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Urea is successful in treating inappropriate antidiuretic hormone secretion in an infant

Running head: Inappropriate antidiuretic hormone secretion

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The syndrome of inappropriate antidiuretic hormone (SIADH) consists of a number of key features, namely hyponatraemia, inappropriate urinary concentration and clinical euvolaemia or hypervolaemia. It is caused by inappropriate secretion of the antidiuretic hormone (ADH), which activates the vasopressin type 2 receptor (AVPR2) in the principal cells of the collecting duct of the kidney and leads to increased reabsorption of water through aquaporin 2 channels. Common causes of SIADH in children include trauma, asphyxia, pain, stress, certain drugs and recent neurosurgery (1). The first line of therapy is simply fluid restriction (1). Unfortunately, this is often unsuccessful in patients with free access to fluids and thirst is reportedly increased in SIADH (2). Moreover, it is not feasible for infants for prolonged periods of time, as their caloric intake is directly coupled to milk and thus fluid intake and fluid restriction would lead to starvation. A simple treatment option is the so-called vaptans, which are specific antagonists of the AVPR2 receptor, with tolvaptan providing an orally active form (3). While tolvaptan has not yet been formally assessed in children, we previously reported its successful use in two infants with chronic SIADH in *Acta Paediatrica* (4). A drawback to long-term tolvaptan use is cost, namely £896 for 10 tablets of 15mg each in the UK, and the potential for liver function abnormalities (5). An alternative treatment option is urea, which leads to osmotic diuresis (6). Urea is a key constituent of the so-called osmotic load, which are the solutes that need to be cleared by the kidney and thus obligate accompanying water excretion (7). The main disadvantage of urea supplementation is its foul taste, although mixing it with citrate has been reported to result in better acceptance by patients (8). Here we report on the successful use of urea treatment in our previously reported child with chronic SIADH (4) at the age of 16 months. The boy has a congenital form of chronic SIADH associated with an ectopic posterior pituitary. He had been successfully

treated with tolvaptan for approximately one year, but alternative treatments were considered due to concerns about the cost and potential liver injury, due to borderline elevated aspartate transaminase (AST), with a maximum of 74IU/l being recorded and an upper limit of normal of 67IU/l. All other liver function tests remained normal throughout. Urea was obtained in the form of sachets containing 15g (16.7mmol) of urea mixed with citric acid and flavourings (Nutricion Medica, Spain: www.nutricionmedica.com).

He was electively admitted at the age of 15 months so that his treatment could be converted from tolvaptan to urea. The pertinent data are given in Table 1. First we established the persistence of SIADH by withdrawing tolvaptan, which led to a recurrence of hyponatraemia (126mmol/l) within two days. Urea was initially commenced at 1g/kg/day, divided into two doses. There was a small increase in plasma sodium to 128mmol/l after two doses and to 129mmol/l after a total of four doses. The frequency of dosing was subsequently increased to three times a day, providing a total of 1.5g/kg/day. The following day, after three doses, the boy's plasma sodium had increased to 136mmol/l. Initially, the patient had difficulties in tolerating the urea and vomited after every dose, but this improved when we minimised the volume in which the contents of the sachets were dissolved. The parents eventually identified a way to make it palatable for him by dissolving the contents of the sachet in 5ml of fruit puree, instead of the 100ml of water recommended by the manufacturer. They then split the resultant volume, of approximately 20ml, into four doses. Since the start of urea treatment, our patient has remained well. As expected, his plasma urea level has increased from around 1-5mmol/l on tolvaptan to 8-10mmol/l with urea supplementation. His plasma creatinine has remained unchanged, at around 20μmol/l.

Urea has been extensively described as an inexpensive and safe treatment option for adults with chronic SIADH (9). A prospective long-term study showed similar efficacy for urea and vaptans in the long-term treatment of hyponatraemia secondary to SIADH (6). Within the peadiatric population, its effectiveness has only been detailed in case reports (10, 11). However, those studies seem promising and also reported the successful treatment of hyponatraemia in children with chronic SIADH.

The reported difficulties in taking urea due to its unpalatable taste and potential purgative effects were also clearly observed in our patient, even though the formulation that was provided was already mixed with citrate and flavourings. Nevertheless, with persistence and some experimentation with the preparation, the patient learned to accept the supplementation and now tolerates it without any difficulties. Based on the current dose of urea, his annual treatment cost is approximately £500, which compares favourably to tolvaptan, at £16,350 per year. The tolvaptan cost had already been reduced by splitting the 15mg tablet in half to provide dosing for two days, a process not recommended by the manufacturer. Using a new tablet each day would obviously have doubled the cost to £32,700 per year.

