South Manchester University Hospitals NHS Trust

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Low dose tolvaptan (7.5 mg) is effective in the management of SIADH in oncology patients (a retrospective audit at The Christie Hospital and Wythenshawe Pulmonary Oncology Unit)

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Introduction

Tolvaptan (a selective V2 receptor antagonist) is licensed for the inpatient management of SIADH induced hyponatraemia, a common complication in patients with malignancy. Licensed daily doses start at 15mg but there is some evidence to suggest that some cancer patients have a rise in serum sodium [Na] of >12mmol/l/24h in response to this and a 7.5mg starting dose may therefore be more appropriate. Too rapid increases in [Na] can cause osmotic demyelination with potential life-threatening consequences. Patients are at higher risk of demyelination if they are malnourished, as many cancer patients are.

Methods

A retrospective case note audit was performed of patients initiated on tolvaptan at The Christie Hospital and the Pulmonary Oncology Unit at Wythenshawe Hospital between November 2009 and September 2013.

Results

	No. of patients (%)
Total number of patients	34 (100%)
Male	15 (44%)
Female	19 (56%)
Mean age: 67 years (±9 SD)	
Diagnosis:	
SCLC	26 (76%)
Renal cell carcinoma	2 (6%)
Oesophageal cancer	2 (6%)
Myeloma	1 (3%)
Testicular teratoma	1 (3%)
Cholangiocarcinoma	1 (3%)
Adrenal liposarcoma	1 (3%)

Table 1. Patient demographics

Nineteen (56%) patients met the full biochemical criteria for SIADH (plasma osmolality <280 mOsm/kg, urine osmolality >100 mOsm/kg, urinary sodium >20 mmol/L). Three patients died during the hospital admission. No incidents of central pontine myelinosis were recorded.

	No. of patients (%)
Specialist endocrine input sought	29 (85%)
Demeclocycline discontinued prior to tolvaptan	19 (79%)
Fluid restriction discontinued prior to tolvaptan	17 (61%) (8 not stated)
Therapies given prior to tolvaptan:	
Demeclocycline	24 (71%)
Fluid restriction	28 (82%)
None	3 (13%)

Table 2. Pre-tolvaptan data

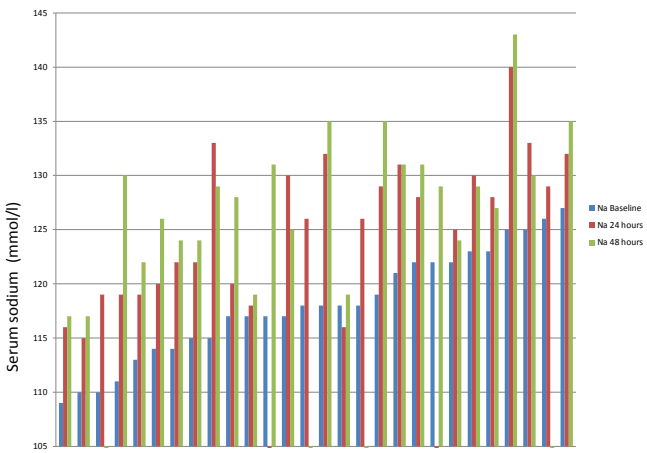
The initial starting dose was 7.5mg in 82% (n=28) of patients and 15mg in the remaining 18% (n=6). To achieve [Na] >130mmol/l, 3 patients required escalation from 7.5mg to 15mg dose.

	7.5mg Tolvaptan (n = 28)	15mg Tolvaptan (n = 6)
Mean (±sd) baseline [Na]	118 (±5) mmol/l	114 (±4) mmol/l
Mean (±sd) increase in [Na]/24h	7 (±4) mmol/l	14 (±4) mmol/l
N° pts with rise in [Na]/24h	27 (96%)	6 (100%)
N° pts with [Na] rise ≥12mmol/l/24h	4 (14%)	5 (83%)
N° pts achieving [Na] ≥130mmol/l in 48h	12 (43%)	3 (50%)
Mean (±sd) [Na] on discharge	131 (±6) mmol/l	136 (± 5) mmol/l

Table 3. A comparison of patients initiated on 7.5mg vs 15mg Tolvaptan

Baseline [Na] (mmol/l)	Number of patients (%)
Mild (130 – 135)	0 (0%)
Moderate (125 – 129)	4 (12%)
Profound (<125)	30 (88%)

Table 4. Baseline sodium



Graph 1. The rise in serum sodium in patients given 7.5mg tolvaptan

Initial Tolvaptan dose	Baseline [Na] (mmol/l)	24h [Na] (mmol/l)	Rise in [Na]/24h (mmol/l)	Plasma osmolality (mOsm/kg)	Urine osmolality (mOsm/kg)	Urinary sodium (mmol/l)
15mg	114	126	12	240	834	107
15mg	110	122	12	232	576	26
15mg	110	123	13	Not done	Not done	Not done
15mg	113	126	13	230	541	65
15mg	114	136	22	Not done	Not done	Not done
7.5mg	125	140	15	Not done	434	79
7.5mg	115	133	18	242	448	80
7.5mg	118	132	14	250	456	56
7.5mg	117	130	13	244	612	Not done

Table 5. Patients who had a rise in [Na] ≥ 12mmol/l

Conclusion

•Tolvaptan 7.5mg is effective in increasing serum [Na] in patients with cancer and SIADH.

•Tolvaptan 15mg frequently resulted in a rise of serum [Na] > 12mmol/24 hours, potentially increasing risk of osmotic demyelination.

•Rapid rises in serum sodium were less frequent in patients receiving tolvaptan 7.5mg but were still observed and therefore the safety of this lower dose is still in question.

•New European Guidelines[1] on the diagnosis and treatment of hyponatraemia recommend against the use of tolvaptan in profound hyponatraemia due to the risk of overcorrection without proven benefit in terms of improved survival or improved quality of life.

•Anecdotally, cancer patients with SIADH have benefitted from tolvaptan however there is an absence of data proving any benefit in terms of quality of life. This is an area for further research.

•Not all patients in this audit were fully evaluated before receiving tolvaptan and although SIADH was the likely diagnosis, this should not be assumed.

Reference

Spasovski G, Vanholder R, Allolio B, Annane D, Ball S, Bichet D, Decaux G, Fenske W, Hoorn E, Ichai C, Joannidis M, Soupart A, Zietse R, Haller M, van der Veer S, Van Biesen W, Nagler E; Hyponatraemia Guideline Development Group. Eur J Endocrinol. 2014 Feb 25;170(3):G1-G47. doi: 10.1530/EJE-13-1020. Print 2014.