

Original papers

QJM

Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series

J.D. MACKAY¹ and P.T. BLADON²

From the ¹Department of Medicine and ²Department of Biochemistry, Victoria Hospital, Blackpool, FY3 8NR, UK

Address correspondence to J.D. Mackay Department of Medicine, Victoria Hospital, Blackpool, FY3 8NR, UK.
email: dr.mackay@bfwhospitals.nhs.uk

Received 24 November 2009 and in revised form 29 January 2010

Summary

Background: Reports since 2006 have identified proton-pump inhibitor (PPI) therapy as a cause of hypomagnesaemia, in a total of 13 cases.

Aims: To summarize the clinical course of 10 patients (one male, nine female) identified with severe hypomagnesaemia, all of whom were on PPI therapy. A case report illustrates the experience of a severely affected patient.

Methods: Clinical and biochemical review. Severe hypomagnesaemia was defined as 0.54 mmol/l or less, >4 SD below the mean.

Results: Patients were 68.8 ± 8.6 years old when they presented with severe hypomagnesaemia, having been on PPI therapy for a mean of 8.3 ± 3.5 years. Eight patients were on diuretics at initial presentation. There was significant morbidity as eight patients remained on PPI therapy after presentation for a mean of 2.75 ± 1.54 years. There were

18 emergency hospital admissions with severe hypomagnesaemia. Oral and parenteral magnesium supplements were relatively ineffective at correcting the problem, but stopping PPI therapy lead to prompt resolution of the hypomagnesaemia (within 2 weeks in five carefully monitored patients), with symptomatic benefit. Hypomagnesaemia recurred if PPI therapy was re-introduced because of troublesome dyspepsia. However, pantoprazole, the least potent PPI, largely relieved dyspepsia and hypomagnesaemia did not inevitably develop when combined with oral magnesium supplements.

Conclusions: These cases confirm that long-term PPI therapy can cause severe, symptomatic hypomagnesaemia, which resolves when PPI therapy is withdrawn. The serum magnesium should be checked annually in patients on long-term PPI therapy, or if they feel unwell.

Introduction

Proton-pump inhibitor (PPI) drugs (e.g. omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole) are potent inhibitors of gastric acid secretion, by blocking the hydrogen–potassium

adenosine triphosphatase enzyme system (the ‘proton pump’) of the gastric parietal cell. They are widely used for the treatment and prevention of dyspeptic symptoms, associated with peptic ulcer disease, gastritis and oesophagitis. In general they are well tolerated, but side effects can occur some of

which are potentially serious. There are concerns that PPI therapy, by decreasing gastric acidity, can increase the risk of gastro-intestinal infections, including *Clostridium difficile* enterocolitis.¹ In addition, there is increasing evidence that long-term PPI therapy can cause severe hypomagnesaemia, associated with significant morbidity (e.g. fatigue, unsteadiness, paraesthesia, tetany, fits); but as yet this has not been included in the list of side-effects of PPI therapy in the manufacturers' summary of product characteristics (SPC) or the British national formulary (BNF).

In 2006, Epstein *et al.*² reported two patients on PPI therapy who presented with tetany, which they attributed to hypomagnesaemic hypoparathyroidism, and where withdrawal of the PPI normalized the metabolic abnormalities. They speculated that these two cases represented the 'tip of an iceberg among patients with hypomagnesaemia'.

In 2008, Agarwal *et al.*³ reported a 43-year-old man, on high-dose omeprazole for reflux oesophagitis for 3 years, who developed symptomatic hypomagnesaemia and hypocalcaemia. Oral and parenteral magnesium replacement was unsuccessful in correcting the problem, yet withdrawal of PPI therapy led to normalization of his biochemistry in 6 weeks and symptoms in 12 weeks. Cundy and Dissanayake⁴ described two patients with severe hypomagnesaemia who presented with hypocalcaemic seizures, and who were long-term users of PPI therapy. Their investigations demonstrated that these patients were severely magnesium depleted, with avid renal magnesium retention after intravenous magnesium infusions. The hypomagnesaemia was corrected partially by high-dose oral magnesium supplements and resolved on withdrawal of PPI therapy. They concluded that PPI therapy can inhibit magnesium intestinal absorption. Reports on a further eight cases have been published,^{5–8,16} giving a total of 13 cases reported in the literature.

This article presents information on 10 patients symptomatic from severe hypomagnesaemia. All were on PPI therapy which in eight patients was not recognized at the time as the cause of the hypomagnesaemia: PPI therapy was continued for years, with significant morbidity in consequence. The experience of these patients after stopping PPI therapy is also reported. A case report illustrates the experience of a severely affected patient.

Methods

Our laboratory normal range for serum magnesium is 0.7–1.0 mmol/l, with a mean value 0.85 mmol/l. In this article hypomagnesaemia refers to a serum

magnesium of 0.55–0.69 mmol/l (2–4 SDs below the mean); with severe hypomagnesaemia defined as ≤ 0.54 mmol/l (>4 SD below the mean). Our laboratory routinely checks the serum magnesium when hypocalcaemia is detected. All calcium readings are corrected for serum albumin (CCa), with the normal range 2.12–2.63 mmol/l. Serum and urine magnesium was measured by Xylidyl blue at pH 11.4. The purple complex produced is proportional to the magnesium concentration and is measured at 520/800 nm. Calcium interference is removed by GEDTA.

