CHANGES IN HAEMATOLOGICAL AND BIOCHEMICAL PARAMETERS IN PATIENTS DUE TO LONG-TERM USE OF OMEPRAZOLE

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ABSTRACT

Introduction: Omeprazole (OMZ) is the most frequently used PPI in conditions of Gastroesophageal Reflux Disease (GERD), gastric/duodenal ulcer, erosive esophagitis, H. pylori infection, in addition to being prescribed as a gastric protector in case of use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) (Sambugaro et al., 2021). Drugs of this class are often well tolerated, their adverse effects are usually manifested with the prolonged use of PPIs (Haastrup et al., 2018). Biochemical alterations may occur, such as hypocalcemia, hypokalemia, hypomagnesemia (Isse; Hashimoto, 2020). Methodology: For the construction of the present research, a systematic review of the qualitative literature was carried out. In this review study, in the search phase, the search was carried out in journal articles, books and dissertations. Results and discussion: According to the study carried out, the prolonged use of omeprazole can generate a series of complications, among them we can mention the decrease in the absorption of vitamin B12, important for hormonal development and for the formation of red blood cells (red blood cells), and iron deficiency, as its use affects the intestinal absorption capacity of micro-elementary nutrients. In addition to affecting the absorption of vitamins and minerals, prolonged use of omeprazole can cause hematological changes such as MCV (Mean Corpuscular Volume), HCM (Mean Corpuscular Hemoglobin) and MCHC (Mean Corpuscular Hemoglobin Concentration). Conclusion: Taking into account the preference for the use of omeprazole as a proton pump inhibitor in the treatment of acid-peptic disorders, attention should be paid to the harm caused by the prolonged use of this drug.

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INTRODUCTION

The gastrointestinal tract is made up of a set of organs (mouth, pharynx, esophagus, stomach, small intestine, large intestine, rectum and anus) that have the function of promoting the digestion of food, in order to absorb nutrients, such as water, macronutrients, micronutrients and electrolytes, necessary for the full functioning of the body, from the conversion of food into absorbable molecules (Tortora; Derrickson, 2017).

The stomach is a fundamental organ for the functioning of the digestive system. It is composed of four regions (cardia, gastric fundus, gastric body and pylorus), and has gastric glands that help its performance. Peristalsis waves favor the digestion of food in smaller sizes, contributing to the process of digestion and stomach absorption (Tortora; Derrickson, 2017).

The gastric glands, responsible for releasing substances that make up gastric juice, are composed of 3 types of cells: mucous cells of the colon, main and parietal. The mucous cells of the cervix secrete mucus, the main cells secrete gastric lipase and pepsinogen, and the parietal cells produce hydrochloric acid, which transforms pepsinogen into pepsin, the enzyme responsible for the digestion of proteins (Tortora; Derrickson, 2017).

The use of Proton Pump Inhibitors are effective and allow for prolonged therapy, however, users are not exempt from adverse effects over time; calcium deficiency is an adverse effect due to the ability of this class to reduce calcium absorption. Omeprazole (OMZ) is the most frequently used PPI in conditions of Gastroesophageal Reflux Disease (GERD), gastric/duodenal ulcer, erosive esophagitis, *H. pylori infection*, in addition to being prescribed as a gastric protector in case of use of Non-Steroidal Anti-inflammatory Drugs (NSAIDs) (Sambugaro et al., 2021).

Drugs of this class are often well tolerated, their adverse effects are usually manifested with the prolonged use of PPIs, such as the appearance of enteric infections, due to their mechanism of action resulting in hypochlorhydria, which is summarized in a reduction of hydrochloric acid, favoring bacterial colonization; another adverse effect related to hypochlorhydria is its interference in the ionization of calcium that facilitates its absorption, as a consequence of this process hypocalcemia arises, which favors the emergence of other diseases, such as osteoporosis (Haastrup et al., 2018).

