REVIEW ARTICLE

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Safety of Potent Gastric Acid Inhibition

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Abstract

The proton pump inhibitors are a very effective drug group for the control of gastric acid secretion, which makes them of great use in the medical practice setting, while at the same time they represent one of the treatment groups widely used in Western European countries. These factors lead to this drug group being prescribed in all age populations, quite often in polimeticated patients and with pluripathology, and on many occasions during prolonged periods of time. All these determinant factors sometimes make the safety profile of proton pump inhibitors disputable. In this respect all of them have been shown to have little adverse events and are safe in long-term treatment. The risk of drug interactions when prescribed in association with other drugs is low and their repercussion in the medical practice setting is quite exceptional as they require few dosage adjustments in patients with severe concomitant diseases and in elderly patients. Finally, their safety is high in pregnant women and in children, although further studies in this population are required to corroborate this evidence.

1. Introduction

The proton pump inhibitor (PPI) drugs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) have caused a revolution in the management of gastric acid-related diseases. There is no doubt about the clinical efficacy of these drugs, which have caused their consumption to burgeon in the Western world. In Spain, the consumption of anti-secretory drugs (overall) in the year 2003 represented 6.7% of the total drug consumption, and 87% of this fraction corresponded to the PPIs.[1] However, despite the multiple data published corroborating their therapeutic potential, their highly effective profile as inhibitors of gastric acid secretion and the introduction of new generations of these drugs over a very short period of time have given rise to a certain degree of confusion regarding their safety profile when given for long periods, their possible interactions when given at the same time as other drugs, and their safety in aged patients and in patients with severe co-morbidities that might affect their metabolism. This article shall review, in a practical manner, these various aspects as related to the PPIs as a group and, when differences do exist, the peculiarities of such differences between the various PPIs. Degrees of evidence and recommendation are rated according to the criteria established in the Introduction of this issue.

2. Drug Interactions between the PPIs and Other Drugs

All the PPIs are metabolised in the liver through the action of the cytochrome CYP450 enzyme system. Two of the six main isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) are involved in PPI metabolism: CYP2C19 and CYP3A4.[2]

The PPIs have, generally speaking, greater affinity for CYP2C19 than for CYP3A4, the latter isoenzyme functioning as a reserve metabolisation pathway when the main one (CYP2C19) becomes saturated.[3] However, the affinity of the various different PPIs for each of these two isoenzymes in the process of their metabolisation is different, and

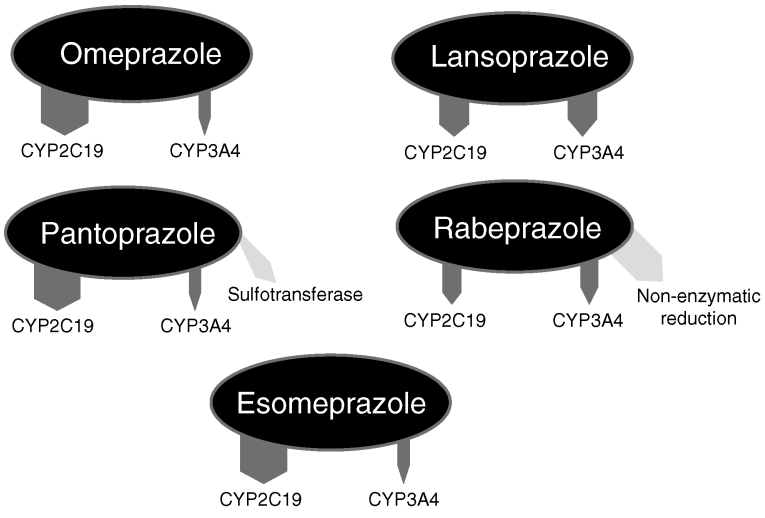

Fig. 1. Major metabolic pathways for the various proton pump inhibitors (PPIs). The pantoprazole sulfotransferase does not belong to the cytochrome CYP450 system and is not saturable.

it should be stressed that rabeprazole, although it is also metabolised by the two stated isoenzymes of the CYP450 system, is essentially metabolised through a non-enzymatic pathway (figure 1). The CYP2C19 isoenzyme has two genotypes, providing two different phenotypes: poor metaboliser and rapid metaboliser.[4–6] The frequency of the 'poor metaboliser' phenotype ranges between 2% and 6% among the Caucasic population, and is about 20% in the Asian populations.[7] The effects of these genotypes vary according to the precise PPI; generally, and in decreasing order, they are: omeprazole > lansoprazole ≥ esomeprazole > pantoprazole > rabeprazole.[7,8] Poor metabolisers have higher plasma PPI levels, which in theory might represent an advantage in terms of better control of acid secretion and of a better profile in relation to drug interactions, although it might also generate unpredictable adverse side effects.

