Tolvaptan and urea in paediatric hyponatraemia

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Abstract

Background: The syndrome of inappropriate antidiuretic hormone (SIADH) is usually treated with fluid restriction. This can be challenging in patients with obligate fluid intake for nutrition or medication. Pharmaceutical treatment with tolvaptan and urea is available but minimal paediatric data are available. We review the efficacy and safety of tolvaptan and urea in paediatric patients with SIADH.

Methods: Retrospective review of paediatric inpatients with clinical diagnosis of SIADH. Patients were identified from pharmacy records, based on tolvaptan and urea prescriptions. Relevant information was extracted from patient electronic records.

The main outcome measures included: number of days to sodium normalisation, daily change in plasma sodium concentration and maximum increase of plasma sodium concentration in 24hrs. Reported side effects were captured.

Results: Thirteen patients received tolvaptan and six urea. Five patients had both agents (tolvaptan converted to urea.) Tolvaptan led to plasma sodium normalisation in 10/13 (77%) within six days (median 2.5 days, range [1,6]) with a median change of sodium concentration of 7 mmol/L(-1,14) within the first 24 hours of treatment. Three patients experienced a change in plasma sodium >10 mmol/l/day but had no apparent side effects.

Urea led to sodium normalisation in 5/6 (83%) patients. Median number of days to normalisation with urea was 2 (1,10) with a median change of plasma sodium concentration of 2 mmol/L (-1,6) within the first 24hours. All patients tolerated tolvaptan and/or urea without unexpected side effects.

Conclusions: Tolvaptan and urea appear to be safe and effective when fluid restriction is challenging in paediatric SIADH.

Introduction

The syndrome of inappropriate antidiuretic hormone (SIADH) is characterised by hypoosmolality in a euvolaemic or hypervolaemic patient with inappropriately concentrated urine due to excess secretion of antidiuretic hormone (ADH) from non-osmotic stimuli [1]. ADH acts via 2 receptors: the type 1 receptor, mainly expressed in the vasculature, causing vasoconstriction; the type 2 receptor (AVPR2), primarily expressed in the principal cells of the kidney collecting duct, regulating reabsorption of water and therefore urine concentration [2]. Non-osmotic stimuli for ADH release include a variety of conditions, such as infections, pain, stress, medications, brain injury and congenital malformations [1].

Whenever the kidneys cannot adequately provide homeostasis by adjusting urine volume and composition to match intake, clinicians need to adjust intake to match the output [3]. Consequently, the first step in managing SIADH is usually fluid restriction, but this can be challenging. Patients with SIADH tend to be thirsty and may maintain increased fluid intake [4]. Moreover, small infants depend on fluid intake (milk) for their caloric needs and prolonged fluid restriction therefore risks malnutrition. Some patients with complex medical backgrounds may also have been prescribed large fluid volumes, for instance to minimise toxicity when receiving chemotherapy.

For pharmacological treatment of SIADH, urea has long been used as an osmotic diuretic, but reported experience in children is limited to case reports [5-8]. With the availability of specific AVPR2 antagonists, the "vaptans", another pharmacologic treatment modality for SIADH has become available [9]. Because of their specific effect on water excretion, these drugs are also called "aquaretics". Tolvaptan, an oral aquaretic is arguably the most used vaptan and is predominantly metabolised in the liver by CYP3A4 [10]. Efficacy has been demonstrated in adult medicine, but, again, descriptions of use in paediatrics is restricted to single case reports [11, 12]. In this study we reviewed our experience with tolvaptan and urea in a cohort of paediatric patients with a diagnosis of SIADH.

Methods

This is a retrospective cohort study looking at the efficacy and safety of tolvaptan and urea use for SIADH in paediatric inpatients at the Great Ormond Street Hospital for Children NHS Foundation Trust, a London based tertiary paediatric hospital, and the Portland Hospital, a private specialised paediatric hospital in London. Patients were identified from pharmacy records based on tolvaptan and urea prescriptions. The prospectively collected electronic patient records during the inpatient stay were reviewed and relevant demographic information and laboratory results were extracted, including primary diagnosis leading to SIADH, dose of treatment, blood and urine osmolality, creatinine and electrolyte results. The follow-up inpatient and outpatient documentation was also reviewed aiming to identify any observed adverse reactions.

