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Optimising Acid Inhibition Treatment

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Abstract

Acid inhibition is safe and useful in several clinical settings. Proton pump inhibitors are more effective than H_2-receptor antagonists in virtually all cases. Proton pump inhibitors should be used in: the eradication of *Helicobacter pylori*; the treatment of non-*H. pylori*-related peptic ulcer healing; for the prevention and treatment of non-steroidal anti-inflammatory drug-induced upper digestive lesions; for bleeding peptic lesions; and, especially, in the short-term and long-term control of gastro-oesophageal reflux disease. The timing, the dosing and the specific drugs should be adapted to the particular patient, clinical situation and local factors. For instance, in a patient with active bleeding from a duodenal ulcer, intravenous constant infusion should be the preferred treatment. When seeking oral 'potent' acid inhibition (refractory gastro-oesophageal reflux disease, and perhaps Barrett's oesophagus), available data suggest that the pharmacological and clinical profiles of esomeprazole are slightly better.

1. Introduction

As extensively reviewed in Chapter 3, the clinician treating a patient who requires acid inhibition has available scientific evidence for the following:

- Inhibition of gastric acid secretion is effective in healing peptic lesions and in improving their symptomatology, and in the prevention of lesions induced by NSAIDs.[1,2]
- There exists a quantitative relationship, which is different for each disease condition, between inhibition of acid secretion and therapeutic efficacy.[3,4]
- Inhibition of acid secretion maintains its efficacy over time without relevant side effects.[1,2,5,6]

However, when faced with the need to take a therapeutic decision, the clinician must still answer a number of questions: Which drug? Which dose? Which administration schedule? How long should I maintain treatment? How should I assess the response? Furthermore, for each decision he must also consider local circumstances, availability of other therapies, characteristics of the particular patient, and cost. Sometimes, there are clinical practice guidelines that may facilitate his work, such as those of the Spanish Gastroenterology Association (Asociación Española de Gastroenterología, AEG) (www.guiasgastro.net). We provide, here, brief answers to a number of questions that may arise in daily practice, accompanied by the most recent and highest quality supportive scientific evidence. As in all the other chapters in this Supplement, the scientific evidence will be categorised according to the proposals of the Centre for Evidence-Based Medicine in Oxford (UK), which have been adopted by the Ibero-American Cochrane Centre (see the Introduction to this Supplement).

2. Histamine$_2$ Receptor Antagonists or Proton Pump Inhibitors?

Proton pump inhibitors (PPIs) are more effective inhibitors of gastric acid secretion in all clinical circumstances and present no disadvantages as compared with the histamine$_2$ (H_2) receptor antagonists as regards safety. There seem to be no indications for the use of H_2 receptor antagonists in present-day digestive diseases, perhaps with the exception of the management of occasional heartburn, possibly in association with an antacid, or in the exceptional patient who is hypersensitive (allergic) to all PPIs.[1,2,7-11]

3. Eradication of *Helicobacter pylori*

There is clear evidence that the use of single doses of PPIs reduces the efficacy of *H. pylori* eradication treatment;[12] PPIs should therefore be used at double the standard doses (with the exception of esomeprazole, for which the 20mg twice daily dose is effective) when given as part of the eradication procedures recommended by the therapeutic guidelines and by the national and international consensus conferences[2,13,14] (evidence level 1a; degree of recommendation A). There are no data available that might suggest one PPI to be preferable to another in this indication[2,15] (evidence level 1a; degree of recommendation A).

