REVIEW ARTICLE

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Potent Acid Inhibition: Summary of the Evidence and Clinical Application

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1. Introduction

This issue has carried out an in-depth, detailed review of the significance of potent inhibition of gastric acid secretion in its different aspects: pharmacological, physiological, diagnostic, and therapeutic. Each of the chapters has addressed a specific subject, in an attempt to provide the greatest amount of scientific knowledge and evidence. The work done by the different authors is undoubtedly of great value for making a detailed analysis of the clinical significance of profound acid secretion inhibition. However, we thought it would be useful to highlight the concepts from each chapter that might be more relevant in clinical practice and that often arise as isolated questions in the context of our professional activity. An attempt has been made to make questions and answers as concise as possible in order to allow for rapid reading. Readers who require additional information will be able to find it in the relevant chapters of the issue, together with literature references, evidence levels and grades of recommendation.

2. General Aspects of Proton Pump Inhibitors

2.1 What progress has been made with drugs intended to control gastric acid secretion?

Tremendous progress has been made over the past 25 years. We have evolved from alkaline antacids, having a short, weak action, to secretion inhibitors. Moreover, as regards the latter, the advent of the proton pump inhibitors (PPIs) involved a great quantitative and qualitative change from the histamine H_2 receptor antagonists (anti-H_2). Few therapeutic areas of gastroenterology have seen such significant scientific progress.

2.2 Do PPIs Achieve the Same Acid Inhibition as Anti-H_2?

No. Among anti-secretory drugs, PPIs can inhibit gastric acid secretion with a greater efficacy than anti-H_2.

2.3 What is Potent Acid Inhibition?

The concept of 'potent acid inhibition' is relative, and is applied in a different way in each clinical setting, depending on the intended therapeutic objective.

2.4 What is the Definition of Potent Acid Inhibition?

Potent acid inhibition is arbitrarily defined as inhibition that achieves maintenance of an intragastric pH higher than 4 for at least 16 h out of 24 h.

2.5 What is the Relationship between Gastric Acid Inhibition and Therapeutic Response?

A direct relationship was shown many years ago between the time during which the gastric pH remains above 4 and the rapidity in lesion healing, both for gastric or duodenal ulcers and for oesophagitis.

2.6 Are Better Results Obtained if Additional Inhibition of Gastric Acid Secretion is Achieved?

It has been shown that the healing rate of oesophagitis, *Helicobacter pylori* eradication, peptic ulcer healing, or the extent of mucosal damage induced by non-steroidal anti-inflammatory drugs are clearly related to the acid inhibition level achieved with the corresponding treatment.

2.7 How Should the Ideal Drug to Achieve a Potent Acid Inhibition Be?

The ideal drug to achieve potent acid inhibition should be able to maintain pH above 4 for 16 h or more per day. Such acid inhibition level would guarantee a consistent response to treatment, and would be sufficient even for the most refractory cases of peptic acid disease. Efficacy of the drug would also have to be consistent, so that such potent acid inhibition levels might be achieved in all patients, regardless of their basal acid secretion, metabolic capacity, or the presence or absence of *H. pylori* infection.

2.8 What are the PPIs Currently Available?

Omeprazole was the first PPI marketed, followed by lansoprazole and pantoprazole, which together represent the first generation of PPIs. The most recent PPIs are rabeprazole and esomeprazole, both considered second-generation PPIs.

2.9 For How Long are the Different PPIs Able to Maintain Gastric pH Above 4?

Administration of PPIs at standard doses for five consecutive days achieves maintenance of an intragastric pH above 4 as follows: on average, 14 h with esomeprazole, 12 h with rabeprazole, 12 h with omeprazole, 11.5 h with lansoprazole, and 10 h with pantoprazole. Thus, a gain from 20% to 40% is achieved when comparing esomeprazole with other PPIs.

2.10 What is the Variability in Individual Response when PPIs are Used?

At low doses of conventional PPIs there is a wide inter-individual variability in effectiveness, but at higher doses, or with second-generation PPIs such as esomeprazole, higher levels of acid inhibition are achieved, and responses are much more consistent.

2.11 What is the Comparative Anti-secretory Efficacy of the Different PPIs?

Among the different PPIs administered at standard doses, esomeprazole 40 mg/day has a greater anti-secretory potency than all other PPIs. Among the latter, rabeprazole 20 mg/day and lansoprazole 30 mg/day show a faster action, and perhaps a slightly greater acid inhibition capacity than omeprazole 20 mg/day and pantoprazole 40 mg/day.

