Drug-Induced Nutrient Depletions

The Truth about Antacids and Ulcer Medications

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Mechanisms of Drug-Nutrient Interactions (DNIs)

- Side effects from drug therapy may not be directly due to the drug itself
- Mechanisms responsible for the depletion of nutrients include interference with
  - Absorption
  - Synthesis
  - Transport
  - Storage
  - Metabolism
  - Excretion

Where does this information come from?

- A great many studies in the scientific literature reporting the drug-induced depletion of nutrients.
- Some health care professionals are not aware that many drugs can cause or exacerbate nutritional deficiency-related health problems.
- Awareness of DNIs can reduce the incidence of deleterious or even lethal outcomes.

Pharmaceutical Treatments

Antacids and Ulcer Medications

- Magnesium and Aluminum
  - Tums, Rolaids, Maalox, Mylanta
- Sodium bicarbonate
  - Alka Seltzer, Baking soda
- Histamine H2 Receptor Antagonists
  - Axid, Pepcid, Tagamet, Zantac
- Proton Pump Inhibitors
  - Prilosec, Nexium, Prevacid, Acifex, Protonix
- *Helicobacter pylori* (*H. pylori*) Agents

Magnesium and Aluminum Hydroxides

e.g., *Tums, Rolaids, Maalox, Mylanta*

Nutrients Depleted

- Calcium
- Phosphorus
- Folic Acid
- Iron
- Magnesium

- Other minerals such as **zinc** and **copper** maybe depleted due to reduction in gastric acid

Histamine H2-Receptor Antagonists

Axid, Pepcid, Tagamet, Zantac

Nutrients Depleted

- Vitamin B12
- Vitamin D
- Folic acid
- Zinc
- Iron

Also

- May inhibit gastric alcohol dehydrogenase activity.
- May induce food allergy.
- ↓ Intrinsic Factor caused by low stomach acid

H2RAs Cause Vitamin B12 Deficiency

- H2RAs decrease acid secretion by the gastric parietal cells.
- Gastric acid and pepsin produced by these cells are required for the cleavage of vitamin B12 from dietary sources.
- Intrinsic factor (IF), also produced by gastric parietal cells, is required for vitamin B12 absorption from the gastrointestinal tract.
- Although H2RAs have not conclusively been shown to decrease IF secretion, studies have demonstrated a significant reduction in food-bound vitamin B12 absorption secondary to decreased acid secretion in patients taking these drugs.

Ann Pharmacother. 1992 Oct;26(10):1283-6.

Interventions

Vitamin B12

- Methylcobalamin is the bioactive form of vitamin B12 in the body.
- Unlike cyanocobalamin, it requires no conversion to be biologically active.
- Oral supplementation raises serum B12 levels and is efficacious.

Acid balance

- Hydrochloric acid (HCl) can be taken in supplement form as from betaine HCl and L-glutamic acid HCl
- Also consider protein-digesting enzymes, such as pepsin and/or acid stable proteases.

J Altern Complement Med 2006;12:881-5.
Br J Clin Pharmacol 2003;56:635-8.
Am Fam Physician 2003;67:979-86.

Cimetidine Disrupts Vitamin D Metabolism

- The H2RA cimetidine has been shown to inhibit vitamin D-hydroxylase and thus decrease hepatic metabolism of vitamin D in humans and animals
- These hydroxylation steps are required to convert vitamin D3 into its physiologically active form.

Digestion. 1990;46(2):61-4.
J Lab Clin Med. 1984 Oct;104(4):546-52.
Nutr Rev. 1985 Jun;43(6):184-5.

Intervention

- Apart from supporting bone health, **vitamin D** is well researched as a critical immune modulator.
- Suboptimal levels of vitamin D intake have been documented, especially among older adults. Approximately 38-60% of elderly institutionalized adults have been found to be lacking in vitamin D intake (depending on time of year tested).
- Elderly individuals taking cimetidine are particularly at risk and should supplement at least 2,000 IU per day.

J Am Geriatr Soc. 1997;45:598-603.
JAMA. 1995;274:1683-6.

Cimetidine Inhibits Nonheme Iron Absorption

- Radioiron absorption tests in human volunteers demonstrated a 28% reduction in the absorption of dietary nonheme iron from a meal that was preceded by the administration of 300 mg cimetidine.
- More pronounced decreases of 42% and 65% were observed with 600 and 900 mg cimetidine, respectively.

Gastroenterology. 1981 Dec;81(6):1068-71.