It might be possible to predict, *a priori*, to what degree the PPIs would or would not interact with other drugs if the following data were known: (a) which isoenzyme(s) in the CYP450 system is (are) responsible for the metabolism of the other drug given; (b) the relative contribution of the various isoenzymes in the CYP450 system to the overall metabolism of the drugs given; (c) the relative affinity of the drugs involved for the CYP450 isoenzymes; and (d) the relative concentrations of the various drugs within the hepatocytes based on their plasma concentrations.[9] However, not all interactions can be explained in terms of these premises.

2.1 Omeprazole

Omeprazole can, in theory, alter the absorption, metabolism and excretion of a large number of drugs and other substances, among them bismuth, caffeine, carbamazepine, diazepam, digoxin, mephenytoin, methotrexate, nifedipine, phenytoin and warfarin.[10] From a clinical point of view, the most important interaction of omeprazole is a 25–50% reduction in diazepam clearance (level of evidence 1a), an effect not observed in poor metabolisers (level of evidence 1a).[2,11,12] Isolated interactions have been reported with other benzodiazepines (level of evidence 1c).[13,14] Although pharmacokinetic studies have demonstrated that omeprazole increases the area under the curve (AUC) of plasma concentration *versus* time of phenytoin, and reduces its plasma clearance, studies carried out in epileptic patients receiving

phenytoin who were given omeprazole have not demonstrated changes in the plasma phenytoin levels (level of evidence 1b).[15–17] As for warfarin, there are few data supporting a clinically significant interaction of omeprazole. Warfarin constitutes two enantiomers, *R*-warfarin (mainly metabolised by CYP2C19) and *S*-warfarin (the more active isomer, which is mainly metabolised by CYP2C9). Although isolated cases have been reported of increased prothrombin time in anticoagulated patients given omeprazole (level of evidence 1c),[18] randomised studies have not disclosed clinically significant interactions. In healthy volunteers and in patients given warfarin and omeprazole the S-warfarin activity has not been observed to increase significantly (level of evidence 1a).[19–21] On the other hand, there are data that show that ketoconazole and clarithromycin (two drugs with high affinity for CYP3A4) are able to increase the plasma omeprazole concentrations (levels of evidence 1b and 1a, respectively).[22,23] The affinity of omeprazole for the P-glycoprotein of the small intestine increases digoxin bioavailability by 10% (level of evidence 1a) and that of nifedipine by 26% (level of evidence 1a), although in no case did these interactions achieve clinical significance.[24,25] Table I illustrates the observed levels of evidence for the interactions between omeprazole and other drugs.

2.2 Lansoprazole

Lansoprazole has been demonstrated to be a potent competitive inhibitor of CYP2C19 *in vitro*.

Table I. Major possible drug interactions induced by omeprazole

Drug	Interaction	Level of evidence	Reference
Diazepam	+	A	[11]
Phenytoin	−	B	[17]
Warfarin	−	A	[21]
Propranolol	−	A	[59]
Theophyllin	−	A	[60]
Quinidine	−	A	[61]
Cyclosporin	−	A	[62]

+ = interaction; − = no interaction.

Table II. Major possible drug interactions induced by lansoprazole

Drug	Interaction	Level of evidence	Reference
Diazepam	−	A	[26]
Phenytoin	−	A	[28]
Warfarin	−	A	[29]
Theophyllin	−	A	[27]
Tacrolimus	+	C	[63]

+ = interaction; − = no interaction.

However, it causes no significant inhibition of the metabolism of diazepam.[26] Similarly, the available data do not reveal significant drug interactions with theophylline, phenytoin and warfarin[27–29] (table II).

2.3 Pantoprazole

Pantoprazole exerts less inhibitory activity on the CYP450 enzyme system than omeprazole or lansoprazole.[30] Pantoprazole has a good safety profile with regards to drug interactions (table III).

2.4 Rabeprazole

As already pointed out, rabeprazole is metabolised primarily through a non-enzymatic pathway. This leads to this drug posing — at least in theory — fewer problems of interactions with drugs that are metabolised by the CYP450 system. The data available in the literature show, similar to the previously discussed PPIs, a high level of safety of rabeprazole as regards drug interactions (table IV).

Table III. Major possible drug interactions induced by pantoprazole

Drug	Interaction	Level of evidence	Reference
Diazepam	−	A	[64]
Phenytoin	−	A	[65]
Warfarin	−	A	[66]
Theophylline	−	A	[67]
Nifedipine	−	A	[68]
Carbamazepine	−	A	[69]

+ = interaction; − = no interaction.

Table IV. Major possible drug interactions induced by rabeprazole

Drug	Interaction	Level of evidence	Reference
Diazepam	–	A	[68]
Phenytoin	–	A	[32]
Warfarin	–	A	[33]
Theophylline	–	A	[33]

+ = interaction; − = no interaction.

