (11.5%) | 9 (17.6%) | 0.328 |
| ICH/CVA | 31 (39.7%) | 10 (19.6%) | **0.016** |
| Malignancy | 3 (3.8%) | 4 (7.8%) | 0.327 |
| Fracture | 4 (5.1%) | 4 (7.8%) | 0.532 |
| Fall | 4 (5.1%) | 4 (7.8%) | 0.532 |
| ACS/Arrhythmia | 2 (2.6%) | 2 (3.9%) | 0.664 |
| Elective | 2 (2.6%) | 5 (9.8%) | 0.076 |
| Other | 17 (21.8%) | 15 (29.4%) | 0.362 |
| Comorbidities | | | |
| CCF | 4 (5.1%) | 3 (5.9%) | 0.780 |
| AKI/CKD | 8 (10.3%) | 7 (13.7%) | 0.315 |
| CLD | 4 (5.1%) | 2 (3.9%) | 0.768 |
| Contributing medications | | | |
| ACEI | 9 (11.5%) | 6 (11.8%) | 0.969 |
| ARB | 12 (15.4%) | 8 (15.7%) | 0.963 |
| Antidepressant | 14 (18.0%) | 17 (33.3%) | **0.046** |
| Antipsychotic | 2 (2.6%) | 3 (5.9%) | 0.340 |
| Antiepileptic | 23 (29.5%) | 14 (27.5%) | 0.803 |
| Pregabalin | 2 (2.6%) | 6 (7.7%) | **0.034** |
| ARNI | 1 (1.3%) | 0 | — |
| Thiazide | 3 (3.8%) | 3 (5.9%) | 0.591 |
| Frusemide | 7 (9.0%) | 5 (9.8%) | 0.874 |
| Spironolactone | 2 (2.6%) | 1 (2.0%) | 0.824 |
| Amiloride | 1 (1.3%) | 0 | — |
| Cause of hyponatraemia | | | |
| SIADH | 70 (89.7%) | 51 (100.0%) | — |
| Hypervolaemia | 7 (9.0%) | 0 | — |
| Nonrenal salt depletion | 4 (5.1%) | 0 | — |
| Diuretics | 6 (7.7%) | 0 | — |
| Cause of SIADH | | | |
| CNS pathology | 45 (64.3%) | 27 (52.9%) | 0.209 |
| Small cell lung cancer | 7 (10.0%) | 0 | — |
| Respiratory pathology | 5 (7.1%) | 5 (9.8%%) | 0.600 |
| Other malignancy | 3 (4.3%) | 7 (13.7%) | 0.063 |
| Medications | 7 (10.0%) | 6 (11.8%) | 0.757 |
| Surgery | 1 (1.4%) | 0 | - |
| None found | 5 (7.1%) | 10 (19.6%) | **0.040** |
| Duration of hyponatraemia | | | |
| Acute | 32 (41.0%) | 16 (31.4%) | 0.267 |
| Chronic | 35 (44.9%) | 18 (35.3%) | 0.280 |
| Unknown | 11 (14.1%) | 17 (33.3%) | **0.010** |

Bold indicates statistically significant difference ($P < 0.05$)

ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; AKI, acute kidney injury; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker-neprolysin inhibitor; CCF, congestive cardiac failure; CKD, chronic kidney disease; CLD, chronic liver disease; CNS, central nervous system; CVA, cerebrovascular accident; ICH, Intracranial haemorrhage; SIADH, syndrome of inappropriate antidiuretic hormone.

Patients with multiple reasons for admission, comorbidities, causes of hyponatraemia or SIADH and multiple medications were counted for each. Age reported as median (IQR) and compared with Mann-Whitney U test, all other variables reported as n (%) and proportions compared with chi-square tests.

