ORIGINAL ARTICLE

OMEPRAZOLE: A CAUSE OF VITAMIN B12 DEFICIENCY - A HOSPITAL-BASED STUDY

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Editorial received on: 05-06-2019

Editorial accepted on: 28-11-2019

ABSTRACT

This cross sectional prospective research study was done in the Department of Medicine, Indus Medical College, Tando Muhammad Khan. Study duration was from 05 February 2018 to 06 February 2019. It included all patients both female and male. All patients above 15 years of age, of either gender with history of recurrent abdominal pain, dyspepsia or abdominal discomfort, heartburn, GERD, H. Pylori positive patients, patients with gastritis, esophagitis, peptic and duodenal ulcer, bloating and halitosis through outdoor patient department (OPD), were enrolled in the study. The detailed history of all such patients was taken and complete physical and relevant clinical examination was performed. Vitamin B12 deficiency was considered when serum B12 level was <350 pg/ml. The informed consent was taken from every patient or from attendants of patients after full explanation of procedure regarding the study and all such manoeuvres was performed under medical ethics and through the cooperation of whole research team. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. Venous blood samples were collected in the morning after an overnight fast from 11.00 pm for Vitamin B12 levels. During one year study period, 250 patients on long term use of omeraparzole were studied for vitamin B12 deficiency, of which 143 (57.2%) were males and 107(42.8%) were females. The observed symptoms included recurrent abdominal pain in 38(15.2%), dyspepsia or abdominal discomfort in 40(16%), heartburn in 50(20%), bloating in 13(5%), halitosis in 08(3.2%) and combined / mixed symptoms in 17(11%) patients. Of two hundred fifty patients, 120 (48%) had raised MCV with vitamin B12 deficiency.

Article Citation:
Suthar RK, Bai K, Zaki M. Omeprazole: A Cause of Vitamin B12 Deficiency – A Hospital – Based Study. JIMC. 2019; 2(2): 15-22

INTRODUCTION

Proton-pump inhibitors (PPIs) such as omeprazole are one of the most widely prescribed classes of drugs worldwide. PPIs are indicated for treatment of ulcers with or without Helicobacter pylori infection; for treatment of gastroesophageal reflux, Zollinger-Ellison disease, dyspepsia, esophagitis and gastritis; and for prevention of peptic ulcers in patients receiving non-steroidal inflammatory agents (NSAIDs) and in patients with upper gastrointestinal bleeding.[1-2]

Proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H_2RAs) suppress the production of gastric acid and thus may lead to malabsorption of vitamin B_{12}. Vitamin B_{12} deficiency was more common among persons with a 2-year or greater supply of PPIs compared with nonusers. [3] Mechanism of action of omeprazole centers on inhibition of the H^+/K^+ ATPase enzyme in gastric mucosal parietal cells, which is responsible for hydrogen ion secretion in exchange for potassium ions in the gastric lumen. [4]

B_{12} is a protein-bound vitamin introduced mainly through dairy products and meat that requires the presence of gastric acid and pepsin to be liberated in the stomach. It subsequently binds to R factors forming a non-absorbable complex present in saliva and gastric juice. In the duodenum, the alkaline pancreatic juice that contains proteases brakes up the binding between B_{12} and R factor allowing the cobalamine to bind with the intrinsic factor, a necessary step for it to be absorbed in terminal ileum.[5]

