Topiramate induced renal tubular acidosis
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Topiramate is a drug used for the treatment of generalised tonic-clonic seizures, migraine prophylaxis and many other off-label indications such as bipolar disorder and post-traumatic stress disorder. With increasing use of topiramate, reports have emerged of biochemical derangements attributable to this medication which may preclude or limit its use. We report a case of a 51-year-old female found to have incidental hypokalaemia and on further investigation, renal tubular acidosis (RTA) for which searches incriminated topiramate as the likely cause. Biochemical abnormalities normalised following drug cessation.

Case report
A 51-year-old female was incidentally found to have mild hypokalaemia on a routine insurance medical, with potassium 3.4mmol/L, bicarbonate 18mmol/L [reference 22–28] and raised chloride at 117mmol/L [reference 95–110]. Venous blood gases showed a low normal pH of 7.39 [reference 7.34–7.44], bicarbonate low at 16.3mmol/L, base excess -8mmol/L [reference -3 to +3] and confirmed chloride of 117mmol/L. Urine anion gap was positive, in this context supportive of a distal as opposed to proximal RTA. Urine citrate was low with a ratio of 0.03 [reference >0.15], also consistent with distal [or type 1] RTA. Searches for possible drug-related causes implicated topiramate, which she had been taking as a potential cause. Biochemical abnormalities normalised following cessation of this drug.

Discussion
The biochemical picture was consistent with mild type 1 distal RTA with a positive urine anion gap and low urine citrate supportive of a distal tubular mechanism. Urine anion gap is calculated as [(sodium + potassium) – chloride] and a value greater than zero is positive and supportive of distal RTA. Conversely, in proximal or type 2 RTA, renal tubular ammonia production is increased to buffer the excess hydrogen ions, chloride production is increased and hence urine anion gap is negative. Topiramate is a classic cause of this biochemical disorder with studies suggesting that up to 30% of outpatients on topiramate had low serum bicarbonate concentrations. The mechanism, however, is thought to involve both proximal tubular mechanisms with impaired reabsorption of filtered bicarbonate and distal tubular mechanisms with impaired hydrogen ion secretion. Inhibition of carbonic anhydrase activity, that catalyses the conversion of carbon dioxide to bicarbonate and hydrogen ions is thought to underlie the proximal tubular effects. Classical hypokalaemic distal RTA has a very broad differential diagnosis, including hereditary, sporadic, auto-immune diseases such as Sjogren's syndrome and many drugs including topiramate.

The hypokalaemia in our case was mild and asymptomatic. The caveat, however, is that this may become more severe with any intercurrent illness that may involve diarrhoea or vomiting. There are also potential adverse effects of long-term acidosis on reducing bone density and increasing the risk of renal calculi. Topiramate is associated with increased risk of nephrolithiasis. Compared with an expected incidence of stone formation in the general population of around 0.2%, this may be increased up to 1.5% on topiramate. Urinary citrate is a recognised inhibitor of urolithiasis, and its deficiency, along with decreased acidification of urine, may contribute to an environment that supports calcium phosphate stone formation. Importantly, the biochemical abnormalities are completely reversible on discontinuing topiramate, as was observed in our case.
This case was triggered by the discovery of incidental and asymptomatic hypokalaemia. The cause was identified through further investigations of acid base status, indicating a hyperchloremic normal anion gap acidosis followed by a literature search of possible offending drugs that implicated topiramate. There were 810 patients receiving topiramate in Canterbury in 2016, which reinforces the need for clinicians using this agent to be vigilant for possible adverse metabolic effects.

**Competing interests:**
Nil.

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