The median initial serum sodium was 127 mmol/L (IQR 122-128), initial plasma osmolarity (calculated) 264 mmol/L (IQR 257-269), nadir serum sodium 122 mmol/L (IQR 118-126) and baseline urine osmolality 551 mOsm/kg (IQR 422-724; prior to initial treatment). Fifteen patients had an initial serum sodium ≤120 mmol/L and 29 had a nadir serum sodium in that range. Two patients were mildly hypothyroid, and one patient was found to be cortisol deficient (four patients inappropriately did not have a cortisol measured). Biochemical and treatment response parameters and comparison to the fluid restriction only group are shown in Table 2.

Fluid restriction was first-line treatment in 51 patients (65.4%). The median maximum fluid restriction was 500 mL/24 h (IQR 500-750), in 34 treatment episodes (43.6%) the fluid restriction was breached. This was higher compared to the fluid restriction alone group (23.5%; $P = 0.02$) and was due to intravenous treatment (antibiotics, other medications; 21 episodes) or patient noncompliance (13 episodes). Urea was administered as first-line treatment in 17 patients (21.8%) and as second line in the remaining 61 treatment occasions (78.2%). Eleven patients (14.1%) developed hyponatraemia during treatment with the local Neurosurgical Department subarachnoid haemorrhage (SAH) protocol (3 L intravenous 0.9% saline per 24 hour period to prevent vasospasm), of which seven received urea as first-line treatment. These patients developed moderate hyponatraemia, a mean of 8.4 ± 3.0 days after the haemorrhage. Aside from those on the SAH protocol, only two other patients received urea without concomitant fluid restriction. One of these was noncompliant with fluid restriction despite close nursing supervision; the other was deemed to have multi-factorial hyponatraemia with concomitant salt depletion and SIADH (thus treated with a combination of intravenous 0.9% saline and urea). The initial urea dose range was 15-90 g daily (mode 30 g, 55.1%), median maximal dose 45 g (IQR 45-60, range 15-145) and median treatment duration 6 days (IQR 4-8, range 1-21).

In 50 treatment episodes (64.1%), the patient achieved a serum sodium ≥130 mmol/L at 72 hours postinitiation of urea treatment,

**TABLE 2** Biochemical parameters for patients treated with urea (n = 78) and fluid restriction alone (n = 51)

| Measure | Urea Median (IQR) or N (%) | FR Median (IQR) or N (%) | Units | *P* |
|---|---|---|---|---|
| Initial serum Na | 127 (122-128) | 126 (124-128) | mmol/L | 0.840 |
| Initial serum osmolarity | 264 (257-269) | 265 (259-268) | mmol/L | 0.918 |
| Nadir serum Na | 122 (118-126) | 125 (122-127) | mmol/L | **0.024** |
| Initial urine osmolality | 551 (422-724) | 470 (346-605) | mOsm/kg | **0.046** |
| Initial fluid restriction | 750 (500-1000) | 1000 (950-1500) | mL/d | **0.001** |
| Maximal fluid restriction | 500 (500-750) | 1000 (750-1250) | mL/d | **<0.001** |
| Proportion Na ≥130 mmol/L at 72 h | 50 (64.1%) | 27 (52.9%) | Patients | 0.121 |
| Days until Na ≥130 mmol/L | 2 (1-4) | 3 (1-5) | Days | 0.060 |
| Days until Na ≥135 mmol/L | 5 (3-7) | 5 (3-10) | Days | 0.763 |

Bold indicates statistically significant difference ($P < 0.05$)
FR, fluid restriction; Na, serum sodium.
Nonnormal continuous variables compared with Mann-Whitney U test, proportion of patients with serum sodium ≥130 mmol/L at 72 h (primary outcome) compared using chi-square test.

of which 16 (20.5% total) reached ≥135 mmol/L. The median time to achieve serum sodium ≥130 mmol/L was 2 days in the urea-treated group compared to 3 days in the fluid restriction alone group, which just failed to reach statistical significance (Table 2, $P = 0.06$). The urea-treated group had already either failed a first-line treatment or were deemed not suitable to be fluid restricted. In 56 patients who received other treatment prior to commencement of urea, the mean sodium change in the 72 hours following urea treatment initiation (6.9 ± 4.8 mmol/L) was significantly greater than with the preceding treatments (−1.0 ± 4.7 mmol/L, $P < 0.001$); cumulative change in serum sodium over time is shown in Figure 1.

