DOI: https://doi.org/10.22516/25007440.150

Vitamin B_{12} Deficiency Associated with Consumption of Proton Pump Inhibitors

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Received: 01-08-16
Accepted: 28-07-17

Abstract

Introduction: Vitamin B_{12} deficiencies have been linked to chronic consumption of proton pump inhibitors (PPIs). The aim of the study is to determine serum levels of vitamin B_{12} in patients receiving proton pump inhibitors and to describe vitamin B_{12} levels according to type of PPI, time of use, dosage, patient age and patient gender. **Materials and methods:** Patients older than 18 years of age at the outpatient clinic of the gastroenterology department of Clínica Fundadores (a third-level institution) who had been diagnosed with gastrointestinal disease and who took PPIs were included. Vitamin B_{12} levels were determined. The collected information was described and analyzed using conventional statistical techniques with analysis stratified according to variables. **Results:** One hundred nine patients were recruited, 78.9% were women, and the average age was 58.9 years. Patients who had been treated with PPIs for more than three years had significantly lower vitamin B_{12} levels than did patients who had been treated for less than three years ($p = 0.022$). No statistically significant differences were found according to the type of PPI ($p = 0.881$ for Esomeprazole, $p = 0.098$ for Omeprazole, and $p = 0.131$ for Lansoprazole), age ($p = 0.937$) or gender ($p = 0.519$). **Conclusions:** Using PPIs for more than three years is related to decreased serum levels of vitamin B_{12}. The age, gender, type of PPI and dosage used are not independent factors related to these decreases.

Keywords

Vitamin B12 deficiency, proton pump inhibitors, gastrointestinal diseases.

INTRODUCTION

Proton pump inhibitors (PPIs) are the most potent suppressors of gastric acid secretions. At normal doses, acid production decreases by 80% to 95%. (1) These drugs are among the most frequently prescribed drugs in the world and are usually used in the long-term treatment of various acid peptic disorders including gastroesophageal reflux disease (GERD), peptic ulcers and hypersecretory states such as Zollinger-Ellison syndrome. (1, 2)

Vitamin B12 (also known as cobalamin) is a cofactor for two enzymes: methionine synthetase and Methylmalonyl-CoA mutase (MCM). (3, 4) The spectrum of diseases associated with vitamin B12 deficiency is broad and ranges from the absence of symptoms to malabsorption syndrome, pancytopenia and neurological symptoms including paresthesias and signs of myelopathy and/or neuropathy. (3, 4, 5) Long-term use of PPIs is effective and safe. However, there is evidence that suggests long-term use may lead to decreased serum levels of Vitamin B12. (4, 5, 6, 7, 8).

Theoretically, inhibition of gastric acid secretion by PPIs can promote Vitamin B12 malabsorption by several mechanisms. (4, 5) One of them is elevation of intragastric pH which alters the extraction of Vitamin B12 from

dietary proteins. The reduction of gastric acid then alters the intestinal microbiota. In addition, it may predispose to small intestinal bacterial overgrowth (SIBO) which increases bacterial consumption of Vitamin B12. (4, 5) Another mechanism involved is reduction of parietal cell activity which may reduce the secretion of intrinsic factor. (4)

The objective of this study is to determine serum levels of Vitamin B12 in adult patients chronically treated with PPIs in the gastroenterology department of the Clínica Fundadores in Bogotá.

MATERIALS AND METHODS

This is a cross-sectional study which included patients over 18 years of age who had histories of gastrointestinal disease and who had been continuously treated with PPIs for a period of 6 months or more. Before entering the study, patients read and signed informed consent forms. Participants were recruited at the outpatient gastroenterology clinic. The protocol and informed consent form were approved by the institution's ethics committee.

Exclusion Criteria

Patients on strict vegetarian diets, those who had pernicious anemia, intestinal malabsorption syndrome, chronic diarrhea, exocrine pancreatic insufficiency, gastrectomy or intestinal resection, gastric cancer, chronic autoimmune atrophic gastritis, chronic gastritis with OLGA III-IV, and those who had recently used calcium supplements, metformin and/or Vitamin B12 were excluded.

The sample size of 86 people was calculated using STATA 12.0 in order to find a difference of 35 pg/mL between a group of patients who had used PPIs for three years or less and a group of patients who had used PPIs for more than three years, with a standard deviation of 50 pg/mL, an alpha value of 0.05 and a power of 90%.

The data were collected on a specific questionnaire which included the following patient data: demographic characteristics, type of PPI, dosage, duration of treatment, Vitamin B12, comorbidities, and recent intake of calcium supplements, metformin and/or Vitamin B12.