The clinical criteria applied by our team for the diagnosis of SIADH conform to current definition [1]:

a) hyponatraemia as defined by a sodium concentration <133mmol/L for patients less < 15years of age or <137mmol/L for patients > 15years of age), with concurrent plasma osmolality below the normal range, defined by our laboratory as <282 mosm/kg

b) hypervolaemia or euvolaemia based on clinical assessment (including examination and regular body weights)

c) an inappropriately concentrated urine (osmolality >100mosm/kg)

The end points of this study were:

a) Number of days to plasma sodium normalisation

b) Daily change of plasma Na concentration [Na]

c) Maximum increase of plasma sodium concentration in 24hrs

d) Reported side effects

In addition, all children had their thyroid function checked to exclude other potential causes of hyponatraemia. Timing of electrolyte testing varied between patients and depended on the choice of the treating clinicians. As plasma osmolality was not obtained at the same frequency as sodium, we followed plasma sodium levels for follow-up instead. For consistency, plasma electrolyte results were gathered around set time points, including

at diagnosis of SIADH and every day thereafter up to 6 days following commencement of treatment with tolvaptan.

Urea was used as an alternative drug either by clinician choice or because treatment was converted from tolvaptan to urea as a more cost-effective option in persistent SIADH.

Similar data collection was followed for those children and a comparison made between the two approaches in the number of treatment days until normalisation of plasma sodium was achieved.

Continuous data were summarised with medians and range (min, max). Group comparisons were performed with non-parametric tests allowing for paired sampling (Wilcoxon and Friedman tests). Statistical analysis and graph preparation were performed with GraphPad Prism (version 8 for MacOS).

As this was a retrospective review of clinical and laboratory data obtained as part of routine clinical care, ethical approval by the National Research Ethics Service was not required but departmental approval was provided.

Results

We identified 14 patients who received tolvaptan and /or urea as part of their routine clinical care for treatment of SIADH between 2015 to 2020. These included four infants with ages: five weeks, three, five and six months. One of them had been reported previously [6, 12]. All patients were diagnosed with SIADH as per inclusion criteria and were reviewed by a paediatric endocrinologist or nephrologist. The patient demographics are presented in table 1.

At time of SIADH diagnosis									During treatment with tolvaptan			During treatment with urea		
P	**Sex**	**Age**	**Underlying diagnosis**	**Prior treatment**	**Plasma [Na]**	**Plasma Osmolality**	**FENa**	**Urine Osmolality**	**Days to normal [Na]**	**Max Δ Na/24h**	**Max dose mg/kg/day**	**Days to normal [Na]**	**Max Δ Na/24h**	**Max dose g/Kg/day**
1	M	5 w	Neonatal listeria meningitis, hydrocephalus	Fluid restriction	128	268	1.0	298	5	9	0.2	N/A	N/A	N/A
2	F	6m	Optic pathway pilocytic astrocytoma	Fluid restriction NaCl supplements	128	274	3.2	685	3	9	0.7	2	6	1
3	M	2y	Pilocytic astrocytoma	Fluid restriction	127	-	3.9	608	1	14	0.2	N/A	N/A	N/A
4	F	9y	Ovarian teratoma	Fluid restriction NaCl supplements	123	255	1.6	622	N/A	5	0.1	1	2	0.75
5	F	5m	Supra and infra tentorial teratoma	Fluid restriction NaCl supplements	122	250	2.1	525	N/A	7	1.3	N/A	3	1.7
6	M	3m	Panhypopituitarism, chronic SIADH	Fluid restriction	131	268	-	391	1	13	0.9	3	3	0.6
7	M	6y	XIAP deficiency, HLH, skin GVHD	Fluid restriction	125	263	2.0	525	1	13	0.2	N/A	N/A	N/A
8	M	7y	Optic pathway, hypothalamic glioma	Fluid restriction NaCl supplements	127	261	2.3	784	3	5	0.2	10	4	1.5
9	M	16y	Hypothalamic, chiasmatic glioma	Fluid restriction	130	272	0.1	612	2	4	0.2	N/A	N/A	N/A
10	M	6y	Acute Lymphoblastic Leukaemia	Fluid restriction	121	247	1.6	719	N/A	8	1.4	N/A	N/A	N/A
11	F	6y	Intestinal failure, sepsis	Fluid restriction NaCl supplements	122	253	0.1	580	6	12	0.35	N/A	N/A	N/A
12	M	6y	Neonatal HIE, chest infection	Fluid restriction NaCl supplements	124	264	0.6	246	1	7	0.2	N/A	N/A	N/A
13	M	2y	Suprasellar Tertodermoid lesion	Fluid restriction	130	273	0.6	850	4	8	0.3	N/A	N/A	N/A
14	M	7y	Pilomyxoid astrocytoma	Fluid restriction NaCl supplements	134	281	1.2	708	N/A	N/A	N/A	1	6	0.5

Table 1: Summary table of patient cohort (P: Patient number, M: Male, F: Female, y: years, m: months, N/A: Not Applicable, XIAP: X-linked inhibitor of apoptosis protein, HLH: haemophagocytic lymphohistiocytosis, GVHD: graft versus host disease).