2.12 Does the Presence of *H. Pylori* Influence the Degree of Acid Inhibition?

It has been reported that acid secretion inhibition caused by omeprazole is greater in patients with *H. pylori*, and that eradication treatment reduces the ability of PPIs to increase gastric pH.

2.13 Does Esomeprazole Efficacy Depend on Whether the Patient is Infected by *H. Pylori*?

PPIs show a decreased efficacy in patients not infected by *H. pylori*. This often requires the use of

higher doses of the PPI. However, esomeprazole has shown a high efficacy regardless of the presence or absence of *H. pylori*.

2.14 Do PPIs have Some Antibacterial Activity against *H. Pylori*?

Unlike anti-H_2, PPIs have an intrinsic antibacterial activity against *H. pylori*, and also cause a synergic pharmacokinetic interaction with some antibiotics.

2.15 What Happens When the Administration of PPIs is Discontinued?

When treatment is discontinued, several days are required to recover normal acid production levels, and no cases of acid secretion rebound have been reported.

2.16 Does Tachyphylaxis Occur after Long-term Use of a PPI?

No. Continued PPI administration does not induce tachyphylaxis, but an improved efficacy as previously spared enzymes are disabled.

2.17 Do PPIs Have a Good Safety Profile?

PPIs have a good safety profile, and there is no evidence that they cause direct toxic effects. The most common adverse reactions include episodes of diarrhoea, nausea, abdominal pain, dizziness, headache, or skin rash. These manifestations are most often transient and moderate in severity, not requiring reductions in compound dosage.

2.18 Is Continued Use of PPIs Dangerous?

It has been observed that prolonged PPI therapy in *H. pylori*-infected patients results in some changes in gastric histology, mainly chronic atrophic gastritis; whether this is clinically relevant or not remains a matter of discussion. However, clinical evidence accumulated for over 15 years confirms that continued use of PPIs does not result in changes in clinical, laboratory or gastric cytology parameters, and rules out any reservation about the continued use of PPIs for prolonged periods.

2.19 At What Time Should PPIs be Administered?

PPIs should preferably be administered while fasting and before a meal — so that at the time the peak plasma concentration is reached, there is also a maximum of proton pumps activated (i.e., secreting acid).

2.20 Is it the Same to Administer PPIs in the Morning or Evening?

A PPI administered in the morning reduces acid secretion more effectively than when the drug is administered in the evening, at the expense of reducing diurnal acid secretion, but not affecting nocturnal secretion. On the other hand, administration before lunch achieves more effective inhibition of nocturnal secretion than administration before breakfast.

2.21 Is there any Difference between Administration of PPIs in One or Several Doses?

Administration in divided doses appears to be more effective than a single daily dose, but the clinical significance is low in most cases.

3. Pharmacologic Aspects of PPIs

3.1 What are the Essential Pharmacological Effects of PPIs?

PPIs dose-dependently inhibit basal acid secretion and acid secretion induced by any stimulus, including food. PPIs somewhat decrease pepsinogen secretion and, due to the increase in intragastric pH, inhibit the proteolytic activity of pepsin.

3.2 What are the Similarities between the Different PPIs?

These drugs share the same mechanism of action and many pharmacokinetic and pharmacodynamic properties, having a common structural nucleus, 2-pyridyl methyl sulfinyl benzimidazole, with different substituent groups.

3.3 What is Esomeprazole?

Esomeprazole is the *S* isomer of omeprazole. Pharmacokinetic and pharmacodynamic studies suggest that this isomer undergoes less first-pass metabolism in the liver and has a lower plasma clearance as compared with omeprazole.

3.4 How can it be that PPIs have a Short Half-life and a Long-lasting Effect?

Despite their short plasma half-life, PPIs exert a persistent pharmacological action because by irreversibly binding to the proton pump they render necessary the synthesis of new enzymes to re-establish gastric acid secretion.

3.5 What is the Relationship between PPI Plasma Levels and their Effect?

A good correlation exists between the degree of inhibition of gastric acid secretion and the area under the plasma concentration curve.

3.6 How are PPIs Metabolised?

PPIs undergo extensive first-pass metabolism in the liver, resulting in various inactive metabolites that are excreted in the urine or bile. With the partial exception of rabeprazole, which has a significant non-enzymatic metabolism component, PPIs are metabolised by the cytochrome P450 system (mainly by isoenzymes CYP2C19 and CYP3A4).

