ORIGINAL

Vasopressin receptor antagonist in the treatment of the syndrome of inappropriate antidiuretic hormone in general hospital practice

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Abstract. Hyponatraemia (serum sodium concentration <135 mmol/L) is the most common electrolyte disorder in hospitalised patients. We analysed the safety and efficacy of tolvaptan in the treatment of hyponatraemia in hospitalised inpatients and report the first consecutive retrospective clinical case series report based on a single centre experience from the United Kingdom. We sought out the case records of all patients treated with tolvaptan for hyponatraemia over a period of 19 months; 15 episodes of treatment with tolvaptan in 14 patients were analysed. There were 8 women and 6 men (age 72 ± 16 , (mean $\pm$ standard deviation), range 36 to 90 years, mean BMI 24.9 ± 8.67 , 13.9 to 46.4 kg/m²). Thirteen patients were diagnosed with euvoalaemic hyponatraemia. One patient had hypovolaemic hyponatraemia. The median duration of tolvaptan therapy was 3 days (1 to 21 days). A serum sodium level of 130 mmol/L was targeted during therapy and fluid restriction was discontinued. There was a significant change in sodium level from baseline (mean sodium 120.1 ± 4.6 , 108-126 mmol/L) to cessation of tolvaptan therapy (mean sodium 131.9 ± 3.6 , 125-139 mmol/L, $P < 0.0001$). The maximum rate of change of sodium was observed in the first 24 hours of therapy (mean 6.7 ± 2.8 , 1 to 11 mmol/L) with no patient exceeding 12 mmol/L in 24 hours and 18 mmol/L in 48 hours at any point whilst on tolvaptan. No patient developed the osmotic demyelination syndrome. Tolvaptan appears to be safe and effective in the management of hospitalised inpatients with definitive euvoalaemic hyponatraemia when close monitoring is observed.

Key words: Tolvaptan, Hyponatraemia, Syndrome of inappropriate antidiuretic hormone (SIADH), Vasopressin receptor antagonist, Euvoalaemia

HYPONATRAEMIA (defined as a serum sodium <135 mmol/L) is the most common biochemical abnormality seen in hospitalised patients [1], occurring in 15% to 30% of such patients [1, 2] and in nearly 7% of ambulatory patients [3]. Severe hyponatraemia (serum sodium <125 mmol/L) is associated with an in-hospital mortality of between 23% and 50%, depending on the serum sodium concentration at presentation [4], and with increased mortality extending to 6 months of follow-up [5]. The length of hospital stay was also significantly prolonged in hyponatraemic patients [4]. Waikar *et al.* prospectively studied 98,411 patients with outcomes measured up to 5 years after hospital discharge, and found that even mild hyponatraemia (serum sodium

<135 mmol/L) independently predicted mortality [1]. Though traditionally only severe hyponatraemia (serum sodium <125 mmol/L) was considered to be symptomatic and requiring treatment [6], it has been shown that even mild hyponatraemia is associated with attention deficits, falls and unsteadiness, and that these can be improved with correction of hyponatraemia [7]; hyponatraemia may also predispose to an increased risk of fractures in the ambulatory elderly [8].

The syndrome of inappropriate antidiuretic hormone (SIADH) is a common cause of hyponatraemia [9], although most cases of hyponatraemia are associated with hypovolaemia and diuretic use. Non-suppressible relatively higher levels of arginine vasopressin (antidiuretic hormone (ADH), arginine vasopressin (AVP)) are associated with the pathogenesis of hyponatraemia in euvoalaemic patients (SIADH), as vasopressin acts on the V2 receptor in the kidney allowing water to be reabsorbed [10] with consequential free water retention; a

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subsequent fall in serum osmolality and serum sodium occur in this situation. The traditional therapy for the condition has been fluid restriction, but this may be unpleasant for the patient and is often difficult to ensure on non-specialist wards. Recently, several AVP receptor antagonists have been developed, and it has been suggested that they may become the mainstay of treatment of SIADH as these agents predictably cause an aquaresis leading to increased serum sodium in the majority of patients with SIADH [11]. The possibility of rapid correction has been of significant concern in all of the AVP receptor antagonist clinical trials [11], but so far osmotic demyelination syndrome has not been reported with any of these agents. There has also been concern that these agents may be inappropriately used in hypovolaemic patients when the AVP release is homeostatic, and blockade may be deleterious.

