EDITORIAL

Safe use of proton-pump inhibitors

Proton-pump inhibitors (PPIs) are one of the most widely used drug classes worldwide. Their discovery goes back to the 1980s, when the significance of H+/K+-ATPase in gastric acid production was established. The market launch of PPIs, which inhibit this enzyme by direct, irreversible binding, paved the way to a new age in the management of gastrointestinal conditions related to stomach acid secretion (1).

PPI INDICATIONS

The primary indications of these drugs are summarized in table 1 (2-4). For the prophylaxis of non-steroidal anti-inflammatory drug (NSAID)-induced gastroenteropathy or stress ulcer, their indication involves a number of specific scenarios. In the former case, patients older than 60 years with prior peptic ulcer history when high-dose NSAIDs are used or there is concomitant use of anti-coagulants, anti-aggregants or glucocorticoids, amongst others; in the latter case, seriously ill patients admitted to intensive care units who have additional risk factors such as acute renal failure, coagulopathy or severe sepsis (2-4).

Table 1. *PPI indications*

Peptic ulcer disease
Helicobacter pylori eradication
Upper gastrointestinal bleeding
Uninvestigated dyspepsia
Symptomatic GERD. Esophagitis, Barrett's esophagus, and peptic stricture
Eosinophilic esophagitis
Stress ulcer prevention
Prevention of NSAID- or ASA-induced gastroduodenal injury
Zollinger-Ellison syndrome
Exocrine pancreatic insufficiency

PPI: proton-pump inhibitor; GERD: gastroesophageal reflux disease; NSAID: non-steroidal anti-inflammatory drug; ASA: acetyl-salicylic acid.

CURRENT USE IN SPAIN

According to the Spanish Ministerio Nacional de Sanidad, in 2022 PPIs were the most widely used drugs in number of packages, followed by HMG CoA-reductase inhibitors, anilides and benzodiazepine derivatives. A total of 71,528 million PPI containers were dispensed, 1.47 % more than in 2021, representing 6.51 % of all medications and a health expenditure over € 490 million (5).

Since their introduction in clinical practice the use of these drugs has exponentially increased, which was partially fostered by price reductions at patent's end, the development of generics, and the fact that in some countries such as the USA they may be dispensed over the counter (2). These figures have raised concern on potential inappropriate prescription as there is overuse in scenarios with uncertain indication, often in high doses long-term, which entails considerable healthcare costs and increased risk for potential side effects (3). According to data reported in the medical literature, inappropriate use rates are above 57 % among inpatients and over 50 % among primary care outpatients in developed countries (2).

ADVERSE EFFECTS

Over the last decade literature reports have been numerous associating PPIs with a host of adverse events, which triggered alarm among the population and even safety concerns among the scientific community (6,7). Some of these effects are supported by robust studies and show biological plausibility, but many others lack high-quality scientific evidence. Most associations are based on observational, retrospective studies using heterogeneous patient samples, which provides low-quality evidence-supported results. Therefore, such results should be interpreted with caution, and their context should be considered (7,8).

Infections

PPIs reduce gastric acidity, which impairs intestinal microbiota and facilitates pathogenic bacteria growth. An association has been seen between PPI use and enteric infection with *Salmonella*, *Campylobacter*, and particularly *Clostridioides difficile* (CD) (9). In patients with risk factors or active infection with CD, PPIs should only be used for a true indication and the shortest time possible (3,10). Their relation to other infections such as community-acquired pneumonia involves conflicting findings in the literature (11).

Micronutrient deficiency

PPI use has been associated with deficiency of micronutrients such as iron, vitamin B_{12} and magnesium because of interference with intestinal absorption. Vitamin B_{12} deficiency is biologically plausible since pepsin, whose activation requires an acidic pH, plays a role in separating the vitamin from food. While the magnitude of this interference on absorption and its clinical relevance remain unclear, it is advisable to measure vitamin B_{12} levels in patients with other concurrent deficiency risk factors (3,12). As regards magnesium, the Spanish Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) recommends measuring magnesemia at treatment onset and then regularly in some settings such as concomitant administration of digoxin or diuretics (13). The precise mechanism of magnesium absorption impairment remains unknown; it may be due to changes in carrier proteins and intestinal microbioma composition (14).

Increased fracture risk

In vitro studies have associated long-term, high-dose IPP use with reduced bone mineral density from osteoclast dysfunction, although such effect has not been clearly observed in prospective studies in humans (15). However, an increase in fragility fractures, particularly hip, wrist and spine fractures, has been reported in association with PPI use in several observational studies. While in this association confounding factors may play a role, caution is advisable when prescribing for patients with additional risk factors for bone fracture by only using the minimum effective dose and regularly assessing the need for continuation (6,12,16).

