Case Report

Unrecognised free water loss in a patient with lithium-induced nephrogenic diabetes insipidus can cause acute kidney injury and near fatal hypernatremia...

Abstract

Lithium is the commonest cause of drug induced nephrogenic diabetes insipidus (NDI),[1] a condition in which the patient passes large amounts of dilute urine due to the kidney's loss of the ability to concentrate the urine in response to anti diuretic hormone (ADH). Affected patients may satisfy their polydipsia and avoid dehydration and hyper natremia if they have access to water, but severe hypernatremia can develop if they become acutely unwell or if oral intake of water is restricted. We report a patient on long -term lithium therapy for bipolar disorder who presented with severe confusion, dysarthria and disorientation, and subsequently developing severe hyper natremia and coma despite intravenous saline infusions. She was intubated and ventilated and successfully treated with initial volume expansion and subsequently with intravenous 5% dextrose in water.

Keywords: lithium, hypernatremia, coma, diabetes insipidus

Volume 3 Issue 5 - 2015

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Received: December 08, 2015 | **Published:** December 17, 2015

Abbreviations: ACE, angiotensin-converting enzyme; ITU, intensive therapy unit; ADH, anti diuretic hormone; NDI, nephrogenic diabetes insipidus

Introduction

Acquired nephrogenic diabetes insipidus is most frequently caused by lithium which is used to treat bipolar disorder. The reported incidence of acquired NDI in patients on long term lithium treatment is as high as 55%.[2] Lithium-induced NDI results from inactivation of adenylyl cyclase and thus the phosphorylation of cytoplasmic urinary aquaporin 2 AQP2 by protein kinase A, and consequently ADH-induced translocation of cytoplasmic urinary aquaporin 2 (AQP2) to the apical membrane.[3] Lithium also down regulates the protein abundances of urea transporter, UT-A1, UT-B, thus reducing medullary interstitial osmolality.[4-6] Lithium induced NDI should be suspected in any patient on long-term lithium therapy who develops unexplained hyper natremia so that prompt treatment can be instituted.

Case report

A 57-year-old woman was taken to the accident and emergency department because of a chesty cough, confusion, disorientation and slurring of speech. She was taking modified release lithium 600mg once daily for 15 years for bipolar affective disorder. She also had a history of hyperparathyroidism, hypercalcaemia, nephrocalcinosis, ischaemic heart disease, recurrent urinary tract infections and hypertension. She was treated for non- ST elevation myocardial infarction treated 3 weeks earlier with aspirin, ticagrelor, bisoprolol, and fond aparinux. She was also started on Ramipril 2.5mg once daily. Serum lithium level at the time of the NSTEMI was normal (0.25 mmol/l). She was allergic to penicillin. She smoked 40 cigarettes a day. Physical examination revealed a confused patient with generalised bruising, with a blood pressure of 124 /60mmHg, a heart rate of 54 beats per minute, spo2 of 98% in air, and a respiratory rate of 18/minute. She was afebrile (temperature 36.9oC) and examination of her respiratory system revealed few bilateral basal crackles. Neurological examination revealed severe confusion, disorientation and severe dysarthria.

Initial laboratory investigations revealed high parathyroid hormone level (16.5pmol/l) with hypercalcaemia (serum adjusted total calcium 2.73 mmol/l), normal plasma lithium level (0.86 mmol/l), normal serum sodium (sodium 139mmol/l), urea (urea 5.9mmol/l) and creatinine (creatinine 106 micromole/l). A repeat lithium level on the day of admission was 1.81 mmol/l. Her coagulation screen, full blood count and infection markers were within normal limits. To rule out intracranial pathology, a brain CT was performed which was negative.

She was admitted to the ward and treated with oral clarithromycin for presumed chest infection and over the next 4 days, because of her hyper calcaemia she was kept hydrated with 2 litres of intravenous 0.9% sodium chloride daily. By day 2, her serum sodium concentration had increased to 149mmol/l. Prior to Intensive Therapy Unit (ITU) admission on day 4, serum sodium and chloride concentrations had increased to 176 mmol/l and 143 mmol/l respectively and she was now comatose (GCS5/15; M=3,O=1,V=1) and dehydrated with cool extremities. Laboratory investigations revealed acute kidney injury (serum urea 15mmol/l and serum 207umol/l). She was intubated and controlled mechanical ventilation was instituted after which she was admitted to the intensive care unit. Abdominal examination revealed a distended bladder. When her bladder was catheterised, 1500 mls of urine was drained immediately. Nephrogenic diabetes insipidus due to lithium and hypercalcaemia was suspected and she was managed with intravenous 5% dextrose based on the calculated water deficitusing the following formulas:[7]

Equation 1: Total Body Water = Body weight in kg x correction factor (0.5 for nonelderly female) = 0.5x 65=32.5 Litres. Equation 2 -change in serum Na+ with infusion of 1 litre of 5% dextrose = (infusate Na+ - serum Na+) ÷ (TBW + 1) = (0 - 176) ÷ (32.5 + 1) =-5.25 mmols. Therefore to reduce the serum sodium level by no

more than 10 mmol/l in 24 hours requires 10/5.25= 1.90litres of 5% dextrose; add 1-1.5 litres for insensible loss, so that the total fluid required is about 3-3.5 litres in 24 hours or 125 to 145 mls of 5% dextrose hourly), guided by frequent measurement of serum sodium level).