No patient who started on <30 g daily urea achieved a serum sodium of ≥135 mmol/L at 72 hours. The starting dose of urea correlated significantly with the subsequent change in serum sodium; $r = 0.291$, $P = 0.012$. Using binary logistic regression, when controlling for age, gender, duration of hyponatraemia, presence of comorbidities, contributing medicines, urine osmolality and serum sodium at time of treatment initiation (patients without SIADH excluded), a higher initial urea dose increased the likelihood of the primary outcome (OR 1.135 per 1 g increase in dose, 95% CI 1.015-1.269, $P = 0.027$).

Figure 2 shows the trend in serum sodium for the 72 hours following initiation of urea in 3 patient subsets: patients on the local SAH protocol (unable to be fluid restricted), acute onset hyponatraemia with mild-moderate symptoms, and patients with a serum sodium <120 mmol/L but without severe symptoms. All three groups showed significant improvement in serum sodium over time. Those patients in the SAH group had a median time to serum sodium ≥130 mmol/L of 1 (IQR 0-1) day and ≥135 mmol/$^{L}$ of 4 (IQR 2-5) days.

Seventeen patients (21.8%) had side effects, distaste the most common (7), followed by nausea (6) and hypokalaemia (4). None were severe or led to discontinuation of treatment. Seven patients were admitted to a high-dependency or intensive care unit after initiation of urea treatment, none due to symptomatic hyponatraemia or side effects from the treatment. No patients developed hypernatraemia, overcorrection, osmotic demyelination or died.

## 4 | DISCUSSION

Here we reported the second largest case series of urea treatment, and the largest outside of an intensive care setting. We have shown that urea is a safe and effective second-line therapy for those patients in whom fluid restriction has failed or is impractical. The primary outcome of serum sodium ≥130 mmol/L achieved in 64.1% of treatment occasions is higher than any other second-line agent in the multinational hyponatraemia registry for patients who had failed fluid restriction.[4] The improvement in serum sodium after commencement of urea was consistent with that reported in three previous case series (two from intensive care settings) using similar dose ranges.[10,12,16] When compared to a contemporaneous group of patients with SIADH who were managed with fluid restriction alone, neither the proportion achieving serum sodium ≥130 mmol/L nor the time to achieve a serum sodium ≥130 or ≥135 mmol/L were significantly different. However, the urea-treated patients were either not able to be fluid restricted or had clearly failed to increment their serum sodium prior to urea initiation (Figure 1). In addition, they required a tighter fluid restriction and had a lower nadir serum sodium, indicative of a self-selected, more severe group. High urine osmolality is a known predictor of failure of fluid restriction as was seen in these patients.[17]

The benefits seen from urea treatment were consistent in the three subsets demonstrated in Figure 2. The European Clinical Practice Guidelines make the distinction between biochemically profound hyponatraemia (defined as a serum sodium <125 mmol/L) and clinically severe—based on severity of symptoms.[6] In our institution, hypertonic (3%) saline had been often used in patients with a serum sodium <120 mmol/L, even in the absence of severe

