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Proton pump inhibitor associated hypomagnasaemia - a cause for concern?

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The FDA and MHRA have issued drug safety warnings regarding the use of proton pump inhibitors (PPIs) and the risk of hypomagnesaemia, recommending regular serum magnesium monitoring but are unable to specify how regularly to do so.
- With so many patients prescribed both short and long term PPI therapy, regular blood test monitoring could represent a significant logistical and financial burden on the NHS.

WHAT THIS STUDY ADDS

- We demonstrate the limited benefit in annual measurement of serum magnsesium in all patients on PPI therapy, as recommended by previous authors.
- We were able to identify patients on concurrent diuretic therapy as being at greatest risk of hypomagnesaemia.

AIMS

In recent years, there have been a number of case reports of severe hypomagnesaemia associated with proton pump inhibitor (PPI) use, such that both the FDA and MHRA have issued drug safety warnings. They have recommended periodic serum magnesium testing in patients prescribed PPIs but provide no guidance on timing of these measurements.

METHODS

To our knowledge, we are the first to perform a prospective study to explore specifically proton pump inhibitor associated hypomagnesaemia (PPIAH). We followed 56 patients new to PPIs prospectively as well as a further 100 patients on long term PPIs cross-sectionally to identify what factors may be influencing the development of significant hypomagnesaemia.

RESULTS

For the prospective arm of the study, we measured serum magnesium levels prior to starting a PPI and again at regular intervals for the next 8 months. For the cross-sectional arm of the study we measured serum magnesium levels on patients on PPI therapy ranging from less than 1 year to over 5 years.

CONCLUSION

We found that, although there was a significant downward trend in serum magnesium levels in patients new to PPI therapy with time, clinically relevant hypomagnesaemia was not readily identifiable on regular blood testing. We did however identify patients on concurrent diuretic therapy as being at higher risk and so would recommend regular serum magnesium testing alongside their regular renal function monitoring on a more frequent basis such as annually.

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Introduction

The proton pump inhibitor (PPI) class of drugs inhibits the gastric hydrogen–potassium ATP-ase proton pump of the stomach, responsible for normal acidification of stomach contents following food ingestion [1]. Since first introduced in the 1980s, PPIs have proved effective in the management of peptic ulcers and a variety of gastro-oesophageal reflux disorders [2]. They are now the mainstay of treatment for these conditions and their use has greatly expanded [3]. While enerally considered safe [4], concerns have been raised over inappropriate prescribing [5, 6] and side effects [7].

In 2006, Epstein *et al*. described two cases of severe, symptomatic hypomagnesaemia presenting with carpopedal and truncal spasms associated with the use of PPIs. Following magnesium replacement, normal serum magnesium levels were maintained off PPI therapy (managed on ranitidine) but would become depleted again on PPI re-instatement [8]. Since then, a number of other case reports have linked the use of proton pump inhibitors to the onset of profound hypomagnesaemia [9–20].

Such reports resulted in the issue of safety warnings by both the United States Food and Drug Administration (FDA) [21] and the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) [22]. Both agencies recommend the measurement of serum magnesium before and periodically after the initiation of PPIs, though neither have been explicit on periodicity or whether this should be the case for all patients irrespective of individual risk factors.

Indeed, very little is known about the prevalence or mechanism of action of PPI associated hypomagnesaemia (PPIAH). PPIs can cause renally mediated hyponatraemia as well as acute intersitial nephritis [23], and so it was posited that hypomagnesaemia might share similar pathophysiological mechanisms. However, reports of PPIAH have consistently demonstrated normal renal magnesium handling [11, 16, 17]. Alternatively it has been thought that acid suppression might impair nutrient absorption in the gut [24] though this too has not been reliably demonstrated [25].

To date, we know of only three cross-sectional studies exploring PPIAH in critical care [26], emergency department [27] and community [28] settings. We undertook an exploratory study to determine whether serum magnesium changes could be seen in patients newly started on PPIs as well as those established on long term PPIs. Specifically, we believe our study is the first to monitor serum magnesium prospectively in a cohort of PPI naïve patients, as recommended by Ito *et al*. [29]. Our aim was to see whether asymptomatic PPIAH could be identified on blood testing and if so what timeframes were involved. In doing so, we hope to give further guidance on the FDA and MHRA recommendations [21, 22].

Methods

Participants were recruited from patients attending the Endoscopy Unit for routine diagnostic or follow-up endoscopy. This study had a both a cross-sectional arm and prospective arm.