The date of presentation for each patient is taken as the first recorded severe hypomagnesaemia (≤ 0.54 mmol/l) measurement. The 10 patients were included by the clinician (J.D.M.) in this study for the following reasons: four (P1, P4, P7 and P9) had an in-patient stay under his care; four (P2, P3, P6 and P8) were referred as out-patients by their general practitioners; and two (P5 and P10) were referred by consultant physician colleagues. Several patients with severe hypomagnesaemia, on PPI therapy, but known to have ileal disease (previous resections for Crohn's disease or for gut ischaemia) were not included.

All patients gave informed, written consent to being included in this report.

Case report

Patient P4, 73-year-old at presentation in June 2005, was started on PPI therapy in 1994 for reflux symptoms with Barrett's oesophagitis, initially lansoprazole 30–60 mg daily, but omeprazole 20–40 mg daily from 1999. She was on bendroflumethiazide 2.5 mg once daily (o.d.) in 2001, and furosemide in low dosage (20–40 mg o.d.) in 2005, as treatment for hypertension. A hospital admission in June 2005 with TnI-negative chest pain, abdominal pain and cramps was associated with severe hypomagnesaemia (Mg 0.29 mmol/l) and hypocalcaemia (CCa 1.83 mmol/l). She was discharged on calcium and vitamin D supplements. Severe hypomagnesaemia (Mg 0.23 mmol/l) was still evident during an admission in November 2005 with generalized arthralgia, precise cause unclear, but which responded well to pulse steroid therapy. She was discharged on oral magnesium supplements but readmitted in December 2005 with collapse and tetany (Mg <0.21 mmol/l; CCa 1.75 mmol/l). Over the next 2 years she was symptomatic most of the time with paraesthesia, cramps, lethargy and unsteadiness, despite attempts at correction with magnesium supplements. Oral magnesium supplements (24 mmol/day) were prescribed, with higher doses

causing unacceptable diarrhoea. In addition, she had 35 magnesium sulphate infusions over a 28 month period (total 400 g or 1600 mmol), yet severe hypomagnesaemia was recorded in two-third of 66 measurements (Table 3). These measures failed to prevent another admission to hospital in April 2007 with unsteadiness and a fall (Mg 0.36 mmol/l, CcCa 2.06 mmol/l). Her four admissions to hospital, associated with metabolic problems, totalled 52 days; and she had 35 day hospital visits for magnesium infusions.

Urine magnesium excretion was low (0.61 and 0.57 mmol/24 h, with corresponding serum magnesium 0.57 and 0.52 mmol/l), despite magnesium infusions. Extensive investigations (four gastroscopies, with jejunal and duodenal biopsy; colonoscopy; small bowel enema; CT scan abdomen; capsule endoscopy; gut hormone profile) failed to identify a gastro-intestinal cause for the hypomagnesaemia.

Treatment with ranitidine or cimetidine instead of a PPI lead to a prompt resolution of symptoms (in days) and a steady rise in serum Mg levels, but at the cost of a rash (ranitidine) or troublesome dyspepsia (cimetidine, even in high dosage);

whereas re-introduction of another PPI (esomeprazole, pantoprazole) led to recurrence of hypomagnesaemia (Figure 1). She developed an itchy rash on re-introduction of pantoprazole and persevered with dyspeptic symptoms on cimetidine 800 mg thrice daily (t.d.s.) from December 2008. In July 2009, the serum Mg was normal (0.81 mmol/l) on cimetidine, but not on magnesium supplements or diuretics. Successful laparoscopic oesophageal surgery in August 2009 ameliorated her reflux symptoms, although she persevered with cimetidine.

Summary of cases on PPI therapy

The mean (\pm SD) age of the 10 patients was 68.8 ± 8.6 (range 53–76) years at presentation. Nine of the patients were female. The mean duration of PPI therapy before presentation was 8.3 ± 3.5 (range 2.2–12.3) years. The majority of patients were on PPI therapy for gastro-oesophageal reflux (GORD). Eight patients were on a diuretic at presentation (Table 1).