Therefore, since the prolonged use of omeprazole results in biochemical alterations, it is necessary to evaluate these parameters in patients with prolonged use of this proton pump inhibitor, because commonly, in this context, biomarkers undergo alterations, such as hypocalcemia, hypokalemia, hypomagnesemia, respectively, reduction of serum calcium

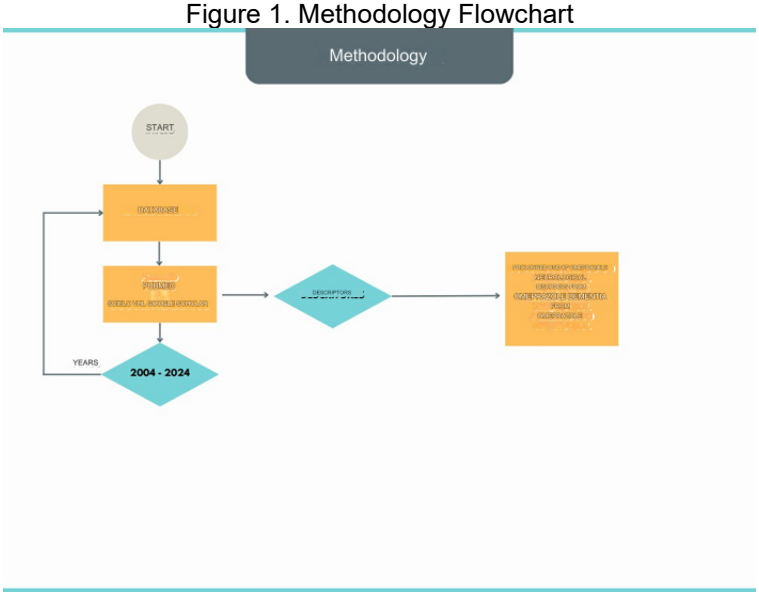
levels, reduction of potassium levels and below-normal levels of magnesium value (Isse; Hashimoto, 2020).

METHODOLOGY

The present work is a systematic review of the qualitative literature. In this review study, in the search for literature, the search was carried out in journal articles, books and dissertations. In this phase, we used descriptors such as "omeprazole", "neurological disorders", "dementia", "PPIs", correlating through the Boolean operator AND. For this, the search engines VHL (Virtual Health Library), Scielo (Scientific Electronic Library Online); PubMed (U.S. National Library of Medicine) and Google Scholar.

Publications between the years 2004 and 2024, articles in English, Portuguese, and Spanish, which directly addressed the mentioned descriptors, and to direct the search, the filter for articles with full and free texts was added. As an exclusion criterion, we eliminated articles that analyzed the theme from another perspective, prior to 2004 and duplicate articles among the databases, totaling 34 articles used for this review.

Figure 1. Methodology Flowchart



Source: The author.

THEORETICAL FRAMEWORK

DRUGS USED IN THE TREATMENT OF ACID-PEPTIC DISORDERS

Disturbances in the secretion of gastric acid or in the action of this compound on the mucosa of the gastrointestinal tract are related to several diseases and aggravations, such as gastric or duodenal ulcers, gastritis, and gastroesophageal reflux disease. Depending on the symptoms, treatment is carried out with proton pump inhibitors or H2 receptor

antagonists. In cases with mild to moderate symptoms, antacids may be used in addition to treatment with antisecretors. They are also used for the treatment of gastric heartburn, a sensation of heat or burning in the stomach (Ministry of Health, 2023).

Gastroesophageal reflux disease (GERD) is a chronic disorder that significantly affects quality of life, requiring effective treatment to relieve symptoms. The first-line drugs are proton pump inhibitors (PPIs), which act by inhibiting gastric acid secretion and increasing intragastric pH. Esomeprazole, the S-isomer of omeprazole, may demonstrate better results compared to other PPIs, as it has a longer half-life, which results in higher plasma concentrations (Lim, 2023).

