DR JACK LOCKETT (Orcid ID : 0000-0002-6175-985X)

PROFESSOR WARRICK J INDER (Orcid ID : 0000-0001-5078-4980)

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Urea treatment in fluid restriction-refractory hyponatraemia

Jack Lockett[1,2,#], Kathryn E Berkman[1], Goce Dimeski[2,3], Anthony W Russell[1,2], Warrick J Inder[1,2]

1. Department of Diabetes and Endocrinology, Princess Alexandra Hospital, Woolloongabba, QLD, Australia.
2. Faculty of Medicine, the University of Queensland, Brisbane, QLD, Australia.
3. Department of Chemical Pathology, Pathology Queensland, Brisbane, QLD, Australia.

Corresponding Author.

Address: Department of Diabetes and Endocrinology, Princess Alexandra Hospital, 199 Ipswich Rd, Woolloongabba, QLD 4102, Australia.

Email: jack.lockett@outlook.com.

Summary

Objective

Hyponatraemia in hospitalised patients is common and associated with increased mortality. International guidelines give conflicting advice regarding the role of urea in the treatment of SIADH. We hypothesised 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 2016-17. Primary endpoint: proportion of patients achieving a serum sodium ≥130mmol/L at 72h.

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 122mmol/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 ≥130mmol/L at 72h. In 56 patients who received other prior treatment, the mean sodium change at 72h (6.9±4.8mmol/L) was greater than with the preceding treatments (-1.0±4.7mmol/L; p<0.001). Seventeen patients (22.7%) had side effects

(principally distaste), none were severe. No patients developed hypernatraemia, over-correction (>10mmol/L in 24h or >18mmol/L in 48h), or died.

Conclusions

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

Keywords

Hyponatraemia, urea, Inappropriate ADH Syndrome, fluid restriction, sodium

Introduction

Hyponatraemia, defined as a serum sodium <135mmol/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] Anti-diuretic hormone (ADH) secreted from the posterior pituitary regulates free water excretion in the nephric collecting ducts. Non-osmotic 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 48h), 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.[8-12] Urea is readily absorbed from the gut and freely filtered at the glomerulus; in a patient with normal renal function the entirety of a 15g dose is excreted within 12h 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 3,087 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 hypothesised that urea is a safe, effective treatment for hyponatraemia due to SIADH in fluid restriction-refractory patients, or those unable to be restricted.

Methods

Inpatients with moderate hyponatraemia (serum sodium <130mmol/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 whom received urea. This was divided into doses of 15-45g (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 ≥ 130mmol/L at 72h post-initiation of urea as a categorical variable. Secondary outcomes were change in serum sodium pre- and post-initiation of treatment as a continuous variable, overcorrection of hyponatraemia (defined as >10 mmol/L rise in serum Na in 24h or >18 mmol/L rise in 48h) and frequency of adverse events from urea treatment.

Normality of continuous variables was assessed by the Shapiro-Wilk test. Non-normally 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, USA) and Prism 7 (GraphPad Software, San Diego, CA, USA). 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.

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 multi-factorial causes for their hyponatraemia, including some patients who had a contribution of salt depletion or diuretic use. In such cases, correction of hypovolaemia/non-renal salt depletion was undertaken prior to free water restriction or urea treatment. Other differences compared to the non-urea group include a lower proportion on

antidepressants and pregabalin, and fewer with no cause found for the SIADH or unknown duration of hyponatraemia.

The median initial serum sodium was 127mmol/L (IQR 122-128), initial plasma osmolarity (calculated) 264mmol/L (IQR 257-269), nadir serum sodium 122mmol/L (IQR 118-126), and baseline urine osmolality 551mOsm/kg (IQR 422-724; prior to initial treatment). Fifteen patients had an initial serum sodium ≤120mmol/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 500mL/24h (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 non-compliance (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 (3L intravenous 0.9% saline per 24h 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 2 other patients received urea without concomitant fluid restriction. One of these was non-compliant 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 15-90g daily

(mode 30g, 55.1%), median maximal dose 45g (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 ≥130mmol/L at 72h post-initiation of urea treatment, of which 16 (20.5% total) reached ≥135mmol/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 72h following urea treatment initiation (6.9 ± 4.8mmol/L) was significantly greater than with the preceding treatments (-1.0 ± 4.7mmol/L, $p<0.001$); cumulative change in serum sodium over time is shown in Figure 1.

No patient who started on <30g daily urea achieved a serum Na of ≥135 mmol/L at 72h. The starting dose of urea correlated significantly with the subsequent change in serum Na; $r = 0.291$, $p = 0.012$. 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 1g increase in dose, 95% CI 1.015-1.269, $p=0.027$).

Figure 2 shows the trend in serum sodium for the 72h 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 < 120mmol/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 ≥130mmol/L of 1 (IQR 0-1) day and ≥135mmol/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, over-correction, osmotic demyelination, or died.

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 ≥130mmol/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 ≥130mmol/L nor the time to achieve a serum sodium ≥130 or ≥135mmol/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 Na <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 Na <120 mmol/L, even in the absence of severe 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, 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 (>30mmol/L in 24h) 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 non-emergent 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 metabolised 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.[29-32] Additional to the safety benefits, treatment with urea is cost effective, costing our centre approximately AU$4 per 30g dose, compared to approximately AU$83 per 15mg 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 pre-urea 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 (<130mmol/L; 62% SIADH) of 5.1 days after cerebral insult and median time to normalisation 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]

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 30g/day. 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 randomised 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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Ethics Approval

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

Conflict Of Interest

There is no conflict of interest to declare.

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No funding was sourced or utilised to undertake this study.

Author Contributions

J.L. – study design, literature review, data collection and entry, statistical analysis, manuscript drafting and revision.

K.B. – study design, literature review, manuscript revision.

G.D. – biochemical data retrieval, manuscript revision.

A.R. – study design and supervision, manuscript revision.

W.I. – study design and supervision, manuscript revision.

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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	-
Non-renal 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*

Table 1: Demographics of patients treated with urea (n=78) and fluid restriction alone (n=51). Patients with multiple reasons for admission, co-morbidities, 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. *Abbreviations*: ICH, Intracranial haemorrhage; CVA, cerebrovascular accident; ACS, acute coronary syndrome; CCF, congestive cardiac failure; AKI, acute kidney injury; CKD, chronic kidney disease; CLD, chronic liver disease; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker-neprolysin inhibitor; SIADH, syndrome of inappropriate anti-diuretic hormone; CNS, central nervous system.

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/day	0.001*
Maximal fluid restriction	500 (500-750)	1000 (750-1250)	mL/day	<0.001*
Proportion Na ≥130mmol/L at 72h	50 (64.1%)	27 (52.9%)	patients	0.121
Days until Na ≥130mmol/L	2 (1-4)	3 (1-5)	Days	0.060
Days until Na ≥135mmol/L	5 (3-7)	5 (3-10)	Days	0.763

Table 2: Biochemical parameters for patients treated with urea (n=78) and fluid restriction alone (n=51). Non-normal continuous variables compared with Mann-Whitney U test, proportion of patients with serum sodium ≥130mmol/L at 72h (primary outcome) compared using Chi-square test. *Abbreviations*: Na, serum sodium; FR, fluid restriction.

Figure 1: Cumulative change in mean (SD) serum sodium over each 24h 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 pre-urea is during fluid restriction, prior to urea treatment. *Abbreviations*: 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 ≤120mmol/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 (3L 0.9% saline per 24h; n=11; one-way ANOVA p=0.0004) from time of urea treatment initiation. *Abbreviations*: Na, serum sodium; SAH, subarachnoid haemorrhage.