Severe hypomagnesaemia was evident in eight patients (P1, P3–7, P9 and P10) on emergency admission to hospital. Six of these eight patients had

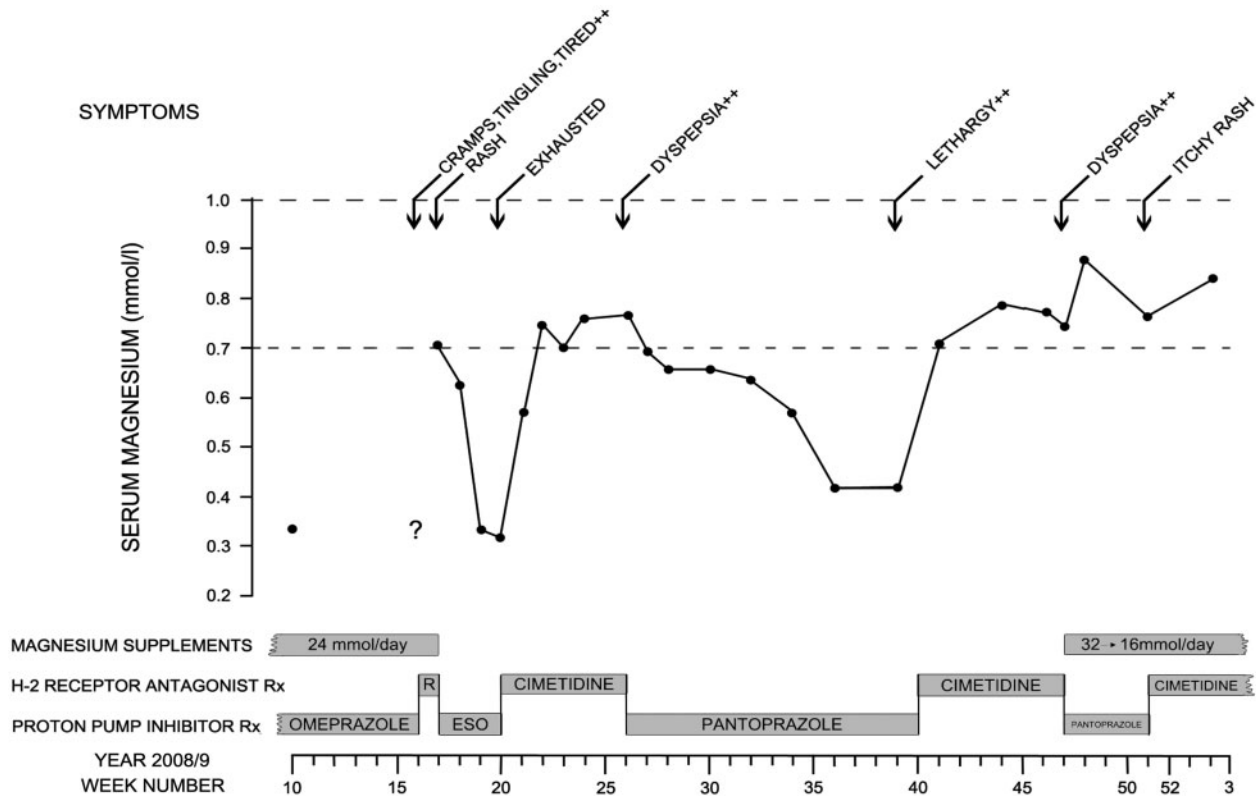


Figure 1. Symptoms, serum magnesium trends and treatment details on patient P4 in 2008–09. R, ranitidine 150 mg twice daily (b.d.); ESO, esomeprazole 20 mg o.d.; omeprazole and pantoprazole both prescribed at 40 mg o.d., and cimetidine at 400 mg b.d. to 800 mg tds.; ?, serum magnesium not measured—laboratory error. Serum magnesium normal range 0.7–1.0 mmol/l.

Table 1 Summary of the 10 patients at presentation

Patient	Sex	Age	PPI therapy			Diuretic Rx		At presentation		
			Type	Indication	Duration (years)	Type	Indication	CCa (mmol/l)	Mg (mmol/l)	Date (m/y)
P1	F	57.9	O	GORD	10.0	BF	HT	1.78	0.15	11.03
P2	F	72.4	O	PUD	12.3	F	HT	1.88	0.46	9.04
P3	F	75.7	O	NSAID	2.2	BF	HT	1.95	0.21	11.04
P4	F	73.6	O	GORD	10.5	F	HT	1.83	0.29	6.05
P5	F	72.5	E	GORD	9.9	BF	DO	1.85	<0.21	11.05
P6	F	53.4	O	GORD	5.6			2.02	0.30	1.07
P7	F	76.9	O	GORD	10.0			1.66	0.30	8.07
P8	F	69.4	O	GORD	2.9	BF	HT	1.66	0.30	10.07
P9	F	76.4	O	NSAID	10.5	F	DO	1.43	<0.21	9.08
P10	M	59.5	O	GORD	9.6	BF	HT	1.92	<0.21	3.09
Mean \pm SD		68.8 \pm 8.6			8.3 \pm 3.5					

O, omeprazole; E, esomeprazole; GORD, gastro-oesophageal reflux disease; PUD, peptic ulcer disease; NSAID, gastro-protection for non-steroidal anti-inflammatory drug therapy; BF, bendroflumethiazide; F, furosemide; HT, hypertension; DO, dependent oedema.