The global prevalence of heartburn and reflux in adolescents and adults is about 15%. Proton Pump Inhibitors are the standard treatment for patients with persistent heartburn and reflux. They have better symptom control and mucosal healing compared to histamine-2 receptor antagonists (H2RAs). Refractory GERD occurs in patients who have persistent symptoms despite twice-daily PPI administration. In this case, it is indicated to add an H2RA, such as famotidine, as needed before bedtime for patients with nocturnal symptoms (Provenza, 2024).

Children and infants have a relatively high prevalence of gastroesophageal reflux. The most effective therapies are proton pump inhibitors (omeprazole, esomeprazole, pantoprazole, lansoprazole, dexlansoprazole, and rabeprazole), with only esomeprazole approved for use in neonates, pantoprazole can only be used in children >5 years of age, and the other four PPIs in children >1 year of age; and H2 receptor antagonists (ranitidine and famotidine/cimetidine), which are approved for use in children aged ≥1 month and ≥1 year, respectively (Masarwa, 2024).

Proton pump inhibitors (PPIs), such as omeprazole, are widely used in gastrointestinal disorders, such as: ulcers with or without *Helicobacter pylori infection;* prevention of peptic ulcers in patients receiving nonsteroidal inflammatory agents (NSAIDs), treatment of gastroesophageal reflux, Zollinger-Ellison disease, dyspepsia, esophagitis, and gastritis (Forgerini, 2018).

Peptic ulcer disease is the most common cause of intestinal bleeding, accounting for about 50% of episodes. Since gastric acid contributes to the hemorrhagic effect by promoting clot lysis, the use of PPIs is favorable in these cases, as it reduces the risk of recurrent bleeding, in view of the suppressive action on acid secretion (Zhang, 2021).

Proton pump inibiter drugs

The proton pump is responsible for maintaining stomach acidity, which happens by the exchange of hydrogen (H+) and potassium (K+) in an energetic process with the use of ATP. PPIs block the action of the enzyme in the exchange of protons, which confers an increase in the pH of the gastric juice, inhibiting the production of hydrochloric acid. Irreversible inhibition of the enzyme occurs by connecting to the receptor by covalent bonding, ensuring an action of 24 hours to 48 hours (time for the synthesis of a new enzyme to occur) (Morschel et al., 2018).

Within this class, the most commonly used omeprazole (OMZ) stands out among its peers, such as: esomeprazole, lansoprazole, pantoprazole, rabeprazole, with dexlansoprazole being the most recent. They are available in the pharmaceutical market and are known for their metabolism carried out by the isoenzyme CYP2C19 (Picoli et al., 2018).

Omeprazole (OMZ) is the main representative of the class of proton pump inhibitors, in clinical use it is part of the treatment for patients with ulcers, usually duodenal or gastric, such as peptic disease, those that arise from *Helicobacter pylori* infection or from the prolonged use of non-steroidal anti-inflammatory drugs. An ASTRONAUT study, carried out with 541 patients with erosions and ulcers, under drug therapy, obtained healing results of these lesions after eight weeks, and 80% healed with the dose of omeprazole 20mg/day (Wannmacher, 2004).

Two endocrine cells are important for the maintenance of gastric acid secretion, G and D cells. Therapy using PPIs contributes to an increase in serum gastrin levels, due to the emergence of acid inhibition and an increase in gastrin (which is produced by G cells), this alteration deregulates the mechanism for the synthesis of hydrochloric acid. Increased gastrin levels are usually higher in PPI users for more than 3 years (Camilo et al., 2020).

According to Chinzon et al (2022), PPIs are (in their chronic use) drugs that strongly interfere with calcium absorption, this is due to the fact that this class acts on its mechanism of action, raising gastric pH, this interference is due to the fact that salts are insoluble at basic pH, this relationship favors bone mining density (Chinzon et al., 2022).

