Systematic review: hypomagnesaemia induced by proton pump inhibition

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SUMMARY

Background
Proton pump inhibitors (PPIs) are a mainstay therapy for all gastric acid-related diseases. Clinical concerns arise from a small but growing number of case reports presenting PPI-induced hypomagnesaemia (PPIH) as a consequence of long-term PPI use. Current opinion is that reduced intestinal magnesium absorption might be involved, but nothing is known on the molecular mechanism underlying PPIH.

Aim
To investigate whether or not PPIH is a true, long-term drug-class effect of all PPIs and to scrutinise a possible role of comorbidity in its aetiology. Therefore, the primary objective in particular was to investigate serum magnesium dynamics in trials drug withdrawal and re-challenge. The secondary objective was to profile the ‘patient at risk’.

Methods
We reviewed systematically all currently available case reports on the subject and performed a statistical analysis on extracted data.

Results
Proton pump inhibitor-induced hypomagnesaemia PPIH is a drug-class effect and occurred after 5.5 years (median) of PPI use, onset was broad and ranged from 14 days to 13 years. Discontinuation of PPIs resulted in fast recovery from PPIH in 4 days and re-challenge led to reoccurrence within 4 days. Histamine-2-receptor antagonists were the preferable replacement therapy in PPIH and prevented reoccurrence of hypomagnesaemia. In PPIH no specific risk profile was identified that was linked to the hypomagnesaemia.

Conclusions
The cases of PPIH show severe symptoms of magnesium depletion and identification of its causation was only possible through withdrawal of the PPI. Clinical awareness of PPIH is key to avoid putting patients at risk.

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INTRODUCTION
Proton pump inhibitors (PPIs) were introduced onto the market for peptic ulcer disease in 1989. Today, they are the mainstay therapy in gastro-oesophageal reflux disease (GERD), gastritis and duodenal or gastric ulcers.1–4 Omeprazole is the prototype drug and it is still the most prescribed PPI worldwide. Since the introduction of omeprazole, other molecules have followed suit such as lansoprazole (1995), pantoprazole (1997), rabeprazole (1999) and esomeprazole (2001).5, 6 PPIs are highly effective and given the fact that a huge number of patients are in need for control of gastric acid made them to one of the top-selling pharmaceuticals of the last decade.7–9 PPIs have a number of side effects. Epidemiological studies have demonstrated that their use is associated with an increased risk for pneumonia, enteric microbial overgrowth and sepsis, although the attributed risk may be dependent on confounding factors.10–13 Clinical cross-sectional studies identified PPI use also to be associated with a higher risk of bone fracture, and in postmenopausal women the use of omeprazole was identified to be a risk factor for the incidence of vertebral fractures, independent from osteoporosis and age.14, 15 A directed retrospective data analysis of hospitalised patients identified PPI use to be associated with lower serum magnesium levels.16 A few case reports, show the use of PPIs resulting in profound, but reversible, isolated hyponatremia, hypocalcaemia and hypokalemia.17

PATIENTS AND METHODS
Literature review methods
We reviewed the published cases on PPIH listed in MEDLINE (National Library of Medicine, Bethesda, MD) and PubMed published up to 1 December 2011. In addition, we performed an exhaustive search using Web of Knowledge and Google Scholar to uncover possibly missed case reports. We included all articles that were written in English, German, Dutch, French or Spanish language. All duplicates were removed. Two reviewers (M.H. and J.D.) independently evaluated the eligibility of all studies retrieved from the databases on basis of the predetermined selection criteria. Disagreements were resolved by discussion with a third party (J.H. and R.B.). To ensure that our search included all published articles, cross-citation screening was manually performed in the reference sections of included articles and within PubMed. We used the following MESH terms for our systematic search: hypomagnesemia, hypomagnesaemia, PPI, proton pump inhibitor, pharmacology, pharmacokinetics, magnesium, omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole, H⁺,K⁺-ATPase, intestine, malabsorption, acid suppression, depletion, drug induced.

Data extraction and analysis
As we were interested in the course of serum magnesium levels in patients receiving PPIs we focused on 2 clinical situations: (i) serum magnesium changes in relation to withdrawal of PPI; and (ii) serum magnesium levels in relation to re-challenge with PPI. Data from the reports were extracted from original text or tables and/or by digitising the original published graphs.