multiple hospital admissions with severe hypomagnesaemia, as the role of PPI therapy in causing the problem was not recognized. In total there were 18 hospital admissions from the time of presentation up to and including the admission when PPI therapy was discontinued, in three different hospitals and under 11 different physicians, with an average length of stay of 9.6 ± 7.5 (range 1–24) days (Table 2). Of the 18 admissions, 15 (83%) were associated with a wide range of symptoms, some non-specific but others clearly attributable to severe hypomagnesaemia. These included nausea, anorexia, vomiting, diarrhoea; weakness and fatigue; dizziness, unsteadiness, decreased mobility, falls; incontinence; inability to cope; paraesthesia, cramps, tetany and collapse, sometimes with seizures. One patient (P3) was admitted with recurrent grand-mal fits (CCa 1.64 mmol/l, Mg 0.27 mmol/l), complicated by pulmonary and glottic oedema, and needed intensive care for 11 days (Table 2). Two patients (P2 and P8) presented with hypomagnesaemic symptoms (paraesthesia, cramps), but never required emergency hospital admission.

Correcting the hypomagnesaemia with magnesium supplements was difficult. Four patients were prescribed oral magnesium supplements (magnesium glycerophosphate or Slow Mag). These were partially effective in preventing severe hypomagnesaemia in two patients, ineffective in two patients, and with side-effects (diarrhoea) in three of these patients. Parenteral magnesium sulphate was administered to all patients when severe hypomagnesaemia was identified during their emergency hospital admissions; but, in addition, five patients

had a total of 61 day case admissions (range per patient 3–35 admissions) for elective magnesium infusions, when a total of 2380 mmol of magnesium sulphate was infused, the majority to patient P4 (Table 3).

The last two patients (P9 and P10) were switched from PPI to H-2 receptor antagonist (H2RA) therapy within days of presentation, but for the other eight patients (P1–8) the mean duration of PPI therapy from presentation until the switch to H2RA therapy was 2.75 ± 1.54 (range 0.5–5.3) years (Table 3).

These eight patients had 200 magnesium measurements before PPI therapy was discontinued, the majority (73%) in out-patient or day-case settings. Four-fifth of these measurements were below normal, with 59% of readings in the severe hypomagnesaemic range. Normal magnesium readings were evident within a few days of intravenous magnesium infusions (Table 3).

Out-patient contact between emergency hospital admissions was variable, but six patients complained of symptoms, particularly tingling and cramps; with lethargy, weakness and unsteadiness additional symptoms in three of them (P1, P4 and P8).

Consistently low urine magnesium excretion was documented in seven patients (P1–6, P8), despite attempts to correct the hypomagnesaemia with intravenous infusions (Table 4). Seven patients (P1, P3–6, P9 and P10) had gastro-intestinal investigations but no structural cause for hypomagnesaemia was identified. Tests included gastroscopy (P1, P4–6 and P10), small bowel radiology (P1, P4, P10) and colonoscopy/flexible sigmoidoscopy (P3, P4, P9 and P10). Coeliac disease was excluded in five patients

Table 2 Hospital admissions, with symptoms and/or diagnoses in eight patients

Patient	Hospital admission			CCa (mmol/l)	Mg (mmol/l)
	Date (m/y)	Days	Symptoms and/or diagnoses		
P1	11.03	6	Nausea, vomiting, dizziness, paraesthesia, collapse	1.78	0.15
	3.09	4	Nausea, vomiting, paraesthesia, cramps, weakness, exhaustion	1.88	0.30
P3	4.05	21	Recurrent fits, pulmonary oedema, glottic oedema	1.64	0.27
	8.07	3	Collapse, probable fit	2.07	0.41
P4	6.05	24	Tnl negative chest pains, cramps	1.83	0.29
	11.05	14	Generalized arthralgia, weakness	1.99	0.23
	12.05	6	Collapse, tetany	1.75	<0.21
P5	4.07	8	Unsteadiness, fall	2.06	0.36
	11.05	19	Diarrhoea and vomiting. <i>Campylobacter</i> enteritis	1.85	<0.21
	12.05	2	Vomiting, tetany, dizziness	2.01	0.07
P6	1.06	14	Vomiting, dizziness, weight loss	2.17	<0.21
	1.07	5	Exacerbation of COPD	2.02	0.30
P7	3.07	1	Paraesthesia, cramps	2.01	0.29
	7.07	13	Exacerbation of COPD, paraesthesia	1.66	0.30
P9	2.09	1	Exacerbation of COPD	1.56	0.26
	2.09	10	Paraesthesia, fatigue	1.43	<0.21
	9.08	19	Dizziness, decreased mobility, falls, nausea, anorexia, diarrhoea	1.43	<0.21
P10	3.09	2	Fatigue, paraesthesia, anorexia, nausea, vomiting, diarrhoea	1.92	<0.21

Patients P2 and P8 not included as they had no hospital admissions with severe hypomagnesaemia.