Tolvaptan, an orally active vasopressin V2-receptor antagonist was first reported to be safe and effective in increasing serum sodium in patients with euvolaemic and hypervolaemic hyponatraemia by the study of ascending levels of tolvaptan (SALT) investigators in 2006 [12, 13]. However, concerns have been expressed over its safety, efficacy and cost effectiveness over conventional treatments in its use in the acute general hospital setting [14]. Tolvaptan has been licensed for treatment of adult patients with hyponatraemia secondary to SIADH in Europe [15], and for the treatment of clinically significant hypervolaemic and euvolaemic hyponatraemia (serum sodium <125 mmol/L or less marked hyponatraemia that is symptomatic and has resisted cor-

rection with fluid restriction), including patients with heart failure, cirrhosis and SIADH, in the U.S. [16].

Tolvaptan was approved for use in Queen Alexandra Hospital (QAH), Portsmouth, in April 2010, by Portsmouth and South East Area Hampshire Prescribing Committee, and added to the formulary for prescribing by named consultants (endocrinologists) only with maximum treatment duration of 10 days and on condition that it would not be continued on discharge of patients from hospital. QAH is a 904-bedded hospital that provides secondary care to an ethnically and socio-economically diverse population of approximately 600,000 within its catchment area of Portsmouth City and South East Hampshire [17]. Local guidelines were prepared for its usage at QAH (Table 1). The aim of our study was to assess the safety and efficacy of tolvaptan in an acute clinical setting in hospitalised inpatients.

Materials and Methods

This was a retrospective consecutive clinical case series study. Clinical and laboratory data were extracted for all patients treated with tolvaptan whilst hospitalised at QAH from 28th April 2010 (when tolvaptan was first approved for use in QAH) until 30th November 2011.

All patients prescribed tolvaptan during their admission were recorded on the pharmacy stock control and dispensing system (JAC version 4.43), and 15 patients were identified from their records. It was not possible to trace the case records for one patient. Data on the remaining 14 patients were collected from clinical case

Table 1 Local QAH guideline for use of tolvaptan in the treatment of hyponatraemia in hospitalised patients with SIADH⁺⁺

Before Initiation of Therapy	
1	Confirm SIADH (exclude glucocorticoid deficiency and hypothyroidism)
2	Serum Sodium < 125 mmol/L despite 48 hours of fluid restriction
3	Serum Sodium < 125 mmol/L and falling despite 24 hours of fluid restriction
4	Symptoms/risks associated with 2 or 3 preventing discharge
5	Serum sodium < 110 mmol/L is better treated with hypertonic saline (3%) after which tolvaptan is indicated for hyponatraemia as per 3.
After Initiation of Therapy	
6	Stop fluid restriction
7	Monitor serum sodium levels every 6 hourly for 36 hours, then 12 hourly whilst on therapy
8	Review usage of tolvaptan at 3, 6, and 9 days
9	If serum sodium rises by ≥ 12 mmol/L in 24 hours or if serum sodium reaches 130 mmol/L, tolvaptan to be discontinued and serum sodium to be monitored 12 hourly for further 36 hours
10	Patient to be carefully monitored for signs of osmotic demyelination syndrome

⁺⁺These are guidelines only and the final decision on its use and monitoring in individual patients is best judged by the prescribing physician.

notes, pathology computer systems (iSOFT iLAB Apex and Sunquest ICE), patient observation tracking system (VitalPAC) and patient letters management system. The following data were retrieved and entered on a proforma: demographics, length of hospital stay, diagnosis, co morbidities, in-hospital mortality, location, symptoms on admission, duration of hyponatraemia, treatment given for hyponatraemia prior to commencement of tolvaptan therapy, duration and dose of tolvaptan therapy, and laboratory data including such serum sodium, potassium, calcium, glucose, urea, creatinine, osmolality, 09.00h cortisol, T4, TSH, urine osmolality and urine sodium.

This information was entered on an Excel spreadsheet, and results were analysed statistically using Graphpad (www.graphpad.com). Continuous variables were expressed as means $\pm$ standard deviations or medians with interquartile ranges and tested by the Student's *t*-test or Wilcoxon rank sum test, as appropriate. Categorical variables are described as proportions and compared using the chi-squared test. All *P* values are two-tailed. We acknowledge the limitations of a retrospective case series study [18] but our data accuracy has been verified across different sources to minimise data collection errors. The study was approved as an audit by the Trust (audit reference number 2018).