4. Functional Dyspepsia

No particular drug has demonstrated a significant consistent (lasting over time) and clinically relevant difference as compared with placebo in functional dyspepsia. In spite of this, a reasonable option is to use a PPI at standard doses, because: (a) PPIs have a good safety profile; (b) in a number of studies PPIs have been superior to placebo, probably because a proportion of patients are suffering from non-diagnosed gastro-oesophageal reflux disease (GORD); and (c) in the case of a diagnostic error – a patient who actually has a peptic ulcer – this treatment would be effective and reduce the probability of complications.[2] For these reasons, the Clinical Practice Guideline for Dyspepsia from the AEG recommends the use of PPIs as an alternative pharmacological option in patients with functional dyspepsia.[2] In these patients, the duration of treatment will depend on the symptomatic response.[2] No direct comparative studies between different PPIs are available that would allow the selection of any particular one in this indication.[13]

5. Duodenal and Gastric Ulcer

In most cases, duodenal and gastric ulcer can be resolved with the eradication of *H. pylori*, although omeprazole is a better option when NSAIDs or aspirin is also needed.[2] However, in some patients there is no infection. In these individuals, the administration of a PPI is the most effective option, as it rapidly ameliorates symptoms, hastens healing, prevents complications and even improves most of the lesions termed 'refractory'.[16] In many cases the standard dose of the PPI suffices, but instances in which the dose has to be doubled are not infrequent. This has been shown to be a useful strategy particularly in gastric ulcer, although in only a limited number of studies.[16,17] There are no comparative studies available between the various PPIs in this indication.

6. Prevention and Treatment of NSAID-Induced Lesions and Symptoms

Although misoprostol is the only drug that has been demonstrated to reduce the rate of complications (bleeding and perforation), its use in actual clinical practice is negligible, both because of dosing disadvantages (at least two doses a day are required for effectiveness) and, most particularly, because of the high rate of side effects (up to 40% of the patients develop diarrhoea).[18,19] In contrast, there is ample indirect evidence that PPIs reduce complications, derived both from confirmed epidemiological data and from observational studies in high-risk population groups.[20] Furthermore, there is definitive evidence that PPIs reduce the

incidence of ulcers and erosions and heal them when they have already developed, even if use of the NSAID persists.[19] Although this is probably a drug class effect, the one PPI for which there is greatest evidence in this indication is omeprazole, a drug with which many studies have been carried out. Remarkably, the 20mg dose is as effective as the 40mg, so that there is no indication for the use of double doses, except in the healing of refractory lesions.[21] Further to the prevention and management of complications and ulcers, it is clinically relevant to attempt to ameliorate the dyspepsia associated with NSAID use.

7. Upper Digestive Tract Bleeding

Proton pump inhibitors have been shown to be effective in the management of upper digestive tract bleeding in patients with lesions at high risk of re-bleeding, either as the only treatment or in association with local haemostatic procedures.[22,23] Although it has been demonstrated, in undeveloped countries, that even the oral route is effective (omeprazole 40mg twice daily),[24,25] in our environment patients at high risk of re-bleeding are provided with a venous access;[26,27] until oral intake can be resumed, the drug should be administered as a continuous infusion. In Spain, both omeprazole and pantoprazole are available for intravenous use. Both omeprazole and pantoprazole are given as an initial 80mg bolus, followed by continuous infusion at a rate of 8 mg/h,[22] although there is no uniform consensus as to the dose. After 72 h, and when the patient has resumed oral intake, it is probably advisable to maintain a dosage equivalent to omeprazole 40mg twice daily by mouth.

8. Gastro-Oesophageal Reflux Disease

It is in the indication of GORD that most doubts and questions as to the treatment modality arise. Initially, the marketed dose of omeprazole (20 mg/day) was shown to be so evidently superior to H_2 receptor antagonists or to sucralfate that it rapidly became the gold standard of treatment. Later on, equivalent evidence accrued for the standard doses of lansoprazole (30 mg/day), pantoprazole (40 mg/day) and rabeprazole (20 mg/day). However, it was soon observed that a significant number of patients did not achieve adequate healing of the lesions or continued having clinically relevant symptoms. Interestingly, symptoms are sometimes more difficult to control in patients without lesions.[28]