Table V. Major possible drug interactions induced by esomeprazole

Drug	Interaction	Level of evidence	Reference
Diazepam	–	A	[31]
Phenytoin	–	A	[31]
Warfarin	–	A	[31]
Cisapride	–	A	[31]

+ = interaction; − = no interaction.

2.5 Esomeprazole

Esomeprazole is the last PPI to have become available in the market, and the data regarding drug interactions are therefore more scarce for this molecule than for the other PPIs. Controlled, double-blind studies show that esomeprazole is able to inhibit the metabolism of diazepam through competitive inhibition of CYP2C19 to a similar degree as omeprazole, causing a fall by approximately 45% in the clearance of that drug (level of evidence 1a).[31] However, this finding is thought not to be clinically relevant.[31] Although pharmacokinetic studies have demonstrated that esomeprazole increases the AUC of phenytoin and reduces its plasma clearance,[31] studies in epileptics receiving phenytoin who were given esomeprazole have failed to demonstrate changes in the plasma phenytoin levels (level of evidence 1a).[31] In the case of warfarin, and similar to omeprazole, there are few data supporting a clinically significant interaction. Esomeprazole seems to produce a marginal inhibitory effect on the metabolism of R-warfarin but not on that of S-warfarin (level of evidence 1a).[31] However, randomised studies in which warfarin and esomeprazole or placebo were given have disclosed no modifications in the analytical parameters of anticoagulation control.[31] On the other hand, clarithromycin has been observed to significantly reduce esomeprazole metabolism and to double its AUC as both drugs share the CYP3A4 metabolic pathway.[31] Table V summarises the interactions of esomeprazole on the metabolism of other drugs.

The high anti-secretory efficacy of the PPIs increases the absorption of digoxin and reduces that of ketoconazole[32,33] as the absorption of these drugs may be influenced by the intragastric pH. Although there are no controlled studies that might explain whether these interactions are significant for the bioavailability of digoxin and ketoconazole, prudence counsels that the plasma levels of these drugs be monitorised in patients receiving PPIs.[30]

Among all the possible drug interactions of the PPIs discussed, the modification of the effects of warfarin might probably be the one with greatest clinical relevance because of the risk of inducing severe haemorrhagic complications. As previously discussed, there does not appear to exist a significant interaction between warfarin and the PPIs in controlled studies. Furthermore, a recent and extensive retrospective study analysing the data recorded by the US Food and Drug Administration on possible drug interactions in patients treated with omeprazole, lansoprazole and pantoprazole states that, although the most frequently reported interaction is that with warfarin, the overall numbers of this interaction are quite low and important complications are practically absent.[34] Furthermore, the numbers of observed interactions were similar for the three PPIs studied, suggesting that this interaction is a class effect or a random coincidence rather than a specific phenomenon associated with one PPI.

3. PPI Dose Adjustment in Patients with Liver Failure or Renal Failure, or in Aged Patients

As previously pointed out, the PPIs are metabolised in the liver and excreted by the kidney. Renal failure has little or no repercussion on PPI elimination, and there is no need to modify

or adjust the dosage of these drugs in renal failure patients.[3,35]

In patients with severe liver failure, however, the AUC of the PPIs increases seven-fold to nine-fold and their half-life increases to 4–8 h.[3] Thus, a reduction of the standard dosage of these drugs is recommended in these patients.

The plasma clearance of the PPIs is reduced in advanced age. The AUC of pantoprazole, lansoprazole and rabeprazole increases by approximately 50–100% in the aged population.[36–38] The plasma clearance of esomeprazole is not significantly modified in this patient group.[39] However, all the PPIs have a short plasma half-life of about 1 h, and accumulation is improbable even when the plasma clearance is reduced.[3] Thus, no dosage adjustment is necessary in aged patients treated with PPIs; however, such an adjustment should be considered when important hepatic or renal failure is added to advanced age.

4. Safety of PPIs During Pregnancy

Medicinal use of drugs is rather frequent during pregnancy; it has been calculated that 85% of all pregnant women use at least one drug during this period.[40] Gastro-oesophageal reflux disease is quite frequent during pregnancy, and the prescription of drug therapy represents a problem for the clinician because of the potential risk of foetal toxicity. The symptoms and complications of peptic ulcer disease may also be frequent during pregnancy. It is usually recommended that treatment of dyspepsia and heartburn during pregnancy be initiated with hygienic–dietetic measures together with antacids and sucralfate. The administration of histamine H_2 receptor antagonists and PPIs should be restricted to pregnant patients whose symptoms are refractory to the aforementioned therapy, even though their use during pregnancy is not yet approved.[41,42]

The PPIs cross the human placental barrier.[43] The US Food and Drug Administration currently states omeprazole in class 'C' of pharmacologic safety during pregnancy, which means that animal reproduction studies have not unequivocally demonstrated the safety of this drug for the foetus and that there are as yet no sufficient studies of its safety during pregnancy in humans.

