1.1. Hypomagnesaemia following the concomitant use of proton pump inhibitors and bumetanide

Introduction

Proton pump inhibitors (PPIs) strongly reduce gastric acid secretion. The pharmacological mechanism of action is based on inhibiting the H^+/K^+-ATP-ase (the so-called proton pump) in the parietal cell of the stomach mucosa. PPIs are widely approved for *the treatment of oesophageal reflux disease, treatment and prophylaxis of (NSAID-associated) duodenal and benign gastric ulcers and relief of dyspeptic symptoms*. Omeprazole, the first PPI has been registered in the Netherlands since 1988. Currently there are five PPIs registered in the Netherlands, namely omeprazole, esomeprazole, pantoprazole, rabeprazole, and lansoprazole [1-5].

Bumetanide belongs to the class of loop diuretics and has been registered in the Netherlands since 1972 and is indicated for *acute pulmonary edema and edema because of congestive heart failure, cirrhosis of the liver, nephrotic syndrome and drugs. Diuretic therapy in chronic renal failure and drug intoxications for which forced diuresis is desired* [6]. Loop diuretics inhibit the reabsorption of NaCl in the the loop of Henle. They enhance the excretion of potassium, calcium and magnesium [7].

Magnesium is a relatively small divalent cation which is crucial as a co-factor in many enzyme reactions, particularly those involving the transfer of high energy phosphate [8]. It is the second most abundant intracellular cation and its homeostasis is intricately regulated by intestinal absorption and renal excretion. Maintenance of adequate intracellular magnesium levels is essential for normal physiological and metabolic processes [8].

Normal total serum levels of magnesium are between 0.6 and 1.1 mmol/l for men and women [9]. Personality changes, muscle weakness, tremor and dysphagia may occur at concentrations < 0.6 mmol/L in serum, while confusion and obtundation develop at concentrations < 0.4 mmol/L. Severe hypomagnesaemia can be associated with malignant cardiac arrhythmias, tetany, generalized seizures and other metabolic disturbances such as hypokalaemia and hypocalcaemia [10].
Low magnesium levels are a well-known adverse drug reaction (ADR) of PPIs that usually occurs after long-term use and monitoring of magnesium serum levels is therefore advised [3,11]. Diuretics, loop but also thiazide diuretics, are associated with hypomagnesaemia, however, routine monitoring and treatment, are not required [7].

Reports

On 3 June 2015, the database of the Netherlands Pharmacovigilance Centre Lareb contained 3 reports of patients hospitalized for hypomagnesaemia following concomitant use of a proton pump inhibitor and bumetanide.

Case A (160879)
This report from a specialist doctor describes a male aged 71 years and older with hypomagnesaemia that led to hypocalcaemia and convulsion following administration of pantoprazole for angiodysplasia of cecum (off-label) and bumetanide for cardiac failure with a latency of 4 years after start of pantoprazole and 1 year after start of bumetanide. The patient was hospitalised and the drug pantoprazole was withdrawn, the dose for bumetanide was reduced. The patient was treated with intravenous magnesium and calcium and recovered. After 5 days the magnesium and calcium levels were back to normal but the patient acquired a hospital infection requiring a prolonged stay (total of 12 days) in the hospital. Concomitant medications were eplerenone, paracetamol, acenocoumarol, allopurinol, bisacodyl, metoprolol, simvastatin, zolpidem, tamsulosin, lisinopril.

Case B (177409)
This report from a specialist doctor describes a male aged 60-71 years, with muscle spasms caused by hypocalcaemia and hypomagnesaemia following administration of esomeprazole and bumetanide (both for unknown indication) with a latency of 1 week after dose increase of the bumetanide and years after start of the esomeprazole. The drug esomeprazole was withdrawn and the patient was treated with magnesium supplementation. The esomeprazole was substituted to famotidine. The patient recovered. Concomitant medications were atorvastatin, spironolactone, lisinopril, metoprolol, acenocoumarol.

The medical history indicates that the patient had gout, gastritis, decompensated heart failure, heart valve replacement twice, ischemic cerebrovascular accident, coronary artery bypass twice and atrial fibrillation.

Case C (192506)
This report from a consumer describes a female aged 71 years and older, with magnesium (and other electrolytes) decreased following a possible drug interaction after administration of pantoprazole and bumetanide with a latency of 2.4 years after start of the bumetanide and 15 years after start of the pantoprazole (both for unknown indication). The drug pantoprazole was withdrawn; the dose for bumetanide was not changed. The patient was admitted to the Intensive Care Unit with a seizure and serious arrhythmia. She also suffered from fatigue and nausea for some time. She was hospitalized for 7 days and was recovering at time of notification. Concomitant medications were acenocoumarol, allopurinol. The patient has no known medical history. The patient has no known past drug therapy.

Unfortunately none of these 3 cases included serum magnesium levels but since all patients were hospitalized the reported hypomagnesaemias are regarded as confirmed. One patient used spironolactone, a potassium sparing diuretic, which is associated with electrolyte disorders but not particularly with hypomagnesaemia [12]. Additionally, the Netherlands pharmacovigilance centre Lareb received 7 cases of low magnesium levels in association with the use of a PPI and furosemide. However, the warnings for low magnesium in the SmPC of furosemide are more comprehensive and therefor these reports are beyond the scope of this signal.

Other sources of information

SmPCs

All SmPCs of PPIs registered in the Netherlands warn for hypomagnesaemia following long term use of these drugs especially when risk factors such as the use of diuretics are present [1-5].