Interventions

- Multivitamin with Iron
- Iron supplements
  - Heme iron
  - Nonheme iron

H2RAs Inhibit Zinc Absorption and Decrease Zinc Plasma AUC

- Gastric acid secretion plays a role in the regulation of zinc absorption in humans.
- Zinc absorption was reduced after high-dose cimetidine administration (1 g/d).
- AUC for zinc plasma concentration was significantly reduced after ranitidine (300 mg/d) but not after cimetidine (500 mg/d) administration.

J Am Coll Nutr. 1991 Aug;10(4):372-5.

H2RAs Inhibit Alcohol Dehydrogenase

- Inhibition of gastric alcohol dehydrogenase activity by cimetidine, ranitidine and nizatidine results in elevated blood levels of ethanol after moderate consumption.
- In another study, ranitidine increased the mean peak concentration and the area under the curve of blood alcohol concentrations by 34% .
- Famotidine does not produce this effect.
  - Therefore, famotidine might be preferable in alcoholics and social drinkers who require treatment with H2-receptor antagonists.

Dig Dis Sci. 1991 Dec;36(12):1673-9.
JAMA. 1992 Jan 1;267(1):83-6.

Antacid medications inhibit digestion of dietary proteins and may cause food allergy

- Digestible food proteins are assumed to be irrelevant for oral sensitization and induction of food allergy.
- However, administration of antacid meds inhibits digestion of certain dietary proteins (e.g., parvalbumin from fish).
- In an animal study, subjects receiving antacid drugs tested positive for specific IgE auto-antibodies to the tested dietary proteins, whereas feeding of the proteins alone was well tolerated.
- **Intervention**: Acid-stable enzyme supplementation

J Allergy Clin Immunol. 2003 Sep;112(3):616-23.

Proton Pump Inhibitors

Prilosec, Nexium, Prevacid, Acifex, Protonix, …

Nutrients Depleted

- Vitamin B12
- Vitamin C
- Iron
- Minerals
  - Hypocalcemia
  - Hypomagnesemia

Also

- ↑ acid reflux
- ↑ gastrointestinal tract mucosal permeability (leaky gut syndrome)
- ↓ gall bladder function
- ↑ risk of *C. difficile*
- ↑ risk of community acquired pneumonia
- ↑ risk of hip fracture
- Weight gain
- Protein maldigestion

Omeprazole and Vitamin B12 Deficiency

- Omeprazole therapy decreases absorption of vitamin B12 by preventing its cleavage from dietary proteins.
- Example: At the end of a 2-week treatment period, cyanocobalamin absorption decreased from 3.2% to 0.9% ($P = 0.031$) in participants receiving 20 mg of omeprazole daily. In patients taking 40 mg of omeprazole daily, cyanocobalamin absorption decreased from 3.4% to 0.4% ($P < 0.05$).
- Under certain circumstances, the treatment may lower serum vitamin B(12) levels.

Ann Pharmacother. 1999 May;33(5):641-3.
Ann Intern Med. 1994 Feb 1;120(3):211-5.
Am J Med. 1998 May;104(5):422-30.

PPIs, Vitamin C, and Iron

- PPIs decrease the [vitamin C] in gastric juice and the proportion of the vitamin in its active antioxidant form i.e., ascorbic acid.
  - This results in increase gastric juice nitrite levels. More marked in H. pylori pts.
- PPIs may reduce bioavailability of ingested vitamin C.
- PPIs reduce the absorption of non-heme iron and may delay clinical response to iron supplementation.

Am J Gastroenterol. 2009 Mar;104 Suppl 2:S5-9

Intervention

- Vitamin B12
- Vitamin C
- Iron

PPIs and Mineral Malabsorption

- Widely reported association between PPI use and hip fractures.
- Probably because PPIs can induce hypocalcemia.
- PPI-induced hypomagnesemia is common and may occur within 1 year of PPI therapy initiation with serious clinical consequences.

Maturitas. 2009 Sep 20;64(1):9-13. Epub 2009 Aug 11.
CMAJ. 2008 Aug 12;179(4):319-26.
JAMA. 2006 Dec 27;296(24):2947-53.
J Bone Miner Metab. 2009;27(6):635-42. Review.
Am J Kidney Dis. 2010 Feb 25. [Epub ahead of print].