3.7 What is the Significance of the Metabolic Pathway of the Different PPIs?

The CYP2C19 pathway is more commonly used than the CYP3A4 one and has a different kinetic speed. Small changes in the per cent use of one of these pathways result in significant changes in their effects. Esomeprazole, for instance, has greater affinity for the CYP3A4 isoenzyme, which also metabolises it more slowly. This allows esomeprazole to undergo a less extensive first-pass metabolism in the liver and to achieve higher plasma levels than those seen with an equivalent dose of omeprazole.

3.8 What Interactions do PPIs have with Other Drugs?

Theoretically, their influence on phenytoin, carbamazepine, warfarin, and diazepam should be monitored. However, as confirmed by a recent analysis of cases recorded by the US Food and Drug Administration (FDA), the clinical impact of these potential interactions is very low (rates lower than 0.1–0.2 per 1 000 000 prescriptions), with no differences between the different PPIs.

3.9 Are There Any Differences in Drug Interactions of the Different PPIs?

A recent, large retrospective study analysing the data collected by the US FDA on possible drug interactions in patients treated with omeprazole, lansoprazole, and pantoprazole reported that while the most commonly reported drug interaction occurs with warfarin, the overall figure for such interaction is very low, and significant complications are virtually absent. The results were similar with the three PPIs studied.

3.10 Are Adverse Side Effects Related to PPI Treatment Common?

No. The frequency of mild adverse effects is around 1–3%, with headache, diarrhoea, skin rash,

and constipation the main effects. Their frequency is similar to that seen with placebo or Anti-H_2.

3.11 Are Serious Adverse Side Effects Related to PPI Treatment Common?

No. Serious adverse effects occur uncommonly with PPIs, although cases have been reported of toxic hepatitis, interstitial nephritis, and severe eye disease.

3.12 What is the Influence of Renal Failure on PPI Dosage?

Renal failure has a low or absent impact on the elimination of PPIs, and no change is required in the doses of these drugs administered to patients with renal failure.

3.13 What is the Influence of Liver Failure on PPI Dosage?

In patients with severe liver failure, the area under the plasma curve for PPIs increases seven-fold to nine-fold, and their half-life is prolonged to 4–8 h. A decrease in the usual dose of these drugs is recommended in this group of patients.

3.14 Should the PPI Dosage be Decreased in Elderly Patients?

Plasma clearance of most PPIs is reduced in advanced age. However, since PPIs have a short plasma half-life, no adjustment of PPI dose is required in healthy elderly patients.

3.15 Do PPIs Have a Good Safety Profile in Children?

Available data suggest that PPIs have a good safety profile in children. However, additional safety studies are required to confirm this information, particularly long-term studies.

3.16 Can PPIs be Used During Pregnancy?

PPIs cross the human placental barrier. Omeprazole is currently classified by the US FDA in category 'C' for safety during pregnancy: there is no unequivocal evidence of safety. However, a recent meta-analysis examining administration of PPIs, particularly omeprazole, during the first trimester of pregnancy showed that it was not associated with a teratogenic risk. The overall malformation rate was 2.8% (95% confidence interval, 1.8–3.8), lower than that reported in the general population.

3.17 Can PPI Intake Induce a Vitamin B_{12} Deficiency?

In some patients continuously taking PPIs, a mild vitamin B_{12} deficiency has been seen as the result of decreased vitamin absorption. This is due to impaired release of the vitamin from food, because this is a process enhanced by the presence of an intragastric acid environment.

3.18 Is There an Increased Risk of Intestinal Infection in Patients Taking PPIs?

The potential risk of enteral infections as a result of hypochlorhydria caused by potent PPI treatment is not supported by the currently available scientific information.

3.19 Is PPI Intake Associated with the Occurrence of Gastric Carcinomas or Carcinoids?

There is no report to date on the association of PPI use with such types of tumours in humans, and only cases of hyperplasia or redistribution of gastric enterochromaffin cells have been reported.

3.20 Have Patients with *H. Pylori* Infection who Receive Long-term PPI Treatment an Increased Risk of Suffering Gastric Cancer?

There is currently no scientific evidence that patients with *H. pylori* infection who receive

long-term treatment with PPIs have an increased risk of suffering gastric cancer.

4. Gastro-oesophageal Reflux Disease and PPIs

4.1 What is the Degree of Correlation between Symptom Severity and Grade of Oesophagitis?

No correlation exists between symptom severity and the presence and grade of endoscopic lesion; there is even a certain trend to an inverse correlation, so that the most symptomatic patients usually have mild or even no endoscopic lesions.

4.2 What Impact has the Symptomatic Improvement Obtained with PPIs on Gastro-oesophageal Reflux Disease Treatment?

Symptom improvement achieved during treatment with PPIs is associated with a marked improvement in quality of life parameters.