For digitising the graphs we captured a high-resolution snapshot of the portable document file (PDF) with Adobe Photoshop CS3. To assure proper and reproducible digitising, digitised measurement points were marked by cross-hairs intercepting the centre, and this template for digitising was subsequently stored as high quality JPG image. Subsequently, each measurement point of the graphs was digitised three times by the first author and by an independent colleague. Averages were pooled and the maximal point-to-point variation was 2%. As a quality measure, we compared the original data obtained from two case reports with captured digitised data. This procedure revealed absence of significant differences between either datasets. The timescale was always transformed into days. Further clinical data, such as age, gender, PPI-type, doses (data not shown), symptoms due to hypomagnesa-
emia, co-morbidity and medical history were extracted from the original text and/or tables.

Biochemical data
Data were derived from the published case reports. To develop a comprehensive overview we obtained additional information using a structured questionnaire send to the first/corresponding authors from six different case reports. We obtained additional patient data from three authors (see Acknowledgements). We designed an electronic data extraction form in MS Excel and used this for data entry. We extracted the following biochemical data from the case reports: serum magnesium, calcium, potassium and parathyroid hormone (PTH) (data not shown) as well as the urinary excretion of magnesium. The following cut-off values to indicate the severity of the electrolyte disturbances were used (all numbers in mmol/L): Hypomagnesaemia was defined by serum concentrations <0.7 (mild) and severe (symptomatic) hypomagnesaemia was defined by a serum value of <0.5. Hypocalcaemia was categorised into three levels, mild hypocalcaemia with plasma levels of 1.80–2.10, moderate hypocalcaemia 1.50–1.79 or severe hypocalcaemia <1.50. Mild hypokalemia was defined by serum values of 3.1–3.5, moderate hypokalemia 2.5–3.0 or severe hypokalemia <2.5.

Quality measures & demographical data
All cases were investigated for the causality between the administration of PPIs and hypomagnesaemia evaluation of the case descriptions. From all case reports, data concerning age, gender, type, dosage and timescale of PPI usage, nadir of hypomagnesaemia under PPI use, the calcium levels and the presence of hypokalemia, renal magnesium handling, serum magnesium after withdrawal/change in therapy and important medication and comorbidity, type of follow-up therapy and the use of magnesium supplementation were collected (partially shown in Table S1).

Study endpoints
This review was guided by two endpoints. Primary goal was to investigate short-term changes of serum magnesium in selected magnesium-depleted cases upon (i) withdrawal of the PPI (maximum 28 days); and (ii) at re-challenge with the PPI maximum (maximum 21 days).

(1) In case of withdrawal we focused on the nadir of serum magnesium and the mean recovery time needed to reach 0.6 mmol/L after discontinuation of the PPI, as lower values hallmark symptomatic hypomagnesaemia.

(2) In case of re-challenge we focused on the mean time needed for serum magnesium to intersect 0.6 mmol/L towards lower values within the sequels of PPI re-challenge.

The secondary goal was to identify a risk profile in cases with PPIH. Therefore, the traits age, gender, hypertension and the use of drugs were statistically tested with respect to nadir of magnesium under PPI regimen.

Statistical analysis
Changes in serum magnesium were assessed by an analysis performed for each of the two endpoints. All data were stored in an MS Excel spread sheet and subsequent statistical analysis and plotting was all done with GraphPad Prism (version 5; GraphPad Software Inc., La Jolla, CA, USA). (1st Endpoint): exponential regression analysis was performed on all suitable withdrawal (observation 28 days) and re-challenge events (observation 21 days). We included curve fitting and regression analysis and numbers with the graphs including means ± S.E.M. (standard error of the mean) and 95% confidence intervals (95% CI) and sample size (n). (2nd Endpoint): To detect possible correlations between the serum magnesium nadir under PPI regimen and the traits present in the cases a one-way-ANOVA analysis (95% confidence intervals and Kruskal–Wallis with Gaussian approximation) was performed. The different group-combinations are described in the results section. Subsequent Bonferroni’s, Dunn’s or Tukey’s multiple comparison test was applied to detect differences between these groups (P < 0.05). Possible relationships between patient traits in respect to serum magnesium nadir were tested by Pearson’s correlation analysis, significance level P = 0.05). Values are given as means ± S.E.M. and 95% confidence intervals (95% CI) and sample size (n).