The majority of patients were under the care of the paediatric oncology team (12/14, 86%). SIADH was attributed to a brain lesion or neurosurgical procedure (brain tumour, debulking or shunt revision, n= 7), medications (vincristine, n=3), infection (n=3) and panhypopituitarism (n=1). Often more than one triggers could be identified. None had abnormal thyroid function.

The median plasma [Na] at the time of SIADH diagnosis was 127 mmol/L (121 – 134). Relevant laboratory results are summarised in table 2.

	At SIADH diagnosis	**At starting tolvaptan**
	Median (min, max)	**Median (min, max)**
plasma [Na] (mmol/L)	127 (121, 134)	126 (111,133)
plasma [Cr] (mmol/L)	18 (13,28)	19 (15, 32)
urine [Na] (mmol/L)	192 (40, 369)	164 (40, 352)
urine [Cr] (mmol/L)	2 (1, 9.5)	2.1 (0.9, 34)
plasma osmolality (mosmol/kg)	264 (247, 281)	259 (228, 278)
urine osmolality (mosmol/kg)	612 (246, 850)	529 (302, 889)
FeNa (%)	1.61 (0.1, 3.90)	1.712 (0.039, 3.45)

Table 2: Laboratory results at SIADH diagnosis and at tolvaptan commencement, summarised as medians, followed by range (min: minimum, max: maximum).

Tolvaptan was received by 13 patients. All had had a period of fluid restriction before commencing tolvaptan. The length of restriction varied depending on underlying condition and clinician preference [median: 2 days (1,60)]. One patient had intestinal failure and experienced episodes of severe hypoglycaemia with fluid restriction. Median [Na] at the time of starting tolvaptan was 126 (111 – 133) (table 2). The median starting dose was 0.2mg/kg/day (0.1-1.4). Sodium supplements were stopped if they had been previously prescribed. Fluid intake was liberalised when tolvaptan was started.

Tolvaptan was associated with [Na] normalisation in 10/13 (77%) within six days (median 2.5 days, range [1,6]) with 70% of the patients having achieved this endpoint by day 3. One patient (patient 5) did not have a normal sodium by day 6 and this was attributed to induction of CYP3A4 by the concomitant medication phenobarbitone. This patient's treatment was converted to urea (also without apparent effect), but this was shortly thereafter stopped as patient commenced palliative care. Interestingly, this was also the only patient

who was clinically hypervolaemic with oedema of unclear aetiology. Thus, whether the treatment failure did indeed reflect CYP3A4 induction by phenobarbitone or a different aetiology of hyponatraemia is unclear. There was one patient on concomitant ribociclib (potent CYP3A4 inhibitor) and plasma [Na] increased by 6mmol/L within six hours while urine osmolality dropped from 648 to 104mosmol/kg, following the first dose of 0.1mg/kg of tolvaptan. It was therefore decided to change tolvaptan to urea. The third patient (Patient 10, Figure 1) received a high dose of tolvaptan (1.4mg/kg/day) for 2 days with a subsequent increase in [Na], yet tolvaptan was stopped before normalisation. Sodium normalised 3 days later.

In one of the patients (Patient 3, Figure 1) plasma [Na] increased by 13mmol/L within 10hrs. The patient was neurologically stable and the drug was continued. Repeated sodium results remained stable and the child asymptomatic. Tolvaptan dose was reduced from 0.2mg/kg/day to 0.075mg/kg/day on day 5. One infant (Patient 6, Figure 1), on 0.9mg/kg/day, had a sodium increase of 13 mmol in 24 h on day 3 of treatment. The patient remained clinically well and the dose was reduced to 0.2 mg/kg/day. In another patient (Patient 12, Figure 1) an increase of 7 mmol/L in 5 h was observed on a starting dose of 0.2 mg/kg/day. Again, the patient remained clinically well and neurologically stable. Tolvaptan was stopped, as sodium normalised after the first dose. One patient (Patient 2, Figure 1) had an episode of seizure following starting treatment. This was not associated with significant sodium changes but attributed to their medical background of acute hydrocephalus and neurosurgical intervention. Tolvaptan was continued.