1 The cross-sectional aspect of the study enrolled patients with established Barrett's oesophagus. These were patients attending for routine follow-up endoscopy, having already been established on longer term PPI therapy.
2 The prospective arm enrolled patients listed for diagnostic endoscopic investigation of dyspepsia and who were found to have gastro-oesophageal reflux disease or peptic ulceration. These were patients who were to be newly commenced on PPI therapy as part of their clinical management.

The aim of the study was to determine whether there was any abnormality of magnesium status in patients established on PPIs and also to determine whether changes in magnesium status can be observed over time in patients commenced on PPIs. No data currently exist to enable formal statistical evaluation or power calculation. For the purpose of this pilot study we aimed to recruit 100 patients in the cross-sectional arm and 50 in the prospective arm.

Potential recruits were identified from the endoscopy listings and were given information about the study with their endoscopy appointment. On attendance, they were met by a research nurse who explained the nature of the study and obtained consent for participation. Exclusion criteria were age < 18 years, an inability to consent, any significant bowel or renal disease and, in the case of the prospective arm, any condition affecting ability to attend for follow-up testing. In addition, those in the prospective arm who ceased taking PPIs had no further follow-up testing. Details of the patient's current medical complaint, indication for PPI prescription, duration of PPI therapy, past medical history and current medication, in particular, any medication that might affect magnesium turnover [30], were noted. None of the patients was taking magnesium supplements though two patients in the cross-sectional group and one patient in the prospective group admitted to taking over the counter multivitamin supplements, the exact nature of which could not be determined.

Patients attended for endoscopy, having fasted overnight as per the routine endoscopy procedure. For the prospective arm of the study, if the endoscopy was consistent with the need for initiation of PPI therapy, blood was drawn for measurement of serum magnesium, renal function, potassium, calcium and phosphate. Patients were also asked to provide a urine sample, while still fasting, for measurement of magnesium and

creatinine and calculation of the fractional excretion of magnesium (feMg) [31].

An assessment of urinary magnesium excretion was made by calculation of the feMg in a second void fasting sample. This estimates urinary clearance in relation to creatinine clearance by the formula:

$$\text{feMg} = \frac{\text{urine magnesium} \times \text{serum creatinine}}{(0.7 \times \text{serum magnesium}) \times \text{urine creatinine}} \times 100$$

where all measurements are in mmol l^{-1} and the factor of 0.7 corrects for the fact that 70% of magnesium is free and filterable [31].

The patients in the prospective arm of the study then commenced the PPI as prescribed and had repeat blood and urine measurements at 2, 4 and 8 months, timed to coincide, where possible, with follow-up endoscopy and/or assessment.

Patients in the cross-sectional arm of the study attended for a routine follow-up endoscopy, and fasting blood and urine samples were collected for tests described above, as a single one off occasion only. The duration of PPI treatment was noted. The baseline characteristics of the PPI-naïve prospective group served as a control group.

All analyses were undertaken in the Clinical Biochemistry Department, Royal Bournemouth Hospital on a Cobas Modular Clinical Chemistry analyzer (Roche Diagnostics, Burgess Hill, UK).

For the cross sectional study, serum magnesium measurements and calculated feMg were tested for normality and compared with the control group (PPI naïve prospective group at baseline). As not all study variables were normally distributed, non-parametric test statistics were used where appropriate. For the prospective group, non-parametric repeated measures analysis of variance (Friedman's test) was used to assess changes over time for participants having measurements on all four occasions.

The Dorset Research Ethics Committee reviewed and confirmed a favourable opinion for this research study (approval number 09/HO21/3). The study was compliant with the principles of the World Medical Association Declaration of Helsinki (1996) and MRC/good clinical practice.

Results

Over an 18 month period, 100 consecutive patients, established on PPIs, consented to inclusion in the cross-sectional arm of the study. In the same period, 56 patients consented to inclusion in the prospective arm of the study. Baseline characteristics of these patients are listed in Table 1. Table 2 shows serum and urine measurements levels from the 100 participants in the cross-sectional arm of the study and for the control group (baseline measurements of the 56 PPI naïve patients in the prospective arm of the study prior to initiation of PPI therapy).