RESULTS

Literature research:
Our comprehensive literature search identified in total 36 cases of PPIH since 2006, distributed over 18 articles (Figure 1) including one abstract (Weegh et al.), one review and one paper that was not accessible in full text to the authors (Francois et al.) (see also Table S1).

Demography
Our sample size consisted of 24 female (66.7%) and of 12 male individuals (33.3%). The age of the patients ranged from 30 to 83 years with a mean of
67.4 ± 1.9 years. In 75% of the cases omeprazole was observed to elicit hypomagnesaemia, in 25% esomeprazole, in 14% pantoprazole, and in a few cases by lansoprazole and rabeprazole (total is more than 100% because in individual cases different PPIs were able to elicit PPIH, see Table S1). Most likely this reflects the market share of the different available PPIs. The time that elapsed between the start of PPI use and first clinical detection of PPIH ranged from 2 weeks up to 13 years, with a median duration of 5.5 years (n = 30).

Primary endpoint:

**PPI withdrawal and re-challenge.** The screening of the case reports revealed nine papers containing data describing the short-term effects of withdrawal (Figure 2: 17 episodes in nine individuals) and/or re-challenge (Figure 3: 19 episodes in seven individuals) suitable for intended analysis.

Figure 2 depicts the course of recovery of mean serum magnesium values after withdrawal of the PPI in nine different cases. The recovery halftime from the mean magnesium nadir of 0.41 mmol/L (intercept with vertical axis) was 4.1 days (95% CI = 2.9–7.5 days). A serum magnesium of 0.6 mmol/L was reached after 4 days of withdrawal, the plateau of 0.81 mmol/L within 14 days after withdrawal.

Figure 3 depicts the course of mean serum magnesium values after re-challenge with PPI in seven different cases. Halftime from the mean magnesium peak of 0.72 mmol/L (intercept with vertical axis) was 5.6 days (95% CI = 2.4–infinite days). After 4 days, 70% of the sampling points have fallen below the serum magnesium of 0.6 mmol/L cut-off. The calculated onset of plateau phase after re-challenge 0.38 mmol/L (95% CI = 0.20–0.56 mmol/L) is comparable to that after withdrawal. The plateau phase starts early on day 4 (see dotted vertical line Figure 3). The nadir of serum magnesium was 0.44 ± 0.05 mmol/L (95% CI = 0.35–0.54 mmol/L).
Systematic review: PPI-induced hypomagnesaemia

After intervention, magnesium levels returned to normal. Secondary aim of this systematic review was to sketch a picture of the (classical) patient at risk. All PPIH cases suffered from considerable co-morbidity. Hypertension was most frequently described (55%) and there was widespread use of diuretics (36%). The cases were, therefore, grouped into ‘control’, ‘pure hypertensive’, ‘pure diuretic’ users and combined ‘hypertensive & diuretic’ users, and by stepwise univariate analysis we tested whether or not nadirs of serum magnesium values between these groups (and all possible combinations thereof) were different. Furthermore, the same analysis assessed whether gender or age were predisposing risk factors. We could not detect significant differences (at $P < 0.05$) between the ‘control’ group (‘no diuretic’ & ‘no hypertension’) and ‘pure hypertensive’ with respect to mean nadirs of serum magnesium concentration (control: mean $= 0.26 \pm 0.04$ mmol/L, 95% CI 0.16–0.36 mmol/L, $n = 13$ vs. pure hypertensive: mean $= 0.17 \pm 0.02$ mmol/L, 95% CI 0.12–0.23 mmol/L, $n = 11$) or patients on diuretics but not hypertensive (mean $= 0.13 \pm 0.03$ mmol/L, 95% CI 0.02–0.23 mmol/L, $n = 4$). Gender was no risk factor; women (mean $= 0.24 \pm 0.03$ mmol/L, 95% CI 0.19–0.30 mmol/L, $n = 24$); men (mean $= 0.17 \pm 0.02$ mmol/L, 95% CI 0.12–0.21 mmol/L, $n = 12$). There was no correlation between age and nadir magnesium levels (Pearson’s $r = -0.1651$, $P = 0.34$, $n = 36$). Stepwise Bonferroni’s multiple comparison did not detect any differences between all groups (control, all combinations of hypertensive, diuretics users, non-diuretics users, women and men) at significance level $P < 0.05$.

