Omeprazole Therapy Causes Malabsorption of Cyanocobalamin (Vitamin B12)

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Objective: To evaluate protein-bound cyanocobalamin (vitamin B12) sub absorption before and after omeprazole (Prilosec) therapy in healthy male volunteers.

Design: Clinical trial in which each volunteer served as his own control.

Setting: Outpatient department of a university medical center.

Participants: Ten healthy, male volunteers 22 to 50 years old.

Intervention: Each participant had a modified Schilling test (protein-bound cyanocobalamin) and a gastric analysis, as well as measurements of serum vitamin B12, gastrin, and folate levels. Five patients were then randomly assigned to take 20 mg or 40 mg of omeprazole daily. After 2 weeks of omeprazole therapy, these tests were repeated.

Measurements: The modified Schilling test, gastric analysis, serum gastrin level, folate level, and cyanocobalamin level.

Results: At the end of the 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).

Conclusions: Omeprazole therapy acutely decreased cyanocobalamin absorption in a dose-dependent manner.

Omeprazole, a substituted benzimidazole, is a potent, long-lasting inhibitor of gastric acid secretion [1]; it is now approved in the United States for the treatment of the Zollinger-Ellison syndrome, gastroesophageal reflux disease, and peptic ulcer disease. Omeprazole (Prilosec) is not yet approved for prolonged maintenance therapy of gastroesophageal reflux and peptic ulcer disease as it is in certain European countries. Nevertheless, omeprazole is used in the United States for maintenance therapy of refractory gastroesophageal reflux disease by a substantial number of patients.

A decrease (P < 0.05) in serum cyanocobalamin levels develops after 3 to 4 years of omeprazole therapy [2]. However, in patients with the Zollinger-Ellison syndrome receiving omeprazole for up to 4 years, no hematologic abnormalities were noted, but cyanocobalamin levels were not measured [3]. Cyanocobalamin deficiency in humans can result in potentially fatal hematologic and neuropsychiatric abnormalities [4]. Unfortunately, hematologic abnormalities are only seen in severe advanced cyanocobalamin deficiency and, thus, a normal complete blood count can occur in the presence of cyanocobalamin deficiency [5]. Little information is currently available about the potential effect of prolonged oral omeprazole therapy on cyanocobalamin absorption.

Cyanocobalamin (vitamin B12) is a water-soluble vitamin derived from certain microorganisms; the vitamin is tightly bound to dietary protein. Hydrochloric acid and pepsin release cyanocobalamin from dietary protein in the stomach where it binds to salivary R proteins [6]. After alteration of R proteins by pancreatic enzymes [7], cyanocobalamin is rapidly transferred to intrinsic factor to form a complex that is resistant to proteolysis [8]. Once the intrinsic factor-cyanocobalamin complex is formed in the upper jejunum, it remains intact until it adheres to specific receptors in the distal ileum.

Omeprazole acts by inhibiting the H+K+ adenosine triphosphatase, a proton pump that seems to be specific to the gastric parietal cells [9-13]. Prolonged omeprazole treatment can result in cyanocobalamin deficiency by three possible mechanisms: 1) In hypo- or achlorhydria, protein-bound cyanocobalamin may not be adequately released from food for transfer to R proteins and intrinsic factor; 2) omeprazole may decrease intrinsic factor secretion after long-term therapy even though no effect on intrinsic factor secretion occurred after a single intravenous dose of omeprazole [14] and 3) achlorhydria causes gastric bacterial overgrowth that may accelerate the development of cyanocobalamin deficiency by producing vitamin B12 analogs that compete with absorption and use of the vitamin [15].

We analyzed the effect of omeprazole on cyanocobalamin absorption, because neurologic disorders caused by cyanocobalamin deficiency are often irreversible and can occur in the absence of any hematologic abnormalities [4].

Methods

Ten healthy male volunteers with no known gastrointestinal disorders were recruited for this study. All were nonsmokers.
Five of the volunteers received 20 mg of omeprazole, and the other five received 40 mg of omeprazole (Prilosec; Merck & Company, Inc., West Point, Pennsylvania) daily for 2 weeks. Participants had modified Schilling tests (protein-bound cyanocobalamin) and gastric analyses, as well as measurements of serum cyanocobalamin, gastrin, and folate levels before and after 2 weeks of omeprazole therapy.