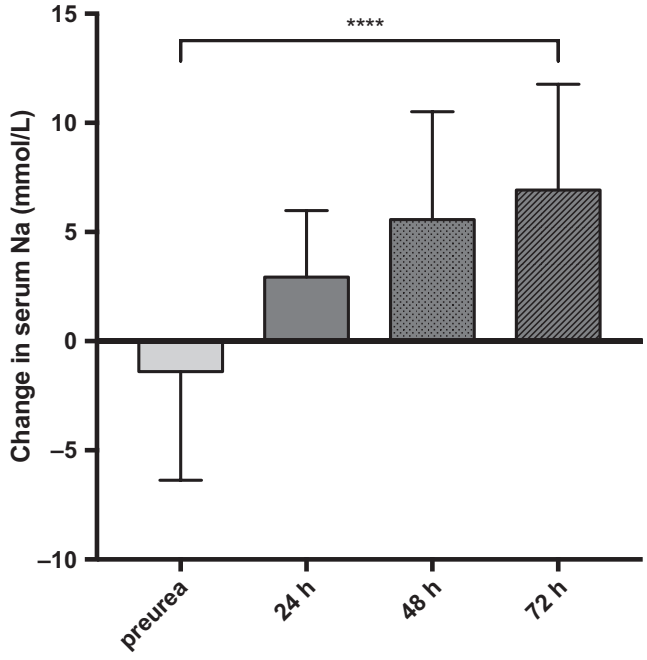


**FIGURE 1** Cumulative change in mean (SD) serum sodium over each 24 h period from baseline after commencement of urea for those patients who failed fluid restriction (n = 56), ****one-way ANOVA $P < 0.0001$ for improvement over time. Change preurea is during fluid restriction, prior to urea treatment. Na, serum sodium

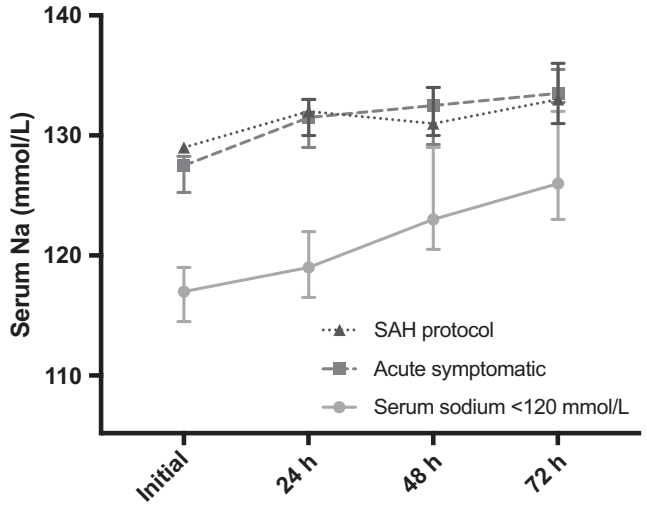


**FIGURE 2** Median (IQR) serum sodium for patients with acute, symptomatic hyponatraemia (n = 10; one-way ANOVA $P = 0.0011$), serum sodium ≤120 mmol/L at commencement of urea (n = 21; one-way ANOVA $P < 0.0001$), and those who developed SIADH while being treated on local subarachnoid protocol (3 L 0.9% saline per 24 h; n = 11; one-way ANOVA $P = 0.0004$) from time of urea treatment initiation. Na, serum sodium; SAH, subarachnoid haemorrhage

symptoms. While hypertonic (3%) saline is the treatment of choice in severe symptomatic hyponatraemia,[6,7] this study has demonstrated the safety and efficacy of using urea in patients with biochemically profound hyponatraemia (<120 mmol/L) without severe symptoms and those with acute onset hyponatraemia with moderate symptoms. Our recently published experience treating moderate to severe hyponatraemia included hypertonic saline for severe symptomatic hyponatraemia where a median increase in serum sodium of 11 mmol/L was observed over the total treatment period.[15]

