A misleading, underestimated side effect of a commonly used therapy. Following your stomach may hurt your heart

O. Amatruda

Abstract We report a case of resistant hypokalaemia with hypertension and arrhythmias. The clinical history included chronic gastro-oesophageal reflux treated with proton pump inhibitors. Blood test revealed hypocalcaemia and hypomagnesaemia. Treatment with magnesium and withdrawal of proton pump inhibitors resulted in complete recovery; however, when the patient was readministered proton pump inhibitors because of epigastric pain, the whole syndrome reappeared. Treatment with proton pump inhibitors was then stopped definitively with release of both hypertension and hypocalcaemia. Proton pump inhibitors induce intestinal magnesium wasting and related cardiovascular complications.

Keywords Hypokalaemia · Hypocalcaemia · Hypomagnesaemia · Hypertension · Proton pump inhibitors

A 67-year-old man came to our observation on 31 December 2007 because of persistent hypokalaemia resistant to replacement therapies. Both parents were affected by end-stage renal failure, his only daughter was healthy. The patient had smoked for many years but quit at the age of 40. When he was 47, gastro-oesophageal reflux was diagnosed and treated with H2-receptor agonists for 4 years and then switched to proton pump inhibitors.

At the age of 59, he developed arterial hypertension initially treated with ace inhibitors replaced by angiotensin-II-receptor antagonist (candesartan cilexetil 16 mg per day). In December 2006 hypokalaemia (2.6 mEq/L) and hypercholesterolaemia were occasionally found: accordingly, oral potassium replacement and statins were administered. Arterial pressure was high, and the dose of candesartan cilexetil was doubled (32 mg per day).

Serum creatinine was 1.2 mg/dL; abdominal ultrasound revealed microlithiasis of the left kidney with regular kidney structure and dimensions. The abdominal aorta was not dilated.

After 6 months the patient complained of tachycardia and fatigue. The dynamic ECG showed sinus rhythm, left bundle branch block, U waves and sporadic supraventricular ectopic beats, sometimes in short runs. On ultrasound the left ventricular wall appeared hypertrophic (septal thickness 14 mm) and dilated (diastolic diameter 62 mm, ejection fraction 50%). The dose of oral potassium was increased to 3.6 grams/day and amlodipine added to control hypertension.

Two months later ankle oedema developed; hypokalaemia (2.96 mEq/L) and hypertension were still present. Daily urinary potassium (81 mEq/day) indicated loss of this ion with urine (U\text{K}, > 20 mEq in the presence

of hypokalaemia). However, renin and aldosterone levels were low: 24 pg/mL (nv.70–300) and 2.5 µU/day (nv.7–76), respectively.

Potassium canrenoate at the dose of 300 mg/day was added to the ongoing therapy but with no beneficial effect on either serum potassium levels or blood pressure. Moreover, the patient began to complain of paresthesias and cramps in both upper and lower extremities.

Primary hyperaldosteronism or Liddle syndrome were both excluded, the first on the basis of hormone levels, the second because of advanced age.

When the patient finally came to our observation, he appeared overweight (BMI 28) but in good condition. Physical examination was unremarkable.

Blood analysis: pH 7.40; HCO₃ 24.7 mEq/L; Na 142 mEq/L; K 2.7 mEq/l; unexpectedly low ionized calcium serum levels were found (0.75 mmol/L). Based on this new element, calcitriol was administered (0.50 mcg/day) and in 15 days paresthesias disappeared, ionized calcium reached 1.05 mmol/L, total calcium 9 mg/dL.

But what about the magnesium levels?

Magnesium is present mainly in the intracellular compartment. Hypomagnesaemia induces inhibition of the tubular reabsorption of potassium and of PTH secretion, which result in both hypokalaemia and hypocalcaemia; however, resistant hypokalaemia with or without hypocalcaemia or even the presence of arrhythmias alone can be a reflection of intracellular depletion of magnesium, even when blood levels are normal (>1.8 mg/dL).

A daily excretion of magnesium less than 10 mg or an excretion fraction (EFMg) less than 2% indicates increased renal reabsorption consequent to intracellular depletion. EFMg can be easily calculated: EFMg= U_Mg x Pcr/(0.70 x P_Mg) x Ucr x100.

In the presence of hypomagnesaemia, a urinary excretion higher than 20 mg/day or EFMg higher than 4% indicates urinary loss of magnesium. Indeed our patient had severe hypomagnesaemia (pMg: 0.8 mg/dL) with very low urinary Mg-excretion (uMg: 2.45 mg/day, EFMg: 0.36%), as consequence of a elevated renal reabsorption. The patient then received 6.75 g/day of magnesium pidolate.

After one month arterial pressure was 105/60 mmHg, despite the withdrawal of amlopipine, and electrolytes were as follows: pK: 4.5 mEq/L, pCa++:1.21 mmol/L; pMg: 1.7 mg/dL. However, despite blood magnesium being slightly below the normal range, urinary magnesium was still less than 10 mg/day, with a low excretion fraction (EFMg: 0.22%), thus indicating persistent intracellular magnesium depletion.

The patient had neither the most common causes of intestinal loss of magnesium, such as diarrhoea, vomiting, nasogastric suction, gastrointestinal fistulas or stoma, nor was he receiving any of the drugs frequently associated with hypomagnesaemia: loop diuretics, amphotericin B, aminoglycosides, pentamidine, capreomycin, viomycin, foscarnet, chemotherapeutic agents such as cisplatin, or immunosuppressants, i.e. tacrolimus or cyclosporine.

Which is the culprit?

It has been reported that proton pump inhibitors may induce hypomagnesaemia [1, 2]. Indeed, our patient had been undergoing pantoprazole therapy for years. The drug was withdrawn to be replaced by ranitidine. Potassium canrenoate was withdrawn as well. One month later blood magnesium was normal, urinary magnesium was slightly over 10 mg/day and EFMg was 0.78% indicating a suboptimal recovery of intracellular magnesium load. After 3 months the main data were the following: AP 120/80 mmHg; pK 4.59 mEq/L; pCa 9.3 mg/dL; pMg 2.2 mg/dL; uMg 18mg/day; EFMg 0.78%.

In the following days, however, the patient once more began to complain of epigastric pain. Since other treatments had failed to give any relief, the patient was given omeprazol. The gastric symptoms disappeared, but fatigue and hypertension recurred after 20 days. Blood tests again showed hypokalaemia (pK: 2.9 mEq/L) and hypomagnesaemia (pMg 1.2 mg/dL) with low magnesium excretion (uMg: 2.25 mg/day, EFMg: 0.28%).

Proton pump inhibitors were then withdrawn for good and replaced by H2-receptor antagonists. After 45 days arterial pressure was 95/50 and accordingly any hypotensive drugs were withdrawn, and blood tests were repeated: pK: 4.4 mEq/L, pMg 2.2 mg/dL.

One year later the patient is doing well: epigastric pain is somehow tolerated; arterial pressure is normal.

Is this side effect of proton pump inhibitors so uncommon?

Few cases of hypomagnesaemia induced by proton pump inhibitors have been reported [3, 4]. It is likely that years of treatment with these drugs result in a slow depletion on intracellular magnesium. The mechanism is unknown, but it should be observed that Mg replacement therapy alone was effective in correcting the ion deficiency (without withdrawing the proton pump