Results

Fourteen patients were treated with tolvaptan. Each episode of treatment was analysed separately. One patient was treated twice, on successive admissions. Thus, there were 15 episodes of treatment in 14 patients. Tables 2 and 3 summarises the characteristics of each episode of treatment.

There were 8 women and 6 men (mean age 72 ± 16 (mean $\pm$ standard deviation), range 36 to 90 years) with a mean BMI of 24.9 ± 8.67 , 13.9 to 46.4 kg/m². On admission to hospital, hyponatraemia was present in all 15 episodes, whilst severe hyponatraemia [4] (serum sodium < 125 mmol/L) was present in 12/15 episodes (80%). The duration of hyponatraemia [19] was unknown in 8 episodes, acute (≤ 48 hours) in 3 episodes and chronic (> 48 hours) in 4 episodes. On review all 15 episodes were associated with confusion at the point of admission, although this was initially attributed to hyponatraemia in only 8 episodes [6]. Irritability, mood change and falls were recorded in 11 of the 15 episodes. Sepsis was present in 6 episodes on admission.

Hyponatraemic patients were diagnosed as having

syndrome of inappropriate anti-diuretic hormone (SIADH) based on their clinical volume status, serum osmolalities, urine sodium and osmolalities [19]. All patients had a normal 09.00h serum cortisol, T4 and TSH during all the episodes. One patient developed acute severe very hyponatraemia (serum sodium < 120 mmol/L) following vigorous large volume fluid resuscitation for acute renal impairment. The remaining 13 patients were diagnosed with SIADH prior to 14 episodes of treatment with tolvaptan. The mean length of stay for the 14 episodes (excluding one episode where the patient died as an inpatient on the 27th day of admission) was 25.4 ± 12.3 (12-48 days).

The initial therapy for 12 episodes was fluid restriction [19] to 1 litre (mean duration 5.9 ± 3.1 , 2-12 days) prior to commencement of tolvaptan. Demeclocycline [19] was used in two episodes in conjunction with fluid restriction, and once without any fluid restriction, prior to tolvaptan therapy. One patient had been treated with 100 mL of 3% hypertonic saline infusion [19] once, 3 days prior to tolvaptan therapy.

Tolvaptan was initiated when conventional methods were considered to be ineffective. A serum sodium level of 130 mmol/L was targeted during therapy according to locally agreed guidelines (Table 1); fluid restriction was discontinued [12] when tolvaptan therapy was commenced. The median duration of tolvaptan therapy in the 15 episodes was 3 days (1 to 21 days): 15mg of tolvaptan was used in 14 episodes with no dose changes, while 30mg of tolvaptan was used in one episode in a patient who had previously been treated with 15mg of tolvaptan and was readmitted with hyponatraemia. Only a single patient, who was treated with 15mg of tolvaptan for 3 days in the intensive care unit for acute severe hyponatraemia following large volume fluid resuscitation to apparent clinical euvolaemia but with no evidence of inappropriate natriuresis, complained of thirst during therapy [15]. No patient developed osmotic demyelination syndrome [20] as a consequence of hyponatraemia treatment in our study.

There was a significant rise in serum sodium level before (mean sodium 120.1 ± 4.6 , 108-126 mmol/L) and after (mean sodium 131.9 ± 3.6 , 125-139 mmol/L, $P < 0.0001$) tolvaptan therapy. The maximum rate of change of sodium was observed in the first 24 hours of therapy (mean 6.7 ± 2.8 , 1-11 mmol/L), with 2 patients requiring just one dose of 15mg of tolvaptan to achieve a target sodium of ≥ 130 mmol/L. In the first 48 hours of therapy, the rate of change of sodium was 9.6 ± 3.4 ,

