

## Treatment of infantile SIADH with a vasopressin-receptor antagonist: 2 cases

**Running title:** tolvaptan in infantile SIADH

**Authors:** Daniela Marx-Berger<sup>1</sup>, David V Milford<sup>2</sup>, Meenakshi Bandhakavi<sup>3</sup>, William van't Hof<sup>4</sup>, Robert Kleta<sup>4,5</sup>, Mehul Dattani<sup>6</sup>, Detlef Bockenhauer<sup>4,5</sup>

### Affiliations

1. Department of Paediatrics, Children's Hospital of Eastern Switzerland, St. Gallen, CH
2. Department of Nephrology, Birmingham Children's Hospital, Steelhouse Lane, Birmingham UK
3. Department of Paediatrics, Sandwell and West Birmingham Hospitals NHS Trust
4. Renal Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
5. UCL Centre for Nephrology, London, UK
6. Endocrine Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

### Corresponding author:

Prof D Bockenhauer

UCL Centre for Nephrology and

Renal Unit, Great Ormond Street Hospital for Children NHS Foundation Trust

Great Ormond Street

London, WC1N 3JH, UK

Email: [d.bockenbauer@ucl.ac.uk](mailto:d.bockenbauer@ucl.ac.uk)

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## **Abstract**

### Aim

Treatment for the Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) includes fluid restriction to adjust fluid intake to the diminished water excretion. This is potentially hazardous in infants, as fluid and caloric intake are coupled. Antagonists for the type 2 vasopressin receptor have demonstrated efficacy in adult patients with SIADH, but evidence in children is lacking. Moreover, the current unavailability of a liquid preparation makes the administration of these drugs challenging especially in small children. We aimed to review our experience from 2 recent cases.

### Methods

Retrospective review of clinical data of 2 patients diagnosed with SIADH in infancy and treated with the oral vasopressin receptor antagonist tolvaptan.

### Results

Persistent hyponatraemia was noted in both patients in the first month of life and eventually led to a diagnosis of SIADH. Initial salt supplementation in one patient resulted in severe hypertension, treated with four anti-hypertensive drugs. Tolvaptan was commenced at 2 and 4 months of age, respectively and was associated with normalisation of plasma sodium values and blood pressure without the need for anti-hypertensive treatment. There was transient hypernatraemia in one patient, which normalised with dose reduction. Tolvaptan was administered by crushing the tablet and mixing in water.

### Conclusion

Tolvaptan was effective for the treatment of SIADH in both infants and could be administered orally.

**Key notes:**

- SIADH is difficult to treat with fluid restriction in infants due to the coupling of fluid and caloric intake.
- Tolvaptan, an oral vasopressin receptor antagonist was effectively used in 2 infants reported here.
- Administration of tolvaptan was achieved by crushing the tablet and dispersing in water.

**List of abbreviations:**

ADH: Antidiuretic hormone

AVPR2: type-2 vasopressin receptor

DOL: Day of life

IGF1: Insulin-like growth factor -1

IGFBP3: insulin-like growth factor-binding protein-3

MRI: Magnetic Resonance Imaging

NSIAD: Nephrogenic Syndrome of Inappropriate Antidiuresis

SIADH: Syndrome of Inappropriate Antidiuretic Hormone secretion

TPN: total parenteral nutrition

## **Introduction**

The Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) is characterised by eu- or hypervolaemic hyponatraemia with inappropriately concentrated urine. The excess secretion of the Antidiuretic hormone (ADH) leads to activation of the type-2 vasopressin receptor AVPR2 in the kidney, which mediates urinary concentration (1). Excess ADH secretion can be triggered by pain, stress, numerous medications, brain injury or be associated with brain malformations (2). The resulting hyponatraemia is associated with substantial morbidity and mortality both in adult and paediatric patients (3, 4). SIADH is mainly treated with fluid restriction to adjust fluid intake to the decreased renal water excretion (5). This is potentially hazardous in young infants as their nutrition mainly consists of milk, so that fluid and caloric intake are coupled and long-term fluid restriction risks malnutrition. Other treatment options include oral urea to provide an increased osmotic load, but this can be poorly tolerated due to its taste (6). Recently, oral AVPR2 antagonists have become available, which specifically block AVPR2 to prevent activation by ADH and their efficacy has been demonstrated in adult patients with eu- or hypervolaemic hyponatraemia (7). Evidence from paediatric patients with SIADH, however, is lacking. Moreover, there is currently no liquid formulation of an oral AVPR2 antagonist available, complicating their use in smaller children. We therefore aimed to review our experience from 2 recent cases.