Table 3 Serum magnesium measurements from presentation until PPI therapy discontinued

Patient	Total no. of Mg readings	Duration of observation (weeks)	Severe hypoMg (≤ 0.54)	HypoMg (0.55–0.69)	NormoMg (0.7–1.0)	Intravenous magnesium (Total-mmol)	Oral Mg
			N (%)	N (%)	N (%)		
P1	27	276	14 (52)	11 (41)	2 (7)	48	Yes
P2	21	194	8 (38)	7 (33)	6 (29)	148	
P3	33	184	18 (55)	7 (21)	8 (24)	400	
P4	66	151	45 (68)	11 (17)	10 (15)	1600	Yes
P5	22	161	10 (45)	8 (36)	4 (19)	152	Yes
P6	15	70	12 (80)	2 (15)	1 (7)	408	
P7	9	82	5 (56)	2 (22)	2 (22)	118	Yes
P8	7	27	5 (71)	0 (0)	2 (29)	120	
Total	200	1145	117 (59)	48 (24)	35 (17)	2994	
Mean \pm SD	25 \pm 19	143 \pm 80					

143 \pm 80 weeks is equivalent to 2.75 \pm 1.54 years.

Patients P9 and P10 not included as switched from PPI to H2RA therapy within 2 days of presentation.

by duodenal histology (P4, P6 and P10) or negative antibodies (P1, P3).

Hypocalcaemia was evident in association with severe hypomagnesaemia. Simultaneous calcium and magnesium measurements in the 10 patients (total 301) revealed that severe hypomagnesaemia (≤ 0.54 mmol/l) was associated with hypocalcaemia in 64% of 101 measurements. Serum calcium levels rose when hypomagnesaemia was corrected. Serum magnesium readings >0.54 mmol/l were

associated with normal calcium levels in 97% of 200 measurements. Serum parathyroid hormone (iPTH; normal range 8–73 pg/ml) was measured in all 10 patients when hypomagnesaemic and usually hypocalcaemic (Table 5). The majority of readings were at the lower end of the normal range. iPTH measurements were raised in two patients (P2 and P9). A iPTH reading of 102.5 pg/ml in patient P9 rose to 559.0 pg/ml 3 days later, following an intravenous magnesium infusion. Simultaneous

Table 4 Urine magnesium excretion in seven patients, with concurrent serum magnesium

Patient	Date (m/y)	Urine magnesium		Serum Mg (0.7–1.0 mmol/l)
		Spot (mmol/l)	24 h (3.0–5.0 mmol/24 h)	
P1	3.05	0.28	0.4	0.66
P2	4.08	1.04	0.71	0.74
P3	5.06	<0.99	<0.6	0.44
P4	12.06	0.35	0.61	0.57
P5	7.06	0.29		0.68
P6	6.07	0.10	0.30	
P8	4.08	0.68	1.64	0.80

Table 5 Serum calcium, magnesium, parathyroid hormone and 25-OH vitamin D measurements in the 10 patients

Patient	Date (m/y)	CCa	Mg	iPTH	Vit D	Comment
P1	3.09	1.88	0.30	32.0	40	
P2	11.07	1.71	0.39	159.6		
P3	3.05	1.74	0.19	51.1		
P4	6.05	2.04	0.23	11.7		On oral vitamin D
P5	4.06	2.40	0.49	13.6	81	On oral vitamin D
P6	5.07	2.01	0.36	11.4		
P7	8.07	1.47	<0.21	20.9		
P8	10.07	1.68	0.29	36.2		
P9	9.08	1.43	<0.21	102.5	20	
P10	3.09	1.92	<0.21	20.4	79	

CCa, corrected calcium: normal range 2.12–2.63 mmol/l.

Mg, serum magnesium: normal range 0.7–1.0 mmol/l.

iPTH, intact parathyroid hormone: normal range 8–73 pg/ml.

25-OH vitamin D: normal range 50–200 nmol/l.

vitamin D data is included in Table 5, where available.

Serum magnesium response after PPI withdrawal

PPI withdrawal study⁹

Serum magnesium levels were measured before and at 1–2-week intervals after withdrawal of PPI therapy in five patients. These were patients P2–P4, P6 and P8. They were selected for this study when it

was realized that PPI therapy could be responsible for their chronic hypomagnesaemia; and they were willing and able to co-operate with out-patient investigations. All of them had been treated previously with intermittent day-case intravenous magnesium infusions, and none of them were on oral magnesium supplements at the time of this study. They were switched from PPI therapy (omeprazole 4, esomeprazole 1) to H2RA therapy (ranitidine 4, cimetidine 1). The baseline Mg of 0.50 ± 0.10 mmol/l rose significantly to 0.70 ± 0.09 one week after PPI withdrawal (paired *t*-test, $t=7.53$, $P<0.01$), and to 0.77 ± 0.03 at week 2 ($t=8.04$, $P<0.01$). Serum Mg remained in the normal range at 6 weeks (0.77 ± 0.06) and at 12 weeks (0.75 ± 0.07 , four patients). Well-being improved within 1–2 weeks of stopping PPI therapy, but four patients suffered troublesome dyspepsia on H2RA therapy and for this reason one patient (P4) was switched back to a PPI (pantoprazole) by her general practitioner after 6 weeks on cimetidine (Figure 2).