The maximum sodium change was observed in the first 24hrs after initiating tolvaptan treatment (Figure 2). The median change of sodium concentration within the first 24 hours of treatment was 7 mmol/L (-1,14).

The available urine osmolality values were reviewed. The maximum osmolality drop from baseline was observed at approximately 6-8 hrs. Tolvaptan was typically stopped after 7-10 days to assess for the ongoing presence of SIADH. If plasma sodium and osmolality dropped in the context of an inappropriately elevated urine osmolality, urea treatment was considered.

Tolvaptan was converted to urea in 5 (38%) patients after a median time of 8 days (0,352). One patient received urea as first line treatment due to clinician choice. Median plasma [Na] at starting urea was 128 mmol/L (123-134). The dose was increased as necessary to maintain an acceptable plasma [Na]. The maximum dose prescribed ranged between 0.5 to 1.7 g/kg/d with a median dose of 0.875 g/kg/d. Median number of

days to normalisation was 2 (1,10) (Figure 3). In the first 24 hours, the median change of plasma sodium concentration was 2 mmol/L (-1,6). This change was numerically lower to that observed with tolvaptan (n=5, p=0.062). Plasma urea concentration increased following commencement of treatment [baseline: 4.4mmol/L, range (2.3, 5.2), day 3: 9.1mmol/L (6.2, 13.7) and day 5: 5.4mmol/L [(3.1, 8.5), n=6, p=0.0001].

Discussion

Hyponatraemia due to SIADH is a common complication in hospitalised children but can usually be treated successfully with fluid restriction. Yet, in some patients, restriction is either unsuccessful or unsuitable and alternative treatments should be considered. While there is ample evidence from adult medicine on efficacy and safety, few paediatric data are available in the literature. We first started using tolvaptan in our hospital in 2015 with approval from the drugs and therapeutics committee, obtained on a case-by-case basis [6, 12]. Discussion about permanent inclusion of tolvaptan into our pharmacy provided the opportunity to review our current experience. Considering a literature-reported background incidence of 20% for hospital acquired hyponatraemia and that our hospital has on average about 7000 admissions per year, yet we only used this drug in 12 patients, it becomes apparent that tolvaptan was given to a very select group of patients, who had either failed standard therapy or for whom long-term fluid restriction was unsuitable. With increasing experience with this drug in our hospital, we subsequently developed a prescribing guideline, which recommends an initial starting dose of 0.1-0.15 mg/kg (maximum 15mg). While our mean treatment dose was 0.2mg/kg/d, this lower starting dose was deliberately chosen to minimise the risk of an excessive increase in plasma osmolality with consequent risk of osmotic demyelination. The variable starting dose (0.1-0.15 mg/kg) was chosen to facilitate dose preparation: tolvaptan is available only in tablet form and these tablets are poorly soluble in water. The variable starting range allows to pick a simple fraction of a tablet, which is then crushed and dispersed in a small volume (5ml) of water. Nevertheless, 2 patients showed an excessive increase in plasma sodium of 13mmol/l in 10 hours and another of 7mmol/l in 5 hours. Fortunately, both patients remained neurologically stable and plasma sodium did not rise further, due to adjustment of tolvaptan dose and concurrent fluid administration. As the half-life of tolvaptan is approximately 8 hours, a sustained aquaretic effect is usually only seen with concurrent administration of CYP3A4 inhibitors and this should be checked prior to starting tolvaptan. To further mitigate against the risk of excessive rise in [Na], our guideline also recommends close monitoring of weight and fluid balance. A 5% change in weight or a discrepancy between fluid intake and output equivalent to >5% of body weight in a 24-h period should prompt a careful clinical and biochemical assessment of the patient. Assuming an acute weight change is attributed to total body water change, a 5-8% change in weight is roughly equivalent to a 10mmol/l change in plasma sodium, which is usually considered safe over 24-h.

The diagnosis of SIADH can be challenging even for the experienced paediatrician and is frequently confused with cerebral (renal, pulmonary) salt wasting. This is reflected in the finding that 50% of our patients initially

received salt supplements for treatment of the hyponatraemia. The existence of the entity of cerebral salt wasting and its diagnosis are controversial [13]. Yet, the administration of tolvaptan in patients with hyponatraemia from salt wasting could seriously compound hypovolaemia mediated by salt losses with additional water losses. For this reason, tolvaptan was only prescribed if the consultant nephrologist at the time had personally examined the child and diagnosed euvolaemia or hypervolaemia. Arguably, the most common reason for a misdiagnosis of cerebral salt wasting is an elevated urinary sodium excretion. Our data clearly show that this is not a suitable diagnostic feature. Absolute urine sodium concentration was as high as 369 mmol/l and FENa as high as 3.9%. As none of the patients experienced hypovolaemia after tolvaptan, we assume that our diagnosis of SIADH was correct and that the elevated sodium excretion reflected the physiological attempt of the kidneys to restore volume homeostasis in the context of hypervolaemia mediated by the inappropriate water retention [14]. Obviously, urinary sodium excretion will have been further augmented in those patients receiving initial salt supplements.