Treatment with urea at our centre was well tolerated, and there were no grade 3/4 toxicities from treatment. The most common side effect of distaste can be ameliorated by mixture with sweet or carbonated liquids (there is a more palatable recipe published),[18] and no patient in our study discontinued treatment as a result of this or any other side effect. The biggest concern with treatment of hyponatraemia is that of overly rapid correction and the subsequent risk of osmotic demyelination syndrome (ODS). Overly rapid correction has been shown to be a risk with use of hypertonic saline[4,19,20] and vasopressin receptor antagonists ("vaptans"),[4,21,22] and has been seen previously in some urea series,[10,11] but not others.[12,16,23] ODS has been reported in one case of vaptan use[24] but not to date with urea. Furthermore, experimentally induced rapid correction (>30 mmol/L in 24 hours) of serum sodium in rats with urea, lixivaptan and hypertonic saline treatments showed lower rates of neurological symptoms, mortality and histological hallmarks of ODS in the urea group.[14] It is this high risk of overcorrection (and subsequent ODS risk) and the associated need for close monitoring in a HDU/ICU setting that leads to reluctance to administer hypertonic saline and the search for alternative treatment options in the nonemergent setting. Long-term tolvaptan treatment (at higher doses than for hyponatraemia) has an increased risk of reversible, idiosyncratic drug-induced liver injury, leading to both the FDA and Australian Therapeutic Goods Administration limiting treatment to 30 days.[25,26] Vaptans are metabolized by CYP3A4 (conivaptan is also a potent inhibitor of the enzyme) resulting in a number of important drug interactions.[27,28] Both of these issues raise concerns regarding the long-term safety of vaptans to treat chronic SIADH. Urea has been shown to be a safe and well-tolerated treatment for this indication in both adults and children, with published cases of up to 8 years treatment duration.[29,30] Additional to the safety benefits, treatment with urea is cost effective, costing our centre approximately AU$4 per 30 g dose, compared to approximately AU$83 per 15 mg dose of tolvaptan.

This study is limited by its retrospective nature and the reliance on information documented in the medical record. Despite this, overall there was a low volume of missing data and all urea-treated patients had the involvement of clinicians familiar with the investigation and treatment of hyponatraemia. Despite only two patients not receiving the involvement of the Department of Diabetes and Endocrinology, there was significant inter-prescriber variability in dosage of urea, threshold for initiation and dose escalation, and duration of treatment. This may mask predictors of response to treatment and could be improved by implementation of practical guidelines for prescribing urea. The majority of patients did not have a measured serum osmolality; instead, the calculated osmolarity available for all patients was used in defining SIADH. This provides consistency between patients for a small risk of error. Despite a robust improvement

in serum sodium after initiation of urea treatment, the comparison to preurea change in serum sodium is limited by the wide range of time between onset of hyponatraemia and treatment with urea. A number of patients received ineffective treatment with limited monitoring for portions of this time (15 patients received no treatment initially and three patients with SIADH received isotonic [0.9%] saline), which is likely to magnify the treatment effect. The benefit to hyponatraemia from resolution of the inciting event can also not be discounted when considering the improvement seen, neither can the more stringent fluid restriction used in the urea patients compared to the contemporaneous fluid restricted group. This may be more relevant in the subarachnoid haemorrhage group. A previous study of a heterogenous group of 187 neurosurgical patients (33% with SAH) showed a mean onset of hyponatraemia (<130 mmol/L; 62% SIADH) of 5.1 days after cerebral insult and median time to normalization serum sodium of 3 days (no details of the presence or absence of treatment for hyponatraemia are reported).[33] This is earlier and quicker than in our data and may support resolution of SIADH contributing to a return to eunatraemia. However, in our clinical experience, patients on the local neurosurgical SAH protocol do not have spontaneous resolution of hyponatraemia until the intravenous fluid loading is ceased, which can be up to weeks in duration. The study is relatively small thereby diminishing the strength of the statistical inferences. However, it is the second largest case series published to date, and there is only one small prospective study of urea which shows comparative efficacy to vaptans in 12 patients with chronic SIADH.[9]