4.3 What is the Essential Factor in the Genesis of Oesophagitis?

The action of acid on oesophageal mucosa is currently considered as the main pathogenetic factor involved in the occurrence and maintenance of oesophagitis.

4.4 What Relationship Exists Between the Extent of Acid Secretion Inhibition and Healing of Oesophagitis in Gastro-oesophageal Reflux Disease?

Various pathophysiological studies have supported the existence of a linear correlation between the extent of gastric secretion inhibition and the healing rate of oesophagitis in Gastro-oesophageal reflux disease (GORD).

4.5 What is the Main Factor Determining Therapeutic Response in GORD?

A recent meta-analysis of clinical trials comparing two or more PPIs for acute treatment of GORD showed that the differences between them depended more on the dosage given than on the specific PPI used: higher doses achieved a greater efficacy. These data support the significance of potent acid inhibition in GORD treatment. Nevertheless, another meta-analysis concluded that, at the standard doses marketed, only esomeprazole surpasses the gold standard of efficacy established by omeprazole.

4.6 What is the Optimum Threshold for Inhibition of Gastric Acid Secretion in GORD?

There are indirect data suggesting that maximum efficacy is achieved in GORD when the intragastric pH is above 4 for longer than 16 h per day.

4.7 At What Should a Treatment Aim to be Effective in GORD Oesophagitis?

The most effective treatment to achieve healing of oesophagitis consists of the use of drugs inhibiting acid secretion, which, in addition to rapidly controlling symptoms, suppress and counteract the harmful effects of acid and pepsin on the oesophageal mucosa.

4.8 What is the Efficacy of Anti-H_2 for Healing the Different Grades of Oesophagitis?

It can be summarised that the Anti-H_2 are effective in 70% of patients with mild oesophagitis (grades I and II of the Savary–Miller classification), but efficacy decreases to 35–40% in severe oesophagitis (grades III and IV).

4.9 What are the Healing Rates of Oesophagitis Achieved with Omeprazole *versus* Lansoprazole?

A recently published meta-analysis compared the efficacy of omeprazole at a dose of 20 mg/day *versus* lansoprazole at 30 mg/day in the treatment of erosive oesophagitis. The healing rate at 4 weeks was 74.7% in the group treated with omeprazole, as compared with 77.7% in the lansoprazole group; at 8 weeks, the rates reached were 81.3% and 83.3%, respectively, with no significant differences.

4.10 Are Different Results Achieved when GORD is Treated with Omeprazole, Lansoprazole, or Pantoprazole?

The therapeutic efficacy of the first PPIs introduced into the market at the standard doses used (omeprazole 20 mg/day, lansoprazole 30 mg/day and pantoprazole 40 mg/day) is very similar, with no significant differences being seen between them in the healing rate achieved or the symptom relief for patients.

4.11 Are Different Results Achieved when GORD is Treated with Omeprazole or Rabeprazole?

Rabeprazole achieves a fast and effective symptom relief in patients with erosive oesophagitis. Symptom relief at the dose of rabeprazole 20 mg/day is superior to the relief obtained with omeprazole 40 mg/day.

4.12 What are the Healing Rates of Oesophagitis Achieved with Esomeprazole *versus* Omeprazole?

A controlled study showed a higher healing rate at week 8 with esomeprazole 40 mg/day (94.1%) and esomeprazole 20 mg/day (89.9%) as compared with omeprazole 20 mg/day (86.9%), with statistically significant differences by intention to treat.

4.13 What are the Healing Rates of Oesophagitis Achieved with Esomeprazole *versus* Lansoprazole Depending on its Severity?

In the largest study published to date, including over 5000 patients, healing of oesophagitis was achieved at 8 weeks in 97%, 92%, 88%, and 81% of patients treated with esomeprazole 40 mg/day (oesophagitis grades A, B, C and D, respectively), while in the group treated with lansoprazole 30 mg/day the healing rates decreased as the severity of oesophagitis increased — the corresponding figures being 97%, 91%, 77%, and 64%. Thus, the healing rate of erosive oesophagitis with esomeprazole treatment was 11% higher as compared with lansoprazole in grade C patients, and the difference increased to 17% in grade D patients.

4.14 What are the Healing Rates of Oesophagitis Achieved with Esomeprazole *versus* Pantoprazole?

In a comparative, controlled study including over 3000 patients, oesophagitis healing rates were seen to be greater with esomeprazole 40 mg/day as compared with pantoprazole 40 mg/day both at 4 and 8 weeks. Differences became more evident as the severity of oesophagitis increased; thus, at 4 weeks of treatment, healing rates were as follows: 84% *versus* 83% for oesophagitis grade A, 80% *versus* 76% for oesophagitis grade B, 71% *versus* 60% for oesophagitis grade C, and 61% *versus* 40% for oesophagitis grade D.