Proton pump inhibitors are among the most commonly prescribed classes of drugs, and their use is increasing, in particular for long-term treatment, often being over-prescribed and used for inappropriate conditions. In recent years, considerable attention has been directed towards a wide range of adverse effects, and even when a potential underlying biological mechanism is plausible, the clinical evidence of the adverse effect is often weak. Several long-term side effects have been investigated ranging from interaction with other drugs, increased risk of infection, reduced intestinal absorption of vitamins and minerals, and more recently kidney damage and dementia.[6] Recent studies have suggested that long-term treatment with PPIs may accelerate the development of atrophic changes of the gastric mucosa, especially in H. pylori-infected individuals.[7] Vitamin B_{12} (B_{12}; also known as cobalamin) is a B vitamin that has an important role in cellular metabolism, especially in DNA synthesis, methylation and mitochondrial metabolism. [8] Vitamin B_{12} deficiency is a common cause of megaloblastic anemia, various neuropsychiatric symptoms, and other clinical manifestations. Screening average-risk adults for vitamin B_{12} deficiency is not recommended. Screening may be warranted in patients with one or more risk factors, such as gastric or small intestine resections, inflammatory bowel disease, use of metformin for more than four months, use of proton pump inhibitors or histamine H_2 blockers for more than 12 months, vegans or strict vegetarians, and adults older than 75 years.[9]

There is also an association of decreased absorption of vitamin B_{12} in elderly population. Therefore, patients utilizing long-term PPIs and/ or elderly populations will have decreased absorption of vitamin B_{12} from food sources. [10-11] To reduce the likelihood of low levels of B_{12}, it is recommended to take B_{12} supplements or ingest B_{12} fortified foods to counteract malabsorption. Side effects associated with low vitamin B_{12} levels include anemia, fatigue, weakness, constipation, loss of appetite and weight loss. [12] To prevent the development of these side effects, it is important to have B_{12} levels monitored when on long term PPI therapy.

The rationale of this study is to explore the association of vitamin B_{12} in the patients taking omeprazole for long duration.There is no data to assist particular care in prescribing omeprazole therapy due to concerns about risk of vitamin B_{12} deficiency with the long-term use of omeprazole. Long-term use of omeprazole does not lead to vitamin B_{12} deficiencies, except possibly in the elderly, or in persons with Zollinger-Ellison Syndrome who are on high doses of omeprazole for prolonged periods of time. There is no convincingly proven data available in our population that omeprazole increase the risk of vitamin B_{12} deficiency so this study has been conducted to determine the frequency of vitamin B_{12} deficiency in patients on long term omeparazole.

It is hypothesized that vitamin B_{12} levels alter in the patients who are taking omeprazole for long duration.

METHODOLOGY

This cross sectional prospective research study was done in the Department of Medicine, Indus Medical College, Tando Muhammad Khan. Study duration was from 05 February 2018 to 06 February 2019. It included all patients both female and male. All patients above 15 years of age, of either gender with history of recurrent abdominal pain, dyspepsia or abdominal discomfort, heartburn, GERD, H. Pylori positive patients, patients with gastritis, esophagitis, peptic and duodenal ulcer, bloating and halitosis through outdoor patient department (OPD), were enrolled in the study. The detailed history of all such patients was taken and complete physical and relevant clinical examination was performed. Vitamin B_{12} deficiency was considered when serum B_{12} level was <350pg/ml.[17] The informed consent was taken from every patient or from attendants of patients after full explanation of procedure regarding the study and all such maneuvers was performed under medical ethics and through the cooperation of whole research team. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. Venous blood samples were collected in the morning after an overnight fast from 11.00 pm for Vitamin B_{12} levels. Long-term use of omeparazole (ATC codes A02BC01 through A02BC05) was defined as prescription of >270 Defined Daily Doses (DDD) of PPIs per year for 3 years or more (>810 DDD in 3 years).

The exclusion criteria of the study were; (1) Non-cooperative patients who refused to give consent or participate in the study (2) Patients on metformin therapy, (3) Patients who were on long-term uric acid lowering therapy, and patients who were on potassium intake (4) Anemic patients with the primary disease, such as hepatic disease, haemolytic anemia, cancer, aplastic anaemia, myeloproliferative disease, red cell aplasia, multiple myeloma, leukemia, chronic lung disease, chronic kidney disease and those using immunosuppressive or chemotherapeutic drugs, (5) Pregnant females and alcoholics, (6) Patients with history of resection of stomach or small bowl surgery, (7) Vegetarian population and (8) Patients with malabsorption syndrome and folic acid deficiency. Whereas, to control confounders of the study all patients were also interviewed to exclude known medical problems that couldaffect vitamin B^{12} status and to determine that they had not received cyanocobalamin treatment parenterally.