PPIs have similar efficacy, but the levels of improvement in the condition of some pathologies change from drug to drug of this class, pantoprazole, for example, has greater efficacy after 8 weeks of treatment to treat duodenal ulcer, reflux esophagitis (obtaining the highest percentage of efficacy), with about 90-96% (Costa et al., 2023).

Pantoprazole in association with antibiotic therapy, as an adjuvant in the prevention of symptoms in relation to *Helicobacter pylori* infection, can reach 100% efficacy, which

suggests that it is an ideal adjuvant of choice to accompany its eradication, in the same sense, in second place of efficacy with 90% is esomeprazole, followed by rabeprazole (77%) and omeprazole in last place with 75%. Pharmacokinetic processes are related to the efficacy of PPIs (Costa et al., 2023).

CONSEQUENCES OF LONG-TERM USE OF PROTON PUMP INHIBITORS

Long-term use of proton pump inhibitors has been associated with adverse consequences, including chronic kidney injury, acute kidney injury, acute interstitial nephritis, hypomagnesemia, *Clostridium difficile* infection, community-acquired pneumonia, bone fracture, and increased risks of developing and dying gastric cancer (Yang et al., 2020).

Several studies have suggested an association between long-term use of proton pump inhibitors (PPIs) and potential adverse effects, including iron and vitamin B12 deficiency, hypomagnesemia, risk of bone fracture, particularly hip fracture, *Clostridium difficile* infections, cognitive impairment, and dementia in elderly patients (Mumtaz, et al 2022).

PPIs are often prescribed to people who have already received other medications, and while considered safe, several concerns have been raised about their safety in long-term use (Cena et al., 2020).

According to numerous studies, PPIs have been linked to hyperprolactinemia, which can lead to a variety of sexual and reproductive problems (Ashfaq, et al 2022).

Other studies have commented that PPIs can substantially affect sperm quality parameters, including sperm count, sperm motility, sperm viability, and capacitation, which can lead to male infertility (Mumtaz et al., 2022).

Although serious side effects are very rare, they include liver problems, joint pain due to subacute cutaneous lupus erythematosus due to prolonged use, and allergic reaction (Hadeel et al., 2022).

PPI users tend to have a less healthy gut microbiota than non-users, with a significant increase in *Enterococcus*, *Streptococcus*, *Staphylococcus,* and *Escherichia coli* (Yang et al., 2020).

The change in gastric acidity can also affect the intestinal absorption capacity of micro elemental nutrients in a way that can result in iron deficiency and decreased concentration of zinc, selenium and copper (Hadeel et al., 2022).

In view of this, we postulate that chronic PPI use can lead to the accumulation of unhealthy gut microflora and disrupt the normal functions of the gallbladder and bile ducts, inducing biliary tract diseases (Yang et al., 2020).

Other signs of long-term use may include a decrease in blood magnesium levels after taking omeprazole for more than 3 months. (Hadeel et al., 2022).

Dementia and Other Neurological Disorders Associated with Long-Term Use of Omeprazole

Proton pump inhibitors (PPIs) are widely recognized as one of the most commonly prescribed classes of drugs globally for the control of stomach acidity. These medications play a crucial role in managing conditions associated with excess stomach acid, such as gastritis, gastric ulcers, and reflux esophagitis. Among the various drugs available within this class, omeprazole stands out for its remarkable effectiveness. This drug is able to reduce stomach acid production by up to 95%, offering significant relief from symptoms related to hyperacidity and promoting the healing of gastric and esophageal lesions (Hoefler et al., 2009).

Long-term use can lead to the occurrence of adverse reactions of concern and unknown to the majority of the population. For example, use for a period equal to or greater than 2 years can lead to a decrease in the absorption of vitamin B12, an important vitamin for hormonal development and for the formation of red blood cells (red blood cells). Clinically, the effects caused by vitamin B12 deficiency can manifest as dementia, neurological problems, anemia and other complications, sometimes irreversible (Santos, 2016).