4.15 Which is the PPI of Choice in Cases of Mild Oesophagitis?

In mild oesophagitis (grades A and B), no significant differences are seen in healing rate or symptom relief between esomeprazole and all other PPIs. However, it should be mentioned that no adequately addressed studies have been performed to evaluate differences in terms of symptom relief or early oesophagitis healing.

4.16 Which is the PPI of Choice in Cases of Severe Oesophagitis?

Esomeprazole has been shown to be significantly more effective than other PPIs for cases of grade C and D oesophagitis according to the Los Angeles endoscopic classification.

4.17 What are the Healing Rates of Oesophagitis Achieved with Double-dose Omeprazole *versus* Lansoprazole?

The 40 mg/day dose of omeprazole has the same clinical and lesion healing efficacy as lansoprazole 30 mg/day for all grades of oesophagitis.

4.18 What is Refractory GORD?

Refractory GORD is that in which healing is not achieved with a standard dose of omeprazole (20 mg/day) for 12 weeks. Thus, the standard dose has an inadequate potency in some cases.

4.19 Do all patients with GORD respond to double doses of PPIs?

Up to 20% of GORD patients have an inadequate anti-secretory response to omeprazole 20 mg/12 h. Although no data are available, these results can probably be extrapolated to all other PPIs of similar potency. Higher omeprazole doses (80 mg/day) achieve a reduction in acid secretion in these refractory patients.

4.20 What Approach Should be Taken when Faced with a Patient with GORD not Responding to Standard PPI Treatment?

Up to 30% of patients with GORD treated with a PPI in a single daily dose continue to experience heartburn at any time of the day or night. These patients usually respond to twice-daily administration of PPIs (before breakfast and dinner). However, replacing that PPI by a single dose of esomeprazole 40 mg has been shown to be as effective as doubling the dose of the original PPI.

4.21 What Would be the Approach to be Taken in a Patient with Suspected GORD Refractory to Treatment?

Esomeprazole at a dose of 40 mg/12 h would achieve an even greater response than omeprazole 80 mg/day, and would be a practical choice to rule out that the lack of symptomatic response is due to an inadequate effect of PPIs in patients refractory to treatment.

4.22 What is the Role of Esomeprazole in the Treatment of Refractory GORD?

In a group of patients with persistent symptoms despite receiving lansoprazole 30 mg/day, a switch to esomeprazole 40 mg/day has been reported to be as effective as increasing the lansoprazole dose to 30 mg/12 h.

4.23 What is the Comparative Clinical Efficacy of the Different PPIs in GORD Treatment?

At standard doses, omeprazole, lansoprazole, rabeprazole, and pantoprazole are equivalent as regards therapeutic efficacy, in both symptom control and healing of lesions. Esomeprazole, at a dose of 40 mg/day, is more effective for both symptom improvement and lesion healing, with a therapeutic gain of approximately 5–10%.

4.24 Is Esomeprazole Superior to Omeprazole for Treating GORD?

A systematic review of the literature shows esomeprazole to be the only PPI that is more effective than omeprazole for the acute treatment of GORD, both at 4 and 8 weeks of treatment.

4.25 Is Esomeprazole Superior to other PPIs for Treatment of GORD?

Yes. This superiority has been documented in comparative, controlled, randomised, and

double-blind clinical trials of esomeprazole *versus* omeprazole, lansoprazole, and pantoprazole.

4.26 What is the Most Efficient Long-term Treatment for GORD?

PPIs represent the best long-term medical therapy, and the most effective therapy is the most efficient.

4.27 What is the Evidence Showing that PPIs are Better than H_2 Receptor Antagonists for Preventing Symptomatic Relapse in GORD Patients?

Six clinical trials including approximately 1000 patients and analysed in a systematic review have shown the superiority of PPIs over anti-H_2 for preventing symptomatic relapse in GORD patients.

4.28 Which is the Dose to be Used in Maintenance Treatment to Prevent GORD Relapse?

Daily maintenance treatment may be given using the conventional daily dose (20 mg/day for omeprazole and rabeprazole, 30 mg/day for lansoprazole, and 40 mg/day for pantoprazole and esomeprazole), or one-half of the conventional dose administered daily (15 mg/day for lansoprazole, 20 mg/day for esomeprazole and pantoprazole, and 10 mg/day for rabeprazole). A systematic review of the literature shows that any PPI is more effective at full doses than at half doses. Among the different PPIs at half doses, esomeprazole is the only one that is more effective than lansoprazole and pantoprazole.