Other findings

Electrolytes under PPI regime. Nine patients had severely low plasma calcium in phase with nadir hypomagnesaemia, 16 were moderately low, 8 showed a mild hypocalsemia. One was ‘normo-calaemic’ and 1 was hypercalcemic due to hypoparathyroidism (Table S1, marked*). Severe hypokalemia was present in only one case: $< 2.5$ mmol/L, 20 cases were mildly to moderately hypokalemic (Table S1), in six cases the potassium levels were not affected. To investigate a possible correlation between the magnesium nadir and other electrolytes, the recorded calcium and potassium levels under PPI therapy were re-assessed. We were not able to detect a significant relationship between magnesium nadir and total plasma calcium (Pearson’s $r = 0.127$, $P = 0.482$) nor potassium (Pearson’s $r = -0.05$, $P = 0.86$) (not shown).

According to the secondary aim we subsequently also tried to detect a possible effect of hypertension and/or diuretics on the correlation between serum magnesium nadir and calcium levels. Therefore, we analysed if there

![Figure 3 | Short-term effect of pump inhibitors (PPI) re-challenge on serum magnesium in PPI-induced hypomagnesaemia. The horizontal axis reflects the number of days since PPI restart. The vertical axis denotes serum magnesium levels in mmol/L (normal range 0.75–1.25 mmol/L, hypomagnesaemia < 0.70 mmol/L). All single observations are plotted as open dots. The exponential regression line was derived from fitting of the means $[r^2 = 0.40, n = 59$, $Y_0 = 0.72$ mmol/L (95% CI = 0.65–0.79 mmol/L), plateau = 0.38 mmol/L (95% CI = 0.20–0.56 mmol/L)].
are significant differences in magnesium and calcium between hypertensive, hypertensive diuretic users, only diuretic users and cases with neither hypertension nor diuretic use (control). No correlations within these groups between magnesium nadir and calcium values were detected and there were no significant differences between these groups (ANOVA & Tukey’s multiple comparison test, significance level $P < 0.05$, data not shown).

**Symptoms at magnesium nadir.** Most cases ($n = 35$) came to clinical attention when patients developed signs of symptomatic hypomagnesaemia. The description of symptoms in episodes of severe PPIH included neuronal/mental, neuromuscular, cardiovascular and metabolic manifestations. Most commonly described were seizures (40%), followed by nausea or dizziness (36%), paresthesias (30%), vomiting and diarrhea (28%), muscle cramps and spasms (20%) and tetany (17%). Symptoms of weakness, fatigue or lethargy were present in 30% of the cases. Changes in cardiac rhythm were recorded in 30% of the cases. There was one case of epilepsy and one case of loss of consciousness reported. Some 20% of the cases presented other neurological impairments like numbness, perception problems, needles and pins feeling in feet and hands or hallucinations (one case). In three of five cases there was an exacerbation of COPD (chronic obstructive pulmonary disease) linked to PPIH.33, 43, 44

**Renal magnesium excretion.** Renal magnesium excretion was documented in 33 cases and fell appropriately during the periods of PPIH (see Figure S2). Magnesium excretion over 24 h was measured in 24 cases and varied between 6.42 mmol/24 h (possibly outlier) and ‘immeasurable low’ indicating adequate renal magnesium retention. Mean magnesium excretion was $0.24 \pm 0.05$ mmol/24 h (95% CI means: 0.14–0.34 mmol/24 h; three outliers were discarded: $n = 21$). Urinary magnesium correlated positively with low serum magnesium in state of magnesium depletion (Pearson’s $r = 0.60$, 95% CI = 0.23–0.82, two-tailed $P = 0.038$, $r^2 = 0.36$).

