ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 14, Issue, 07, pp. 66292-66295, July, 2024
https://doi.org/10.37118/ijdr.28542.07.2024

REVIEW ARTICLE **OPEN ACCESS**

THE INDISCRIMINATE USE OF OMEPRAZOLE: A SYSTEMATIC REVIEW

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ARTICLE INFO

Article History:
Received 14th April, 2024
Received in revised form
09th May, 2024
Accepted 13th June, 2024
Published online 30th July, 2024

Key Words:
Proton pump inhibitors; Adverse effects; Drugs interactions.

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ABSTRACT

Proton Pump Inhibitors (PPIs) constitute an important drugs class, one of the most used in the world, with omeprazole being the best known representative. PPIs act by inhibiting the proton pump, which reduces gastric acidity and contributes to the treatment of diseases such as peptic ulcer disease, gastroesophageal reflux and esophagitis. They are most used through self-medication indiscriminately and often wrongly prescribed. Studies have associated the use of omeprazole for long periods with diseases such as interstitial nephritis, bone demineralization, nutritional deficiencies, decreased immunity and harmful drug interactions. The objective is to discuss the misuse of omeprazole. The search was performed in the Pubmed, EMBASE, LILACS, SciELO and MEDLINE databases, using the terms: "proton pump inhibitors" AND "omeprazole" AND "proton pump inhibitor" AND "nonprescription drugs" AND "adverse effects". Based on the results, the study reaffirms the health risk arising from prolonged use of omeprazole, requiring measures to ensure the rational use of this medication.

Citation*: *Gustavo Roque de Queiroz; Pedro Somma Pereira; Patrick Mega Guerra Peixe; Enzo Zattera Gonçalves de Oliveira et al. 2024. *"The indiscriminate use of omeprazole: A Systematic Review". International Journal of Development Research*, 14, (07), 66292-66295.

INTRODUCTION

Proton Pump Inhibitors (PPIs) are part of the most commonly used drug arsenal in gastroenterology, and are the first line of treatment for diseases such as duodenal ulcers and reflux esophagitis, in addition to acting as an adjuvant in the *Helicobacter pylori* eradication scheme (CUI *et al*., 2001; GUIMARÃES; MARGUET; CAMARGOS, 2006). The following are representatives of this class: omeprazole, lansoprazole, pantoprazole, rabeprazole, dexlansoprazole and esomeprazole, with omeprazole being its main representative, given its low cost and easy access (ARAI; GALLERANI, 2011). As they present little or no adverse effects in clinical practice when managed correctly, PPIs have come to be used not only for acute symptoms, even if their limits are debatable in the long term (HYUN et al., 2010). PPIs have their primary action on chloropeptide inhibition, acting on the parietal cells of the stomach where they irreversibly inhibit the proton pump. This acid suppression can last 48 hours or more, until new enzyme synthesis occurs and its incorporation into the luminal membrane of parietal cells (WAGNER, 2011). According to the World Health Organization (WHO), regarding the problem of medication safety, more than half of prescribed medications are used incorrectly by the population (HOLLOWAY; VAN DIJK, 2011). The irrational use of medicines is often driven by cultural aspects, inadequate prescriptions or simple lack of knowledge. Among the various problems that the irrational use of medications can cause, the following stand out: drug interactions, polypharmacy, self-medication, adverse reactions, therapeutic failure, prolonged hospitalizations and deaths (MANSO; BIFFI; GERARDI, 2015). Furthermore, PPIs are part of the National Relationship of Essential Medicines of Brazil (RENAME) being recommended by the National Health Surveillance Agency (ANVISA), and its sale must only be carried out through medical prescription, yet its use for self-medication constitutes a major problem (LIMA; NETO FILHO, 2014; BRAZIL, 2015). To compound the dilemma, De -La- Coba *et al*. (2016) reveal an estimate that 54 to 69% of PPIs prescriptions are incorrect. Carranza Caricol (2015) and Cristellys and Mateos (2017), the use of so-called "gastrolesives", such as non-steroidal anti-inflammatory drugs (NSAIDs), is an important factor linked to the frequent use of PPIs, in especially omeprazole. This is due to the recognized association of NSAIDs with peptic ulcer disease. Other

factors that explain its continuous use are advanced age and the excessive number of medications used, the so-called "polypharmacy". It is therefore necessary to discuss the proposed topic, taking into account the precarious access to specialized healthcare, associated with the high prevalence of disorders of peptic origin, and free access to PPIs which, according to studies, are not harmless, when used for the long term.