4.29 What is Intermittent Treatment for GORD?

Intermittent treatment for GORD consists of administration of short treatment courses (approximately 2 weeks) with standard PPI doses when symptoms relapse. This can be considered in young adults with non-erosive GORD or grade A–B oesophagitis.

4.30 When is On-demand Treatment Recommended?

On-demand treatment consists of taking the medication only when GORD symptoms occur, rather than every day. It has mainly been recommended in GORD without oesophagitis.

4.31 What Characteristics Should a PPI Have to be Used on Demand?

The drug to be used in an on-demand regimen should cause a potent inhibition of gastric acid secretion, and should have a fast onset of action, a prolonged action, and a predictable inter-individual response. Esomeprazole meets all these criteria.

4.32 Is Esomeprazole Useful when Used On Demand in GORD Patients without Oesophagitis?

Yes, because over 90% of patients in which symptoms respond to esomeprazole are subsequently controlled with an on-demand esomeprazole regimen, requiring a mean of one tablet every 3 days. This is associated with a direct cost reduction by up to 61% when compared with a PPI in a daily dosage regimen.

4.33 What can be Expected in the Evolution of Patients with Non-erosive GORD?

In a small group of patients, followed up for 7–14 years, it was shown that 75% required antisecretory agents, 40% continuously and 60% intermittently or on demand; in addition, 62% of patients undergoing a repeat endoscopy had signs of mild to moderate oesophagitis.

4.34 Have Patients with Non-erosive GORD any Particular Clinical Characteristic?

Generally, patients with non-erosive GORD are younger, non-obese patients, more frequently women, and do not have hiatus hernia; in addition, they do not usually progress to the erosive form or experience complications, even after follow-up periods of 15–20 years.

4.35 What is the Prognosis for Patients with Severe Oesophagitis?

Patients with grade C–D oesophagitis have a high risk of mid-term to short-term complications, and it is in these patients where the benefit of anti-secretory treatment is easier to document.

4.36 How should GORD be Treated in Elderly Patients?

In elderly patients, who are also usually taking drugs aggravating gastro-oesophageal reflux, GORD should be treated with full PPI doses daily and for life.

4.37 What is the Adequate Therapeutic Regimen for the Treatment of Supra-oesophageal Manifestations of GORD?

A PPI at double the standard dose for not less than 3 months is the therapeutic regimen to be used in supra-oesophageal signs due to gastro-oesophageal reflux. While a standard esomeprazole dose is more effective than an omeprazole dose to treat GORD, it seems reasonable to also recommend a double dose of esomeprazole.

4.38 Is PPI Treatment of Patients with Non-cardiac Chest Pain Useful?

It can be stated that non-cardiac chest pain is the extra-oesophageal condition where more evidence exists about the value of PPIs. When PPIs are used at double doses, the response rate is up to 81%, as compared with 6% in the control group.

4.39 Is PPI Treatment of Asthma Patients Useful?

A systematic review of the literature shows no results favouring anti-reflux treatment in asthmatic patients either in clinical or functional parameters. However, PPIs may be indicated in some cases, and the best results are obtained with high PPI doses administered twice daily for 2–3 months. Efforts should be made to detect those patient subgroups that could benefit from treatment with PPIs, for which future studies should be aimed at identifying response predictors.

4.40 Is PPI Treatment of Patients with Cough Useful?

A controlled study has shown that omeprazole 40 mg/day for 8 weeks is superior to placebo in cough relief. Until further studies are conducted to define treatment duration and dosage, a PPI at a double dose for at least 8–12 weeks is currently recommended.

4.41 Is PPI Treatment of Patients with Laryngitis Useful?

Controlled clinical trials of PPIs *versus* placebo for the treatment of laryngitis do not provide very optimistic data as regards clinical or laryngoscopical response. Only one trial, conducted with lansoprazole 30 mg every 12 h, showed a 50% response in the treatment group, as compared with 10% in the group treated with placebo. In three other studies, with a small number of patients, no significant differences were noted between the treatment groups, but PPIs are usually effective for initial symptom control.

4.42 Is Esomeprazole Treatment of Patients with Laryngitis Useful?

In a multicentre study conducted in 145 patients who were randomised to esomeprazole 40 mg twice daily or placebo, no significant differences were seen in clinical or laryngoscopical response.