She required intravenous Actrapid insulin to control hyperglycaemia. Arterial blood gases on admission to the ITU revealed mixed acidosis (pH 7.25, base excess - 5, serum lactate 1.1, PCO2 6.6 kpa, Po2 11kpa; FIO2 0.8). Her urine osmolality on admission to the intensive care unit was 232mosmol /kg. Her serum osmolality was 336 mosmol/kg. Her urine output increased about 12 hours after ITU admission to 300 to 500 mls/hour and intravenous desmopressin 40micrograms was ineffective in reducing the urine output. Actrapid insulin infusion was used to treat hyperglycaemia resulting from the large intravenous glucose load.

She was started on ibuprofen 200mg 8 hourly orally and co-amilozide (amiloride hydrochloride 2.5mg, hydrochlorothiazide 25mg) which promptly decreased her urine output to less than 120mls/hour. On the third day of ITU admission, her serum sodium had decreased to150 mmol/l (serum chloride had decreased to 126mmol/l). She was started on a low sodium feed by nasogastric tube (nutrison low sodium®). On the fifth day, serum sodium had decreased to 149 mmol/l (serum chloride 123mmol/l). On the 4th day in ITU, sedation was discontinued and her Glasgow Coma Score gradually increased to 13- 15/15 over several days. After percutaneous tracheostomy on the 10th day, she was gradually weaned off respiratory support. Ibuprofen was discontinued, and although her adjusted total calcium increased to 2.95 mmol/l, her polyuria did not recur. Her neurological status remained normal.

Discussion

We have described a patient who developed near fatal severe hypernatremia, dehydration, acute kidney injury and coma due tolithium- induced nephrogenic diabetes insipidus which was unmasked by severe acute mental status changes limiting free water ingestion. Lithium is recommended for prophylaxis and treatment of bipolar disorder and is the commonest cause of acquired nephrogenic diabetes insipidus.[1,2] Lithium- induced impairment of urinary concentrating ability, while present in over half of the patients treated with the drug, only causes overt polyuria in about a fifth of cases.[2] Lithium –induced nephrogenic DI is due to at least 2 mechanisms: Lithium prevents AVP-induced translocation of cytoplasmic urinary aquaporin 2 (AQP2) to the apical membrane of the principal cells of the collecting duct by inactivating adenylyl cyclase and thus the phosphorylation of AQP2 by protein kinase A.[3-6] Lithium induced-NDI can become chronic and irreversible if not recognised quickly and lithium therapy stopped.[8,9] Hypercalcaemia also causes acquired NDI by down regulating the expression of AQP2 protein in the medulla and interfering with ADH mediated water reabsorption.[4]

We believe that our patient may have hadpolyuria during her ward admission which was not obvious because she was not catheterised and subsequently developed dehydration, prerenal azotaemia and hypernatremia. Review of her ward charts revealed that hypernatremia developed soon after admission (serum sodium increased from 139 mmol/l on day 1 to 146 mmol/l on day 2). Although she presented with confusion and dysarthria which are signs of lithium toxicity,[1] her serum lithium levels were not elevated initially but was in the toxic range soon afterwards (0.81mmol/l). It has been shown that Angiotensin-converting enzyme (ACE) inhibitors which enhance tubular reabsorption of lithium can cause acute-on chronic toxicity.[9] Our patient had been started on Ramipril 2.5mg following her NSTEMI 3 weeks previously. Despite receiving 2 litres of intravenous normal saline daily for 4 days, dehydration, hypernatremia and prerenal azotaemia developed as her free water deficit was not corrected. With the development of acute kidney injury, less free water reached the collecting ducts, with consequent decrease in urine output.[10] However polyuria developed after fluid resuscitation with Hartmann's solution. It was unresponsive to vasopressin 40micrograms intravenously but showed a marked response to ibuprofen 200mg 8 hourly and hydrochlorothiazide and amiloride25mg/2.5mg.

NSAIDs have been shown to be rapidly effective in treating lithium-induced N DI. They act through inhibition of prostaglandin E^2 which increases CAMP in the distal collecting duct, increasing AQP2 transportation to the cell surface with consequent improvement in renal concentrating ability. NSAID- inhibition of prostaglandins can also decrease glomerular blood flow and therefore glomerular filtration rate.[10] Amiloride has been shown to ameliorate lithium-induced NDI by binding to the epithelial sodium channel, ENaC located in the renal collecting duct and abolishing its uptake of lithium. The end result is release of lithium- induced inhibition of cAMP generation by AVP and increased AQP2 transportation to the cell surface with consequent improvement in renal concentrating ability.[11] Hydrochlorothiazide also upregulates AQP2 and distal renal Na (+) transporters in the collecting ducts.[12] Using the two drugs have been shown to be more effective and well tolerated.[13]

Lithium is the commonest cause of drug –induced NDI and if NDI is not recognised and the water intake is restricted, severe dehydration, acute kidney injury and severe hypernatremia can result. Hospitalised patients who have or are taking lithium chronically needs to be carefully monitored for signs of diabetes insipidus so as to allow prompt diagnosis and treatment. It might also be prudent to temporarily reduce the dose of lithium or discontinue it. NSAIDs can rapidly control polyuria but they are for short-term use only. NSAIDs can be combined with amiloride and or hydrochlorothiazide, although the latter can increase lithium toxicity.

Acknowledgments

None.

Conflicts of Interset

None.

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Citation: Ayeko M. Unrecognised free water loss in a patient with lithium-induced nephrogenic diabetes insipidus can cause acute kidney injury and near fatal hypernatremia... *J Anesth Crit Care Open Access.* 2015;3(5):343–345. DOI: 10.15406/jaccoa.2015.03.00114