



**BRIEF QUESTIONS
AND ANSWERS
ON CURRENT
CLINICAL
CONTROVERSIES**

Q: Should patients receiving long-term gastric acid inhibition therapy be evaluated for vitamin B₁₂ deficiency?

JOEL E. RICHTER, MD

Chairman, Department of Gastroenterology, Cleveland Clinic

A: THE PROTON PUMP INHIBITORS (PPIs) have an excellent safety profile. However, there has been some concern recently that their long-term use may depress levels of serum vitamin B₁₂ (cobalamin).

■ HOW VITAMIN B₁₂ IS ABSORBED

The main dietary sources of vitamin B₁₂ are meat and eggs. The US Recommended Daily Allowance (RDA) is 2 µg per day, but the usual daily intake is much higher, ranging from 5 to 15 mg per day. Body stores of cobalamin are usually a substantial 2 to 3 mg. Hence, even strict vegans who eat no animal proteins will not deplete their body stores of vitamin B₁₂ for many years.^{1,2}

Dietary vitamin B₁₂ is tightly protein-bound. Gastric acid releases it, and the free cobalamin then binds to salivary R proteins in the stomach. In the proximal small intestine, pancreatic enzymes degrade the R protein, allowing cobalamin to bind to intrinsic factor (IF) and subsequently to be absorbed in the distal ileum. Cobalamin appears in the portal circulation bound to transcobalamin II, and some enterohepatic recycling occurs.

■ TWO MECHANISMS OF MALABSORPTION

Prolonged acid inhibition by PPIs could promote vitamin B₁₂ malabsorption by two possible mechanisms.

First, an increased gastric pH could impair the body's ability to extract vitamin B₁₂ from the dietary proteins to which it is bound. Some studies confirmed that PPIs reduce the absorption of protein-bound cobalamin. For example, Marcuad et al³ gave a 2-week course

of omeprazole to 10 healthy subjects. The proportion of protein-bound cobalamin absorbed decreased from 3.2% to 0.9% in patients given 20 mg per day and from 3.4% to 0.4% in patients given 40 mg. Saltzman et al⁴ suggest that the degree of impairment may be greater in elderly patients.

Second, in theory, reduced acidity could promote bacterial overgrowth in the proximal small intestine, which could increase bacterial consumption of this nutrient. (It is even possible that inhibiting parietal cell function could reduce IF secretion. However, this effect has not been reported during PPI therapy.)

■ DEFICIENCY IS UNLIKELY

However, the human diet typically contains more cobalamin than is needed; it is unlikely that partly inhibiting the absorption of protein-bound cobalamin would produce vitamin B₁₂ deficiency. Even if the inhibition were complete, deficiency would take many years to manifest because of the body's large functional reserve of vitamin B₁₂. In addition, PPI treatment does not affect the absorption of unbound cobalamin,⁵ such as the crystalline vitamin B₁₂ contained in commercial multivitamins.

■ PPIs DECREASE B₁₂ LEVELS SLIGHTLY

For these reasons, serum levels of vitamin B₁₂ are a more clinically relevant measure of this nutrient than absorption rates. Normal serum levels of vitamin B₁₂ range widely between 115 and 600 pmol/L. Koop et al⁶ reported that serum cobalamin levels decreased from baseline in patients who received unspecified doses of omeprazole daily for up to 4 years. However, the absolute changes were small, reaching significance only at 4 years, and no patient developed subnormal values.

**Inhibiting B₁₂
absorption is
unlikely to
cause
B₁₂ deficiency**



Similarly, Schenk et al⁵ found that cobalamin values decreased, though not statistically significantly, among 25 reflux patients treated with omeprazole 20 to 60 mg for 3 to 7 years.

The degree of acid suppression may affect the cobalamin level. Termanini et al,⁷ in a study of patients with Zollinger-Ellison syndrome treated with high doses of PPIs continuously for at least 5 years, found that mean serum cobalamin levels decreased by 27% ($P = .001$) in the 21 patients with sustained achlorhydria, defined as no demonstrable acid secretion in the preceding 3 years. On the other hand, mean serum cobalamin levels did not decline significantly in the 47 patients without sustained achlorhydria.