However, further research is required on this matter to try and identify those patients who may benefit from potent acid inhibitory treatment.

5. Barrett's Oesophagus and PPIs

5.1 What Should be the Medical Treatment for Barrett's Oesophagus?

Since the presence of Barrett's oesophagus is considered an important and severe complication of GORD, PPI therapy is assumed to be the drug treatment of choice.

5.2 What is the Medical Treatment of Choice for Patients with Barrett's Oesophagus?

Potent and adequate anti-secretory treatment reduces cell proliferation of metaplastic mucosa in Barrett's oesophagus. The risk of developing dysplasia and/or adenocarcinoma might be reduced by deeply inhibiting gastric acid secretion.

5.3 What is the Relationship between Clinical Response and the Suppression of Gastro-oesophageal Reflux Achieved with PPIs in Patients with Barrett's Oesophagus?

Recent data suggest that symptom suppression is often not associated with normalisation of intra-oesophageal pH; up to 50% of patients with Barrett's oesophagus were taking suboptimal doses. This fact supports the need for monitoring intra-oesophageal pH in patients with Barrett's oesophagus taking PPIs in order to optimise therapy at adequate doses, rather than based only on the presence or absence of symptoms.

5.4 Is Treatment with PPIs or Anti-reflux Surgery Associated with a Length Reduction and/or Gradual Normalisation of Barrett's Oesophagus?

Most classical studies suggested that neither PPI therapy nor anti-reflux surgery were associated with regression in the length of Barrett's oesophagus. This concept has been recently challenged by some surgical teams. Moreover, some studies have suggested that intensive PPI treatment is associated with a partial regression of intestinal metaplasia. Nonetheless, we should currently assume that, while partial results are obtained, Barrett's oesophagus does not disappear with these measures.

5.5 Does Treatment with Profound Acid Inhibition Prevent the Development of Adenocarcinoma in Barrett's Oesophagus?

Profound acid inhibition or reduction of gastro-oesophageal reflux does not prevent progression of Barrett's oesophagus to adenocarcinoma, but may reduce the risk of its occurrence.

5.6 Does Treatment with Profound Acid Inhibition Prevent the Development of Dysplasia?

A recent study suggests that the risk of developing high-grade or low-grade dysplasia is correlated with the delay in starting PPI therapy after diagnosis of Barrett's oesophagus.

5.7 Is Profound Acid Inhibition Required in the Management of Patients with Barrett's Oesophagus Undergoing Ablation by Endoscopic Techniques?

Available studies state that profound acid inhibition is required during and after ablative endoscopic treatment in order to provide an acid-free, or at least an acid-reduced, environment in the re-epithelisation process of the oesophageal mucosa by squamous epithelium. These studies have shown that reflux persistence and the length of Barrett's oesophagus are the factors determining the frequency of relapse after ablation.

5.8 What is the Value of Treatment with Esomeprazole in Patients with Barrett's Oesophagus?

A recent study stated that esomeprazole 40 mg twice daily was superior to standard PPI treatment for the control of gastric acidity and for normalisation of intra-oesophageal pH in patients with Barrett's oesophagus. This occurred in virtually all patients treated with esomeprazole, and in only 50% of patients on standard treatment with other PPIs.

5.9 What Dose of Esomeprazole Should be Used in Patients with Barrett's Oesophagus?

Recent data, published as an abstract, suggested that the optimal dose of esomeprazole in patients with Barrett's oesophagus is 40 mg twice daily, because it successfully maintained the intra-oesophageal pH above 4 for 23 h per day.

6. Ulcer Disease, *H. Pylori* and PPIs

6.1 Do PPIs Have any Direct Action on *H. Pylori*?

Yes. PPIs inhibit the urease protecting *H. pylori* from acid and are effective on this microorganism *in vitro*, although *in vivo* they only achieve eradication in 10–15% of cases.

6.2 Do PPIs Promote the Action of Antibiotics in *H. Pylori* Eradication?

In vitro, PPIs have an additive — even synergistic — effect with several antimicrobial agents. Various studies have suggested that the use of high omeprazole doses increases amoxycillin levels in gastric juice, and that a higher dose of the PPI improves *H. pylori* cure rates when dual therapy with PPI and amoxycillin is prescribed. Clarithromycin activity against *H. pylori* is also enhanced as intragastric pH increases.

6.3 What Dose of PPIs Should be Used for *H. Pylori* Eradication?

Esomeprazol should be used at dose of 20 mg twice daily as part of *H. pylori* eradication regimens.

