Proton pump inhibitor-induced hypomagnesemic hypoparathyroidism

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ABSTRACT

Proton pump inhibitors are the one of the most widely used drugs in the world. Hypomagnesemic hypoparathyroidism has been reported with different proton pump inhibitors with prolonged oral use. We report the first reported case of possible such effect with intravenous preparation of proton pump inhibitor. This case report raises awareness among physicians worldwide of this often unknown association, as life-threatening cardiac and neuromuscular complications can arise with unrecognized hypocalcemia and hypomagnesemia with proton pump inhibitors.

KEY WORDS: Hypocalcemia, hypoparathyroidism, proton pump inhibitors, tetany

Introduction

It is often quoted that “all drugs are dangerous and how dangerous a drug is depends on the skill of the prescriber.” The skill includes the knowledge of uncommon adverse effects of drugs that may have huge therapeutic implications for the patient. Over the last few years, there have been increasing case reports of hypomagnesemic hypoparathyroidism with the prolonged oral use of proton pump inhibitors. Until date, there have been no reports of such an association with short-term intravenous use, apart from this case report. Considering the wide use of proton pump inhibitors worldwide, this case report will bring awareness about this rare, but potentially fatal adverse effect of a commonly used drug.

Case Report

A 40-year-old lady underwent a total thyroidectomy for a differentiated thyroid cancer. Postoperative course was uneventful for the first 24 h. The parathyroids were identified and preserved during surgery. The patient was started on calcitriol and calcium as per the local protocol postsurgery. Serum calcium corrected for albumin on day 2 (postoperative) was within normal limits at 9.2 mg/dl (normal range 8.5–10.2 mg/dl). On the afternoon of day 2, patient had persistent epigastric pain and profuse vomiting. Urgent endoscopy showed a peptic ulcer with high-risk stigmata. Patient was commenced on intravenous esomeprazole (bolus of 80 mg intravenously over 30 min followed by 8 mg/h infusion). On the night of day 2, patient started to develop severe parasthesias and tetany [Figure 1]. Intravenous calcium gluconate bolus twice had to be followed by a continuous calcium infusion as the serum calcium dropped to 5.6 mg/dl. In spite of escalating maximum recommended doses of calcium infusion, patient was in persistent severe tetany. Serum magnesium was found to be low at 1 mg/dl (1.6–2.2 mg/dl). Intravenous magnesium was commenced with no improvement in tetany for 18 h since the onset. Serum parathormone was inappropriately normal at 12 pg/ml (normal range 11–54 pg/ml).

Literature search suggested the possibility of proton pump inhibitor-induced hypomagnesemic hypoparathyroidism, though this has been reported only with long-term oral use. However, symptoms rapidly improved following the cessation of intravenous esomeprazole. Serum calcium and magnesium levels returned to normal within 6 h of stopping the infusion. Patient was discharged 48 h later with corrected calcium of 9.2 mg/dl and serum magnesium of 1.8 mg/dl. Postoperative radio-iodine ablation was done for a papillary thyroid carcinoma. She was gradually weaned off the oral calcium and calcitriol at a 3 month follow-up. At a recent clinic visit, she was normocalcemic, normomagnesemic and continues on long-term thyroxine and ranitidine. She has been educated about the need to avoid proton pump inhibitors in the future and this has been “red flagged” in her case record.

Discussion

Proton pump inhibitors are one of the most commonly used and abused drugs in the world. There is an increasing research favoring a possible causal role of proton pump inhibitors in
the development of hypomagnesemic hypoparathyroidism, more so with prolonged use.[1] Initial reports of proton pump inhibitor-induced hypomagnesemic hypoparathyroidism surfaced in 2006,[2] followed by several case reports and review articles.[3,4]

The exact pathophysiological mechanisms of proton pump inhibitor induced hypomagnesaemic hypoparathyroidism are still elusive, but renal and intestinal handling of magnesium is thought to be responsible. The hypomagnesemic hypocalcemia may be related to proton pump inhibitor induced hypochlorhydria or altered regulation of transient receptor potential melastin 6/7 (TRPM 6/7). TRPM 6/7 is an active transcellular channel present in the gastrointestinal tract and kidneys, which conducts cations such as magnesium and calcium into the cells.[5] Variants of TRPM 6/7 may be responsible for hypomagnesaemia in susceptible patients. It is also possible that patients who develop hypomagnesaemia on proton pump treatment may have mutations in genes involved in modulation of magnesium reabsorption in the kidneys, which could result in a persistent magnesium leak through the kidneys.

Causality Assessment

This is the first reported case of possible severe hypomagnesemic hypoparathyroidism following the intravenous preparation of proton pump inhibitors. Causality Assessment with both Naranjo and WHO-Uppsala Monitoring Centre [UMC] Causality scales suggest possible adverse drug reaction (rather than definite or probable) as the hypocalcemia may still be related to postsurgical hypoparathyroidism. One of the key clinical feature in all reported case series with proton pump inhibitor-induced hypocalcemia is the prolonged use of oral preparations in adults (at least 3 months and in most cases more than a year). It could be possible that the hypocalcemia in our case could have been exacerbated by transient hypoparathyroidism after total thyroidectomy but the presence of hypomagnesemia, the normal calcium levels on day 2 postoperative and the temporal sequence of events after the initiation and cessation of intravenous esomeprazole suggest that the effects were due to the medication rather than severe hypoparathyroidism related to the surgery.

References

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