LITERATURE REVIEW

Risk for bone fracture: Studies increasingly point to the association of PPI use as a risk factor for fractures. Lenihan *et al*. (2017) observed a positive association between PPI use and hip fracture. Yang *et al*. (2006) described that the use of omeprazole at a dosage of 20 mg per day was able to significantly reduce bone mineral density. A meta-analysis of eighteen studies revealed that moderate use of PPIs increases the risk of hip fracture, in addition to the spine and other locations (ZHOU *et al*., 2016). Targownik *et al*. (2012) argue that there is no link between the use of PPIs and the change in bone mineral density that leads to a predisposition to fractures. Other factors such as a sedentary lifestyle, smoking, drinking alcohol and low lean mass increase the risk of fractures when they are associated. In studies by Ho *et al*. (2009), with a review of 145 thousand medical records, it was confirmed that the long-term use of PPIs in high doses causes harmful effects on the absorption of calcium from the gastrointestinal tract, which leads to progressive weakening of the bones. It was shown that people using omeprazole for more than a year had a 44% additional risk of having a hip fracture.

Urinary system: A known, but rare, kidney problem related to the use of omeprazole is interstitial nephritis. It is a hypersensitivity reaction, with a clinical picture that is often atypical, and, when diagnosed, the patient should be asked about the use of PPI, with it being withdrawn whenever possible (ANTONIOU *et al*., 2015). The long - term use of PPIs, according to Lazarus *et al*. (2016), it is enough to place these drugs as important etiological agents in the development of acute kidney injury (AKI) and chronic kidney disease (CKD).

B12 Deficiencies: In patients treated with PPIs for six months or more, Lúquez Mindiola *et al*. (2017) compared two groups: for up to three years and for more than three years (chronic user), regarding serum B12 levels. The incidences of vitamin B12 deficiency and threshold B12 deficiency were significantly higher in the group of chronic PPI users. No significant differences were observed between PPIs in relation to serum B12 levels. Vitamin B12 is linked to cellular metabolism, and diseases resulting from its deficiency are already well established. However, Araújo (2017) highlights dementia as one of the direct consequences of poor absorption for a period longer than two years.

Iron and anemia: Increasingly, studies reveal the association between prolonged use of PPIs and iron deficiency, with the direct consequence of developing iron deficiency anemia. The reduction in intestinal iron absorption was linked to reduced gastric acid secretion as a result of chronic use of these drugs. Hashimoto, Matsuda and Chonan (2017) observed an improvement in the anemic clinical condition when PPIs were discontinued, or even after changing the medication (for famotidine, for example). It is the doctor's responsibility, in his practice, to observe the principles of non-maleficence and use such medicines within reason.

Changes in gastric histology: The relationship between the chronic use of PPIs and histological proliferative changes in the stomach has been increasingly analyzed by recent studies. A common point in these studies is the length of treatment in which patients are subjected to this drug as a determining factor, however the temporality in the genesis of the histological change is quite variable in the literature (MENEGASSI *et al*., 2010). The etiopathogenesis observed by Hoefler and Leite (2009), in an animal model, was intense peptic suppression by these drugs, generating a positive feedback that increases gastrin secretion, and, as a consequence of hypergastrinemia, the trophic effect on the gastric mucosa, in addition to the increased expression of enterochromaffin cells, which is a risk factor for the development of gastric tumors related to the use of dose-dependent omeprazole. Menegassi *et al*. (2010), after analyzing gastric biopsies (fundus, body and gastric antrum) from 22 patients, they verified this association between the chronic use of PPI and the presence of proliferative changes in the histology of the oxyntic mucosa. Among the changes macroscopically found are sporadic polyps in the fundus region and microscopically, glandular cystic formation.