## **Case 1**

A 6-day old male was noted to have hyponatraemia (127 mmol/l) on routine bloods. He was born after an uncomplicated pregnancy to healthy, non-consanguineous parents by emergency caesarian section due to fetal bradycardia at 40+6 weeks gestation; birth weight was 3750 g. Postnatally, he was apnoeic with clonic movements. His APGAR score at 5 min was 3 and he was intubated immediately thereafter. Initial investigations on the neonatal intensive care unit revealed a

pneumothorax, and he was treated with a chest drain. Blood tests showed hypoglycaemia (blood glucose 0.9 mmol/l), lactic acidosis (14.6 mmol/l) and elevated ammonia (123  $\mu$ mol/l). He was given a 10% dextrose infusion and with that developed hyponatraemia (121 mmol/l), which normalised with fluid restriction. He was transferred to Great Ormond Street Hospital on the 11<sup>th</sup> day of life (DOL) for metabolic investigations, which eventually revealed no evidence of a specific metabolic disorder. Examination at admission was remarkable for a microphallus (measured at 19 mm, normal 28 – 42), but otherwise no obvious dysmorphism.

During the first 3 weeks, he had labile blood pressure, resulting in intermittent treatment with either vasopressors or anti-hypertensive drugs. Endocrine work-up showed no evidence of hyperinsulinism, but insufficient cortisol peak in a standard synacthen test (basal cortisol 44 nmol/L, 30 minute peak cortisol to synacthen 162 nmol/L) , as well as low concentrations of free thyroxine (6.6 pmol/L; NR 12.5-24.6), TSH (0.3 mU/L), IGF1 (<25 ng/ml; NR 55-327), IGFBP3 (<0.50 mg/L; NR 0.7-3.6), LH (<0.2 IU/L) and FSH (<0.2 IU/L), suggestive of panhypopituitarism. A brain MRI showed a small anterior and an ectopic/undescended posterior pituitary. Treatment with hydrocortisone and levothyroxine was commenced. The hypoglycaemia resolved, and a trial of depot-testosterone (Sustanon 25 mg monthly for 3 months only) was administered, resulting in a significant improvement in the size of the phallus. Growth hormone was commenced at the age of 4 months in view of poor growth, a structurally abnormal pituitary gland, and low concentrations of IGF1 and IGFBP3.

He was again noted to be hyponatraemic (130 mmol/l) on the 15<sup>th</sup> DOL. There were no signs of dehydration, his weight was 3950 g and his blood pressure was 126 mmHg systolic. He received total parenteral nutrition (TPN) plus milk feeds and these were supplemented with up to 8.5 mmol/kg/d of sodium. Associated with this, his blood pressure increased and anti-hypertensive treatment was successively escalated to a total of 4 medications: propranolol, amlodipine, furosemide and captopril.

Investigations into the aetiology of hypertension including urine catecholamines, plasma renin and aldosterone and a renal ultrasound were essentially normal.

He was eventually discharged home on enteral feeds with salt supplementation and 4 anti-hypertensive drugs on DOL 46.

He was re-admitted at the age of 3 months due to failure-to-thrive and for reassessment of his hypertension.

By that time, his weight was 4.49 kg (percentile decreased to <0.4<sup>th</sup>); length was 56 cm (0.4<sup>th</sup> percentile), and head circumference was 40.5 cm (25<sup>th</sup> percentile).

