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RESEARCH NOTES

A COMPILATION OF VITAL RESEARCH UPDATES ON HUMAN NUTRITION

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Proton Pump Inhibitors' Impact on Mineral Nutrition

According to a recent report, [Arch Intern Med. 2010;170(9):747-748], the sales of proton pump inhibitors were $13.9 billion US dollars per year and rising. In the US alone, there are 113.4 billion prescriptions written for these drugs in a year. In addition, there are several popular over- the-counter (OTC) brands that are top selling items. This category is one of the largest selling categories of medications in the world. They had been implicated as a cause for increasing the risk of certain bacterial infections, as well as bone fractures. It is prescribed for 70% of the elderly, during hospital stays, and is a major cause for pneumonia related deaths in these patients, according to several studies published in medical journals over the last 2 years.

Proton pump inhibitors are prescribed for a variety of conditions, but most commonly for the treatment of erosive and ulcerative esophagitis, Barrett esophagus, Zollinger-Ellison Syndrome, and gastro-esophageal reflux disease, in an effort to prevent the stomach acid from backing up into the esophagus, leading to severe end points, such as cancers of the esophagus. It is also prescribed for the treatment and healing of duodenal ulcers and related peptic disorders. Over-the-counter purchasers are using it for common problems, like simple stomach upset due to hyperacidity. Since this category has gone to over-the-counter as well, and the pharmaceutical companies have invested a lot of ad money on promoting the use of these items, people are using this type product far too commonly, and for the wrong indications. In fact, according to a recent article in the Archives of Internal Medicine [Katz M; Arch Int Med; 2010; 170(9):747-748], 53-69% of proton pump inhibitor prescriptions are for inappropriate indications. There has been talk of taking these types of drugs off the OTC market, and making them restricted to prescription only, but that doesn't seem likely to happen, given the economics of the situation. More needs to be done to educate the consumer in a situation like this.

Proton Pump Inhibitors Mode of Action

Proton pump inhibitors work by irreversible inhibition of the hydrogen-potassium adenosine triphosphatase enzyme system (the K+/H+ - ATPase, or more commonly called proton pump) of the gastric parietal cells (stomach acid producers). The proton pump is the final stage of gastric acid secretion, and it is directly responsible for secreting the H+ ions into the stomach cavity, making it a great target for the blocking of acid secretion. By acting in this way, and in irreversible fashion, these types of drugs are much more effective than their predecessors, the H_2 antagonists. Proton pump inhibitors can reduce gastric acid secretion by as much as 99%! The proton pump inhibitors are actually given in their inactive form, as a neutral molecule, which is lipophilic and can easily cross cell membranes, getting inside intracellular compartments, such as the parietal cell canaliculus, which have acidic environments. The acidic environments activate the proton pump inhibitor through protonation. In its active form this drug will bind covalently and irreversibly to the proton pump, thus deactivating it. In the link below, you can see a video representation that demonstrates the mechanism of action for the proton pump inhibitors.

[http://pharmacologycorner.com/proton-pump-inhibitors-ppis-mechanism-of-action-a-video-animation]

Mineral Absorption

The complex mechanism for the absorption of minerals is a subject matter that has had textbooks written in an effort to capture all that is involved in the body's effort to digest and absorb minerals, whether they are from foods, beverages, or supplementation. In general, however, one of the basic tenets on mineral absorption is that minerals require an acid environment, in order for their proper digestion and absorption. Most mineral forms ingested require an acid environment in the upper gut, in order to ionize and be absorbed in the upper small intestine. The table, below, taken from "Intestinal Absorption of Metals Ions and Chelates" (Ashmead HD, Graff D, Ashmead HH,) points out how important an acid pH and ionization are for the most needed mineral nutrients.

The importance to dietary mineral absorption of an acid pH in the stomach and upper small intestine has been well demonstrated. The effectiveness of proton

Table 1. Similarities in Mucosal Membrane Transport of Ions

	Ca	Mg	Fe	Zn	Cu	Mn
Absorption in acid pH of upper intestine	X	X	X	X	X	X
Solubility/ionization essential for absorption	X	X	X	X	X	X
Ion attached to exterior cell membrane	X	X	X	X	X	X
Membrane attachment requires amino acid/peptide molecule	X	X	X	X	X	X
Ion binding to peripheral protein requires chelation	X	X	X	X	X	X
Membrane transport requires energy	X	X	X	X	X	X
Mineral released intra cellularly and rechelated	X	X	X	X	X	X

Intestinal Absorption of Metal Ions and Chelate, HD Ashmead, DJ Graff, HH Ashmead, © 1985.

pump inhibitors in the decreasing of stomach acid production is known (up to 99%). From this it would seem that the chronic long term use of such agents could be a serious detriment to the mineral status of those who must use these agents. Proton pump inhibitors include the following:

Generic Name	Brand Name
Omeprazole	Prilosec, Zegerid
Lansoprazole	Prevacid
Rabeprazole	Aciphex
Pantoprazole	Protonix
Esomeprazole	Nexium
Dexlansoprazole	Kapidex

In line with this basic logic, that long term use of proton pump inhibitors have the potential to disrupt ones' mineral status, are a growing body of published research studies. The first of the findings on the subject have been concerned mostly about calcium metabolic status and aspects of bone health. The following are abstracts of three studies that have given various findings on proton pump inhibitors and bone health. These studies have connected the long term use of proton pump inhibitors with an increase risk for hip fractures, vertebral fractures, as well as forearm, wrist, and total fractures.

Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative

Gray SL, LaCroix AZ, Larson J, Robbins J, Cauley JA, Manson JE, Chen Z. Arch Intern Med. 2010 May 10;170(9):765-71.

Authors Abstract

BACKGROUND: Proton pump inhibitor (PPI) medications have been inconsistently shown to be associated with osteoporotic fractures. We examined the association of PPI use with bone outcomes (fracture, bone mineral density [BMD]). METHODS: This prospective analysis included 161, 806 postmenopausal women 50 to 79 years old, without history of hip fracture, enrolled in the Women's Health Initiative (WHI) Observational Study and Clinical Trials with a mean (SD) follow-up of 7.8 (1.6) years. Analyses were conducted for 130, 487 women with complete information. Medication information was taken directly from drug containers during in-person interviews (baseline, year 3). The main outcome measures were self-reported fractures (hip [adjudicated], clinical spine, forearm or wrist, and total fractures) and for a subsample (3 densitometry sites), 3-year change in BMD. RESULTS: During 1, 005, 126 person-years of follow-up, 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and 21, 247 total fractures occurred. The multivariate-adjusted hazard ratios for current PPI use were 1.00 (95% confidence interval [CI], 0.71-1.40) for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fracture, and 1.25 (95% CI, 1.15-1.36) for total fractures. The BMD measurements did not vary between PPI users and nonusers at baseline. Use of PPIs was associated with only a marginal effect on 3-year BMD change at the hip (P = .05) but not at other sites. CONCLUSION: Use of PPIs was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures.

Increase in vertebral fracture risk in postmenopausal women using omeprazole

Roux C, Briot K, Gossec L, Kolta S, Blenk T, Felsenberg D, Reid DM, Eastell R, Glüer CC. Calcif Tissue Int. 2009 Jan;84(1):13-9. Epub 2008 Nov 21.

Authors Abstract

Proton pump inhibitors are taken by millions of patients for prevention and treatment of gastroesophageal diseases. Case-control studies have suggested that use of omeprazole is associated with an increased risk of hip fractures. The aim of this prospective study was to assess the risk of vertebral fractures in postmenopausal women using omeprazole. We studied 1,211 postmenopausal women enrolled in the Osteoporosis and Ultrasound Study from the general population. Information on omeprazole and other risk factors for fractures including prevalent fractures and bone mineral density was obtained at baseline. Vertebral fractures were assessed on X-rays obtained at baseline and at the end of the 6-year follow-up and analyzed centrally. At baseline, 5% of this population was using omeprazole. Age-adjusted rates for vertebral fractures were 1.89 and 0.60 for 100 person-years for omeprazole users and nonusers, respectively (P = 0.009). In the multivariate analysis, omeprazole use was a significant and independent predictor of vertebral fractures (RR = 3.50, 95% CI 1.14-8.44). The other predictors were age higher than 65 years (RR = 2.34, 95% CI 1.02-5.34), prevalent vertebral fractures (RR = 3.62, 95% CI 1.63-8.08), and lumbar spine T score </= -2.5 (RR = 2.38, 95% CI 1.03-5.49). Omeprazole use is associated with an increased risk of vertebral fractures in postmenopausal women. Further studies are required to determine the mechanism of the association between the underlying gastric disease, omeprazole use, and risk of osteoporotic fractures.

Long-term proton pump inhibitor therapy and risk of hip fracture

Yang YX, Lewis JD, Epstein S, Metz DC. JAMA. 2006 Dec 27;296(24):2947-53.

Authors Abstract

CONTEXT: Proton pump inhibitors (PPIs) may interfere with calcium absorption through induction of hypochlorhydria but they also may reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps. **OBJECTIVE:** To determine the association between PPI therapy and risk of hip fracture. **DESIGN, SETTING, AND PATIENTS:** A nested case-

control study was conducted using the General Practice Research Database (1987-2003), which contains information on patients in the United Kingdom. The study cohort consisted of users of PPI therapy and nonusers of acid suppression drugs who were older than 50 years. Cases included all patients with an incident hip fracture. Controls were selected using incidence density sampling, matched for sex, index date, year of birth, and both calendar period and duration of up-to-standard follow-up before the index date. For comparison purposes, a similar nested case-control analysis for histamine 2 receptor antagonists was performed. **MAIN OUTCOME MEASURE:** The risk of hip fractures associated with PPI use. **RESULTS:** There were 13,556 hip fracture cases and 135,386 controls. The adjusted odds ratio (AOR) for hip fracture associated with more than 1 year of PPI therapy was 1.44 (95% confidence interval [CI], 1.30-1.59). The risk of hip fracture was significantly increased among patients prescribed long-term high-dose PPIs (AOR, 2.65; 95% CI, 1.80-3.90; P<.001). The strength of the association increased with increasing duration of PPI therapy (AOR for 1 year, 1.22 [95% CI, 1.15-1.30]; 2 years, 1.41 [95% CI, 1.28-1.56]; 3 years, 1.54 [95% CI, 1.37-1.73]; and 4 years, 1.59 [95% CI, 1.39-1.80]; P<.001 for all comparisons). **CONCLUSION:** Long-term PPI therapy, particularly at high doses, is associated with an increased risk of hip fracture.