An alternative to urea and tolvaptan would have been no treatment at all and to just accept hyponatraemia. We had repeatedly stopped tolvaptan treatment to assess for ongoing SIADH in this patient. Each time, his plasma sodium settled around 126-130 mmol/l. Chronic hyponatraemia in adults has been associated with impaired psychomotor function (12)) and even osteoporosis (13). Obviously, this is difficult to assess in infants, but neither the parents nor the medical personnel noted an apparent difference in the child's behaviour when he was hyponatraemic. Some patients may have a better tolerance for hyponatraemia and we previously reported the case of a London taxi driver, who had no apparent dysfunction despite presumably having lifelong hyponatraemia (14). Given the inexpensive and benign treatment we have achieved with urea, we have opted to continue with this for the time being.

In conclusion, this case study shows how we achieved successful treatment of chronic hyponatraemia with urea in an infant. Urea should be considered as an alternative and inexpensive treatment option to vaptans in children with chronic SIADH.

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References

1. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med* 2013; 126:S1-42

2. Smith D, Moore K, Tormey W, Baylis PH, Thompson CJ. Downward resetting of the osmotic threshold for thirst in patients with SIADH. *Am J Physiol Endoc M* 2004; 287:E1019-23

3. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *New Engl J Med* 2006; 355:2099-112

4. Marx-Berger D, Milford DV, Bandhakavi M, Van't Hoff W, Kleta R, Dattani M, et al. Tolvaptan is successful in treating inappropriate antidiuretic hormone secretion in infants. *Acta Paediatr* 2016; 105:e334-7

5. Watkins PB, Lewis JH, Kaplowitz N, Alpers DH, Blais JD, Smotzer DM, et al. Clinical Pattern of Tolvaptan-Associated Liver Injury in Subjects with Autosomal Dominant Polycystic Kidney

Disease: Analysis of Clinical Trials Database. *Drug Safety* : an international journal of medical toxicology and drug experience. 2015; 38:1103-13

6. Soupart A, Coffernils M, Couturier B, Gankam-Kengne F, Decaux G. Efficacy and tolerance of urea compared with vaptans for long-term treatment of patients with SIADH. *Clin J Am Soc Nephrol* 2012; 7:742-7

7. Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. *Nat Rev Nephrol* 2015; 11:576-88

8. Vandergheynst F, Gankam Kengne F, Decaux G. Vasopressin Antagonists. *N Engl J Med* 2015; 373:980-1

9. Decaux G, Brimioulle S, Genette F, Mockel J. Treatment of the syndrome of inappropriate secretion of antidiuretic hormone by urea. *Am J Med* 1980; 69:99-106

10. Huang EA, Feldman BJ, Schwartz ID, Geller DH, Rosenthal SM, Gitelman SE. Oral urea for the treatment of chronic syndrome of inappropriate antidiuresis in children. *J Pediatr* 2006; 148:128-31

11. Chehade H, Rosato L, Girardin E, Cachat F. Inappropriate antidiuretic hormone secretion: long-term successful urea treatment. *Acta Paediatr* 2012; 101:e39-42

12. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med* 2006; 119:71 e1-8

13. Upala S, Sanguankeo A. Association Between Hyponatremia, Osteoporosis, and Fracture: A Systematic Review and Meta-analysis. *J of Clin Eendocr Metab* 2016; 101:1880-6

14. Bockenhauer D, Penney MD, Hampton D, van't Hoff W, Gullett A, Sailesh S, et al. A family with hyponatremia and the nephrogenic syndrome of inappropriate antidiuresis. *Am J Kidney Dis* 2012; 59:566-8

Table 1 Pertinent clinical data

Timeline	*On tolvaptan*	*Two days off tolvaptan*	*Urea x 1day*	*Urea x 3days*	*Urea x 1month*
Age (months)	9	15	15	15	16
Treatment	Tolvaptan 0.2mg/kg/day	Tolvaptan off	Urea 1g/kg/day	Urea 1.5g/kg/day	Urea 1.5g/kg/day
Weight (g)	6,050	8,100	8,100	8,000	8,150
Plasma					
Sodium (mmol/l)	136	126	128	136	136
Osmolality (mosmol/kg)	ND	257	270	277	277
Urea (mmol/l)	1.1	5.2	10.2	8.5	9.3
Urine					
Sodium (mmol/l)	<5	96	15	10	14
Osmolality (mosmol/kg)	61	541	618	853	835

Note recurrence of hyponatraemia after withdrawal of tolvaptan, associated with increased urine osmolality, reflecting persistent SIADH. Plasma sodium levels normalised again with urea supplementation. ND: not determined.