FEATURE

Medicinal mishap

Trimethoprim-induced critical hyperkalaemia

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Case

An 88-year-old woman presented for investigation of generalised weakness, collapse, bradycardia and delirium. She had a history of recurrent urinary tract infections and had started trimethoprim five days previously. Her past medical history included hypertension, paroxysmal atrial fibrillation with cerebrovascular accident and stage 4 chronic kidney disease attributed to reflux nephropathy and renovascular disease. Her usual drugs were quinapril, doxepin, atorvastatin, frusemide, nebivolol, pregabalin, hexamine hippurate and warfarin.

On admission the patient's serum potassium was 7.9 mmol/L with acute kidney injury (serum creatinine 300 micromol/L, usual baseline 120 micromol/L). Her ECG showed atrial fibrillation with a ventricular rate of 50 beats/minute.

The hyperkalaemia was managed with intravenous sodium bicarbonate, insulin and glucose plus oral sodium polystyrene sulfonate. There was continuous cardiac monitoring. The trimethoprim was ceased and quinapril, frusemide, pregabalin, nebivolol and doxepin were withheld due to the potential for them to contribute to her overall condition. The patient's symptoms, signs and biochemistry stabilised over five days and she was discharged home.

At a subsequent review her quinapril was stopped. She was advised to avoid trimethoprim because of the risk of precipitating hyperkalaemia.

Four months later the woman developed another urinary tract infection but she was again given trimethoprim. Within six days she was readmitted with critical hyperkalaemia (serum potassium 8.1 mmol/L) associated with acute kidney injury (creatinine 200 micromol/L), bradycardia, lethargy and shortness of breath. She required haemodialysis in the intensive care unit, but made a favourable recovery.

The Naranjo score[1] for predicting adverse drug reactions was 7 in this patient. This means that the hyperkalaemia was a probable adverse reaction to trimethoprim.

Comment

There were several other possible causes for the hyperkalaemia in the initial presentation. These include acute kidney injury, chronic kidney disease and treatment with quinapril. Although hyperkalaemia is associated with weakness and bradycardia, the patient was taking other drugs that may have contributed to these symptoms, notably nebivolol, doxepin and pregabalin. However, on her second presentation the patient had not been taking quinapril.

Hyperkalaemia is now a well-recognised adverse reaction to trimethoprim, however this was not reported until approximately 25 years after the antibiotic was first marketed. Detailed human and animal studies in the 1990s found that trimethoprim interferes with potassium excretion by antagonising the epithelial sodium channel in the distal tubule. This results in an effect like that of the potassium-sparing diuretic amiloride.[2] In addition, trimethoprim antagonises the renal tubular secretion of creatinine, causing an increase in serum creatinine concentration which can be interpreted as acute kidney injury – however, there is no change in glomerular filtration rate.[3]

The Australian Medicines Handbook[4] warns of the risk of hyperkalaemia from trimethoprim in patients with chronic kidney disease and in those taking other drugs that cause potassium retention. It recommends against using trimethoprim in severe renal impairment.

Canadian case-control studies investigated sudden deaths in older outpatients (>66 years old) prescribed antibiotics. Compared to amoxycillin there was an adjusted odds ratio of 1.38 (95% CI* 1.09–1.76) for sudden death in patients prescribed trimethoprim with a renin-angiotensin system inhibitor. The adjusted odds ratio was 2.46 (95% CI 1.55–3.90) in those prescribed trimethoprim and spironolactone (approximately 50% were also prescribed a renin-angiotensin system inhibitor).[5] These deaths were thought to relate to unrecognised critical hyperkalaemia. In another study, co-prescribing of trimethoprim with a renin-angiotensin system inhibitor was associated with an adjusted odds ratio of 6.7 (95% CI 4.5–10.0) for hyperkalaemia-associated hospitalisation, compared to those co-prescribed amoxycillin.[6]

* CI confidence interval

Recommendation

Trimethoprim is a well-recognised cause of hyperkalaemia, particularly in older patients, those with renal impairment or those taking a renin-angiotensin system inhibitor or spironolactone. When possible, alternative antibiotics should be prescribed to susceptible patients. If these patients are prescribed trimethoprim, monitoring of serum potassium is recommended.

Conflict of interest: Darren Roberts is a member of the Australian Prescriber *Editorial Executive Committee.*

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