General comments

Withdrawal of PPI therapy lead to normal magnesium levels in all 10 patients, with normal mean readings in nine patients (Table 6). Two patients were so troubled by dyspepsia that they were switched back to PPI therapy after only 2–3 weeks on ranitidine. The other eight patients were observed off PPI therapy and on H2RA therapy (seven patients) for 37.4 ± 15.1 (range 16–57) weeks, remaining predominantly normomagnesaemic throughout that time. Normal magnesium readings were noted in 58/66 (88%) of the measurements. Oral magnesium supplements were used in four patients (Table 6).

Stopping diuretics did not correct the hypomagnesaemia in five patients (P1, P3–5 and P8) who remained on PPI therapy; and it resolved in two patients (P2 and P9) who remained on a diuretic when PPI therapy was discontinued.

Intra-gastric pH studies suggest that pantoprazole is the least potent PPI at suppressing gastric acid secretion.¹⁰ Six patients, distressed by dyspepsia, were switched from an H2RA to pantoprazole 40 mg o.d. Dyspeptic symptoms were largely relieved (although patient P1 was reliant on regular domperidone as well). The serum magnesium fell at variable rates in the four patients not on magnesium supplements. Magnesium supplements maintained normal magnesium levels in two patients (P5 and P8) for up to one year; but with patient P6 they failed to correct symptomatic hypomagnesaemia, once it had developed (Table 7). The only practical long-term

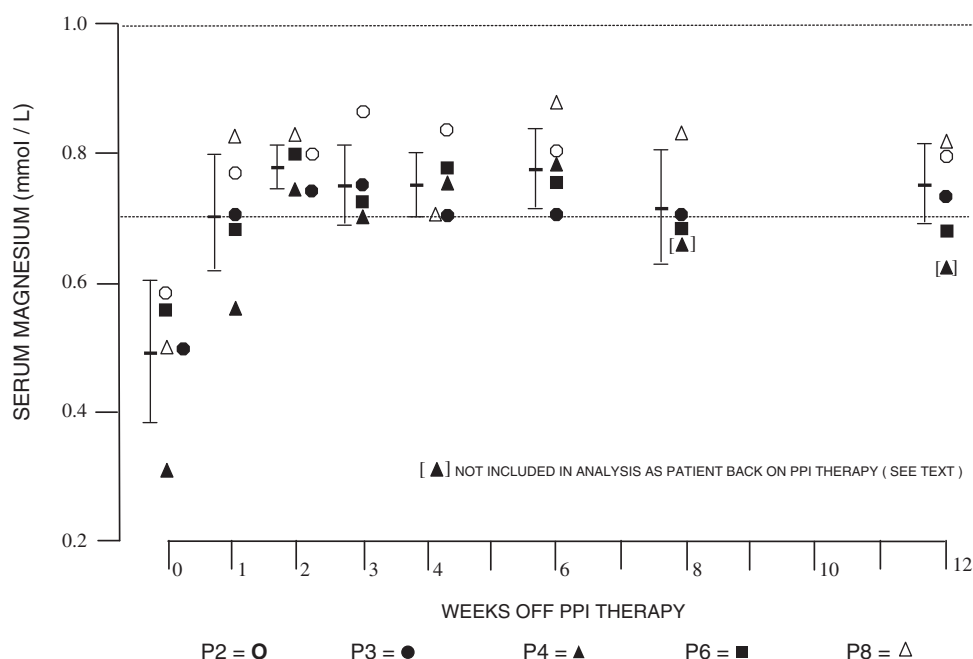


Figure 2. Serum magnesium after withdrawal of PPI therapy in five patients. P2, open circle; P3, filled circle; P4, filled triangle; P6, filled square; P8, open triangle.

Table 6 Serum magnesium results after PPI therapy discontinued

Patient	H2RA	H2RA Intolerance	Off PPI/on H2RA				Comment
			Duration (weeks)	Serum Mg (mmol/l)			
				Mean \pm SD	Range	No.	
P1	R	Yes	3	0.74 \pm 0.05	0.67–0.81	3	On oral Mg 12 mmol/day
P2	R	No	49	0.81 \pm 0.04	0.76–0.86	8	
P3	R	Yes/No	57	0.71 \pm 0.02	0.67–0.74	11	
P4	C	Yes/No	41	0.78 \pm 0.05	0.70–0.91	15	Mg supplements used Intermittently-Case report
P5	R	Yes	2	0.83		1	On oral Mg 24 mmol/day
P6	R	Yes/No	53	0.73 \pm 0.05	0.68–0.79	11	
P7	R	Yes/No	24	0.71 \pm 0.06	0.63–0.79	6	On oral Mg 12 mmol/day; stopped after 14 weeks
P8	R	Yes/No	16	0.81 \pm 0.07	0.70–0.87	5	
P9	None		35	0.83 \pm 0.06	0.78–0.91	3	
P10	R	No	24	0.84 \pm 0.04	0.82–0.88	3	

H2RA, H-2 receptor antagonist therapy; R, ranitidine; C, cimetidine.

Yes/No, persistent dyspepsia, but persevered with H2RA therapy for at least 16 weeks.

option for symptom control in this patient may be oesophageal surgery.