**DISCUSSION**

We reviewed 36 cases with PPIH. This side effect is observed for all currently available PPIs and does not occur with other acid suppressants such as H2RA. All case reports document hypomagnesaemia at different standard daily doses and PPIH reappears invariably when re-challenged with the same or a different PPI. Collectively, this suggests that (i) the PPIH is a class effect and that (ii) once PPIH has established it persists with continuous use and always reappears after re-challenge. Time to onset of hypomagnesaemia is highly variable and ranged from 14 days up to 13 years (mean 5.5 years).

Most of the cases developed a magnesium-depleted state marked by severely low serum nadir (0.22 mmol/L) and strongly reduced renal magnesium retention. Hypomagnesaemia recovered upon withdrawal (within 4 days to 0.6 mmol/L cut-off) whereas re-challenge with PPI’s caused hypomagnesaemia in a very short time frame (70% of magnesium determinations fell below 0.6 mmol/L, cut-off within 4 days). The onset of PPIH in re-challenge is brisk and gets apparent as soon as the body magnesium reserves are depleted. This shows that PPIH is not an intrinsic long-term effect of PPI’s, but likely depends on the patients’ magnesium status.36 A pattern of risk factors uniting all cases of PPIH was not detected. Hypertension and/or the use of diuretics were common features in our population. However, multivariate analysis did not find a correlation between the nadir serum magnesium and these two parameters. In addition, PPIH arose independently from age and gender. An important finding from our study is that the side effect is not induced by other acid inhibiting drugs, because H2RA did not cause hypomagnesaemia after substitution of PPI.28

There was no information on the long-term success rate of the alternative treatment and the need for persistent electrolyte supplementation. It has to be assumed that final outcomes are stable because there are no revisions known of any case reports concerning this matter.

That some cases could not withstand with H2RA and needed continuation of PPI could be explained by insufficient acid blockage or the appearance of other relevant side effects under H2RA antagonist therapy (e.g. rash). Success of acid reduction by H2RA might depend on individual fastening gastrin levels.45 High levels might overrule inhibition of the histamine-2-receptor of parietal cells and may result in insufficient acid reduction and rebound effects.

The majority of published PPIH cases reported herein lag the introduction of PPI almost by two decades. This may suggest that PPIH is less frequent than other forms of drug-induced hypomagnesaemia or suggests that it is missed because many cases are asymptomatic and routine measurement of serum magnesium does not take place. This is of concern because, in consequence of this, the prevalence of PPIH is unknown. Literature emphasises that the importance of magnesium may be underestimated in daily routine at this moment.46, 47 However, serum magnesium only gives limited information on total magnesium balance. On the basis of this study we think that
there is no place for repeated magnesium measurements in the follow-up of all PPI users as the frequency of the side effect apparently is low. In the cases under investigation, magnesium levels prior to the appearance of symptoms of hypomagnesaemia had not been recorded. Therefore, a suggestive benefit of magnesium measurements in all PPI users can only be proven by prospective long-term monitoring of magnesium in PPI users. This type of studies on PPIH have not been performed, but need to be done to investigate to which extend PPIH is also present in subclinical patients.

