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Review Article

A Review on Vitamin B12 and Iron Deficiency Anaemia Linked with Persistent Use of Gastric Acid Suppressants

Arumugavignesh M[1*], Jeya Ananthi J[2], Soffia Mary J[1], Jessica P[1], Nandhini S R[1]

[1]*Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, Tamilnadu, India.*
[2]*Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankoil, Tamilnadu, India.*

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ABSTRACT

Globally Anaemia is a public health hurdle influencing both developing and developed countries at all ages. World Health Organization (WHO) defines Anaemia as the hemoglobin (Hb) levels <12.0 g/dl in women and <13.0 g/dl in men. Etiology of Anaemia is often multi factorial. Among those, prolonged use of acid suppressants in hospitalized, ambulatory and non ambulatory patient setting is a notorious one. Acid suppressants are the therapeutic agents which prove to be effective in the treatment of common gastro intestinal disorders like peptic ulcer, Gastro Esophageal Reflux Disease etc. Acid suppressants can be classified into three pharmacological classes namely histamine-2 receptor antagonists, proton pump inhibitors and miscellaneous. These are often used for prolonged period of time in many a circumstances to inhibit the secretion of gastric acid. The gastric acid is necessary for the absorption of Vitamin-B 12 and Iron. This paves the way for the incidence of Iron and Vitamin-B12 deficiency Anaemia in some patients as an adverse effect. This review exemplifies the mechanism associated with this and also compares the results of various research works, case reports those are similar to this topic. It also sheds light towards the clinical management of different types of Anaemia induced by persistent use of acid suppressants.

1. Introduction

Anaemia is an intercontinental public health hurdle influencing both developing, developed and underdeveloped countries at all ages. World Health Organization (WHO) defines Anaemia as the hemoglobin (Hb) levels <12.0 g/dl in women and <13.0 g/dl in men.[1] Most of the Anaemia is related to the gastro intestinal system by nutritional deficiency, mal absorption, or chronic hemorrhage.[2] Anaemia contributes to 8.8% of the total malady from all conditions in the year 2010. Children less than five years and women are more vulnerable to this. Although iron-deficiency Anaemia is the most common etiology globally, other leading causative factors of Anaemia vary significantly by geography, age, and gender.[3] Besides that Anaemia is often under diagnosed in both clinical and outpatient settings. If left untreated, Anaemia put forth various health risks like sever fatigue, tissue hypoxia, pregnancy complications, heart problems and even sometimes fatal.

Acid suppressants are inevitable agents used in the treatment of gastro intestinal ailments like peptic ulcer, drug induced ulcers and Gastro Esophageal Reflux Disease (GERD).[4] Acid suppressants are pharmacologically classified into two broad categories namely histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs). Other miscellaneous classes of drugs are also used in some clinical conditions. Nevertheless, their prolonged use is attributed to various hematological adverse effects. Among those decreased dietary iron and vitamin B_{12} absorption is a noteworthy one.[5] This review discusses the mechanism associated with acid suppressants induced Vitamin-B_{12} deficiency, Iron deficiency Anaemia and also compares the results of various research works, case reports those are similar to our study topic.

* *Corresponding author.* Tel.: +918072046740.
E-mail address: m.arumugavignesh20@gmail.com

Iron Deficiency Anaemia

Iron deficiency Anaemia (IDA) is the most prevalent form of Anaemia in this earth.[6] Under the morphological classification of WHO, it comes under microcytic hypochromic Anaemia. Menstruating women, pregnant women and children below five years of age who have diet low in iron are at high risk of getting IDA.[7] Patients with gastro intestinal disorders like peptic ulcer, inflammatory bowel disease are also at the same risk. In the human body, iron is ubiquitous in all cells. It has many significant functions such as transporting oxygen to the tissues from the lungs in the form of hemoglobin (Hb). It also promotes oxygen utility and stockpile in the muscles as myoglobin and act as a carrier medium for electrons within the cells in the form of cytochromes. It is also an integral component of enzyme reactions in variety of tissues. Hence it is understood that deficiency of iron can interrupt all these vital functions and results in significant rate of morbidity and mortality.[8] Iron is available in ferric (Fe^{3+}) the most stable form in most of the food substances.[9] Indeed, it is better absorbed in ferrous (Fe^{2+}) form. Stomach hydrochloric acid plays a significant part in the conversion of ferric form to ferrous form.[10] Duodenum and proximal jejunum are the principal sites of absorption for dietary iron.[11]