Table 2 Summary of patient characteristics during all 15 episodes

Episode of tolvaptan use	Age (years)	Sex	BMI on admission (kg/m ²)	Clinical fluid status as assessed by documenting physician	Serum osmolality (285-295 mos/kg)	Urine osmolality (mos/kg)	Serum sodium (135-146 mmol/L)	Urine sodium (mmol/L)	Physician diagnosis of SIADH [‡]	Cause for SIADH [‡]	Duration of hyponatraemia [§]	Treatment given for hyponatraemia prior to tolvaptan [†]	Total length of stay in our hospital (days)
1	79	F	39.8	Euvolaemic	240	252	117	35	Yes	Lung cancer	Chronic	FR- 1 litre for 3 days DC- 14 days	13
2	90	F	25.9	Euvolaemic	241	480	119	106	Yes	Unknown	Unknown	FR- 1 litre for 2 days	13
3	47	F	19.5	Euvolaemic	262	219	122	30	Yes	Neuro-sarcoidosis	Chronic	FR-1 litre for 3 days	23
4	84	M	46.4	Euvolaemic	245	520	118	158	Yes	Unknown	Acute	FR- 1 litre for 9 days	48
5	73	F	21.3	Euvolaemic	216	345	100	100	Yes	Unknown	Unknown	FR- 1 litre for 4 days 3% HS- 100 ml	32
6	70	M	22.9	Euvolaemic	258	318	123	97	Yes	Unknown	Unknown	FR- 1 litre for 4 days	33
7	73	M	25.6	Euvolaemic	252	872	121	32	Yes	Lung cancer	Unknown	FR- 1 litre for 10 days FR- 750 ml for 7 days	27°
8	84	M	23.1	Euvolaemic	256	515	116	58	Yes	Lung cancer	Unknown	FR- 1 litre for 5 days FR- 750 ml for 5 days	12
9 [#]	52	F	21.8	Hypovolaemic / Euvolaemic	258	271	115	<10	No	Not applicable	Acute	Not applicable	45
10	36	F	29.6	Euvolaemic	258	259	122	46	Yes	Unknown	Acute	FR- 1 litre for 7 days	29
11	82	F	20.6	Euvolaemic	248	227	116	36	Yes	Unknown	Unknown	None	12
12	88	F	18.1	Euvolaemic	258	135	126	22	Yes	Unknown	Unknown	FR- 1 litre for 5 days FR- 750 ml for 5 days DC- 7 days	29
13	74	M	13.9	Euvolaemic	233	361	110	55	Yes	Unknown	Unknown	FR- 1litre for 12 days	19
14*	74	M	19.9	Euvolaemic	265	401	125	25	Yes	Unknown	Chronic	FR- 1 litre for 7 days	13
15*	74	M	19.9	Euvolaemic	252	373	121	82	Yes	Unknown	Chronic	DC- 10 days	34

*Episodes 14, 15 occurred in the same patient during successive admissions, [#]Patient was admitted with sepsis and sodium level of 125 mmol/L, following which she developed acute renal failure. She was volume resuscitated to apparent clinical euvolaemia with 3 litres of intravenous normal saline and 3 litres of Hartmann's solution in 24 hours, but she developed acute very severe hyponatraemia. Tolvaptan was used in her with careful monitoring of her electrolytes every 3 hours on intensive care unit, [‡]Syndrome of inappropriate anti-diuretic hormone [19], [§]Duration of hyponatraemia [19] - Acute: ≤48 hours, Chronic: >48 hours, °Patient died whilst in hospital, [†]Treatment for hyponatraemia prior to tolvaptan therapy [19]: FR- Fluid restriction, DC- Demeclocycline, 3% HS- Hypertonic saline

range 4-17 mmol/L. In no patient did the rate of change in serum sodium rise exceed 12 mmol/L in 24 hours and/or 18 mmol/L in 48 hours at any point whilst on tolvaptan, a rate of change above which osmotic demyelination syndrome has been reported [20]. There were small insignificant rises in serum potassium (mean potassium 4.45 ± 0.64 , 3.6-5.8 mmol/L prior to commencement of tolvaptan therapy, 4.5 ± 0.62 , 3.6-5.6 mmol/L at the end of tolvap-

tan therapy, $P>0.05$), serum urea (mean urea 6.2 ± 4.1 , 2.8-18.3 mmol/L prior to commencement of tolvaptan therapy and 7.2 ± 3.4 , 1.4-15.6 mmol/L at end of tolvaptan therapy, $P>0.05$), and serum creatinine (mean creatinine 104 ± 73 , 38-335 umol/L prior to commencement of tolvaptan therapy and 109 ± 82 , 42-382 umol/L at end of tolvaptan therapy, $P>0.05$). Local guidelines (Table 1) were followed for initiation and monitoring of tolvaptan therapy.