The prolonged use of omeprazole by the elderly impairs the absorption of essential vitamins for its nutrition, as the elderly have a slightly deficient immune system, the absence of these vitamins increases the possibility of the emergence of serious diseases, such as dementia and Alzheimer's (Liotti et al., 2015).

In this sense, it is possible to perceive an important contraindication regarding the prolonged use of Omeprazole by the elderly, since it may end up contributing to the advancement or aggravation of a series of complications that already exist or that at least it is already a predetermination, requiring constant care and adequate medical follow-up in order not to aggravate already complicated conditions (Liotti et al, 2015).

In addition, long-term use of omeprazole can lead to significant complications, including severe changes in the balance of electrolytes in the body, particularly hypomagnesemia. This condition, characterized by low levels of magnesium in the blood,

may, in some cases, not have evident symptoms. However, in more severe situations, it can result in a variety of clinical symptoms. Among them are episodes of vomiting, diarrhea, and, in more severe cases, neuromuscular symptoms such as tetany — a condition marked by involuntary muscle spasms and pain (Miyares et al., 2020).

Magnesium is the most abundant divalent cation in the human body. Approximately 60% of magnesium is stored in bones, 38% intracellularly in soft tissues, and approximately only 2% in extracellular fluid, including plasma (Huang et al., 2007). Hypomagnesemia can result in neurological signs and symptoms including lethargy, tremors, confusion, fasciculation, tetany, ataxia, and tremors (Ghosh et al., 2008).

Acidic gastric secretion is necessary for the absorption of vitamin B12 from food. Vitamin B12 is an essential nutrient that needs to be acquired from the diet, it is present in protein-bound foods and the presence of gastric acid is necessary for pancreatic proteases to separate vitamin B12 from proteins, allowing its association with intrinsic factor (IF) and absorption in the terminal ileum (Mccoll, 2009).

Vitamin B12 deficiency can cause neurological diseases, including neuropathy, spinal cord degeneration, gait disorders leading to falls, depression, and dementia, which if diagnosed in time are reversible (Werder, 2010).

Although there is an association between the use of Omeprazole and the risk of dementia, especially Alzheimer's, although the mechanism responsible for its development is not fully understood, prolonged hypochlorhydria seems to potentiate cognitive decline, as well as the increase in β-amyloid levels in the brain, after PPI crosses the blood-brain barrier, leading to degradation and promotion of the formation of anomalous aggregates of TAU protein, abundant proteins in the central nervous system (Viegas; Nabais, 2017).

CHANGES IN LABORATORY TESTS OF PATIENTS UNDERGOING PROLONGED USE OF OMEPRAZOLE

The blood count is one of the most requested laboratory tests by health professionals. This, in turn, evaluates the individual's health in general, providing important information that can help diagnose pathologies such as leukemias, infectious processes, and several other hematological disorders such as anemia, thalassemias, and polycythemias (Rosenfeld et al., 2019).

Studies show that the prolonged use of omeprazole can cause changes in hematimetric indices such as MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin) and MCHC (Mean Corpuscular Hemoglobin Concentration) and in biochemical

parameters, for example the dosage of vitamin B12, Vitamin D and Calcium (Ricardo et al., 2023).

Vitamin B12 is a water-soluble micronutrient, acquired exogenously in foods of animal origin. Its deficiency is common among the elderly, vegetarians, and individuals who adopt a low protein diet or have gastrointestinal absorption problems. In addition, the deficiency may be due to prolonged use of omeprazole. In this way, its deficiency can harm the hematopoietic and nervous system, interfering with the development of cell maturation, which leads to cell lysis. Thus, they can lead to pathological conditions, such as megaloblastic anemia and lesions in the nervous system (Haefliger et al., 2021).

