Gastric protection or bone protection? The dilemma of proton-pump inhibitor

Pino Montes J del

Servicio de Reumatología del Hospital Universitario de Salamanca - Departamento de Medicina de la Universidad de Salamanca (España)

e-mail: jpino@usal.es

The arrival of H2 inhibitors and later the proton-pump inhibitor (PPI) changed the clinical course of gastroesophageal disease, greatly reducing the rate of peptic ulcers and their complications. At present they are used in a high proportion of patients with diverse clinical situations[1]. They are recommended to treat gastro-esophageal reflux, Helicobacter pylori, Zollinger-Ellison syndrome, duodenal ulcer, gastric ulcer and NSAID-induced peptic ulcer. Their proven benefits in preventing ulcers and encouraging good tolerance have led them to be considered as a popular, safe "gastric protector", with little adverse effects and used in many situations without indication.

But do not forget that the blockade of acid secretion by PPIs is the cause of some undesirable effects[2]. Increased intestinal and systemic infections have been attributed to decreased gastric acid secretion and their bactericidal capacity. Other infections, such as pneumonia, are also more common among patients treated with PPIs. B_{12} production capacity and intestinal absorption may be reduced by malabsorption. A reduced of antiplatelet effect of clopidogrel therapy has also been described. Some cancers, especially colon cancer, could be more frequent. Finally, it is worth noting the increased risk of fracture in patients treated with long-term PPI. In this issue, a study by Vera Rodríguez et al.[3] on its possible association with increased fractures in the population of the Canary Islands is presented, confirming the increase in non-traumatic fractures in patients over 50 years undergoing long-term PPI treatment compared to those who have never taken these medications.

PPIs' link to fractures has drawn attention in the past 10 years, long after they came on the market. Several observational studies have shown a relationship between PPI consumption and the presence of osteoporotic fractures of the hip, vertebrae and wrist. Generally, they are associated with high-dose treatments or periods longer than 12 months. The results are contradictory as not all studies have confirmed these findings. The studies are methodologically heterogeneous and have numerous confounding variables, which explained the lack of consistency in the findings. Unfortunately, there are no controlled studies, since this side effect was not detected in clinical trials on long-term use of PPIs, mainly because they were not designed to assess fragility fractures.

In 2011, some meta-analysis based on epidemiological cohort and case-control studies linked chronic use of PPIs to increased fragility fractures in postmenopausal women and older men. Given this evidence, drug regulatory agencies, including the FDA (Food and Drugs Administration) and the EMA (European Medicines Agency), decided to issue warnings about this risk.

In the meta-analysis by Ngamruengphong et al.[4], 10 observational studies (4 cohort and 6 control) with a population of men and women among which more than 200,000 fractures were included. In patients who had used PPIs fracture risk it was increased, with an OR of 1.25 (confidence interval (95% CI: 1.14 to 1.37) for hip fracture, 1.50 (CI 95% CI 1.3 to 1.72) for vertebral fracture and 1.09 (95% CI. 0.95 to 1.24) for the wrist. These studies' heterogeneity limited the analysis of the influence of other factors related to PPI treatment. The results of a second meta-analysis coincided with those of previous two items were included[5] and also analyzed studies with patients treated with H2 receptor inhibitors (IRH2). Their results were consistent with the meta-analysis of Ngamruengphong et al., and also found increased risk of fracture, of similar magnitude in patients with PPI The OR for vertebral fracture was 1.5 (95% CI: 1.32 to 1.72) and hip fracture of 1.23 (95% CI: 1.11 to 1.36), while for the total fractures of 1.20 (95% CI: 1.11 to 1.30). However, it was confirmed that there was no association between treatment with IRH2 and fractures.

In both studies the increase in fractures is proportionally discrete after adjusting for various risk factors. However, to extrapolate these results to the general population, in which the use of PPIs in the population at risk of osteoporosis and fracture is common, the weight of this adverse effect is important. These studies had considerable heterogeneity in relation to risk intensity and duration of treatment until the appearance of fractures, and some variability in relation to confounding factors for which the results were adjusted. Despite these limitations, the occurrence of fractures has been observed especially in patients at higher doses, greater grip and longer duration of PPI therapy. Overall, this increased fracture rate is independent of other risk factors of fracture, including bone mineral density. But some authors have found that in addition to chronic use of PPIs, the use of tobacco is a risk factor for hip fracture in postmenopausal women[6].