## 5 | CONCLUSION

This study adds to the growing body of evidence that urea is a safe, effective, and well-tolerated treatment for hyponatraemia due to SIADH. Based on our data, we recommend urea in patients with SIADH and moderate to profound hyponatraemia (in the absence of severe symptoms) who are unable to undergo, or have failed fluid restriction, with a starting dose of at least 30 g/d. Further prospective studies are needed to confirm safety in biochemically profound hyponatraemia <120 mmol/L in the absence of clinical signs of severity, although this study makes a strong case. A randomized controlled trial comparing fluid restriction alone to fluid restriction and urea would also be useful to determine if urea might even be indicated as first-line therapy. These studies are required to clearly elucidate the place for urea in the treatment of SIADH and help form an easy to use algorithm.

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## CONFLICT OF INTEREST

There is no conflict of interest to declare.

## AUTHOR CONTRIBUTIONS

JL—designed the study, reviewed the literature, collected and entered the data, analysed the statistics, drafted and revised the manuscript. KB—designed the study, reviewed the literature, revised the manuscript. GD—retrieved biochemical data, revised the manuscript. AR—designed and supervised the study, revised the manuscript. WI—designed and supervised the study, revised the manuscript.

## ETHICS APPROVAL

Ethics approval was obtained from the Metro South Human Research and Ethics Committee (reference HREC/16/QPAH/490).

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## REFERENCES

1. Ball SG, Iqbal Z. Diagnosis and treatment of hyponatraemia. *Best Pract Res Clin Endocrinol Metab*. 2016;30(2):161-173.
2. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*. 2006;119(7 suppl 1):S30-S35.
3. Corona G, Giuliani C, Verbalis JG, Forti G, Maggi M, Peri A. Hyponatremia improvement is associated with a reduced risk of mortality: evidence from a meta-analysis. *PLoS ONE*. 2015;10(4):e0124105.
4. Greenberg A, Verbalis JG, Amin AN, et al. Current treatment practice and outcomes. Report of the hyponatremia registry. *Kidney Int*. 2015;88(1):167-177.
5. Cuesta M, Thompson CJ. The syndrome of inappropriate antidiuresis (SIAD). *Best Pract Res Clin Endocrinol Metab*. 2016;30(2):175-187.
6. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Eur J Endocrinol*. 2014;170(3):G1-G47.
7. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med*. 2013;126(10 suppl 1):S1-S42.
8. Decaux G, Brimioulle S, Genette F, Mockel J. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea. *Am J Med*. 1980;69(1):99-106.
9. Soupart A, Coffernils M, Couturier B, Gankam-Kengne F, Decaux G. Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol*. 2012;7(5):742-747.
10. Decaux G, Andres C, Gankam Kengne F, Soupart A. Treatment of euvolemic hyponatremia in the intensive care unit by urea. *Crit Care*. 2010;14(5):R184.
11. Pierrakos C, Taccone FS, Decaux G, Vincent J-L, Brimioulle S. Urea for treatment of acute SIADH in patients with subarachnoid hemorrhage: a single-center experience. *Ann Intensive Care*. 2012;2(1):13.
12. Coussement J, Danguy C, Zouaoui-Boudjeltia K, et al. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone with urea in critically ill patients. *Am J Nephrol*. 2012;35(3):265-270.
13. Sterns RH, Silver SM, Hix JK. Urea for hyponatremia? *Kidney Int*. 2015;87(2):268-270.