Although the SmPC of furosemide warn for hypomagnesaemia in 4.4 (special warnings and precautions for use) and advices regular measurement of electrolytes [13], the SmPCs of bumetanide only mention hypomagnesaemia as an adverse drug reaction in 4.8 (adverse drug reactions) [6]. Neither the SmPC of furosemide or the SmPC of bumetanide mention the use of PPIs as an additional risk factor [6,13].

Literature

So far, only two studies highlighted the increased risk of hypomagnesaemia and concomitant use of PPIs and diuretics [10,14]. Zipursky et al. conducted a population-based case-control study of multiple health care databases in Ontario, Canada, from April 2002 to March 2012. Patients who were enrolled as cases were Ontarians aged 66 years or older hospitalized with hypomagnesaemia (identified with ICD-10 codes E83.42 and E61.2). For each individual enrolled as a case, up to four individuals were identified as controls matched on age, sex, kidney disease, and use of various diuretic classes. Exposure to PPIs was categorized according to the most proximate prescription prior to the index date as current (within 90 days), recent (within 91 to 180 days), or remote (within 181 to 365 days). A conditional logistic regression to estimate the odds ratio for the association of outpatient PPI use and hospitalization with hypomagnesaemia was used. Current PPI use was associated with a 43% increased risk of hypomagnesaemia In a stratified analysis, the risk was particularly increased among patients receiving diuretics and not significantly increased among patients not receiving diuretics [10]. This finding corresponds with the outcomes of Danziger *et. al*, who examined the serum magnesium concentration and the likelihood of hypomagnesaemia (<1.6 mg/dl) of patients with a history of PPI use. PPI use was associated with 0.012 mg/dl lower adjusted serum magnesium concentration compared to users of no acid-suppressive medications, but this effect was restricted to those patients taking diuretics: among the patients concurrently on diuretics, PPI use was associated with a significant increase of hypomagnesemia and 0.028 mg/dl lower serum magnesium concentration. Among those not using diuretics, PPI use was not associated with lower serum magnesium concentrations [14]**.** While PPI-induced hypomagnesaemia is rare and most PPI users are presumably unaffected, patients taking diuretics may be at a higher risk.

Databases

To calculate the disproportionality for adverse drug interactions in Vigibase™, we requested data on the disproportionality measure, omega (Ω), from the Uppsala Monitoring Centre (UMC). The omega describes the relative reporting rate of two drugs and one adverse reaction (adverse drug interaction, ADI) in relation to the background reporting. If the Ω is greater than zero the ADI is reported more often than expected [15,16].
For the reports of hypomagnesaemia where both proton pump inhibitors and bumetanide are reported as suspected, interacting or concomitant drugs the omega is positive for pantoprazole and bumetanide (Ω=1.56).

Prescription data

Table 4. Number of patients using proton-pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole) and loop diuretics (bumetanide and furosemide) in the Netherlands between 2010 and 2014 [17]. Users of fixed dose combinations are excluded. The number of people using both loop diuretics and PPIs is unknown.

	2010	2011	2012	2013	2014
A02BC01 Omeprazole (*Losec* ®)	1,596,000	1,690,000	980,240	1,029,000	1,078,000
A02BC05 Esomeprazole (*Nexium* ®)	340,750	336,130	243,370	233,470	228,320
A02BC03 Lansoprazol (Prezal ®)	18,653	17,416	14,786	13,945	13,260
A02BC02 Pantoprazole (*Pantozol* ®)	622,240	696,690	528,110	581,930	648,820
A02BC04 Rabeprazol (Pariet ®)	60,424	56,376	39,264	34,666	32,140
C03CA02 Bumetanide (*Burinex* ®)	95,118	93,575	92,892	91,273	91,605
C03CA01 Furosemide (*Lasix* ®)	336,970	329,970	326,860	318,490	314,910

Mechanism

Co-administration of several hypomagnesaemia inducing drugs may have an additive effect. The mechanism of hypomagnesaemia in the setting of PPI use is poorly understood but may reflect impaired gastrointestinal absorption of magnesium by inhibition of intestinal TRPM 6 and 7 cation channels which are responsible for active transport of magnesium. In contrast, most other drugs associated with hypomagnesaemia cause renal magnesium wasting. In patients with suspected PPI-induced hypomagnesaemia, renal magnesium handling is often preserved [10].

It is generally accepted that diuretics, due to increased urinary excretion, can cause hypomagnesaemia [18]. The extent and the significance of this effect, however, has sparked controversy for some time although it appears that the hypomagnesaemic effect of thiazide diuretics is more prominent than that of loop diuretics [7,18]. Loop diuretics, by exerting their main action in the ascending part of the loop of Henle, where most of the filtered magnesium is reabsorbed, are liable to produce magnesium deficiency [18]. The age of our patients with hypomagnesaemia is quite high. Since elderly are more prone to the effects of magnesium depletion due to inadequate dietary intake, age can be considered as an additional risk factor for low magnesium serum levels [16].

Discussion and conclusion

The Netherlands' Pharmacovigilance Centre Lareb received 3 cases of patients hospitalized for clinically manifested hypomagnesaemia following the use of a PPI and bumetanide. In all three cases the bumetanide was started after the PPI. Although advice for monitoring magnesium levels is included in the SmPCs of PPIs in 4.4 (especially in the presence of other risk factors e.g. the use of diuretics) and hypomagnesaemia is mentioned as an ADR in the SmPCs of bumetanide in 4.8, warnings and advice for monitoring magnesium levels are lacking and may also be desirable in 4.4 of the SmPCs of bumetanide, at least for cases where other magnesium lowering risk factors (such as age and the use of PPIs) exist.

- Although the SmPCs of bumetanide mention hypomagnesaemia in 4.8, additional warnings should be included in 4.4, mentioning that especially when other risk factors exist hypomagnesaemia could occur.

References

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