Immune system and infections: Regarding the immune system, there is, in the acid secretion of the stomach, a defense mechanism against various microorganisms. Therefore, the chronic and indiscriminate use of omeprazole exposes the patient to an additional risk of infections by microorganisms sensitive to this immunological barrier (DE-LA-COBA *et al*., 2016). Zedtwitz *et al*., (2002 *apud* GARCÍA RODRÍGUEZ; RUIGÓMEZ; PANÉS, 2007) relate the prolonged use of PPIs with reduced leukocyte action, due to the change in the synthesis of oxidant radicals. The bactericidal activity exerted by polymorphonuclear cells against *Escherichia coli* will be reduced by 30%, this occurs with a dosage dose of 40 mg of omeprazole, however it is important to observe the binomial time of use and need. For bacterial growth to occur, it must be related to the number of days in which the gastric pH is greater than 4.0. Physiologically, reducing the pH to titers below 4.0 for a few hours within a 24-hour period is sufficient to inhibit bacterial growth. García Rodríguez, Ruigómez and Panés (2007) report that the pharmacological difference between PPIs and H2 receptor antagonists in their ability to reduce gastric acidity is related to the incidence of infections. The authors also detected that patients treated with omeprazole had more infections than those treated with cimetidine, demonstrating the importance of this defense, which has gastric acidity as a significant immunological defense against ingested organisms.

Drug interactions: A drug interaction (DI) is considered when there is a combination of two or more medications, causing an increase or decrease in the therapeutic or toxic effect of the other or both (PORTO, 2011). This drug interaction is considered in the literature to be a type of adverse drug reaction (ADR). In this sense, it is extremely important that doctors increasingly seek information about the range of adverse effects that the patient will be subject to when prescribing, in order to obtain resolution of the disease and cause minimal or no harm (CARVALHO *et al*., 2013). The drug clopidogrel is a blood anticoagulant, from the class of antiplatelet agents, which must be activated by the liver through cytochrome P450 enzymes. However, studies demonstrate that, in joint therapy with omeprazole, the latter has the power to inhibit this enzyme group, thus modifying the expected effectiveness of the anticoagulant (MADANICK, 2011). Ho *et al*. (2009) revealed that the association of clopidogrel and PPI increased the risk of death or readmission due to acute coronary syndrome by 25%, as well as an increase in revascularization procedures. Warfarin, which is another widely used anticoagulant, with action on the metabolism of vitamin K in the coagulation cascade, also suffers an interaction in its pharmacokinetics when used in conjunction with omeprazole. This happens due to an enzymatic inhibition of the warfarin-metabolizing cytochrome, leading to a decrease in the elimination of the anticoagulant, an ineffective therapeutic action and a risk of hemorrhage (PINTO, 2014; MEIRELLES; SILVA NETO; OLIVEIRA, 2016; MARTÍNEZ LÓPEZ, 2017).

CONCLUSION

The bibliographic evidence that makes up this work discusses the irrational use of omeprazole prescribed by a medical professional or due to its wide empirical use. In this context, it is essential to treat self-medication as a public health problem, as it makes healthcare more expensive and generates other long-term problems. Several studies have shown the association between prolonged use of omeprazole and undesirable health outcomes, ranging from nutritional deficiencies to neoplasms. Drug interaction also

constitutes an important adverse effect on the use of omeprazole for a prolonged period, with its connection being established in the pharmacokinetics of clopidogrel and warfarin, which may lead to their therapeutic failure and, consequently, harm to health. Public health policies are necessary, from assistant doctors to executive bodies, to develop educational strategies aimed at raising awareness among the population about the risks of self-medication. It would be necessary to present a mandatory medical prescription to purchase these medicines in pharmacies. This would help to demystify the idea that omeprazole is problem-free, contributing to therapeutic success.

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