According to Ricardo et al. (2023), the prolonged use of omeprazole may be related to the occurrence of megaloblastic anemia, which leads to reduced absorption of calcium, vitamin B12, and vitamin D. Vitamin B12 is part of the production of blood cells and acts in the synthesis of deoxyribonucleic acid (DNA), which is the genetic material of cells. Therefore, vitamin B12 deficiency causes a delay in the maturation process of the nucleus of cells and results in a lower number of erythrocytes. Consequently, it causes the appearance of abnormally large cells, leading to a condition called megaloblastic anemia.

In addition to vitamin B12, calcium as a fundamental nutrient for the body, also suffers a reduction in absorption with prolonged use of omeprazole. Calcium is an essential mineral for the mineralization of bones and teeth and for the regulation of intracellular events in various tissues (Natasha et al. 2018).

In view of the pointing out of studies on the reduction of nutrients and vitamins due to the prolonged use of omeprazole, it is important to correlate and show the importance of performing laboratory tests to assess people's health, since they provide data and information that allow diagnoses, prognosis, and the characterization of risks for various pathologies (Ricardo et al. 2023).

RESULTS AND DISCUSSION

A study carried out by Oliveira et al. (2019) states that the continuous use of omeprazole, the proton pump inhibitor (PPI), reduces the absorption of vitamin B12 in the body, given that this drug raises stomach pH and interferes with the absorption process, causing a shortage of this nutrient.

Ferreira (n.d.) mentions that the administration of omeprazole is recommended one hour before or two hours after the diets of elderly patients with foods rich in Vitamin B12 (such as meat, chicken and milk), since when administered near or during meals, its absorption is reduced, prevailing the risks of dementia and megaloblastic anemia.

Hipólito et al. (2016) report in their study that patients aged between 60 years and over are the ones who most use omeprazole, due to the high use of drugs with age, increased morbidity and life expectancy, intensifying the use of health services in this population.

Table 1. Profile data of patients who take omeprazole for a long time.

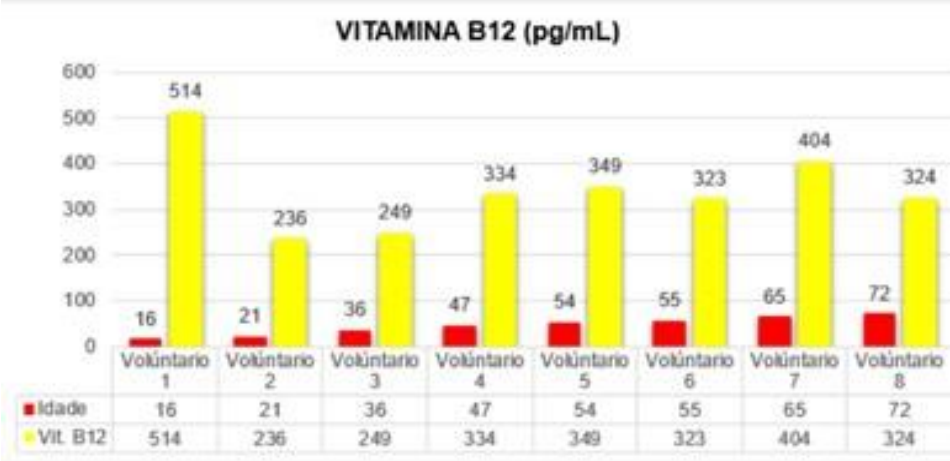
Dados	Voluntário 1	Voluntário 2	Voluntário 3	Voluntário 4	Voluntário 5	Voluntário 6	Voluntário 7	Voluntário 8
Idade	65 anos	74 anos	21 anos	16 anos	36 anos	47 anos	54 anos	54 anos
Sexo	Feminino	Feminino	Feminino	Feminino	Feminino	Feminino	Masculino	Feminino
Escolaridade	Fundamental Incompleto	Fundamental Incompleto	Ensino Médio Completo	Ensino Médio cursando	Superior Completo	Fundamental Incompleto	Ensino médio Completo	Ensino Fundamental Incompleto
Ocupação	Pensionista	Aposentada	Gerente	Estudante	Professora	Dona de casa	Auxílio Doença	Dona de casa
Tempo de uso do omeprazol e posologia	5 anos. 1 comp. 20mg	15 anos. 2 comp. por dia manhã e noite de 40 mg	4 anos. 1 comp. /dia de 20 mg	2 meses 1 comp. de manhã em jejum	10 anos. 1 comp. manhã/ noite 20mg	10 anos. 1 comp./ dia 20 mg	3 anos. 2 comp. /dia 40 mg	5 anos. 3 comp. /dia de 20 mg
Motivo	Gastrite	Gastrite, esofagite e úlcera	Esofagite erosiva grau A, pangastrite	Dor no estômago	Refluxo e hérnia de hiato no esôfago	Gastrite crônica devido aos outros medicamentos	Úlcera e *H. pilory* duodenal	Para poder tomar os outros medicamentos
Outros medicamentos	Losartana 50mg	Rivotril, Losartana, Citalopram	Cloridrato de Fluoxetina	Buscopan e ansiedade	Losartana potássica 50 mg	Danazol, Fluoxetina, Icatibanto e Firazyr (quando crise)	Nilotinibe	Losartana 50 mg, Glibenclamida 5 mg, Metformina 850 mg
Acompanhamento de exames laboratoriais	Não faz	Não faz	Não faz	Não faz	Só quando solicitado pelo médico	Não faz	Faz uso periodicamente para oncologia	Uma vez ao ano