The collected data was analyzed in SPSS version 18.00. The frequency and percentage of gender and serum B_{12} deficiency in Helicobacter pylori patients was calculated. The mean and standard deviation (SD) was calculated for age. The independent-samples t-test was applied between categorical variables, Chi-square was applied to determine the statistical difference in gender and the p-value <0.05 was considered as statistically

significant. The mentioned statistical tests were applied at 95% confidence interval (CI).

RESULTS

During one year study period, 250 patients on long term use of omeraparzole were studied for vitamin B_{12} deficiency, of which 143 (57.2%) were males and 107(42.8%) were females. The observed symptoms included recurrent abdominal pain in 38 (15.2%), dyspepsia or abdominal discomfort in 40(16%), heartburn in 50(20%), bloating in 13(5%), halitosis in 08(3.2%) and combined / mixed symptoms in 17(11%) patients. Of two hundred fifty patients, 120 (48%) had raised MCV with vitamin B12 deficiency. The mean age ±SD (ranged) of overall subjects with statistical difference is shown in Table 1 whereas the mean age ± SD of vitamin B_{12} deficient male as well as female subjects was 45.17±11.86 and 46.12±13.01 (P=0.73).

One hundred and thirty (130/52%) patients on omeprazole had normal vitamin B_{12} level and the mean age ± SD of such category's male and female was 45.38±14.16 and 47.21±12.7 (P=0.62). The mean ± SD of serum vitamin B_{12} level in overall subjects (male and female) was 310.717±223.447 pg/ml and 251.342±31.919 pg/ml (P=0.001) respectively.

The mean vitamin B_{12} level on omeprazole subjects with low vitamin B^{12} (male and female) was 136.250±21.423 pg/ml and 142.625±19.969 pg/ml (P=0.22) where as it was 532.459±157.448 pg/ml and 618.170±141.931 pg/ml (P=0.01) on omeprazole subjects (male and female) with normal serum vitamin B_{12} level. The frequency of vitamin B^{12} deficiency observed in on omeprazole patients is shown in Table 2.

In this series, among the patients taking omparazole for 3 years or more, the mean duration of omeprazole use + SD (ranged) was 4.3 ± 0.71 (3 to 8 years) and mean of daily omeprazole dose was 40 mg per day.

Table 1: Demographic characteristics of the patients (n = 150)

	Number	Percentage (%)
Age (in years), Mean ± SD	44.17 ± 12.9	
Age Range (in years)	15 to 60	
Age in Groups (in years)		
15-30	23	9.2
31-40	102	40.8
41-50	33	18
51-60	45	13.2
>60	47	18.8
Gender		
Male	143	57.2
Female	107	42.8
Duration of Omeprazole Use (in years)	4.3 ± 0.71 (3-8 years)	
Daily Omerprazole Use	40mg	

Table 2: Symptoms and Level of Vitamin B_{12} in Patients Using Omeprazole (n=150)

	Number	Percentage (%)
Symptoms		
Nausea	40	16
Vomiting	28	11.2
Recurrent abdominal pain	38	15.2
Dyspepsia or abdominal discomfort	40	16
Heartburn	50	20
Bloating	13	5
Halitosis	08	3.2
Combined/Mixed Symptoms	17	11
Vitamin B_{12} Deficiency		
Yes	120	48
No	130	52
Normal Vitamin B_{12} Level		
Overall, Mean ± SD	627.361 ± 110.221	
Male	532.459 ± 157.448	
Female	618.170 ± 141.931	
Low Vitamin B_{12} Level		
Overall, Mean ± SD	138.362 ± 18.32	
Male	136.250 ± 21.423	
Female	142.625 ± 19.969	