Other risks of PPIs

- Increased risk of community-acquired pneumonia
- Increased incidence of GERD and acid reflux
- Increased intestinal permeability defects ("leaky gut")
  - Gallbladder motor dysfunction
- Increased risk of *C. difficile* infections
- Undesired weight gain

JAMA. 2004 Oct 27;292(16):1955-60.
Aliment Pharmacol Ther. 2008 Jul;28(1):127-36.
Gastroenterology. 2009 Jul;137(1):80-7, 87.e1.
Aliment Pharmacol Ther. 2008 Dec 1;28(11-12):1317-25.
Surg Endosc. 2006 Sep;20(9):1364-7. Epub 2006 Jul 20.
JAMA. 2005 Dec 21;294(23):2989-95.
World J Gastroenterol. 2009 Oct 14;15(38):4794-8.

Anti-*Helicobacter pylori* (*H. pylori*) Agents

Helidac, Pylera, Prevpac

- Helidac = bismuth subsalicylate, metrondiazole, and tetracycline
- Pylera = bismuth subcitrate potassium, metrondiazole, and tetracycline
- Prevpac = amoxicillin, clarithromycin, and lansoprazole

Antibiotics

- Beta carotene
- Biotin
- Calcium
- Carnitine
- Copper
- Folic acid
- Iron
- Magnesium
- Niacin
- Potassium
- Probiotics
- Vitamin A / retinol
- B1 thiamine
- B2 riboflavin
- B5 pantothenic acid
- B6 pyridoxine
- B12
- C
- D
- K
- Zinc

Alternative Interventions for Ulcers and *H. pylori*

- "Robert's Formula"
  - Geranium, Cabbage, Marshmallow, Okra,…
- Deglycyrrhizinated licorice (DGL)
- Berberine- and hydrastine-containing botanical extracts
  - e.g., *Mahonia aquifolium* , *Hydrastis canadensis*

H. pylori, antibiotics, and probiotics

- *H. pylori* infection is a major cause of chronic gastritis and peptic ulcer and a risk factor for gastric malignancies.
- Antibiotics-based *H. pylori* eradication is effective in a majority of cases. However, it is expensive and causes side effects and antibiotic resistance.
- 7/9 human studies showed an improvement of *H. pylo*ri gastritis and decrease in *H. pylori* density after administration of probiotics.
- No study could demonstrate the eradication of *H. pylori* infection by probiotics but they may reduce the risk of developing disorders associated with high degrees of gastric inflammation.

J Nutr. 2007 Mar;137(3 Suppl 2):812S-8S.

Interventions

- Probiotics
  - *Lactobacillus plantarum*
  - *Lactobacillus acidophilus*
  - *Bifidobacterium longus*
  - *Bifidobacterium lactis*
- Lactoferrin
  - Meta-analysis of 9 trials found lactoferrin supplementation effective in increasing eradication rates of anti-H. pylori therapy.
  - Also found the combination of lactoferrin and probiotics effective.
  - Lactoferrin recommended in cases of antibiotic resistance or failure.
- Deglycyrrhizinated Licorice (DGL)
- "Robert's Formula"
  - Bromelain, cabbage, Althea, Ulmus, Geranium, Echinacea, Goldenseal
- N-Acetyl-D-Glucosamine (NAG)

Helicobacter. 2009 Apr;14(2):119-27.
Dig Dis. 2006;24(1-2):113-30.

Lactoferrin and probiotics enhance efficacy of 'triple therapy'

- Triple therapy with amoxicillin, clarithromycin, and a PPI has an eradication rate of only 74-76% .
- Study: 101 patients (group A) underwent standard triple eradication therapy (esomeprazole, clarithromycin, amoxicillin), while 105 patients (group B) underwent a modified eradication therapy (standard triple eradication therapy plus beta-lactoferrin and probiotics).
- Infection was eradicated in 73/101 patients from Group A vs 93/105 from Group B.
- PP analysis showed 73/96 patients from Group A and 93/101 from Group B to have been successfully treated.
- More patients from group A than from group B reported side effects from their treatment.
- Lactoferrin and probiotics improved standard eradication therapy for H. pylori infection
  - Lactoferrin serving to increase the eradication rate
  - Probiotics to reduce the side effects of antibiotic therapy

Am J Gastroenterol. 2007; 102(5):951-6.

Vitamin C and beta-carotene may help anti-*H. pylori* drugs fight gastric cancer.

- Gastric cancer is the second leading cause of cancer death in the world and five-year survival rates are low.
- *H. pylori* infection associated with increased risk of gastric cancer.
- Anti-*H. pylori* agents have been shown to induce regression of precancerous gastric abnormalities.
- Addition of vitamin C (1 g BID) and beta-carotene (30 mg/d) enhanced the anti-cancer efficacy of *H. pylori* triple therapy.

J Natl Cancer Inst. 2000 Dec 6;92(23):1881-8.