Subsequent data have reinforced this evidence. In recent years, several prospective cohort studies have been published. Including a Canadian cohort study (CaMos) including men and women which found that, after 10 years of follow up, patients who used PPIs presented an increase of non-traumatic incidental fractures independent of many known risk factors. The risk of fracture was calculated by hazard ratio (HR) at 01.75 (95% CI: 1.41 to 2.17) for total fracturas[7]. After adjusting for various risk factors, including bone mineral density of the femoral neck, the link remained significant, with an HR of 1.40 (95% CI: 1.11 to 1.77). In another cohort study in postmenopausal women (Australian Longitudinal Study on Women's Health) data from 4,432 women followed over more than 10 years were evaluated. They found an increase in fractures associated with osteoporosis (HR=1.29 95% CI: 1.08 to 1.55). In this study, this association was evaluated according to the drug used, finding that the risk was increased with the use of any PPI, especially esomeprazole (HR=2.06, 95% CI 1.37 to 3.10)[8]. In a case-control study of more than 6,500 males over 45 years treated with PPIs the relationship with increased risk of fracture, especially those whose long-term consumption was confirmed[9].

The active mechanism by which PPIs increase fracture risk is unknown, but some hypotheses have been proposed decreased intestinal absorption of calcium and vitamin B_{12} or direct action of PPIs on the proton pump of osteoclasts. Decreased intestinal absorption of calcium and other minerals is based on experimental and human studies. Intestinal calcium carbonate absorption is pH-dependent and some studies indicate that in patients with hypo- or achlorhydria, such absorption is reduced, especially in fasting elderly women[10]. This alteration of calcium absorption is unproven in men below 50 years[11]. Inhibition of gastric acid secretion could help reduce vitamin B_{12} absorption and thus facilitate CBS deficiency. Reducing homocysteine could hinder incorporation into bone collagen and therefore facilitate fractures.

Some experimental data indicate that the action of PPIs could have direct influence on bone cells. Here, osteoclastic action may suffer due to the inhibition of proton pump available to osteoclasts. This would lead to limited metabolic remodeling. There is no information on what the actual clinical significance of this action may be. Furthermore, the action of PPIs in the bone could be related to an increase of histamine, as the H1 receptor blockade prevents the increased risk of fracture induced by PPI[12].

However, the increased fracture risk observed in patients treated with these drugs does not seem linked to reduced bone mineral density or bone loss acceleration. Some studies have found that patients starting treatment with PPIs have low bone mineral density, but this does not change significantly during their treatment[13].

In view of all these data, the EMA and the Spanish Agency for Medicines and Health Products (March 2012) issued alerts about the safety of PPIs, which warned of the increased risk to the hip, spine and forearm in patients having long-term treatment (over 1 year) with PPI.

The benefits of PPIs in treating problems associated with gastrointestinal reflux and peptic ulcer disease in general are proven. In these cases, the risk-benefit ratio is favorable to the latter. However, as noted by Vera Rodriguez et al. in their paper[3], in a high proportion of patients treated although treatment indication is not clear. In many cases, it has been assumed that the risk of peptic ulcer prevention in patients treated with NSAIDs could be extrapolated to patients with polypharmacy, but this possibility is not proven. In patients for whom the benefits are uncertain, fracture risk, however small, is not acceptable.

One might suppose that the risk induced by PPIs could be controlled with such anti-fracture medications as bisphosphonates (BSF). However, the available data do not support this hypothesis. In a recent meta-analysis, Yang et al. analyzed four studies involving over 57,000 patients, noting the potential benefits of the combination of PPI and BSF. Contrary to expectations, this combination has more risk of fracture than PPIs alone (OR=1.52). The risk of vertebral fracture has an OR of 1.60 (95% CI: 1.13 to 2.26)[14].