Discussion

These 10 patients, in addition to those reported previously,^{2–8,16} suggest that PPI therapy can cause

severe, symptomatic hypomagnesaemia; and withdrawal of PPI therapy results in resolution of this problem. Cundy and Dissanayake concluded that PPI therapy lead to malabsorption of magnesium.⁴ Our closely monitored PPI withdrawal study on five patients lends support to this view, given the rapid resolution of hypomagnesaemia in 2 weeks.

Table 7 Serum magnesium response in six patients on pantoprazole 40 mg o.d.

Patients	Serum Mg		Duration of Rx (weeks)	Mg supplements	Comments
	Initial	Final			
P1	0.81	0.62	44	No	Reliant on regular domperidone
P3	0.67	0.44	30	No	Tired; no tingling or cramps
P4	0.77	0.42	13	No	See Case report section
P5	0.83	0.81	51	Yes	24 mmol/day Well
P6	0.77	0.44	11	No	Lethargy, paraesthesia, cramps
	0.44	0.56	10	Yes	12 mmol/day Lethargy, paraesthesia, cramps
	0.56	0.40	10	Yes	24 mmol/day Lethargy, paraesthesia, cramps
P8	0.81	0.81	52	Yes	16 mmol/day Well

These patients only presented with symptomatic hypomagnesaemia after taking PPI therapy for many years; and a high proportion (80%) were on concomitant diuretic therapy. Presumably it takes years of PPI-induced magnesium malabsorption, facilitated in many cases by diuretic-induced urinary losses, to deplete the body of so much magnesium that severe, symptomatic hypomagnesaemia develops. Oral magnesium supplements were, at best, only partially effective at correcting the hypomagnesaemia whilst PPI therapy was maintained, unable to override the block in magnesium absorption. Intravenous magnesium infusions provided only short-term relief. The struggle to reverse the hypomagnesaemia of these patients whilst still on PPI therapy contrasts with the ease in achieving this after PPI therapy was discontinued. The associated improvement in general well-being was notable as well.

Some of the patients' symptoms may have been due to hypocalcaemia rather than hypomagnesaemia. The iPTH measurements in this series support the concept of functional hypoparathyroidism as a consequence of severe hypomagnesaemia.¹¹ Serum calcium levels rose when hypomagnesaemia was corrected, helping in the symptomatic improvement.

PPI-induced hypomagnesaemia is not widely acknowledged. The majority of these patients were unwittingly left on PPI therapy for years after their initial presentation with severe hypomagnesaemia, and they suffered significant morbidity in consequence. Later, when feeling better, many of them emphasized the unpleasant nature of their symptoms when they had severe hypomagnesaemia.

The sex distribution in the previously reported 13 cases was roughly comparable (eight males, five females).^{2-8,16} The reason for the female preponderance of patients in this series is unclear, but good compliance with the PPI medication over

many years may have been a factor, particularly in those patients with GORD.

Withdrawal of PPI therapy resulted in biochemical and symptomatic improvement. However, six of the patients (all female) complained of reflux dyspepsia on H2RA therapy and requested to go back on to PPI therapy as previously it had controlled their symptoms. The introduction of pantoprazole, the least potent PPI, resulted in acceptable control of reflux symptoms in most of these patients but with a variable serum magnesium response: hypomagnesaemia did not inevitably develop when combined with oral magnesium supplements. Further studies of this drug in patients with PPI-induced hypomagnesaemia would be worthwhile.

Intestinal magnesium absorption is complex, with two transport systems in the small intestine.¹² First, the majority, ~90%, of magnesium is absorbed passively via paracellular pathways between the enterocytes. The rate of absorption is dependent on the transepithelial voltage gradient and the ionic magnesium gradient, as only free magnesium moves through the paracellular pathway. The permeability of the paracellular pathway is influenced by proteins comprising the tight junction, whose function can be regulated by hormonal and non-hormonal factors acting via intracellular signal pathways. Secondly, a transcellular active transport mechanism permits adaptation to a low magnesium intake by increasing fractional magnesium absorption. This is by means of transient receptor potential melastatin (TRPM) cation channels with protein kinase domains, in particular TRPM6 and TRPM7. These have been described as the gatekeepers of human magnesium metabolism.¹³ TRPM6 is expressed along the entire gastrointestinal tract. Familial cases of hypomagnesaemia with secondary hypocalcaemia have been identified as due to homozygous TRPM6 gene mutations.¹⁴

The mechanism by which PPI drugs reduce the intestinal absorption of magnesium is not

understood. It could be speculated that PPI drugs might affect tight junction function in the paracellular pathway, either directly or as a consequence of intestinal pH changes; or alternatively affect TRPM6 channel function in the active transport pathway. Cundy and Dissanayake suggested, as PPI-induced hypomagnesaemia was partially corrected by high-dose magnesium supplements, that passive magnesium transport was intact and that PPI therapy affected the active transport pathway.⁴ Short-term studies on healthy volunteers suggest that PPI therapy has no detectable effect on magnesium absorption;¹⁵ whereas the evidence from this and another⁴ study suggests the opposite. It raises the possibility that genetic factors result in increased susceptibility to PPI-induced hypomagnesaemia, as might be the case with heterozygous carriers of TRPM6 mutations. Our case series hints at varying degrees of susceptibility, with patients P2 and P8 (who avoided hospital admission) at the more benign end of the spectrum and patients P4 and P6 at the other.