The Recommended Daily Allowance (RDA) of Iron is 13.7–15.1 mg/D in children aged 2–11 years, 16.3 mg/D in children and teens aged 12–19 years, and 19.3–20.5 mg/D in men and 17.0–18.9 mg/D in women older than 19. The median dietary iron intake in pregnant women is 14.7 mg/day.[12] Red meat, pork, poultry, seafood, beans, dark green leafy vegetables such as spinach, dried fruit such as raisins and apricots, Iron-fortified cereals, breads and pastas, Peas are the food products that are found to be rich sources of iron.[13]

The clinical investigation criteria for iron deficiency Anaemia are low hemoglobin (<7.7 mmol/l in men and 7.4 mmol/l in women), a low serum iron (<7.1 µg/l), a low serum ferritin (storage form of iron) (<30 ng/l), a low transferrin saturation (<15%), and a high total iron-binding capacity (>13.1 µmol/l).[14]

IDA can be treated with oral and parenteral therapy. In asymptomatic and mildly symptomatic patients with IDA, oral iron replacement is the common evidence based treatment. Various other oral iron salts like ferrous sulfate, ferrous gluconate, and ferrous fumarate are now available.[15] Ferrous sulfate is used widely among these three products. Parenteral iron therapy is confined to patients who have mal absorptive diseases. High molecular weight dextran, low molecular weight dextran, Iron sucrose, Sodium ferric gluconate complex are the available forms of parenteral iron supplement for the treatment.[16]

Vitamin-B12 deficiency Anaemia

Vitamin-B_{12} deficiency Anaemia is the second most prevalent forms of Anaemia in the recent decade. It is also known as pernicious Anaemia.[17] Cobalamin is another name for Vitamin-B_{12}. Morphologically, it comes under megaloblastic Anaemia. Strict vegans, babies of lactating mothers who have vitamin-B_{12} deficiency, geriatrics, chronic alcoholics are at high risk of developing vitamin B_{12} deficiency Anaemia.[18] Patients who are having atrophic gastritis, people who are lacking intrinsic factors (IF) are also at high risk.[19] Vitamin-B_{12} as a supplement is essential for the production of red blood cells and DNA (De oxy ribo Nucleic Acid), the genetic material in humans. It also especially plays a vital role in the normal functioning of neurons.[20] Deficiency of vitamin-B_{12} affects all these vital functions. In food products, vitamin-B_{12} is present as bounded to protein. Stomach's hydrochloric acid plays a significant role in the separation of vitamin-B_{12} from the bound protein.[21] Then vitamin-B_{12} is conjugated with intrinsic factor (IF) which is secreted by the parietal cells of stomach. Consequently it gets absorbed primarily in distal ileum and then to the systemic circulation for the physiological need.[22]

Recommended daily intake of Vitamin-B_{12} is 0.9 µg in children below nine years, 2.4 µg in children above nine years and adults, 2.6 µg in pregnant women and 2.8 µg in breast feeding mothers.[23] Clams and beef liver are the richest sources of vitamin B-$_{12}$. Fish, eggs, poultry, meat, milk, and other dairy products also contain vitamin-B_{12} in significant quantity.