The US distributors of omeprazole and lansoprazole are not aware of any cases of cobalamin deficiency or megaloblastic anemia developing during prolonged PPI therapy in the United States.² However, a single case report from France describes a patient with megaloblastic anemia attributed to cobalamin deficiency that developed during omeprazole treatment.⁸ The patient was a 51-year-old man who had taken 40 to 60 mg of omeprazole daily for 3 years for severe gastroesophageal reflux disease. He had a macrocytic anemia with megaloblastic bone marrow, normal red cell folate levels, and severely reduced serum cobalamin levels. However, the patient's pretreatment cobalamin level was not reported, and thus it is possible that he could have had subclinical cobalamin deficiency before starting PPI treatment. The patient's anemia responded to cyanocobalamin injections.

■ CLINICAL RECOMMENDATIONS

In summary, no prospective trials are available to guide therapy, but the available evidence suggests that a very small proportion of patients on continuous, long-term PPI therapy may develop reduced cobalamin levels. Nevertheless, vitamin B₁₂ deficiency has been reported only once.

It certainly would not be harmful to recommend commercially available multivitamins, which contain anywhere from 2 to 10 µg of easily absorbed crystalline vitamin B₁₂.

I do not consider it necessary to check or monitor cobalamin levels in young, other-

wise healthy adults on PPI treatment unless they are strict vegans who eat no animal protein.

Elderly patients may be best served by measuring serum cobalamin at baseline after PPI therapy is initiated, and repeating the test every 1 or 2 years.

Patients with borderline low levels of vitamin B₁₂ should also have serum methylmalonic acid (MMA) and homocysteine measured.⁹ Elevated MMA with normal homocysteine levels suggests vitamin B₁₂ deficiency, which can be treated with a single parenteral dose followed by oral supplementation.

If serum cobalamin levels decline on long-term PPI treatment, vitamin B₁₂ supplementation may be sufficient to correct the problem without discontinuing the PPI. However, therapeutic doses of vitamin B₁₂ can mask folate deficiency, so the patient must first be evaluated for folate deficiency.

■ REFERENCES

1. Turnburg LA, Riley SA. Digestion and absorption of nutrients and vitamins. In Sleisenger MH, Fordtran JS, editors. *Gastrointestinal Diseases*. Philadelphia: W.B. Saunders Co, 1993:977-1008.
2. Howden CW. Vitamin B₁₂ levels during prolonged treatment with proton pump inhibitors. *J Clin Gastroenterol* 2000; 30:29-33.
3. Marcuard SP, Albernaz L, Khazanie PG. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B₁₂). *Ann Intern Med* 1994; 120:211-215.
4. Saltzman JR, Kemp JA, Golner BB, et al. Effect of hypochlorhydria due to omeprazole treatment or atrophic gastritis on protein bound vitamin B₁₂ absorption. *J Am Coll Nutr* 1994; 13:584-591.
5. Schenk BE, Festen HPM, Kuipers EJ, et al. Effect of short and long term treatment with omeprazole on the absorption and serum levels of cobalamin. *Aliment Pharmacol Ther* 1996; 10:541-545.
6. Koop H, Bachem MG. Serum iron, ferritin and vitamin B₁₂ during prolonged omeprazole therapy. *J Clin Gastroenterol* 1992; 14:288-292.
7. Termanini B, Gibril F, Sutliff E, et al. Effect of long term gastric acid suppressive therapy on serum vitamin B₁₂ levels in patients with Zollinger-Ellison syndrome. *Am J Med* 1998; 104:422-30.
8. Bellou A, Aimone-Gastin I, DeKorwin JD, et al. Cobalamin deficiency with megaloblastic anemia in one patient after long-term omeprazole therapy. *J Intern Med* 1996; 240:161-164.
9. Snow CF. Laboratory diagnosis of vitamin B₁₂ and folate deficiency: A guide for the primary care physician. *Arch Intern Med* 1999; 159:1289-1298.

ADDRESS: Joel E. Richter, MD, Department of Gastroenterology, S40, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195-5245; e-mail richtej@ccf.org.

Monitor serum B₁₂ levels in elderly patients and vegans taking PPIs