The prevalence of PPI-induced hypomagnesaemia is not known. Symptoms from hypomagnesaemia are either non-specific or could be misinterpreted; and serum magnesium measurements are not part of the routine 'biochemical profile'. These patients illustrate the serious clinical effects of PPI-induced hypomagnesaemia, particularly in females and those on diuretics. The need for long-term PPI therapy in patients should be kept under regular review, just as with patients on non-steroidal anti-inflammatory drugs. However, if PPI therapy is required on a long-term basis, then we suggest that the serum magnesium should be checked annually, or if the patient feels unwell.

Acknowledgements

Thanks to Susan Hainsworth for secretarial support; to Emma Benson, Clinical Pharmacist, for help with the drug histories; to Steven Farley in the Department of Medical Illustration; to Dr M.Y. El Khateeb and Dr M.T. Hendrickse for referring patients P5 and P10, respectively; and to Dr M.T. Hendrickse, Dr P.E.T. Isaacs and Dr S.J. Butler for helpful comments on the manuscript. Finally, thanks are due to the patients for their interest and co-operation.

Conflict of interest: None declared.

References

1. Aseeri M, Schroeder T, Kramer J, Zackula R. Gastric acid suppression by proton pump inhibitors as a risk factor for clostridium difficile-associated diarrhea in hospitalised patients. *Am J Gastroenterol* 2008; **103**:2308–13.
2. Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. *N Engl J Med* 2006; **355**:1834–6.
3. Agarwal N, Rees A, Scanlon M. Hypomagnesaemia related to proton-pump inhibition. *Endocrine Abstracts* 2008; **15**:P24.
4. Cundy T, Dissanayake A. Severe hypomagnesaemia in long-term users of proton-pump inhibitors. *Clin Endocrinol* 2008; **69**:338–41.
5. Shabajee N, Lamb EJ, Sturgess I, Sumathipala RW. Omeprazole and refractory hypomagnesaemia. *BMJ* 2008; **337**:173–5.
6. Francois M, Levy-Bohbot N, Caron J, Durlach V. Chronic use of proton-pump inhibitors associated with giardiasis: a rare cause of hypomagnesemic hypoparathyroidism? *Ann Endocrinol (Paris)* 2008; **69**:446–8.
7. Kuipers MT, Thang HD, Arntzenius AB. Hypomagnesaemia due to use of proton pump inhibitors – a review. *Neth J of Med* 2009; **67**:169–72.
8. Druce MR, Thomas JDJ, Gorrigan RJ, Kelly PA, Coppack SW, Akker SA. Hypomagnesaemia and hypocalcaemia with proton-pump inhibitors: an under-recognised phenomenon. *Endocrine Abstracts* 2009; **16**:P50.
9. Mackay JD, Choudhary N, Bladon P. Withdrawal of proton-pump inhibitor therapy in chronically hypomagnesaemic patients. *Endocrine Abstracts* 2009; **16**:P130.
10. Kirchheiner J, Glatt S, Fuhr U, Klotz U, Meineke I, Seufferein T, et al. Relative potency of proton-pump inhibitors – comparison of effects on intragastric pH. *Eur J Clin Pharmacol* 2009; **65**:19–31.
11. Rude RK. Magnesium metabolism. In: Becker KL, ed. *Principles and Practice of Endocrinology and Metabolism*. 3rd edn. Lippincott, Williams and Wilkins, 2001:673–9.
12. Quamme G. Recent developments in intestinal magnesium absorption. *Curr Opin Gastroenterol* 2008; **24**:230–5.
13. Schlingmann KP, Waldegger S, Konrad M, Chubonov V, Gudermann T. TRPM6 and TRPM7 – gatekeepers of human magnesium metabolism. *Biochim Biophys Acta* 2007; **1772**:813–21.
14. Schlingmann KP, Weber S, Peters M, Neimann Nejsum L, Vitzthum H, Klingel K, et al. Hypomagnesemia with secondary hypocalcemia is caused by mutations in *TRPM6*, a new member of the *TRPM* gene family. *Nature Genetics* 2002; **31**:166–70.
15. Serfaty-Lacrosniere C, Wood RJ, Voytko D, Saltzman JR, Pedrosa M, Sepe TE, et al. Hypochlorhydria from short-term omeprazole treatment does not inhibit intestinal absorption of calcium, phosphorus, magnesium or zinc from food in humans. *J Am Coll Nutr* 1995; **14**:364–8.
16. Broeren MAC, Geerdink EAM, Vader HL, van den Wall Bake AWL. Hypomagnesemia induced by several proton-pump inhibitors. *Ann Int Med* 2009; **151**:755–6.