The conclusive test of serum cobalamin levels which if less than148 pmol/L is highly sensitive for the confirmation of Vitamin-B_{12} deficiency Anaemia.[24] Till today there is no 'gold standard' criteria available for the detection of vitamin-B_{12} deficiency and as a result, the diagnosis requires both clinical manifestations of the patient and the results of investigations. The anti-IF antibody test is a specific investigation for the diagnosis of pernicious Anaemia caused by the insufficient secretion of intrinsic factor from gastric parietal cells.[25]

Oral, parenteral and nasal formulations are available for the management of Vitamin-B_{12} deficiency Anaemia.[26] Patients with no neurological manifestations are treated usually with the regimen of hydroxocobalamin 1 mg on alternate days for two weeks. It is then followed by three-monthly injections of hydroxocobalamin 1 mg.[27] Vitamin-B_{12} is ready for use as a nasal spray for patients in remission succeeding intramuscular administration who have no neurological manifestations.[28] The nasal spray 500 µg/Week is administered once weekly.

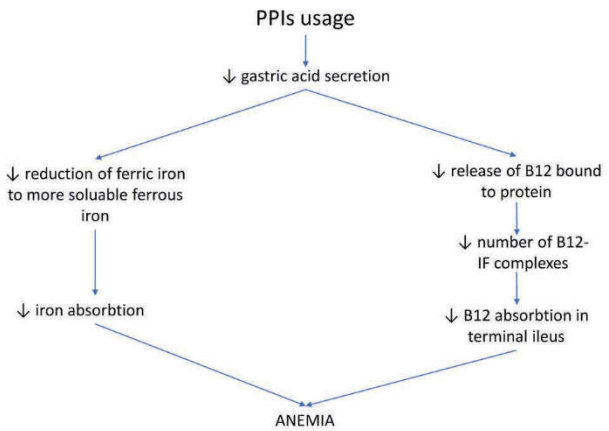

Figure 1. Portraits the mechanism of PPIs induced Iron and Vitamin-B_{12} deficiency Anaemia

Mechanism behind acid suppressants' induced Iron deficiency Anaemia

Acid suppressants are pharmacologically categorized into two types; H_2 blockers and proton pump inhibitors. Histamine-2 blockers are now are in hand both as over the counter drugs and as prescription drugs. Cimetidine was the first introduced H2 blocker.[29] Ranitidine, Nizatidine and Famotidine are the familiar ones. These drugs are antagonists of parietal cell H_2 receptors, declining cAMP (cyclic Adenosine Mono Phosphate) and resultant H^+/K^+ pump activity.[30] H_2 receptor antagonists block basal levels of gastric acid secretion *and may block* meal-stimulated secretion (which is gastrin mediated) to some extent. As a result of stop up of gastric acid secretion and usage of H2 blockers for prolonged period, dietary iron cannot be absorbed properly and finally leads to Iron deficiency Anaemia.[31] This is because of necessity of low pH of gastric acid in the proximal duodenum to allow ferric reductase enzyme and duodenal cytochrome B (Dcytb), on the brush border membrane of the enterocytes to

transmogrify the insoluble ferric (Fe3+) to absorbable ferrous (Fe2+) ions.[32] The gastric acid is also responsible plasma iron homeostasis.

Similarly Proton pump inhibitors (PPIs) like omeprazole, pantoprazole etc impedes the secretion of gastric acid by binding covalently with *H+/K+ ATPase* enzyme which eases the way for hydrogen and potassium exchange through parietal cells, which results in the export of potassium and generation of HCl (gastric acid).[33] This extended inhibition of gastric acid secretion finally leads dwindles iron absorption and results in Iron deficiency Anaemia.[34]

Mechanism behind acid suppressants' induced Vitamin-B12 deficiency Anaemia

Vitamin-B_{12} (cobalamin) in food products is almost found to be bound with proteins. After ingestion, the low stomach pH created by gastric acid liberates cobalamin from other dietary protein. The free cobalamin then aggregates with the gastric R binder (transcobalamin), a glycoprotein in saliva, and the aggregate travels to the duodenum and jejunum.[35]The pancreatic peptidases assimilate the aggregate and release cobalamin. Then, it ties up with gastric intrinsic factor (IF), a glycoprotein produced by gastric parietal cells, secretions of which is equivalent to that of gastric acid secretion.[36] Cobalamin complexed with IF then gets absorbed in ileum of small intestine. Hence, in states of prolonged use of acid suppressants like H_2 blockers and Proton pump inhibitors both IF secretion and gastric acid secretion is reduced.[37] Thus, this mechanism greatly restrains the absorption of Vitamin-B_{12} which eventually leads to the incurrence of Vitamin-B_{12} deficiency Anaemia.[38]