Raw values for serum magnesium measurements were normally distributed (D'Agostino–Pearson test ($P > 0.5$) and are summarized as mean (SD) while feMg values exhibited a significant right-tail skew ($P = 0.0007$) and are summarized as median (interquartile range). The control group was younger ($P = 0.03$, Mann–Whitney test) but there was no difference in the gender balance between the two ($P = 0.62$, Fisher's exact test). There were no significant differences (all Mann–Whitney test) between the two groups in renal function, as measured by serum creatinine and eGFR, calcium, potassium, phosphate or magnesium. In addition, the distribution of serum magnesium results

Table 1

Baseline characteristics for patients and controls (cross sSectional study)

	Patients	Controls
n	100	56
Male/Female	48/52	25/31
Median age (years, range)	68 (23–88)	61 (28–85)
PPI prescribed		
Omeprazole	57 (57%)	46 (75%)
Lansoprazole	35 (35%)	5 (9%)
Esomeprazole	6	3
Pantoprazole	1	0
N/S (not specified)	1	3
Median PPI duration (months) (range)	24 (2–240)	/
Diuretics	15 (15%)	8 (14.3%)
Renal function (eGFR) (ml min^{-1}/1.7 ml min^{-1}/1.73 m^2)		
>90	31 (31%)	17 (30.4%)
60–90	49 (49%)	31 (55.4%)
30–60	20 (20%)	8 (14.3%)
<30	0	0

Table 2

Serum and urine results for patients and controls (cross sectional study)

Serum	Patients Mean (SD)	Controls Mean (SD)	*P*
Creatinine (μmol l^{-1})	78.2 (21.8)	77.29 (21.12)	0.70
eGFR (ml min^{-1}/1.7 ml min^{-1}/1.73 m^2)	68.5 (13.6)	70.64 (12.56)	0.43
Calcium (mmol l^{-1})	2.38 (0.10)	2.40 (0.10)	0.39
Adjusted calcium (mmol l^{-1})	2.32 (0.08)	2.32 (0.09)	0.91
Potassium (mmol l^{-1})	4.7 (0.54)	4.54 (0.43)	0.18
Magnesium (mmol l^{-1})	0.85 (0.06)	0.85 (0.06)	0.86
Phosphate (mmol l^{-1})	1.15 (0.16)	1.10 (0.17)	0.12
Urine	Median (IQR)	Median (IQR)	
Mg : creatinine ratio	0.19 (0.19)	0.23 (0.10)	0.33
Fractional excretion Mg (feMg)	2.19 (2.32)	2.63 (1.54)	0.26

in the participants was identical to that of the control group and also that of the laboratory reference population [32].

When subdividing the cross-sectional arm patients by duration of PPI treatment (<1 year, 1–5 years, >5 years) there were no differences in either serum magnesium levels (P = 0.39) or feMg (P = 0.43, both Kruskal–Wallis test) in Table 3. 15% of patients were taking diuretics and, when compared with the non-diuretic group, they showed higher creatinine levels (median 83 *vs.* 73 μmol l^{-1}, P = 0.01) and lower serum potassium levels (median 4.40 *vs.* 4.65 mmol l^{-1}, P = 0.02) but no difference in serum magnesium levels (median 0.81 *vs.* 0.83 mmol l^{-1}, P = 0.36). feMg for the group overall [median (IQR)] was 2.19% (2.32) with values ranging from 0.18–8.71%. feMg was higher in the group taking diuretics [median (IQR) 3.80 (4.44) *vs.* 2.05 (2.15) %, P = 0.02). Ten of the study participants had a feMg of <1%.

Of the 56 participants enrolled in the prospective arm of the study, 46 attended for visit 2 at 2 months, 37 for visit 3 at 4 months and 31 for visit 4 at 8 months. Within this, 28 participants attended all four visits. The serum magnesium levels and feMg at each visit are documented in Table 4. There was no significant difference in the mean magnesium levels for the groups over the 8 month period of treatment. However, for the 28 patients having measurements for all four visits, there was a significant downward trend in serum magnesium levels (P = 0.020 for linear trend; permutation test on non-parametric repeated measures ANOVA). Similar analysis for the 21 participants for whom there were feMg measurements over all four visits revealed no evidence of a trend (P = 0.44). Numbers taking diuretics in this group (four patients) were too small to determine whether this had any influence on results.

Table 3

Serum and urine magnesium levels related to duration of PPI treatment (cross-sectional study)

Measurement	Result	*P*
Mean serum Mg (mmol l^{-1}) (SD)	0.85 (0.06)	
Serum Mg (mmol l^{-1}) by duration of PPI treatment		0.39
<1 year (28%)	0.87 (0.05)	
1–5 years (49%)	0.86 (0.06)	
>5 years (23%)	0.83 (0.08)	
Median urine Mg : creatinine ratio (IQR)	0.19 (0.43)	
Median feMg (IQR)	2.35 (2.48)	
feMg by duration of PPI treatment		0.43
<1 year (28%)	2.45 (1.96)	
1–5 years (49%)	1.92 (2.30)	
>5 years (23%)	2.30 (2.80)	

Table 4

Serum and urine magnesium levels over sequential visits (prospective study)