The Modified Schilling Test

To measure protein-bound cyanocobalamin absorption in the presence of hypo- or achlorhydria, the Schilling test was modified according to the method of King and colleagues [16]. Protein-bound cyanocobalamin doses were made by mixing 1 mL of radiolabeled cobalt-57 cyanocobalamin (10 microcuries; Amersham Corporation, Arlington Heights, Illinois) with 10 mL of sterile water and with 0.2 mL of unlabeled cyanocobalamin (20 µg B12) with 45 mL of chicken serum (Grand Island Biological Company, Grand Island, New York). Thus, one test dose contained 1 microcuries of cobalt-57 cyanocobalamin and a total of 2 µg of unlabeled cyanocobalamin. After 30 minutes of incubation at room temperature, this mixture was placed in a dialysis membrane with a pore size of 6000 to 8000 molecular weight (PGC Scientifics; Gaithersburg, Maryland). Dialysis was then done for 72 hours at 5 °C to remove the unbound cyanocobalamin. The water was changed three times per day. The adequacy of removal of free cyanocobalamin was then tested with a modified Gottlieb charcoal assay by using albumin-coated charcoal [17].

All patients fasted overnight (at least 8 hours) before the Schilling test. Participants received the test solution containing the protein-bound radiolabeled cyanocobalamin followed by an intramuscular injection of 1 mg of cyanocobalamin. Before ingesting the test solution, the participants urinated and started a 24-hour urine collection. The total urine volume and creatinine concentration were measured. The radioactivity in the urine was determined, and results were expressed as the percentage excretion of the ingested cyanocobalamin. The radioactivity of each test dose was measured within 2 hours before administration of the test.

Gastric Analysis

A nasogastric tube was inserted and advanced until gastric juice could easily be aspirated. The stomach contents were aspirated and, if food or more than 200 mL of liquid was present, the test was canceled. Gastric juice was then collected in 15-minute samples and was placed directly on ice. The pH of each sample was then measured using a glass-tip pH probe (Beckman Instruments, Norcross, Georgia), and the pH was promptly titrated to a pH of 7 to measure total acidity. After the first hour, participants received an injection of 6 µg/kg of pentagastrin subcutaneously (Peptavlon; Wyeth-Ayerst Laboratories, Philadelphia, Pennsylvania). Then, four additional 15-minute samples of gastric juice were collected on ice and were titrated to a pH of 7.

Serum Analyses

Serum cyanocobalamin levels were determined with a protein-binding radioassay using commercially available reagents (Becton Dickinson, Orangeburg, New York). We used a reference range for serum cyanocobalamin of 180 to 960 pg/mL. Gastrin levels in the blood samples were measured using a commercially available radioimmunoassay kit (Becton Dickinson, Orangeburg, New York). Each participant was given a medicine container with 14 doses and was asked to return the container at the end of the study. All studies were carried out using carefully controlled conditions in the gastroenterology laboratory. Informed consent was obtained from all participants, and all investigations were approved by the Policy and Review Committee on Human Research. The Student t-test was used for unpaired and paired samples to determine statistical significance among patient groups. Data are expressed as mean ±SE. A paired Wilcoxon rank-sum test was also used where applicable. A P value of less than 0.05 was considered significant.

Results

The mean age of the ten participants was 30.2 ±2.9 years (range, 22 to 50 years). Their mean height was 1.76 ±0.02 metres (range, 1.65 to 1.87 metres), and their mean weight was 77.9 ±6.2 kg (range, 52.2 to 102.1 kg). For the participants receiving 20 mg of omeprazole daily, the mean basal acid output was 2.5 ±0.6 mEq/h; it decreased to 0.7 ±0.4 mEq/h after 2 weeks of omeprazole therapy. The five participants who received 40 mg of omeprazole daily had a similar basal acid output of 2.8 ±1.3 mEq/h that statistically decreased to 0.09 ±0.08 mEq/h after 2 weeks of therapy. The maximal acid output decreased from 24.7 ±3.8 mEq/h to 5.6 ±2.7 mEq/h in the group receiving 20 mg of omeprazole group and from 19.3 ±5.1 mEq/h to 0.2 ±0.1 mEq/h in the group receiving 40 mg. Figure 1 shows the suppression of basal acid output and the maximal acid output after omeprazole therapy; achlorhydria occurred in the group receiving 40 mg of omeprazole.

Figure 1. Basal acid output and maximal acid output before and after 2 weeks of omeprazole therapy. Means ±SE are shown. *P < 0.01.
Figure 2 shows the results of the modified Schilling test using chicken serum-bound cobalt-57 cyanocobalamin in both groups. One participant in each group had a greater absorption of protein-bound cyanocobalamin than the rest of the participants; we found no explanation for this observation. The mean protein-bound cyanocobalamin absorption at baseline and after 2 weeks of acid suppression with omeprazole is shown in Figure 3. Absorption of protein-bound cyanocobalamin was less than absorption of crystalline cyanocobalamin that is used in the standard Schilling test. As Figure 3 shows, the mean absorption of protein-bound cyanocobalamin at baseline was 3.2% ± 1.4% and 3.4% ± 1.3% in the groups receiving 20 mg and 40 mg of omeprazole, respectively. Protein-bound cyanocobalamin absorption decreased (P < 0.05) to 0.9% ± 0.3% (P = 0.031) and 0.4% ± 0.1% (P = 0.031) after 2 weeks of 20-mg and 40-mg omeprazole groups, respectively. The median values of protein-bound cyanocobalamin absorption were 2.2% and 2.3% at baseline, which decreased to 0.8% and 0.5% after 20 mg and 40 mg of omeprazole.