Adverse effects in the cirrhotic population

In the cirrhotic population PPI use has been associated with the development of hepatic encephalopathy, infection, increased decompensation rate, and even a higher liver-related mortality rate (17). The association with hepatic encephalopathy may be explained by microbiota changes and bacterial translocation, but higher quality evidence is here needed (18). Regarding infection, the strongest association is with spontaneous bacterial peritonitis, but it does not seem to increase infection severity or related mortality (19,20). Furthermore, in a prospective study PPI use was associated with reduced mortality in patients with advanced chronic liver disease with prior GI bleeding (17). These results should prompt extreme caution when using PPIs in patients with cirrhosis while bearing in mind their clear benefit when truly indicated.

Adverse renal effects

The main adverse renal effect of PPIs in the literature is acute renal failure (ARF), at times associated with acute interstitial nephritis from metabolite deposition within interstitial tubules (6,21). While caution is advisable when prescribing PPIs to patients with kidney disease, this adverse effect is not very common in clinical practice and subsequent progression to chronic kidney disease remains unclear.

Drug-drug interactions

The drug-drug interactions of PPIs result on the one hand from increased gastric pH, which impairs absorption and bioavailability for multiple drugs, and on the other hand from competitive inhibition of cytochrome P450, particularly of isoen-

zymes CYP2C19 and CYP3A4 (22). Interacting drugs include clopidogrel, cyclosporin, acenocoumarol, carbamazepine, anti-fungals and direct-acting anti-virals, among others (22). Although the clinical relevance of these interactions is poorly understood, should they develop drug levels may be measured for dose titration (3,4). Taking clopidogrel as an example, while mechanistic studies show it shares with PPIs liver metabolism pathways that decrease active metabolite bioavailability, prospective studies have revealed that cardiovascular events do not increase with the association whereas gastrointestinal events do in patients with double anti-aggregation without an anti-secretory drug (23). In clinical practice, should concomitant therapy be required, administering these drugs separately may be considered to avoid potential interaction.

Other adverse effects

Several studies have warned about a potential increase in the incidence of Alzheimer's disease in patients on chronic PPIs based on their potential to reduce beta-amyloid degradation by interfering with lysosomal acidification (24). However, prospective studies show conflicting findings hence such association has not been demonstrated (24).

Their relationship with gastric cancer is also controversial. An increase was described of neuroendocrine tumors because of enterochromaffin cell hyperplasia, and of gastric adenocarcinoma because of increased gastrin secretion, with a potentially carcinogenic effect (25). Even so, these results were not replicated by a number of studies and confounding factors exist, including infection with *H. pylori*, so scientific evidence lacks robustness in this regard (7,19).

DISCUSSION AND RECOMMENDATIONS

Although PPIs have been associated with multiple adverse effects, the strength of association is low and findings are usually inconsistent in most studies. In some cases, only a potential correlation may be discerned rather than a causal relationship, which highlights the need for further studies, specifically designed to assess these potential adverse effects and to provide higher-quality evidence.

The adverse effects supported by stronger scientific evidence include a higher risk of bone fractures, vitamin B_{12} and magnesium deficiency, increased enteric infections, and more complications in cirrhotic patients. While the likelihood of adverse effects should not be the sole consideration when prescribing a PPI, bearing them in mind and reassessing indications when present is important in clinical practice (Table 2).

Given the currently excessive use of these drugs, it is recommended that the reason for prescription be regularly reassessed while establishing whether a true indication is present. Otherwise, the drug should be discontinued. If a valid indication is present, a dose reduction should be considered, as should whether their prescription needs be long-term, as in erosive GERD or Barrett's esophagus, or may be regularly reassessed.

Table 2. *Main adverse effects of PPI and recommendations*

Enteric infection, particularly with CD	Assess risk-benefit if other risk factors for CD are present
Micronutrient deficiency (vitamin B_{12}, magnesium)	Measure levels, consider supplementation
Increase in frailty-related bone fractures	Assess risk-benefit if other fracture risk factors are present
Drug-drug interactions	Consider measuring drug levels and titration Administer separately
Acute renal failure	Assess risk-benefit if other ARF risk factors are present
Hepatic encephalopathy, infection and decompensation in patients with cirrhosis	Discontinue if no established indication

CD: *Clostridioides difficile;* ARF: acute renal. AIN: acute interstitial nephritis.

CONCLUSION

In view of the currently available scientific evidence and the cumulative experience with PPI use over nearly 40 years, we must consider PPIs a safe drug class with few severe adverse effects, their benefit-risk ratio clearly favoring their use whenever appropriately indicated.

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