Serum Mg (mmol l^{-1})	Visit 1	Visit 2	Visit 3	Visit 4
Mean (SD)	0.85 (0.06)	0.85 (0.06)	0.85 (0.06)	0.84 (0.06
n	56	46	37	31
All four visits (*n* = 28)				
Mean (SD)	0.85 (0.08)	0.84 (0.07)	0.84 (0.05)	0.83 (0.05)
	P = 0.020 for trend across four visits			
feMg	Visit 1	Visit 2	Visit 3	Visit 4
Median (IQR)	2.82 (1.61)	2.64 (1.52)	2.67 (1.60)	2.90 (2.60)
n	53	44	37	27
All four visits (*n* = 21)				
Median IQR	3.08 (1.55)	2.85 (1.65)	2.68 (1.54)	2.90 (2.34)
	P = NS for trend across four visits			

Discussion

None of our 156 participants was found to have clinically relevant hypomagnesaemia whilst on PPI therapy. This is not surprising given the widespread prescription of PPIs in the last few decades and confinement of PPIAH to only a few case reports in the literature [29]. Though its true prevalence remains elusive, PPIAH can be confidently regarded as a rare phenomenon.

Previous cross sectional studies have demonstrated a small decrease in serum magnesium [27, 28] in PPI users. Though we were unable to replicate this finding in either our cross sectional or prospective study arms, we did find a statistically significant downward trend of serum magnesium following initiation of PPI therapy in our cohort of patients who were previously PPI naïve. This would suggest that PPIAH takes many years to develop. Indeed, in a review of the available case reports Hess *et al.* suggests that PPIAH occurred after a median of over 5 years [33].

Neither the FDA or MHRA give guidance on when PPIAH should be checked for during PPI therapy [21, 22]. Some authors recommended annual serum magnesium checks [17], which though a sensible recommendation is not evidence based. Annual checks would likely be logistically and financially cumbersome, given the widespread prescription of PPIs [3] and unlikely to yield many results based on our findings. The question remains, therefore, when should clinicians check serum magnesium levels? Perhaps more useful would be the identification of patients most at risk of PPIAH and targeting these patients for interval serum magnesium checks instead.

The current prevailing theory for PPIAH involves PPI mediated impairment of luminal magnesium absorption. PPIs reduce gastric pH thereby causing dysfunction of transient receptor potential melastatin (TRPM6) protein channels [34–37]. PPIAH may reflect slow depletion of magnesium stores as demonstrated by the significant downward trend in serum magnesium in our study and

it may also explain the great variety in time to hypomagnesaemia [20, 33]. Patients with depleted magnesium stores are therefore likely to be at greater risk of PPIAH. These are likely to include the elderly population, whose dietary magnesium intake is likely limited [38] and have been shown to be at greater risk of PPIAH [39]. It may also explain why some patients, who having suffered PPIAH and been treated with magnesium replacement, have a rapid onset of their hypomagnesaemic state on restarting PPI therapy [8, 17, 33].

Danziger *et al*., in their cross-sectional study, suggested that PPI use was not associated with hypomagnesaemia unless patients were also taking diuretics [26, 40]. Whilst magnesium homeostasis does largely rely on appropriate renal function, patients with PPIAH demonstrate appropriate renal magnesium conservation [11, 16, 17]. Certainly, in our study, we found no relationship between PPI duration and feMg though patients also taking diuretics did demonstrate statistically significant greater renal magnesium losses. Appropriate renal magnesium conservation may protect against severe hypomagnasaemia, which is impaired by diuretic therapy putting these patients at greater risk of PPIAH.

As only a small proportion of our study population were taking diuretics (14 in the cross-sectional group and four in the prospective group), we have been unable to explore this relationship through statistical analysis any further but it would be interesting to do so in future studies. Potassium sparing diuretics lower magnesium excretion in comparison with the mild net magnesium loss caused by loop and thiazide diuretics [31] and so this may be a useful avenue of investigation. Future studies might also investigate a class effect or dose dependent effect of PPI on PPIAH.

In this first prospective study exploring PPIAH, the rarity of this condition limits our study. On the basis of our results we would suggest that annual serum magnesium checks are unwarranted for all (non-selected) patients on PPIs. Rather, clinicians should consider targeting elderly patients and patients on concurrent diuretics for serum magnesium monitoring. Larger, possibly multi-centred population studies would help determine prevalence of PPIAH as well as facilitate focused studies on selected, effected individuals.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Contributors

- JB and TR performed the research.
- JB, TR, TS and PS designed the research study.
- KB enrolled and consented patients.
- JB and TR analyzed the data.
- JB, PS, TR, A A and CS wrote the paper.

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