Diabetes vignette

Patients with diabetes frequently develop urinary tract infection (UTI), particularly if glycaemic control is poor, or the patient is treated with SGLT2 inhibitors. We report a case of a patient with diabetic nephropathy, treated with trimethoprim for UTI, who developed severe hyperkalaemia due to type 4 renal tubular acidosis (RTA).

A 75-year-old woman with a six-year history of poorly-controlled type 2 diabetes, previous left hemiparesis and stage 3 CKD secondary to diabetic nephropathy, presented to the emergency department with non-specific symptoms of generalised weakness and lethargy. One week prior to her hospital presentation she had been prescribed a course of trimethoprim for a lower UTI. Her usual medications included metformin, but she was on no other nephrotoxic agents, including NSAIDs, ACE inhibitors or potassium-sparing agents.

Physical examination revealed evidence of a left-sided hemiparesis, but was otherwise unremarkable. She was clinically euvoalaemic, BP 143/78mmHg with no postural drop, pulse 88 beats per minute and regular; cardiovascular, respiratory and abdominal examination was unremarkable. Plasma biochemistry revealed a marked hyperkalaemia (potassium 8.8mmol/L [3.5–5.3]), and hyponatraemia (sodium 130mmol/L [133–146]). Further admission investigations are detailed in Box 1. These showed evidence of a metabolic acidosis and acute kidney injury.

She was treated with glucose/insulin infusion, IV 0.9% saline and 500ml of 1.4% sodium bicarbonate, while under cardiac monitoring. Metformin was discontinued. Two hours after treatment, acidosis and hyperkalaemia had improved, but not resolved (Box 1).

Urgent renal ultrasonography demonstrated normal appearances of both kidneys without any signs of hydronephrosis or bladder calculi. Serial blood tests over the course of the next 36 hours revealed a persistent hyperkalaemia (potassium 6.0–7.6mmol/L) despite repeated courses of glucose/insulin infusions. Serum aldosterone levels were requested and she was treated with trimethoprim for UTI, who developed severe hyperkalaemia due to type 4 renal tubular acidosis (RTA).

Type 4 RTA is usually a result of true aldosterone deficiency or tubular hypo-responsiveness to its effects.1 The condition generally develops in middle-aged or older patients, and is commonly iatrogenic. Drug-induced type 4 RTA is a previously reported, although perhaps under-recognised, problem. Trimethoprim is a frequently prescribed and generally safe antimicrobial, predominantly used in UTI due to Gram negative bacteria. It may, however, unmask hypoaldosteronism in a predisposed patient, leading to life-threatening hyperkalaemia.2–4 This adverse drug reaction, though more commonly seen with trimethoprim-sulfamethoxazole, must be considered in those who develop type 4 RTA during or shortly after its initiation. Other causative medications include pentamidine, NSAIDs, heparin, ACE inhibitors and angiotensin receptor blockers.5 Withdrawal of the drug usually leads to improvement in the metabolic derangement. Additional medical therapies in those with resistant hyperkalaemia include diuretics in hypovolaemic patients and sodium bicarbonate in euvoalaemic patients.4 Fludrocortisone is effective as an aldosterone analogue, although the dose required may be higher than the typical replacement dose used in patients with adrenal insufficiency.6 Fludrocortisone can generally be stopped after a short period once the hyperkalaemia has settled.

Discussion

Type 4 RTA is usually a result of true aldosterone deficiency or tubular hypo-responsiveness to its effects.1 The condition generally develops in middle-aged or older patients, and is commonly iatrogenic. Drug-induced type 4 RTA is a previously reported, although perhaps under-recognised, problem. Trimethoprim is a frequently prescribed and generally safe antimicrobial, predominantly used in UTI due to Gram negative bacteria. It may, however, unmask hypoaldosteronism in a predisposed patient, leading to life-threatening hyperkalaemia.2–4 This adverse drug reaction, though more commonly seen with trimethoprim-sulfamethoxazole, must be considered in those who develop type 4 RTA during or shortly after its initiation. Other causative medications include pentamidine, NSAIDs, heparin, ACE inhibitors and angiotensin receptor blockers.5 Withdrawal of the drug usually leads to improvement in the metabolic derangement. Additional medical therapies in those with resistant hyperkalaemia include diuretics in hypovolaemic patients and sodium bicarbonate in euvoalaemic patients.4 Fludrocortisone is effective as an aldosterone analogue, although the dose required may be higher than the typical replacement dose used in patients with adrenal insufficiency.6 Fludrocortisone can generally be stopped after a short period once the hyperkalaemia has settled.

Conclusion

Type 4 RTA should be considered in all patients with unexplained hyperkalaemia. Trimethoprim is a widely used antibiotic, and may precipitate type 4 RTA in susceptible individuals. Drugs causing this metabolic derangement should be withdrawn and treatment with fludrocortisone, sodium bicarbonate and/or diuretics should be considered.

References

1. Shazia Hussain, MRCP, Specialist Trainee in Endocrinology and Diabetes
2. Francis C Edozie, MD, FRCP, Consultant in Diabetes
3. Tahseen A Chowdhury, MRCP, Specialist in Diabetes and Metabolism, The Royal London Hospital, UK

References

References are available online at www.practicaldiabetes.com.

Box 1. The patient’s investigation results

- **Haemoglobin:** 13.2g/L (13–17)
- **White cell count:** 9.2x10⁹/L (4–10)
- **Neutrophil count:** 6.7x10⁹/L (2–7)
- **Platelets:** 254x10⁹/L (150–410)
- **Sodium:** 130mmol/L (133–146)
- **Potassium:** 8.8mmol/L (3.5–5.3)
- **Urea:** 15.4mmol/L (2.5–7.8)
- **Creatinine:** 191μmol/L (62–106)
- **Bicarbonate:** 20mmol/L (22–29)
- **Bilirubin:** 10μmol/L (1–21)
- **Alanine aminotransferase:** 16unit/L (10–40)
- **Alkaline phosphatase:** 127unit/L (30–130)
- **Total protein:** 69g/L (60–80)
- **Albumin:** 44g/L (35–50)
- **C-reactive protein:** 13mg/L (0–5)
- **Creatine kinase:** 111unit/L (25–200)
- ** Electrocardiogram:** sinus rhythm, peaked T-waves
- **Chest radiograph:** normal
- **Urinalysis:**
  - pH 5, protein 2+, glucose 2+, ketones 1+
  - Nitrites, leukocytes and blood negative
- **Venous blood gas:**
  - On admission: pH 7.31, potassium 8.8mmol/L, lactate 1.9mmol/L, bicarbonate 18mmol/L, base excess -5
  - 2 hours: pH 7.31, potassium 6.4mmol/L, lactate 1.1mmol/L, bicarbonate 21mmol/L, base excess -2.9
- **9.00am cortisol:** 423nmol/L (200–600)
- **Free T4:** 16.2pmol/L (10.5–24.5)
- **TSH:** 1.10munit/L (0.3–4)
Severe hyperkalaemia due to trimethoprim-induced type 4 renal tubular acidosis

References