Upon admission, his sodium supplementation was stopped and fluid was successively restricted to 80 ml/kg/d, but he remained hyponatraemic with urine osmolality increasing up to 579 mosm/kg (Table 1). In order not to compromise nutritional intake by long-term fluid restriction, a vasopressin receptor antagonist (tolvaptan) was started at a dose of 3.75 mg (0.8 mg/kg) once daily. Urine osmolality dropped with urine output obviously increasing (table 1). His weight decreased, plasma sodium normalised without further sodium supplementation, and all his antihypertensive drugs were stopped. On the second day after receiving tolvaptan he became hypernatraemic with maximum plasma sodium concentration of 153 mmol/l and the dose was subsequently decreased to 1 mg (0.22 mg/kg) once daily. When tolvaptan was withheld, his urine osmolality increased again and his plasma sodium decreased. An ADH level at the time was elevated at 1.3pg/ml with respect to the concomitant plasma osmolality of 265 mosm/kg. Consequently, tolvaptan was restarted and he was discharged on 1 mg daily with stable normonatraemia. He has remained on this dose with most recent follow-up at 7 months of age. He is growing slowly, but with weight and height still <0.4<sup>th</sup> percentile although meeting caloric needs.

## **Case 2**

A 3-day old infant was admitted to her local hospital with persistent jaundice and plasma sodium was noted to be 127 mmol/L on day 8. She was born to consanguineous Pakistani parents, there

was no family history of electrolyte disturbance and physical examination showed bilateral cleft lip and alveolus. Hyponatraemia was initially thought to reflect salt wasting and she was given increasing oral sodium supplementation to a maximum of 22.6 mmols/kg/day without normalisation of plasma sodium. Using intravenous sodium chloride, this was eventually raised to 134 mmol/L on DOL 31-33. Measurement of urinary sodium during the course of her admission showed a progressive increase from <20 mmol/L on day 10 to a maximum of 280 mmol/L on DOL 38. She remained normotensive.

During the admission to her local hospital she had a trial of fludrocortisone commencing DOL 24 but without beneficial effect and discontinued on DOL 66. An endocrine work-up was normal, including a short synacthen test, as well as plasma levels of 17-hydroxyprogesterone, renin and aldosterone levels and a urinary steroid profile. A cerebral MRI scan showed no abnormality. She subsequently was fluid restricted with a progressive reduction in the dose of sodium supplement.

She was admitted for further investigation at 4 months of age and at that time the diagnosis of SIADH was confirmed, based on an elevated urine osmolality of 650 mosm/kg associated with an elevated plasma ADH of 4 pg/ml in the presence of a decreased plasma osmolality of 270 mosmol/kg and clinical euvolaemia. She commenced tolvaptan at a dose of 3.75 mg daily (0.6mg/kg) at 6 months of age with prompt normalisation of her plasma sodium. She had a repair of her bilateral cleft lip at 9 months of age.

She remained on the same dose of tolvaptan until it was discontinued at 13 months of age due to lack of funding. She became hyponatraemic again (130 mmol/l), despite attempted fluid restriction. Latest follow-up was at 13 months of age.

## Discussion

Hyponatraemia is a common complication, seen in approximately 25% of hospitalised children (4, 8). Hyponatraemia can be either due to a deficiency in plasma sodium or an excess of plasma water (9). There is no definitive laboratory test to distinguish between the 2 causes, instead the distinction has to be made on clinical grounds: as sodium is the main constituent of extracellular water, a deficiency in sodium is associated with clinical hypovolaemia, whereas excess water is associated with eu- or hypervolaemia. The distinction is important, as treatment is also different: a deficiency in sodium is typically treated with salt supplementation, whereas water excess is treated by fluid restriction or enhanced water excretion. In the majority of cases of hyponatraemia in hospitalised patients the cause is inappropriate ADH secretion due to non-osmotic stimuli such as pain or certain medications (5). Yet, in clinical practice, hyponatraemia is often equated with salt wasting and consequently treated with salt supplementation, as happened in both cases reported here. Contributing to the misdiagnosis is typically the finding of “elevated” urine sodium levels, which is interpreted as primary renal salt wasting. However, the kidneys use sodium excretion as the primary means to maintain volume homeostasis. Thus, in water excess states, the physiologic response of the kidneys is to excrete sodium to restore euvolaemia. For this reason, urine sodium values in SIADH typically exceed 40 mmol/l, and are of course even higher if salt is supplemented (5). Thus, the diagnosis of SIADH is made in a hyponatraemic patient by combining the clinical findings of eu- or hypervolaemia with an inappropriately elevated urine osmolality (>100 mosm/kg) (2, 9). SIADH can be clinically indistinguishable from Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD), an inherited form of renal water retention (10, 11). Diagnostic clues for this rare disorder are a family history of hyponatraemia and suppressed ADH levels, both of which were absent in our patients. Moreover, patients with NSIAD reportedly do not respond to AVPR2 antagonists (12).