Another treatment of SIADH is urea [5-8]. While tolvaptan also has initial diagnostic potential, as a response (decrease in urine osmolality) confirms a central aetiology, it is costly, making urea an attractive alternative, especially for longer term use [6]. Patient 6 (previously also reported in references [6, 12]
remained on urea treatment until the age of 5 years. At that age he became able to self-regulate his fluid intake and with that his plasma sodium and osmolality again dropped below the reference range (typically around 127-130 mmol/l and 270-280 mosm/kg, respectively). This suggested that the patient may not have chronic SIADH, but rather a reset osmostat. Although no formal testing, such as infusion with hypo- and hypertonic solution was performed, the diagnosis of a reset osmostat was further supported when plasma values remained unchanged (again, typically around 127-130 mmol/l and 270-280 mosm/kg, respectively) after weaning of urea supplementation. The parents reported a lower fluid intake as the only apparent change after stopping urea.

As reported previously, urea costs only a fraction of tolvaptan and we therefore use urea if longer term treatment is anticipated. Nevertheless, we continue to use tolvaptan for the initial treatment of SIADH, as response to the drug confirms the diagnosis of excess ADH and because of its more rapid action compared to urea, as detailed here. We recognise that the speed of action may be a reason for other clinicians to prefer the

use of urea initially, to avoid complications from a potential rapid increase in plasma osmolality. Currently, there is insufficient data for a definitive comparison of safety and efficacy of these two drugs.

Our experience with urea confirms the efficacy of this drug, with 5/6 (83%) patients achieving a normal plasma sodium concentration, within a similar timeframe as tolvaptan. While tolvaptan corrected plasma sodium more rapidly with median sodium change of 7 mmol within 24hrs, this is not necessarily an advantage, as it risks an excessive increase in sodium concentration. Indeed, this was not seen in any of the 6 children treated with urea. However, the smaller sodium change with urea, at least partly, may also reflect our initial inexperience with this drug. The formulation available in our hospital (Ureal NM®) are sachets, sold as a nutritional supplement, containing 15g of urea, equivalent to 250mmol. The advice in the package insert recommends dissolving each sachet in 250ml of water, so as to avoid changes in plasma osmolality. In a subject with a urine osmolality of 1000mosm/kg, administration in this way would not lead to any net removal of water at all: the osmotic diuresis induced by 250mmol of urea would be 250ml, exactly equivalent to the volume of water administered with the sachet. For the treatment of SIADH, the sachet should be dissolved in as small a volume as possible to maximise diuretic efficacy. In practice, this turned out to be between 5 and 15ml per sachet. Based on our experience of using urea we consequently recommended a starting dose of 0.25-0.5g/kg/d, with subsequent titration according to plasma sodium. An increase in plasma urea concentration is usually observed, which reflects the urea treatment and not a kidney function deterioration.

In conclusion, in children and young people with SIADH, in whom fluid restriction is challenging, tolvaptan and urea can be safely used and are highly efficacious. Although we did not observe any cases of osmotic demyelination syndrome, this is a rare side effect of rapid correction of hyponatraemia, which may not be seen in a small case series such as this. Close monitoring and free access to water are therefore essential, particularly with the use of tolvaptan, to avoid excessive changes in plasma osmolality and to inform adjustments in dose or fluid intake.

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Figure legends

Figure 1: Plasma sodium concentration during Tolvaptan treatment

Shown are daily plasma sodium levels for individual patients during the first 6 days of treatment with tolvaptan.

Figure 2. Daily change in plasma sodium concentration during tolvaptan use

Shown is the change in plasma sodium concentration for each patient on the respective treatment days. A positive value reflects a decrease in plasma sodium. Note that the biggest decrease in plasma sodium concentration typically occurs during the first 3 days of treatment.

Figure 3. Plasma sodium concentration during urea treatment

Shown are daily plasma sodium levels for individual patients during the first 10 days of treatment with urea.

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