Because of the widespread and frequent use of PPIs worldwide and because of the fact that many women of reproductive age may be exposed to PPIs during pregnancy, knowledge of the degree of safety of these drugs during that period is necessary.

A recent meta-analysis reviewing the most important studies in the literature, which analyses approximately 600 live births with exposure to PPIs, suggests that the administration of PPIs (and especially omeprazole) during the first trimester of pregnancy is not associated with a significant teratogenic risk. The relative risk was close to one (1.18) with a narrow 95% confidence interval (0.72–1.94), the maximum level of risk increase being less than twice the total relative risk. The overall observed malformation rate was 2.8% (95% confidence interval, 1.8 – 3.8), less than that reported for the general population.[44]

These data lead to the conclusion that the PPIs are a safe medication during pregnancy, particularly if it is borne in mind that the symptoms of gastro-oesophageal reflux disease in the pregnant woman usually become manifest or worsen at the end of pregnancy, when the risk of teratogenesis is much lower.

5. Side Effects of the PPIs

The PPIs have been shown to be well tolerated by the patient and to induce only a few side effects. The frequency of mild side effects is about 1–3%, with headache, diarrhoea, skin rashes, nausea and constipation being those most frequently reported.[3] This frequency of side effects is similar to that reported for placebo or for the H_2 receptor antagonists. Some studies have shown that these PPI-associated side effects are more frequent in the aged population.[45] Although no significant differences have been observed in the frequency and distribution of these side effects among the various PPIs, some isolated studies have reported diarrhoea to be more frequently associated with therapy with lansoprazole.[45]

The induction of severe side effects by the PPIs is infrequent, although cases of toxic hepatitis, interstitial nephritis and severe ophthalmopathies have been reported.[3] Severe ocular lesions in association with PPIs have been mainly, but not exclusively, reported in patients receiving intravenous omeprazole.[46] The fact that they have been reported in polymedicated and aged patients renders caution necessary when considering the certainty of the association of these conditions with this type of drug.

6. Safety of Long-term Therapy with PPIs

The effective and potent inhibition of the gastric secretion of hydrochloric acid has, ever since the introduction of PPIs, posed questions about the safety of long-term therapy with this type of drug.

It is well known that therapy with PPIs is associated, because of the potent inhibition of HCl secretion, with hypergastrinaemia (two to three times the upper level of normality).[47] The hypergastrinaemia levels are variable among the different patients treated but, in any case, usually are not very high and return to the normal range a few days after withdrawing the PPI.[48] As a consequence of this hypergastrinaemia the possibility of carcinoid tumour development in patients receiving long-term PPI therapy has been postulated. Carcinoid tumours have indeed been reported in experimental animals (in the rat);[49] however, to date there is no single report of this type of neoplasm in humans, and only cases of hyperplasia or redistribution of the gastric chromaffin cells have been described.[50]

It is also well known that *Helicobacter pylori* infection is accompanied by chronic gastritis, which is initially predominantly antral. In patients infected by this bacterium and receiving long-term therapy with PPIs, the gastritis extends to the gastric corpus and fundus, and it has been proposed that these changes might lead to increased extension of atrophic gastritis and of intestinal metaplasia, with the ensuing risk of gastric adenocarcinoma development.[51] However, there is at this time no scientific evidence that the risk of gastric cancer may be increased in patients with *H. pylori* infection receiving long-term therapy with PPIs.[52,53]

Potent anti-secretory therapy is associated with an increase of the bacteria concentration in the gastric cavity. The potential carcinogenic effect of the increase of the intragastric nitrosamine concentrations induced by this bacterial overgrowth is highly contradictory, and there is no scientific evidence in support of this theory.[54]

Similarly, the possible risk of enteric infections favoured by the marked hypochlorhydria induced by the potent effects of PPI therapy is not supported by the scientific evidence currently available. Only isolated cases of enteric infection in PPI-treated patients have been reported.[55]

Finally, the possibility has also been put forward that patients receiving long-term therapy with potent gastric secretion inhibitors may evidence nutrient malabsorption (fats, minerals, etc.). Only in a few patients of these characteristics have isolated mild vitamin B_{12} deficiencies been reported; these deficiencies are the consequence of a reduced absorption of that vitamin secondary to impairment of its release from the ingested foodstuffs, as this release process is facilitated by an acidic intragastric environment.[56] For this reason, it does appear advisable to monitor the cyanocobalamin levels in these patients.[57]

7. Safety of PPI Medication in Children

Although a number of studies have reported the use of PPIs in paediatric populations, there are few references in the literature about the pharmacologic safety of this drug group in children. The available data suggest that PPIs are a safe medication in this population group;[58] nevertheless, further safety studies, and particularly long-term safety studies, are necessary for confirmation of this assertion.

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