Figure 2. The modified Schilling test (for protein-bound cyanocobalamin) before and after 2 weeks of omeprazole therapy. B12 = vitamin B12 (cyanocobalamin).

Figure 3. Schilling test results before and after 2 weeks of omeprazole therapy. A statistical decrease (P = 0.031) occurred in cyanocobalamin absorption in both groups. Means ±SE are shown. B12 = vitamin B12 (cyanocobalamin).

Serum gastrin levels Figure 4 increased in the group receiving 40 mg of omeprazole from 42 ± 4 ng/L to 105 ± 15 ng/L after 2 weeks (P < 0.01). The serum gastrin levels slightly increased in the group receiving 20 mg of omeprazole from 49 ± 8 to 96 ± 30 ng/L (P = 0.06). Folic acid levels remained unchanged, from a mean of 52 ± 14 ng/mL to 50 ± 12 ng/mL and from 43 ± 13 ng/mL to 45 ± 14 ng/mL in the groups receiving 20 mg and 40 mg of omeprazole, respectively (data not shown). Serum cyanocobalamin levels increased as shown in Figure 5. Cyanocobalamin levels changed from 300 ± 40 pmol/L to 340 ± 50 pmol/L (P > 0.2) in the group receiving 20 mg of omeprazole and changed from 270 ± 40 pmol/L to 400 ± 20 pmol/L (P > 0.2) in the group receiving 40 mg of omeprazole, probably reflecting the intramuscular cyanocobalamin given during both Schilling tests.

Figure 4. Mean serum gastrin levels before and after 2 weeks of omeprazole therapy. Increases in gastrin levels occurred in both the 20-mg and 40-mg omeprazole groups (P = 0.06 and P < 0.01, respectively). Means ±SE are shown.
Discussion

We found that omeprazole therapy causes a dose-dependent decrease in cyanocobalamin absorption. A similar decrease of protein-bound cyanocobalamin absorption after omeprazole therapy was reported by Kemp and colleagues [18]. They also showed that protein-bound cyanocobalamin absorption was increased by acidic dietary drinks such as cranberry juice. Koop and colleagues [19] studied the effect of long-term therapy with omeprazole on serum cyanocobalamin concentration and reported that levels were stable for about 3 years. However, a statistical decrease in serum cyanocobalamin levels developed after 3 years [2]. In contrast, other investigators [20] found no decreased absorption of liver protein-bound cyanocobalamin; however, intravenous omeprazole induced anacidity only 30 minutes after the Schilling test was administered, and hence sufficient acid and pepsin may have been present for adequate cyanocobalamin liberation from its protein-binding sites.

Cyanocobalamin malabsorption occurs after vagotomy [21] and in patients with achlorhydria [22, 23]. Also, histamine-2-receptor antagonists, such as cimetidine and ranitidine, decrease the absorption of cyanocobalamin [24-27]. In contrast to omeprazole, which causes profound hypochlorhydria, the suppressing effect of the histamine-2-receptor antagonists is greatly reversed by food intake [28] producing possibly sufficient gastric acidity for cyanocobalamin release.

Severe cyanocobalamin malabsorption and decreased serum cyanocobalamin levels occur in patients who have gastric bypass surgery for morbid obesity [29, 30]. The reason for cyanocobalamin malabsorption in patients with achlorhydria may be the lack of necessary gastric acid and pepsin for the release of cyanocobalamin from its protein-binding sites in food. Another explanation may be gastric bacterial overgrowth, because malabsorption of protein-bound cyanocobalamin can be reversed in patients with achlorhydria by using antibiotic agents [31].

Another possible cause of cyanocobalamin malabsorption is the lack of intrinsic factor. However, this possibility is less likely, because adequate concentrations of intrinsic factor have been found in the gastric juice of patients treated with omeprazole [14, 20, 32] or with histamine-2-receptor antagonists [33-35].

Our study shows a dose-dependent malabsorption of protein-bound cyanocobalamin in healthy volunteers receiving omeprazole therapy. This malabsorption is likely caused by drug-induced hypo- and achlorhydria. Because cyanocobalamin deficiency can cause irreversible neurologic and cognitive deficits, it is important to be aware of and understand this complication of omeprazole therapy. Until studies of the effect of long-term omeprazole therapy on cyanocobalamin are completed, we suggest monitoring cyanocobalamin levels in patients who receive long-term therapy.

References


Omeprazole Therapy Causes Malabsorption of Cyanocobalamin (Vita... file:///Cphmedcommon/share/PRIVATE/veronika/E-lib%20april%20...