Table 3 Summary of change in serum electrolytes during all 15 episodes

Episode of tolvaptan use	Sodium level on admission (135-146 mmol/L)	Baseline electrolytes immediately prior to tolvaptan therapy				Electrolytes at end of tolvaptan therapy				Rate of change ⁺ of sodium (mmol/L)		Total change ^Δ in sodium (mmol/L) at end of therapy	Total number of days of tolvaptan usage
		Sodium (135-146 mmol/L)	Potassium (3.5-5 mmol/L)	Urea (2.9-7.1 mmol/L)	Creatinine (60-110 umol/L)	Sodium (135-146 mmol/L)	Potassium (3.5-5 mmol/L)	Urea (2.9-7.1 mmol/L)	Creatinine (60-110 umol/L)	First 24 hours of tolvaptan therapy	First 48 hours of tolvaptan therapy		
1	117	121	4.6	2.8	61	134	4.9	4.9	75	9	11	13	6
2	119	108	5.4	5.2	72	125	5.3	6.6	71	11	17	17	2
3	122	122	5	6.4	144	126	5.6	7.7	177	5	4	4	2
4	118	117	5.3	18.3	154	134	5.1	9.1	78	3	9	17	4
5	100	121	3.7	3.8	38	133	4.6	5.1	47	4	8	12	4
6	123	121	4.2	5.5	93	131	4.5	5.9	109	10	-	10	1
7	121	123	4.1	6.8	74	134	4	9.7	85	8	11	11	2
8	116	123	4.6	5.1	91	132	5.3	6.1	97	9	-	9	1
9	125	115	4.6	11.5	335	128	3.7	15.6	382	7	13	13	3
10	122	125	4.4	2.9	66	139	4.5	7.5	83	10	12	14	3
11	116	117	4.1	2.9	70	133	4	3.8	90	6	11	16	7
12	126	126	3.6	2.9	54	133	3.6	1.4	42	1	6	7	3
13	110	117	5.8	9	148	130	4.2	11.9	127	7	7	13	5
14*	125	123	3.9	5.4	85	131	4	5.4	93	6	8	8	2
15*	121	122	4.1	5.3	70	135	4.2	7.8	85	5	8	13	21 [×]

*Episodes 14, 15 occurred in the same patient during different admissions, ⁺Rate of change of sodium was calculated as follows: First 24 hours of tolvaptan therapy= Sodium level 24 hours after tolvaptan administration minus baseline sodium value just prior to tolvaptan administration; First 48 hours of tolvaptan therapy= Sodium level 48 hours after tolvaptan therapy minus baseline sodium value just prior to tolvaptan administration, ^ΔTotal change in sodium levels at end of tolvaptan therapy was calculated as follows: Sodium level 24 hours after last tolvaptan dose minus baseline sodium value just prior to tolvaptan administration, [×]Only episode where 30mg of tolvaptan was used with intermittent reduction to 15mg, and used for longer than the agreed 10 days with the prescribing committee

Discussion

Hyponatraemia is frequently seen in both outpatients and hospitalised patients, and while there have been a number of reviews and classifications [6, 9, 11, 19, 21], its diagnosis and management are not always straightforward and the key factor remains the clinical assessment of the fluid status of patient [11, 19, 21]. Bartter and Schwartz first described this syndrome in 1957 [22] and while there are differences in the cut-off of natriuresis amongst different reviewers (Hannon *et al.* [21] – urine sodium >40 mmol/L, Reynolds *et al.* [19] – urine sodium >20 mmol/L, and Verbalis *et al.* [11] – urine sodium >30 mmol/L), the other diagnostic criteria remain uncontroversial – the demonstration of hypo-osmolality, inappropriate urine concentration for the serum hyponatraemia and clinical euvolaemia with exclusion of hypothyroidism and glucocorticoid deficiency.