DISCUSSION

The advent of proton pump inhibitors (PPIs) has revolutionized the treatment of acid-related disorders, in particular gastroesophageal reflux disease. These drugs have been always considered highly effective and safe, because of the small number of adverse events reported in medical literature. Nevertheless, in the last years the attention of both physicians and patients has been attracted by a mounting number of publications reporting the occurrence of many serious adverse events, particularly with long-term use of PPI therapy.[13,14] In our study, use of omeprazole for 4.3 years was associated with a subsequent new diagnosis of vitamin B_{12} deficiency. The magnitude of the association was stronger in women and younger age groups.

Omeprazole, a substituted benzimidazole, is a specific inhibitor of the enzyme H^+/K^{+-} ATPase, which is found on the secretory surface of the parietal cell. This enzyme, the "proton pump", catalyzes the final step in acid secretion. [15] Gastric acid is required to cleave vitamin B_{12} from ingested dietary proteins for the essential

vitamins to be absorbed, and it is produced by the same cells that produce intrinsic factor, a compound required for vitamin B_{12} absorption. [16] In this study, among the patients taking omeprazole, the mean duration of omeprazole use was 4.3 years with daily omeprazole dose was 40mg per day and 48% found with deficient vitamin B_{12} levels. Similarly, Lewis JR and coworkers revealed that long-term PPI users were more likely to have low vitamin B_{12} levels versus non-users (50% versus 21%, $p = 0.003$). [17] TS Dharamrajan et al concluded that B_{12} status declines during prolonged PPI use in older adults, but not with prolonged H2 blocker use. PPI use was associated with diminished serum B_{12} levels ($P < .00005$). [18] Lam et al. correspondingly demonstrated that long-term PPI use was associated with a doubling in the risk of clinically diagnosed vitamin B_{12} deficiency. [3] Qorraj-Bytyqi H et al concluded that PPIs use for short term therapy did not result in clinically significant iron and/or vitamin B_{12} deficiency; thus, these findings argue routine screening under normal circumstances, although monitoring in elderly and malnourished may be of precious value. [13]

PPIs work by blocking gastric H^+K^+-ATPase, which is responsible for pumping H^+ ions from within gastric parietal cells into the gastric lumen, where they react with Cl^- ions to form hydrochloric acid. A lack of gastric acid and pepsin decreases the release of vitamin B_{12} from proteins in food and thus reduces its availability for absorption in the ileum. [19] Consequently; omeprazole is PPI and so suppresses the production of gastric acid, may lead to malabsorption of vitamin B_{12}. Vitamin B_{12} (cobalamin) deficiency is a common cause of macrocytic anemia and has been implicated in a spectrum of neuropsychiatric disorders. The role of B_{12} deficiency in hyperhomocysteinemia and the promotion of atherosclerosisis is being explored. [20] Proton-pump inhibitors (PPIs) seem to increase the incidence of cardiovascular events in patients with coronary artery disease (CAD), mainly in those using clopidogrel. [21] The spectrum of diseases associated with vitamin B_{12} 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. [22] According to Green R [23] et al, using PPIs for more than three years is related to decreased serum levels of vitamin B_{12}. 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 ($p = 0.519$).

CONCLUSION

The use of omeprazole for long period was found to be associated with vitamin B_{12} deficiency. To provide more authentic correlation, study on large population is required Clinicians should adopt the exercise for appropriate vigilance while considering such deficiencies in routine practice, and should prescribe these medications at lowest possible effective dose.

References

1. Li W, Zeng S, Yu LS, Zhou Q. Pharmacokinetic drug interaction profile of omeprazole with adverse consequences and clinical risk management. Ther Clin Risk Manag. 2013;9:259-71.
2. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical

implications. Therapeutic advances in drug safety. 2013; 4(3):125-33.

3. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. Jama. 2013; 310(22):2435-42.