Serum levels of vitamin B12 in venous blood were determined. The sample was sent and processed in the institution's clinical laboratory using the Electro-chemiluminescence immunoassay (ECLIA), a competition test in which the sample competes with added biotin-labeled vitamin B12 using purified intrinsic factor. Vitamin B12 deficiency was defined as levels of the vitamin below 200 pg/mL; levels between 200 and 299 pg/mL were considered to be marginal, and levels greater than or equal to 300 pg/mL were considered to be normal. (9)

Specific Objectives

The specific objectives of this study were to describe serum levels of vitamin B12 according to duration of PPI use, to determine serum levels of vitamin B12 according to the type of PPI used, to determine serum levels of vitamin B12 according to the dosages of different PPIs, and to establish serum levels of vitamin B12 according to age and sex.

Statistical Analysis

A descriptive analysis of the variables was carried out. Qualitative variables were expressed in absolute numbers and percentages, and dispersion measures such as averages and standard deviations were used for normally distributed quantitative variables. Other quantitative variable were presented in the form of medians and interquartile ranges. The normality of variables was evaluated with the Shapiro-Wilk test. Student's t-test was used to establish differences in vitamin B12 levels for normal distributions, and the Kruskal-Wallis non-parametric test was used for other distributions. Stratified analysis was done by type of PPI, drug dose, age (less than 65 years and greater than or equal to 65 years) and gender.

RESULTS

We included 109 patients with a mean age of 58.9 years (SD 10.2 years), 78.9% were women (n = 86), and 49.5% of the patients included had used proton pump inhibitors (PPIs) for more than 3 years (n = 54). Characteristics of the population studied are shown in Table 1.

Statistically significant differences of serum levels of vitamin B12 were found between different durations of PPI use (≤3 years or> 3 years) (p = 0.022). Eighty-seven percent of patients had normal levels of Vitamin B12, 15.6% had a marginal deficit (n = 17), and the remaining 4.6% had a Vitamin B12 deficit (n = 5). The proportions of patients in each of these three stages of Vitamin B12 according to duration of PPI use PPI (≤3 years or> 3 years) is shown in Table 2. Evaluation of each of these three categories separately found statistically significant differences in relation to PPI consumption duration, and the group who had used PPIs for more than three years was found to have a higher proportion of patients with vitamin B12 deficiency and marginal deficiency than did the group who had used PPIs for three years or less. The proportions of patients in each of the three stages of vitamin B12 levels according to the type of PPI used are listed in Table 3. Serum levels of vitamin B12 according to the doses of different PPIs are presented in Table 4. It should be noted that, at all doses of the various PPIs prescribed in this population, 50% of the patients

have levels above 300 pg/mL which is the normal level of vitamin B12. In the particular case of esomeprazole at doses of 40 mg, vitamin B12 levels were sometimes in the deficit category (minimum data = 132.7 pg/mL). This was also true for omeprazole at doses/day of 20 mg and 40 mg (minimum data = 188.9 pg/mL and 198.2 pg/mL, respectively) and lansoprazole at doses/day of 60 mg (minimum data = 138.9 pg/mL). No statistically significant differences were found between vitamin B12 levels and the PPI dose used (p = 0.881, p = 0.098 and p = 0.131 for esomeprazole, omeprazole and lansoprazole, respectively).

Table 1. Demographic and clinical characteristics of the study population.

	Use of PPIs	
	3 years or less (n = 55)	More than 3 years (n = 54)
Mean age (SD)	58.4 (11.1)	59.5 (9.2)
Sex, women n (%)	43 (78.2)	43 (79.6)
Serum levels of vitamin B12 (pg/mL)	478.4	434.9
Median (range)	(138.9-1325.0)	(132.7-900.8)
Esomeprazole, dose/day (mg)	n (%)	n (%)
20	4 (7.3)	0 (0.0)
40	8 (14.5)	4 (7.4)
80	11 (20.0)	11 (20.4)
Omeprazole, dose/day (mg)	n (%)	n (%)
20	8 (14.5)	8 (14.8)
40	7 (12.7)	12 (22.2)
Lansoprazole, dose/day (mg)	n (%)	n (%)
30	8 (14.5)	4 (7.4)
60	9 (16.4)	13 (24.1)
90	0 (0.0)	2 (3.7)

Table 2. Serum levels of vitamin B12 according to the duration of use of PPIs in the study population.

Vitamin B12 levels	Three years of less	More than three years	*p*
Deficit (≤200 pg/mL)	1 (1.8)	4 (7.4)	<0.001
Marginal deficit (200-299 pg/mL)	6 (10.9)	11 (20.4)	<0.001
Normal (≥300 pg/mL)	48 (87.3)	39 (72.2)	<0.001

Table 3. Serum levels of vitamin B12 according to the type of PPI used in the study population.

Vitamin B12 Levels	Esomeprazole	Omeprazole	Lansoprazole
Deficit (≤200 pg/mL)	1 (20.0)	2 (40.0)	2 (40.0)
Marginal Deficit (200-299 pg/mL)	8 (47.1)	3 (17.6)	6 (35.3)
Normal (≥300 pg/mL)	29 (33.3)	30 (34.5)	28 (32.2)

No statistically significant differences were found when we analyzed vitamin B12 (yes/no) versus age (<65 years or ≥65 years) and gender (female or male) in the study population (n = 109). The results are shown in Table 5. No megaloblastic anemia, neurological or gastrointestinal manifestations were found in patients with deficit or marginal deficit Vitamin B12 levels.