14. Gankam Kengne F, Couturier BS, Soupart A, Decaux G. Urea minimizes brain complications following rapid correction of chronic hyponatremia compared with vasopressin antagonist or hypertonic saline. *Kidney Int*. 2015;87(2):323-331.
15. Berkman K, Haigh K, Li L, et al. Investigation and management of moderate to severe inpatient hyponatraemia in an Australian tertiary hospital. *BMC Endocr Disord*. 2018;18(1):93.
16. Rondon-Berrios H, Tandukar S, Mor MK, et al. Urea for the treatment of hyponatremia. *Clin J Am Soc Nephrol*. 2018;17:1627-1632.
17. Winzeler B, Lengsfeld S, Nigro N, et al. Predictors of nonresponse to fluid restriction in hyponatraemia due to the syndrome of inappropriate antidiuresis. *J Intern Med*. 2016;280(6):609-617.
18. Vandergheynst F, Gankam Kengne F, Decaux G. Vasopressin antagonists. *N Engl J Med*. 2015;373(10):980-981.
19. Mohmand HK, Issa D, Ahmad Z, Cappuccio JD, Kouides RW, Sterns RH. Hypertonic saline for hyponatremia: risk of inadvertent overcorrection. *Clin J Am Soc Nephrol*. 2007;2(6):1110-1117.
20. Geoghegan P, Harrison AM, Thongprayoon C, et al. Sodium correction practice and clinical outcomes in profound hyponatremia. *Mayo Clin Proc*. 2015;90(10):1348-1355.
21. Rozen-Zvi B, Yahav D, Gheorghiade M, Korzets A, Leibovici L, Gafter U. Vasopressin receptor antagonists for the treatment of hyponatremia: systematic review and meta-analysis. *Am J Kidney Dis*. 2010;56(2):325-337.
22. Jaber BL, Almarzouqi L, Borgi L, Seabra VF, Balk EM, Madias NE. Short-term efficacy and safety of vasopressin receptor antagonists for treatment of hyponatremia. *Am J Med*. 2011;124(10):977.e971-977.e979.
23. Decaux G, Gankam Kengne F, Couturier B, Musch W, Soupart A, Vandergheynst F. Mild water restriction with or without urea for the longterm treatment of syndrome of inappropriate antidiuretic hormone secretion (SIADH): can urine osmolality help the choice? *Eur J Intern Med*. 2018;48:89-93.
24. Malhotra I, Gopinath S, Janga KC, Greenberg S, Sharma SK, Tarkovsky R. Unpredictable nature of tolvaptan in treatment of hypervolemic hyponatremia: case review on role of vaptans. *Case Rep Endocrinol*. 2014;2014:807054.
25. Torres VE, Chapman AB, Devuyst O, et al. Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: the TEMPO 4:4 Trial. *Nephrol Dial Transplant*. 2018;33(3):477-489.
26. Muto S, Okada T, Yasuda M, Tsubouchi H, Nakajima K, Horie S. Long-term safety profile of tolvaptan in autosomal dominant polycystic kidney disease patients: TEMPO Extension Japan Trial. *Drug Healthc Patient Saf*. 2017;9:93-104.
27. Decaux G, Soupart A, Vassart G. Non-peptide arginine-vasopressin antagonists: the vaptans. *Lancet*. 2008;371(9624):1624-1632.
28. Peri A. The use of vaptans in clinical endocrinology. *J Clin Endocrinol Metab*. 2013;98(4):1321-1332.
29. Chehade H, Rosato L, Girardin E, Cachat F. Inappropriate antidiuretic hormone secretion: long-term successful urea treatment. *Acta Paediatr*. 2012;101(1):e39-e42.
30. Huang EA, Feldman BJ, Schwartz ID, Geller DH, Rosenthal SM, Gitelman SE. Oral urea for the treatment of chronic syndrome of inappropriate antidiuresis in children. *J Pediatr*. 2006;148(1):128-131.
31. Renneboog B, Decaux G. Idiopathic hyponatremia in a young patient: look at the sinus. *Am J Med*. 2008;121(5):e5-e6.
32. Decaux G, Genette F. Urea for long-term treatment of syndrome of inappropriate secretion of antidiuretic hormone. *Br Med J (Clin Res Ed)*. 1981;283(6299):1081-1083.
33. Sherlock M, O'Sullivan E, Agha A, et al. Incidence and pathophysiology of severe hyponatraemia in neurosurgical patients. *Postgrad Med J*. 2009;85(1002):171-175.


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