6.4 Are There Differences in *H. Pylori* Eradication Depending on the PPI Used?

The meta-analytical study shows that the results in *H. pylori* eradication are the same irrespective of the PPI used.

6.5 Are There Differences in *H. Pylori* Eradication when Rabeprazole is Used as the PPI?

Some studies have shown that rabeprazole has a greater antibacterial activity against *H. pylori* than other PPIs. However, a meta-analysis of comparative studies shows that rabeprazole is equivalent to other PPIs when administered together with two antibiotics.

6.6 What is the *In Vitro* Antibacterial Activity of Esomeprazole Against *H. pylori*?

Esomeprazole has an *in vitro* activity against *H. pylori* superior to other PPIs, such as omeprazole.

6.7 Are There Differences in *H. Pylori* Eradication when Esomeprazole is Used as the PPI?

Esomeprazole-based combinations are effective for treatment of *H. pylori* infection, with eradication rates similar to those previously reported with other PPIs.

6.8 What is the Therapeutic Strategy for Gastroduodenal Ulcer?

These conditions are resolved in most cases with eradication of *H. pylori*. However, sometimes there

is no infection and the condition should be treated by permanent acid secretion inhibition. The standard PPI dosage is adequate in many cases, but the dose must sometimes be doubled, particularly in the case of gastric ulcer.

6.9 What Degree of Acid Inhibition Should be Achieved to Heal an Ulcer?

It has been reported that a sustained increase in pH to above 3 would be sufficient to heal an ulcer. However, one of the risk factors for refractory gastric ulcer appears to be the impossibility of maintaining gastric pH above 4 for a minimum daily period of 16 h.

6.10 What is the Purpose of Inhibiting Gastric Acid Secretion in Cases of Upper Gastrointestinal Bleeding?

In upper gastrointestinal bleeding, the aim is to achieve the least acid gastric pH possible in order to prevent acid degradation of the clot and accelerate healing as much as possible. Both clinical and experimental studies suggest that an extremely potent inhibition is required to achieve the intended efficacy.

6.11 Is PPI Administration Useful in Cases of Upper Gastrointestinal Bleeding?

PPIs have been shown to be effective for the treatment of upper gastrointestinal bleeding in patients with lesions with a high re-bleeding risk, as single therapy or associated with local haemostatic procedures.

6.12 What is the Best Prevention and Treatment for Upper Gastrointestinal Lesions Induced by Non-steroidal Anti-inflammatory Drugs?

There is conclusive evidence that PPIs decrease the incidence of ulcers and erosions, and heal them when they have occurred, even when non-steroid anti-inflammatory drug administration is continued. Use of a double dose is not indicated, except for healing of refractory lesions.

7. PPIs as a Diagnostic Test

7.1 What is the Value of the Clinical Response to PPIs as a Diagnosis Test for GORD?

A positive clinical response to PPIs cannot be considered an unequivocal diagnosis of GORD, but may be of help. It is simple, convenient, and sensitive enough to be recommended as a first-choice test.

7.2 Is the PPI Test Specific for the Diagnosis of GORD?

The PPI test is poorly specific for diagnosis of GORD (approximately 50–60%), because PPIs are potent anti-secretory drugs that not only improve patients with GORD, but also those with duodenal or gastric ulcer, and 25–50% of patients with functional dyspepsia.

7.3 What is the Value of Esomeprazole Administration for the Diagnosis of GORD?

Administration of esomeprazole 40 mg/day for 1 week and observation for symptomatic response has a high sensitivity for the diagnosis of GORD.

7.4 Is the PPI Test Cost-effective for the Diagnosis of GORD?

Cost analysis studies reveal that using the 'PPI test' for GORD diagnosis, instead of early endoscopy or pH-metry, the number of endoscopies is reduced by 64% and the number of pH-metries by 53%, with savings of €300–400 per patient.

7.5 Is the PPI Test Useful for the Diagnosis of Patients with Non-cardiac Chest Pain?

Yes. A therapeutic test with PPIs for 1 month is useful for the diagnosis of GORD with negative endoscopy in patients with non-cardiac chest pain.

7.6 How Should the PPI Test be Performed for the Diagnosis of Peptic Laryngitis?

In peptic laryngitis, the 'short PPI test' is of no value, and a therapeutic test must be made for at least 3 months and with a profound gastric acid inhibition.

7.7 Is the PPI Test Useful for Diagnosing Chronic Cough as Secondary to GORD?

The best diagnostic method to ascertain whether chronic cough is secondary to GORD, once asthma and posterior nasal drip have been excluded, is treatment with PPIs at high doses for at least 2 weeks.

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