Of note, in both our cases salt supplementation resulted in (near) normalisation of plasma sodium levels, although large doses were used: 22.6 mmol/kg/d of sodium used in case 2 is the equivalent to



a salt intake of more than 90 g per day for a 70-kg adult! The risk of this approach obviously includes hypertension, as demonstrated by case 1: with salt supplementation of 7.5 mmol/kg/d, he remained hypertensive despite treatment with 4 anti-hypertensive drugs.

The current mainstay of treatment for SIADH is fluid restriction, which is often ineffective, as patients with SIADH also have a lowered osmotic threshold for thirst (13). Fluid restriction is especially a problem in infants where fluid and nutritional intake is coupled thus resulting in inadequate caloric intake, as seen in our first case. The advent of selective AVPR2 antagonists, or aquaretics, has provided new treatment opportunities for SIADH, and their efficacy has been shown in adults (7). These drugs prevent tubular water reabsorption by blocking the binding of AVP to the AVPR2 receptor (14). The only oral AVPR2 blocker currently available is tolvaptan, provided solely in tablet form, thus impairing use in infants. According to manufacturers information, tolvaptan is insoluble in water and thus crushing of the tablet and dispensing in water is not advised due to the risk of incorrect dosage. However, in the absence of a liquid formulation, this was the only way to administer the drug and our experience here suggests that this is feasible and effective. Indeed, there are other case reports on the use of tolvaptan in small children with heart failure, albeit without details of administration (15, 16).

The transient development of a nephrogenic diabetes insipidus-like picture with hypernatraemia and very low urine osmolalities in our first case emphasises the need for close monitoring of patients when treatment is commenced so that the dose can be adjusted accordingly. Free fluid intake should be provided with treatment, but is, of course, difficult in patients without free access to fluids. Hypovolaemia and hypotension are further potentially severe complications of AVPR2 antagonists if administered in patients with hyponatraemia due to salt deficiency rather than water excess, emphasising the need for careful clinical assessment prior to administration.

The cause for the prolonged SIADH in these 2 cases is unclear, but probably related to pituitary dysfunction. In the first case, endocrine investigations suggested panhypopituitarism, which can be

associated with hyponatraemia (17). The second case has cleft lip and alveolus, which can be associated with cranial midline defects involving the hypophysis (18), although a cranial MRI was unremarkable and endocrine investigations were otherwise normal.

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<b>Case 1</b>						
<b>Age (days)</b>	105 admission	106 Fluid restricted 80 ml/kg/d	107 Tolvaptan 0.8 mg/kg	110 Tolvaptan 0.8 mg/kg	122 Tolvaptan Off	141 Tolvaptan 0.2 mg/kg
<b>Sodium supplementation [mmol/kg/d]</b>	5	0	0	0	0	0
<b>Weight [g]</b>	4500	4490	4380	4278	4680	4960
<b>plasma</b>						
Sodium [mmol/l]	130	131	138	153	130	139
Osmolality [mOsm/kg]	267	268	288	314	265	287
<b>urine</b>						
Sodium [mmol/l]	99	135	9	<5	75	8
Osmolality [mOsm/kg]	391	579	49	80	415	57

Table 1: Pertinent clinical and laboratory data of case 1