4. Sheen, E., Triadafilopoulous, G. Adverse effects of long-term proton pump inhibitor therapy. Dig Dis Sci. 2011; 56: 931–950.

5. Green, Ralph, Kinsella LJ. "Current concepts in the diagnosis of cobalamin deficiency." Neurology (1995): 1435-1440.

6. Eusebi LH, Rabitti S, Artesiani ML, et al. Proton pump inhibitors: risks of long-term use. Journal of Gastroenterology and Hepatology. 2017; 32(7):1295-302.

7. Li Z, Wu C, Li L, Wang Z, Xie H, He X, Feng J. Effect of long-term proton pump inhibitor administration on gastric mucosal atrophy: A meta-analysis. Saudi Journal of Gastroenterology: Official Journal of the Saudi Gastroenterology Association. 2017;23(4):222.

8. Green R, Allen LH, Bjørke-Monsen AL, Brito A, Guéant JL, Miller JW, Molloy AM, Nexo E, Stabler S, Toh BH, Ueland PM. Vitamin B 12 deficiency. Nature reviews Disease primers. 2017. 29;3(1):1-20.

9. Langan RC, Goodbred AJ. Vitamin B12 deficiency: recognition and management. American Family Physician. 2017; 96(6):384-9.

10. Thomson A, Sauve M, Kassam N, Kamitakahara. Safety of the long-term use of proton pump inhibitors. World J Gastroenterol. 2010; 16(19):2323-30.

11. Ito T, Jenson R. Association of Long-Term Proton Pump Inhibitor Therapy with Bone Fractures and effects on Absorption of Calcium, Vitamin B12, Iron and Magnesium. Curr Gastroenterol Rep. 2010; 12(6):448-57.

12. Alqutub AN, Masoodi I. A case of gastric polyposis in antral area of stomach following prolonged proton-pump therapy. Ger Med Sci. 2010; 2(8):pii Doc19.

13. Qorraj-Bytyqi H, Hoxha R, Sadiku S et al. Proton pump inhibitors intake and iron and vitamin B12 status: a prospective comparative study with a follow up of 12 months. Open Access Macedonian Journal of Medical Sciences. 2018;6 (3):442

14. Savarino E, Marabotto E, Zentilin P, Furnari M, Bodini G, Pellegatta G etail. A safety review of proton pump inhibitors to treat acid-related digestive diseases. Expert Opinion on Drug Safety. 2018; 17(8):785-94.

15. Holt S, Howden CW. Omeprazole. Digestive Diseases and Sciences. 1991. 1;36(4):385-93.

16. Toh BH, van-Driel IR, Gleeson PA. Pernicious anemia. N Engl J Med. 1997;337(20):1441-1448.

17. Lewis JR, Barre D, Zhu K et al. Long-term proton pump inhibitor therapy and falls and fractures in elderly women: a prospective cohort study. Journal of bone and Mineral Research. 2014; 11:2489-97.

18. Dharmarajan TS, Kanagala MR, Murakonda P, Lebelt AS, Norkus EP. Do acid-lowering agents affect vitamin B12 status in older adults? Journal of the

American Medical Directors Association. 2008.1;9(3):162-7.

19. Miller JW. Proton pump inhibitors, H2-receptor antagonists, metformin, and vitamin B-12 deficiency: clinical implications. Advances in Nutrition. 2018; 9(4):511S-8S.

20. Oh R, Brown DL. Vitamin B12 deficiency. American Family Physician. 2003. 1; 67(5):979-86.

21. PelloLázaro AM, Cristóbal C, Franco-Peláez JA, Tarín N, Aceña Á, Carda R etail, Use of proton-pump inhibitors predicts heart failure and death in patients with coronary artery disease. PLoS One. 2017; 12(1):e0169826.

22. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. J Clin Epidemiol. 2004; 57:422-8.

23. Green R. Vitamin B12 deficiency from the perspective of a practicing hematologist. Blood. 2017 May 11; 129(19):2603-11.