2. Discussion

Here with, from our review we discuss and compare the results of various case reports and research articles to espouse the confirmation of prevalence of acid suppressants' induced Iron and Vitamin-B_{12} deficiency Anaemia. A retrospective cohort study conducted by Erin Sarzynski *et al* strongly proves the remarkable decline in hematologic indices from baseline among adult patients who were chronic users of proton pump inhibitors in an outpatients setting. They found a notable decrease in hematologic indices with the inclusion of hemoglobin (P=0.03), hematocrit (P=0.02), and mean corpuscular volume (P=0.05).[39] A community based case-control study conducted by Jameson R *et al* robustly correlates the relationship between prolonged acid suppressants intake and iron deficiency Anaemia. They found that among 77,046 Iron deficiency anemic patients, 2343 (3.0%) were provided with the earlier supply of PPIs and 1063 (1.4%) were received a prior supply of H2RAs for > two years.[40] A case-control study done using CPRD Gold by Tran-Duy A *et al* confirms the positive association between chronic PPI use in terms and conditions of both duration and frequency of pharmacotherapy and soared up risk of iron deficiency Anaemia. The total cases were found to be 26,806 in this study. The quantitative data of full users of proton pump inhibitors, limited users of proton pump inhibitors or non users of proton pump inhibitors in cases and controls are significantly different (p-value< 0.001).[41] A case report of 52 year old man reviewed by Ryosuke Imai *et al* reports the development of Iron deficiency Anaemia in that patient who had been taking omeprazole for the past 25 years.[42]

A case-control study in a University-based geriatric primary care setting conducted by Valuck R J *et al* divulged the increased risk of vitamin-B_{12} deficiency resulted due to use of H2RA/PPI s (OR 4.45; 95% CI 1.47-13.34).[43] A roosted case-control study within the Kaiser Permanente Northern California (KPNC) integrated healthcare system conducted by Lam J R *et al* confirms the relationship between previous and current gastric acid suppressants use with the existence of vitamin B_{12} deficiency.[44] A case report of 78-year-old non vegetarian white woman with symptomatic gastro esophageal reflux reviewed by Ruscin J M *et al* confirms the development of vitamin B_{12} deficiency associated with long-term use (~4½ years) of histamine$_2$ (H_2)-receptor antagonists and a proton-pump inhibitor (PPI).[45] A cross-sectional sample analysis of 659 adult patients done by Dharmarajan T S *et al* reports the downturn of Vitamin-B_{12} level during extensive PPIs use in older adults, but not with extensive H2 blocker use.[46]

3. Conclusion

Iron and Vitamin-B12 deficiency occurs more habitually in patients who are taking acid suppressants for a prolonged period of time. Patients should not be prescribed unnecessarily with acid suppressants without any proper clinical indication. Clinicians should be prudently vigilant while prescribing these drugs and should scrupulously use the lowest possible effective doses as per the individual's requirement. Prescribing doses of acid suppressant drugs should be optimized rationally as per ethical and professional consensus. Regular monitoring of Iron and Vitamin-B12 status in patients who are taking acid suppressants for prolonged period is necessitated. Iron and Vitamin-B12 supplements may not be helpful to overcome this while concomitantly using acid suppressants. However, with drawl of acid suppressants can provide beneficial outcomes. In the near future further studies in these aspects would enhance reduction in the mortality and morbidity of Anaemia.

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Conflict of Interest

The author(s) confirm that this article content has no conflict of interest.

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