The correction of acute and chronic hyponatraemia in SIADH patients can often be challenging and traditionally several strategies such as fluid restriction, demeclo-

cyline, lithium, loop diuretics in combination with salt tablets, urea tablets and hypertonic saline (3%) have been debated and described with no consensus as to the most ideal, safe and effective strategy [6, 9, 11, 19, 21]. It is well known that the rapid correction of serum sodium of ≥ 12 mmol/L in 24 hours and ≥ 18 mmol/L in 48 hours can potentially lead to dangerous neurological complications [20]. Recently-developed aquaretic therapies such as AVP receptor antagonists have been shown to increase serum sodium in SIADH patients [11, 23]. Although to date the osmotic demyelination syndrome has not been reported with any of these agents, the possibility of rapid correction has been of significant concern with all the AVP receptor antagonists [11, 14], and the FDA has issued a “black box warning” indicating that therapy with tolvaptan should be initiated in a hospital setting with close monitoring of serum sodium [16].

Verbalis *et al.* [13] in their subgroup analysis of SIADH patients from the combined SALT population showed similar results to the combined SALT population regarding safety and efficacy of tolvaptan. Of the 110 SIADH patients in the SALT trials randomised to

tolvaptan and placebo therapy, 42 patients completed the full 30-day treatment period in each group. The mean sodium change from baseline was 2.9 mmol/L for placebo and 8.5 mmol/L on day 30 for tolvaptan ($P=0.001$); 3/51 patients exceeded protocol recommended correction limits of a rise in sodium of >12 mmol/L in 24 hours and >18 mmol/L in 48 hours, but none developed the osmotic demyelination syndrome.

Gheorghiadu *et al.* [24] studied the effect of tolvaptan versus fluid restriction plus placebo on serum sodium concentration in hospitalised patients with euvolaemic or hypervolaemic hyponatremia, and concluded that tolvaptan appeared to be more effective than fluid restriction in treating hyponatraemia in this setting. There was no subgroup analysis for the 10 SIADH patients out of 28 patients in this study. Vaghasiya *et al.* [25] studied the effect of a single 15mg dose of tolvaptan in 13 patients with hyponatraemia, of which 8 patients had SIADH. The mean serum sodium rise was 6.4 mmol/L in 24 hours. Three patients, all with SIADH, showed a 8 mmol/L rise in serum sodium within 12 hours, and received small amounts of 5% Dextrose infusion to attenuate changes in serum sodium. There have also been isolated reports of a single 15mg dose of tolvaptan causing a rapid rise in serum sodium of ≥ 12 mmol/L in 24 hours [26, 27], but it was therapeutically targeted in one patient where severe cerebral oedema secondary to hyponatraemia resolved with its correction following tolvaptan therapy [26], whereas in the other patient it caused significant aquaresis leading to symptomatic hypotension [27].

No patient developed rapid correction of sodium or osmotic demyelination syndrome in our study, and they were carefully monitored in keeping with our local protocol. Owing to paucity of data, there is concern for its use in patients with very severe hyponatraemia (serum sodium <120 mmol/L). We had 5 such patients in this cohort where it was safe and effective. Vaptans should not be used for patients with suspected or confirmed hypovolaemic hyponatraemia as it can cause significant aquaresis that can potentially exacerbate the hypovolaemic state and clinical situation despite improve-

ment in serum sodium. There was one patient in our cohort where this occurred.

The most likely role for vaptans in the immediate future is the treatment of in-patient hyponatraemia where fluid restriction has failed, or a shorter length of stay in hospital is desired as they seem more effective than fluid restriction [12, 13, 24]. Besides, fluid restriction on a general medical ward is often not easily or correctly implemented and is more unpleasant to the patient, and therefore patient acceptability of vaptans may be superior to fluid restriction. However, the extent to which vaptans will replace fluid restriction as first-line treatment is likely to depend on appropriate drug pricing to permit its use in the already over stretched therapeutic budgets, although if it can be demonstrated that the length of stay is significantly reduced then its acceptability amongst health care providers might increase.

In conclusion, tolvaptan, a selective oral vasopressin V2-receptor antagonist appears to be safe and efficacious in the management of hospitalised inpatients with definite euvolaemic hyponatraemia, when initiated and monitored in the hospital setting under specialist supervision following appropriate guidelines. We recommend that serum electrolytes are carefully monitored in the first 48 hours of treatment initiation and at least daily thereafter until target sodium levels are achieved and tolvaptan stopped before discharge. However, more clinical studies are needed before it could be recommended for routine use in out-patients and long-term therapy for SIADH.

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Conflict of Interest

The authors declare no conflict of interest with any of the work presented.

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