Table 4. Serum levels of vitamin B12 according to dosages of PPI.

Vitamin B12 levels pg/mL	Median (range)	*p*
Esomeprazole, dose/day (mg)		
20	471.5 (293.4-1148.0)	0.881
40	509.2 (132.7-749.5)	
80	452.3 (202.9-1110.0)	
Omeprazole, dose/day (mg)		
20	439.4 (188.9-655.8)	0.098
40	554.2 (198.2-1325.0)	
Lansoprazole, dose/day (mg)		
30	470.5 (295.7-658.4)	0.131
60	470.8 (138.9-900.8)	
90	240.9 (214.3-267.5)	

Table 5. Vitamin B12 deficiency according to age and sex.

Vitamin B12 levels	Deficit (<300 pg/mL)	No Deficit (≥300 pg/mL)	*p*
Age <65 years (n = 80)	16 (20.0)	64 (80.0)	0.937
Female gender (n = 86)	17 (19.7)	69 (80.2)	0.519

DISCUSSION

This study found statistically significant differences in vitamin B12 serum levels in relation to PPI consumption duration. People who used PPIs for more than 3 years had lower levels of vitamin B12. This finding is similar to those in previously published studies. (8) Vitamin B12 deficiency defined as less than 200 pg/mL was more frequent in patients who had used PPIs for more than 3 years those in those who had used it for three years or less. The percentage of the first group which had deficits was found to be 7.4% and the percentage of the latter group was found to be 1.8% (p <0.001). This study found that the overall percentage of the population studied who had B12 deficits was 4.6% while the overall percentage of the population studied who had marginal deficits was 15.6%. These results contrast with other Latin American studies in which B12 deficits have been found in 40% of the general population, and marginal deficiencies in at least 20% of the general population. (10) No statistically significant differences were found for preva-

lences of alterations in patients older and younger than 65 years. This coincides with previous studies from other parts of the world. (7, 9) Similarly, no significant differences with respect to the B12 levels were found related to the type of PPI used and the dosages used.

Because the study design did not include a control group which did not consume PPIs, levels of Vitamin B12 in that population are unknown. A study conducted in Bucaramanga of 97 people from different socioeconomic strata found that 10.2% of the patients were found to have vitamin B12 intakes below official recommendations, (11) but the absence of a control group prevents determination of the influence of PPIs on the values found. A case-control study has not been carried out since patients who come to the gastroenterology clinic who do not use PPIs are very rare. PPIs are used by these patients either as prophylactic co-therapy with NSAIDs, to treat GERD, or often without any specific indication or prescription.

Nevertheless, we consider that independent evaluation of two subgroups classified by exposure time diminishes the effect related to nutritional issues so that each of the individuals in the study is given the possibility of presenting this bias which homogenizes the population. In addition, the results obtained indicate a need to carry out a more extensive evaluation regarding neuropsychiatric and hematological clinical manifestations in the population with vitamin B12 deficiency. The sample size was not calculated to discriminate among clinical variables in the people with vitamin B12 deficiencies, and a higher number of subjects would probably be needed for this type of research.

Although there are studies that correlate vitamin B12 deficiency with certain neurological, psychiatric and hematological manifestations, these manifestations may vary in the populations studied. (12, 13) It is difficult to determine precisely the percentage of clinical alterations that are explained by this nutritional deficit. In this regard, vitamin B12 deficiencies at hospital admission were found in 7% in a geriatric population in Colombia while anemia was found in 76.4%. (14) However, these isolated data do not allow accurate determination of which patients' anemia might be explained by Vitamin B12 deficiency alone. Based on these limitations, we consider that a cohort study is required to answer these questions. The association of chronic IBD consumption with low levels of vitamin B12 found in this study could stimulate additional research with a larger number of patients and with longer follow-up times on the use of PPIs in order to accurately determine repercussions on hematological and neuropsychiatric parameters.

In conclusion, the use of PPIs for more than three years was found to be associated with decreased serum levels of vitamin B12 with no apparent clinical impact on general physical examinations. Age, sex, type of PPI and dosage used are not independent factors related to this decrease. To establish causality between prolonged use of PPIs and decreased vitamin B12 levels, a study with more patients and with another design is needed.

Financing

The authors declare that they received no financial support for this study.

Declaration of Conflicts of Interest

Dr. William Otero has lectured for, and received fees from, Abbott-Lafrancol, Tecnofarma, La-Santé Laboratories, Procaps and Takeda Laboratories. Drs. Adán Lúquez, Hernando Marulanda and Douglas Rodríguez did not express any conflicts of interest.

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