With all these data, it seems reasonable to assert that PPI therapy presents a risk factor of fracture that is increased by between 9-75%. This undesirable effect is a classic effect because it is maintained when the different PPIs are analyzed separately. This risk may not be annulled by the concomitant use of BSF. There is no contraindication to the use of PPIs in patients with osteoporosis or at risk of fracture. However, in view of the available data, we should act wisely when deciding whether to recommend the blocking the production of gastric acid secretion that PPI use implies, especially in postmenopausal women and men over 50 years.

Bibliography

1. Neila Calvo S, Nan Nan D, García Ibarbia C, Olmos Martínez JM, González Macías J, Hernández Hernández JL. La realidad de la osteoporosis en el paciente hospitalizado en Medicina Interna. Rev Osteoporos Metab Miner 2013;5:141-5.
2. Reimer C. Safety of long-term PPI therapy. Best Pract Res Clin Gastroenterol 2013;27:443-54.
3. Vera Rodríguez J, Martín Bethencourt E, Calvo Hernández LM, Hernández Hernández D, Saavedra Santana P, Gómez de Tejada Romero MJ, et al. Uso inadecuado de inhibidores de la bomba de protones y riesgo de fractura por fragilidad. Estudio preliminar. Rev Osteoporos Metab Miner 2015;7:107-11.
4. Ngamruengphong S, Leontiadis GI, Radhi S, Dentino A, Nugent K. Proton pump inhibitors and risk of fracture: a systematic review and meta-analysis of observational studies. Am J Gastroenterol 2011;106:1209-18.
5. Kwok CS, Yeong JK, Loke YK. Meta-analysis: risk of fractures with acid-suppressing medication. Bone 2011;48:768-76.
6. Khalili H, Huang SH, Jacobson BC, Camargo CA, Diane Feskanich D, Chan AT. Use of proton pump inhibitors and risk of hip fracture in relation to dietary and lifestyle factors: a prospective cohort study. BMJ 2012;344:e372
7. Fraser LA, Leslie WD, Targownik LE, Papaioannou A, Adachi JD, and CaMos Research Group. The effect of proton pump inhibitors on fracture risk: report from the Canadian Multicenter Osteoporosis Study. Osteoporos Int 2013;24: 1161-8.
8. Van der Hoorn MM, Tett SE, de Vries OJ, Dobson AJ, Peeters GM. The effect of dose and type of proton pump inhibitor use on risk of fractures and osteoporosis treatment in older Australian women: A prospective cohort study. Bone 2015;81:675-82.
9. Adams AL, Black MH, Zhang JL, Shi JM, Jacobsen SJ. Proton-pump inhibitor use and hip fractures in men: a population-based case-control study. Ann Epidemiol 2014;24:286-90.
10. Quesada Gómez JM, Sosa Henríquez M. Nutrición y osteoporosis. Calcio y vitamina D. Rev Osteoporos Metab Miner 2011 3:165-82.
11. Sharara AI, El-Halabi MM, Ghaith OA, Habib RH, Mansour NM, Malli A, et al. Proton pump inhibitors have no measurable effect on calcium and bone metabolism in healthy young males: A prospective matched controlled study. Metabolism 2013;62:518-26.
12. Abrahamsen B, Vestergaard P. Proton pump inhibitor use and fracture risk-effect modification by histamine H1 receptor blockade. Observational case-control study using National Prescription Data. Bone 2013;57:269-71.
13. Yang S, Chen Q, Wei H, Zhang F, Yang DL, Shen Y, et al. Bone fracture and the interaction between bisphosphonates and proton pump inhibitors: a meta-analysis. Int J Clin Exp Med 2015;8:4899-910.
14. Targownik LE, Leslie WD, Davison KS, Goltzman D, Jamal SA, Kreiger N, et al. The relationship between proton pump inhibitor use and longitudinal change in bone mineral density: a population-based study [corrected] from the Canadian Multicentre Osteoporosis Study (CaMos). Am J Gastroenterol 2012;107:136-9.