Drug-induced hypomagnesaemia is not unique to PPI’s. Other drug classes such as gentamycin,48 calcineurin inhibitors (cyclosporine A and tacrolimus), platinum-based cytostatics (cisplatin), Epidermal growth factor receptor (EGF-R) targeting drugs (erlotinib and cetuximab), and diuretics (furosemide, torasemide, bumetanide and thiazide-type) have all been associated with hypomagnesaemia.49–53 For example, calcineurin inhibitors, cause hypomagnesaemia in at least 10% of the users.54 Here, hypomagnesaemia is inversely correlated to the dose of cyclosporine A and it is accompanied by low serum calcium. Relative to PPIH, hypomagnesaemia induced by calcineurin inhibitors is less severe, and magnesium wasting is based on diminished renal TRPM6 (Transient Receptor Potential Melastatin 6) expression, which is the magnesium channel facilitating transepithelial magnesium transport under magnesium shortage and by this acts as a gatekeeper of total magnesium homeostasis.55 In contrast to PPI and cyclosporine A, the frequency of cisplatin-induced hypomagnesaemia is exceptionally high. Ninety percent of cisplatin users develop hypomagnesaemia (serum magnesium <0.75 mmol/L) and 50% even severe hypomagnesaemia (serum magnesium <0.58 mmol/L).56 The underlying mechanism is dose-dependent necrotic nephrotoxicity. In some cases, the outcome is persisting isolated renal magnesium wasting that suggests a selective and decisive renal tubular damage. So far, damage of renal epithelia by PPIs has only been observed by a limited number of case reports with idiosyncratic acute tubulo-interstitial nephritis (TIN).57 However, none of the cases reviewed here had TIN. The fact that PPIH is fully reversible suggests that irreversible structural changes do not underlie PPIH. Loop-type diuretics (furosemide) and thiazide-type diuretics have been shown to stimulate renal magnesium loss by lowering either passive magnesium reabsorption in thick ascending limb or indirectly act on magnesium homeostasis by blocking sodium reabsorption.40, 52 Discontinuation of diuretics did not resolve PPIH, indicating their possible confounding role in PPIH to be low or absent.35 We demonstrate that disruption of magnesium handling by PPIs is relatively fast and that the frequency of this side effect (at least severe PPIH) is low, as only documented by a few case reports.36 This supports the assumption of a genetic predisposition possibly underlying PPIH. However, a genetic screen of TRPM6 in one case failed to identify any risk alleles.40 TRPM6 is only one of the candidate genes critically involved in magnesium handling and, therefore, a broad genetic screen might uncover other regulatory genes.58 In vitro experimental evidence suggests that cation transport through layers of colonic cells is strongly reduced at PPI treatment, which may be an observation in line with the clinical picture of PPIH.59 In conclusion, tubular magnesium wasting has been shown for all other forms of drug-induced hypomagnesaemia, but not for PPIH. Reported efficient tubular magnesium retention, therefore, sets PPIH apart from all other forms of drug-induced hypomagnesaemia and suggests an intestinal involvement.

Most cases came to clinical attention because of differential combinations of neuronal, neuromuscular, cardiovascular and metabolic symptoms, typical for hypomagnesaemia. Inadequate secretion of parathyroid hormone was the consequence of severe hypomagnesaemia and resulted in secondary hypocalcaemia in most cases, which was often the first biochemical indicator recognised by clinicians. A link to osteoporosis was suggestive, but only mentioned in one single case.26 This is remarkable, because it is assumable that in this highly comorbid selection of patients it might be more frequently present, independent from a possible involvement of PPI use. Either it was overlooked or beyond the scope of the clinical observation, which bears a concern for failure in treatment as magnesium supplementation then should be accompanied by long-term calcium bisphosphonate administration.

There was no typical patient profile that was unique for PPIH and the final attribution of the symptoms and electrolyte abnormalities to PPIH sometimes took years. In the absence of symptoms, identification of PPIH was purely dependent on chance.33, 39 Proper identification and treatment of PPIH therefore mainly rests on three pillars: First, serum magnesium monitoring on a regular basis. In event of existing hypomagnesaemia discontinuation of PPIs should result in a rapid normalisation, which may be supported by additional magnesium and calcium supplementation.60 This step is crucial to exclude other causes of hypomagnesa-
emia. Second, regular determination of serum magnesium (and concomitant other electrolytes) should be done to monitor the course of recovery. This should be accompanied by urinary magnesium measurements to assure renal magnesium retention. Third, patients with PPIH have the chance to escape hypomagnesaemia by alternative acid suppressants. Therefore, switching to H₂RA should be attempted. In cases of insufficient relief from acid related complains under H₂RA, tapered or intermittent regimes including PPIs might be helpful. Also here, urinary magnesium monitoring is of benefit as it declines prior to the serum magnesium as an early indication in most cases reviewed here, supplementation with electrolytes could be stopped after normal serum magnesium was obtained.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** PPIH - Documented nadir and peak magnesium in cases.

**Figure S2.** PPIH - Urinary magnesium excretion in state of magnesium depletion.

**Table S1.** PPIH - Basic demographics, electrolye values and outcomes.

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