What About Other Minerals?

In an article (Doornebal J, et al. Ned Tijdschr Geneeskd .2009;153; 153:A7110), published in the Netherlands, the authors stated that the long term use of proton pump inhibitors could lead to serious hypomagnesemia. The intestinal absorption of magnesium takes place by passive paracellular and active transcellular transport. The authors report on the hypothesis that proton pump inhibitors impair the active transcellular magnesium transport, which can result in hypomagnesemia. This hypomagnesemia may cause hypoparathyroidism, hypocalcemia, and hypokalemia. This proton pump induced hypomagnesemia can be reversed when the proton pump inhibitors are stopped. Individuals on long term proton pump inhibitors need to be evaluated for this side effect periodically.

Subsequent to this article, the following case series of proton pump inhibitor-induced hypomagnesemia was published, as well, which show further reason for caution.

A case series of proton pump inhibitor-induced hypomagnesemia

Hoorn EJ, van der Hoek J, de Man RA, Kuipers EJ, Bolwerk C, Zietse R.
Am J Kidney Dis. 2010 Jul;56(1):112-6. Epub 2010 Feb 26.

Authors Abstract

Proton pump inhibitor (PPI)-induced hypomagnesemia has been recognized since 2006. Our aim was to further characterize the clinical consequences and possible mechanisms of this electrolyte disorder using 4 cases. Two men (aged 63 and 81 years) and 2 women (aged 73 and 62 years) had been using a PPI (esomeprazole, pantoprazole, omeprazole, and rabeprazole, 20-40 mg) for 1-13 years. They developed severe hypomagnesemia (magnesium, 0.30 +/- 0.28 mEq/L; reference, 1.40-2.10 mEq/L) with hypocalcemia (calcium, 6.4 +/- 1.8 mg/dL), relative hypoparathyroidism (parathyroid hormone, 43 +/- 6 pg/mL), and extremely low urinary calcium and magnesium excretion. One patient was admitted with postanoxic encephalopathy after a collapse likely caused by arrhythmia. The others had electrocardiogram abnormalities (prolonged QT interval, ST depression, and U waves). Concomitant hypokalemia (potassium, 2.8 +/- 0.1 mEq/L) was considered the trigger for these arrhythmias. Hypomagnesemia-induced kaliuresis (potassium excretion, 65 +/- 24 mEq/L) was identified as the cause of hypokalemia. This series of PPI-induced hypomagnesemia shows that this is a generic effect. It also indicates that hypomagnesemia may occur within 1 year of PPI therapy initiation and can have serious clinical consequences, likely triggered by the associated hypokalemia. A high index of suspicion is required in PPI users for unexplained hypomagnesemia, hypocalcemia, hypokalemia, or associated symptoms.

Concern About Iron Interference

In a couple of recent articles, the impact that proton pump inhibitors can have on iron status was highlighted. In the first study [Hutchinson, et al: Gut. 56(9):12915], the researchers point out that during long term treatment of hereditary hemachromatosis, they observed that the use of proton pump inhibitors reduced the requirement for maintenance phlebotomy. Gastric acid plays a crucial role in non-heme iron absorption and the researchers performed a case review and intervention study to investigate the proton pump inhibitor-induced suppression of gastric acid on dietary iron absorption. Their findings were conclusive that the administration of proton pump inhibitors did, in fact decrease the absorption of non-heme dietary iron.

In another article [McColl KE: Am J Gastroenterol. 2009; 104 Suppl 2:55-9], summing recent reports in other studies, it was stated that proton pump inhibitors reduce Vitamin B-12 absorption, reduce the absorption of non-heme iron, and can retard the clinical response to iron supplementation.

A Thought From All of This

In many reports and studies, it has been reported that the absorption of the nutritionally functional mineral amino acid chelate is via a different mechanism than the other mineral forms, and in fact the iron amino acid chelate behaves most closely to heme-iron in the GI tract. The mineral glycinate (bisglycinate) chelates are absorbed in a larger segment of the GI tract and do not require ionization. In fact their stability at the pH ranges of the GI tract involved with their absorption precludes their doing so. This is why they do not suffer from as much absorption interferences as other mineral forms do. It might be a good idea to recommend or formulate mineral products for people who are on a long term proton pump inhibitor using the Albion's brand of mineral glycinate chelate - the TRAACS® brand of chelate. Just a thought!

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