Fonte: Ricardo et al., (2023).

Among the 8 patients interviewed, only two undergo periodic exams, and the male patient, volunteer 7, uses it due to the oncologist's prescription. Prolonged use of the drug ranges from 6 months to 15 years.

Graph 1 shows the result of the age-related vitamin B12 analysis of the selected volunteers on the profile of omeprazole users. However, there were no significant changes in serum vitamin B12 dosages in relation to the prolonged use of omeprazole, regardless of the age of the patients.

Graph 1. Results of vitamin B12 analysis related to the age of the patients.



Fonte: Ricardo et al., (2023).

Araújo et al. (2017) conducted a research related to prescriptions and chronic use of omeprazole. A total of 88 omeprazole prescriptions were analyzed, all of which were chronically used. Regarding age, the age group was between 60 and 69 years old with 45.45%, which intensifies the risk of bone demineralization and the predisposition to fractures. It was observed that females were the ones who most used omeprazole, representing a percentage of 76.13%.

According to Costa and Damascena (2020), women are pointed out as the biggest users of medicines, since they are more careful with their health than men, as they use health services more, and consequently, they are more medicated than men.

CONCLUSION

Therefore, taking into account the preference for the use of omeprazole as a proton pump inhibitor in the treatment of acid-peptic disorders, attention should be paid to the harm caused by the prolonged use of this drug.

In addition, through the research carried out, some of these harmful effects on the patient's health were found, including chronic kidney injury, acute kidney injury, acute interstitial nephritis, hypomagnesemia, other alterations, for example, in laboratory tests, including alterations in hematimetric indices such as MCV (Mean Corpuscular Volume), HCM (Mean Corpuscular Hemoglobin) and CHCM (Mean Corpuscular Hemoglobin Concentration) and in biochemical parameters, for example the dosage of vitamin B12, Vitamin D and Calcium.

In addition, some authors show that the prolonged use of omeprazole can lead to megaloblastic anemia, as well as other harms already mentioned regarding the loss of nutrients and vitamins, requiring laboratory monitoring of this patient.

The empirical and frequent use of PPIs is what results in the adverse effects mentioned above, however, when used rationally, they are the best choice for treatment, prevention and symptoms of gastrointestinal tract diseases, since in general they have a good cost-benefit ratio, in addition to a good absorption and lasting inhibition of gastric acid secretion.

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