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Severe acute hypokalaemia secondary to voriconazole. Uncommon pharmacological causes of hypokalaemia

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To the Editor,
Hypokalaemia is one of the most common metabolic disorders in clinical practice. We report the case of a man who had acute severe hypokalaemia secondary voriconazole, which was resolved without incident.

Hypokalaemia is defined as a decrease in plasma potassium to below 3.5mmol/l and is one of the most common metabolic disorders in clinical practice. Drugs are one of the most common causes of hypokalaemia, primarily through two mechanisms: they promote the movement of potassium into the cell and increase its renal elimination.[1]

We report the case of a 62-year-old man with a 15-year history of sporadic cerebellar ataxia, without other diseases, who arrived at the emergency department with a fever of one week duration. During admission, he had severe acute respiratory failure secondary to bilateral pneumonia. Treatment was initiated with linezolid, amikacin and piperacillin/ tazobactam empirically. A bronchoscopy was performed with sampling, from which *Candida spp*. were isolated, therefore voriconazole was added to the treatment. A control analysis was performed before the introduction of antifungal agents which showed the red cells, white cells, platelets and coagulation were normal. In the biochemical analysis, renal function, liver function and ions showed no abnormalities. At 24 hours after initiation of the voriconazole treatment, the patient had potassium levels of 2.1mmol/l without any associated clinical or electrocardiographic abnormalities. Intravenous replacement with potassium chloride and oral supplements was initiated, and the potassium values returned to normal at 3 days.

In this case, the patient was taking 2 drugs that might predispose a decrease in potassium levels: an aminoglycoside,[2] whose tubular toxicity effect has been widely described, and linezolid, which rarely causes hypokalaemia.[3] The levels were normal with both drugs, but there was a severe, acute fall after adding voriconazole, without severe repercussions for the patient.

Voriconazole is a broad spectrum, antifungal agent in the azole family. It has excellent bioavailability, both orally and intravenously. It is metabolised in the liver by the cytochrome P-450 pathway and its metabolites have no antifungal activity. A dose adjustment is needed in patients with moderate liver function impairment. Renal clearance was 85% as inactive metabolites. In addition, the elimination of unmetabolised voriconazole is slight, so the oral formulation does not require dosage adjustment in kidney failure. However, intravenous administration should be avoided in patients with creatinine clearance below 50ml/min, as its excipient, cyclodextrin, can accumulate.[4]

Voriconazole is well tolerated. The most common side effect, unique among the azoles, is a reversible disturbance of vision, photopsia, which does not usually require discontinuation of the therapy. The following side effects are photosensitivity and increased liver enzyme levels. Less common are vomiting, diarrhoea, abdominal pain and visual hallucinations. Due to its hepatic metabolism, voriconazol can interact with numerous medications.[2]

Table 1. Drugs leading to hypokalaemia

Intracellular movement of potassium
Beta-adrenergic agonists
Adrenaline
Bronchodilators: salbutamol, terbutaline, salmeterol, formoterol, albuterol, isoprotenerol, clembuterol
Tocolytics: phenoterol, ritodrine, orciprenaline
Nasal decongestants: pseudoephedrine, phenylpropanolamine, phenylephrine
Calcium channel blockers
Nifedipine
Intravenous cyanocobalamin
Poison/high doses
Lithium, barium, verapamil, chloroquine and insulin
Methylxanthines
Theophylline, caffeine

Hypokalaemia is not a common side effect. Studies have compared it to amphotericin B, the prevalence of hypokalaemia is 18.8% and only 2.4% have potassium levels below 2.5mmol/l.[3,5]

Many new drugs are increasingly being reported to be involved in various electrolyte disturbances (Table 1). Therefore, the medication that all patients with hypokalaemia receive should be examined, including both drugs traditionally associated with hypokalaemia, such as diuretic agents, beta-adrenergic agonists and amphotericin B, and new antibiotic, antiretroviral and immunosuppressant drugs.

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Extracapillary glomerulonephritis type I with the coexistence of positive anti-GBM and p-ANCA antibodies

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To the Editor,

Extracapillary glomerulonephritis (EGN) is characterised by the presence of potentially pathogenic antibodies or immune complexes in the plasma. These include the antiglomerular basement membrane antibodies (anti-GBM Ab), characteristic of type I EGN, and anti-neutrophil cytoplasmic antibodies (ANCAs), which are usually present in type III EGN.[1,2]

A substantial proportion of patients with EGN are double positive for anti-GBM and ANCA. We report a patient with type I EGN with plasma coexistence of anti-GBM Ab and p-ANCA and severe renal impairment. The patient did not respond to triple therapy with plasmapheresis, corticosteroids and cyclophosphamide.

Case report

A 62-year old man was referred from the emergency department to the nephrology department for general discomfort associated with bilious vomiting and evening fever. He was taking azithromycin. The patient reported a reduction in diuresis in the previous days, without lower urinary tract symptoms. He was not taking NSAIDs or any other nephrotoxic drugs. The medical history showed chronic obstructive pulmonary disease, obstructive sleep apnoea syndrome, chronic otitis media monitored by an otolaryngologist and botulism, which required ICU admission in 2007. No history of hypertension, diabetes mellitus, dyslipidaemia or any known heart disease. The physical examination revealed a normal general state, he was eupneic at rest, conscious, oriented, collaborative, with normal perfusion and hydration. BP was 143/95mm Hg, HR was 75 beats/min, temperature 36.5°C, and oxygen saturation 97%. There were no lesions on the skin or in the mucous membranes.

Cardiopulmonary auscultation: rhythmic without audible murmurs. Vesicular murmur without superimposed noise was found. Abdomen: soft and palpable. No signs of peritoneal irritation. No masses or organomegaly on palpation. The lower extremities showed pitting oedema to the root of the limbs, without signs of deep vein thrombosis (DVT) or chronic venous insufficiency, with positive pulses. The neurological examination found isochoric and normally reactive pupils, normal cranial nerves, and segmentally conserved strength and sensitivity. There were no signs of meningeal irritation.

The analytical results on admission showed: haemoglobin 11g/dl, haematocrit 34.7%, MCV 92fl, WBC 9000 (85% neutrophils, 9.1% lymphocytes), platelets 213 000, glucose 102mg/dl, urea 265mg/dl, creatinine 12.2mg/dl, sodium 137mEq/l, potassium 7mEq/l, chloride 107mEq/l, procalcitonin 0.92mg/dl, protein 7g/l, calcium 9.6mg/dl, corrected calcium 9.8mg/dl, CRP 272.8, total bilirubin 0.6mg/dl, AST 19U/l, ALT 39U/l, GGT 28U/l, ALP 61U/L, amylase 84. Urinalysis: protein 100mg/dl, 300 red cells, negative nitrites, no leukocyte. Chest x-ray showed no signs of condensation or leakage, and normal mediastinum. The plain abdominal x-ray showed non-specific meteorism.

Venous blood gases: metabolic acidosis with pH 7.28, total CO_2 20mmol/l, HCO_3^- 18.8mmol/l, BE -7.5. ECG: sinus rhythm at 75 beats/min, normal PR, narrow QRS, no acute repolarisation changes. Abdominal ultrasound: liver and spleen without ultrasound abnormalities. Enlarged right kidney (15cm), with loss of cortico-medullary