As there is a considerable variability in the response to PPIs, a proportion of the refractory cases may be attributable to an inadequate antisecretory response to PPIs. Studies that have already become classic show that up to 20% of the patients with GORD exhibit an insufficient antisecretory response to omeprazole 20mg twice daily.[29] Although there are no definite data available, these findings can probably be extrapolated to the remainder of the PPIs of similar potency (see Chapter 3). Higher doses of omeprazole (80 mg/day) achieve reduction of acid secretion in these refractory patients.[29] In clinical agreement with these data, observational studies have demonstrated that a proportion of the patients required 40 mg/day of omeprazole, and some others required higher doses – 60 or even 80 mg/day (of course, in the absence of Zollinger-Ellison syndrome).[5] The comparisons between the various PPIs have recently been examined in detail in a meta-analysis,[30] and a systematic review of even more recent literature is given in Chapter 3. Both reviews confirm that:

- At standard dosages, omeprazole, lansoprazole, rabeprazole and pantoprazole are equivalent as to therapeutic efficacy, both in the control of symptoms and in the healing of the lesions.
- An intermediate dose of any one of those drugs is effective (although less than the full dose) in maintenance treatment.
- Esomeprazole (40 mg/day) is more effective both in the management of symptoms and in the healing of lesions, with a therapeutic gain of about 10%.

It has been suggested that the failure of the standard doses might be the result of a phenomenon of 'night-time escape' of the acid secretion,

because in some patients, despite treatment with the standard dose of the antisecretory drug, the intragastric pH decreases to less than 4 for a long period during the night.[31] However, a number of doubts persist regarding the true clinical importance of this phenomenon. Does it really correlate with lack of response? Does the oesophageal pH really change during those periods of insufficient control of acid secretion? Is it necessary to invoke H_2 receptor antagonists in order to palliate this failure of the PPIs in the control of acid secretion? What is the influence of *H. pylori*? Doubts as to the true importance of this phenomenon are at present quite numerous, and some data even suggest that, in practical terms, its clinical relevance is nil.[32] Before changes in therapeutic strategy can be introduced on the basis of this particular point, further scientific evidence is required.

9. Pharmacology for the Practising Physician: 'Tricks' for Achieving Potent Acid Inhibition

As described in Chapter 2, PPIs accumulate within the canaliculi of the oxyntic cell and bind irreversibly to the proton pump, inactivating it permanently. They are, however, unable to inactivate those proton pumps that are in their rest phase and thus not exposed to the canalicular lumen. Furthermore, the parietal cell continuously synthesizes new proton pump molecules, so that acid secretion begins recovering as soon as the PPI concentrations decrease below the threshold for inhibition of the proton pump. After a single dose of a PPI, the acid secretion recovers completely within 72–96 h.[33-37]

PPIs are, to a greater or lesser degree, unstable in an acid environment and must be administered as enteric-coated microgranules in order to prevent their degradation as they pass through the stomach. They are rapidly absorbed in the intestine and achieve peak plasma concentrations 30 min to 3 h after administration. Absorption of PPIs is delayed and sometimes reduced by the presence of food in the gastric lumen. Their bioavailability ranges from 40 to 80% and increases with repeated doses (precisely because of the effect of inhibition of acid secretion). The plasma half-life ranges from 30 min to 3 h, although the pharmacologically significant parameter is the half-life within the parietal cell canaliculus, which is considerably longer. PPIs are rapidly metabolised and excreted through the liver and the kidneys, the elimination mechanisms being highly influenced by genetic variability.[33-37] As will be discussed, all these aspects have practical implications regarding the actual drug to be chosen, the dose and the mode of administration.

9.1 Which PPI?

There are currently five PPIs available: omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. There are some pharmacological differences between them as regards the mechanism of action and the metabolic pathways, and debate regarding the clinical relevance of these differences remains active. We will therefore examine this aspect in greater depth.

First of all, it is usually assumed (despite the insistence of the manufacturers of each product) that the effects of drugs of the same pharmacological group are mostly 'class' or 'group' effects. Thus all statins would have similar clinical usefulness, and all angiotensin-converting enzyme (ACE) inhibitors would be equally useful in the management of arterial hypertension. Independent experts and the Health Authorities, often bearing in mind cost considerations, tend to minimise the differences, whereas the manufacturers tend to exaggerate them. The various points of view may be widely divergent.[38,39] Although it is beyond discussion that a large part of the clinically relevant effects are group effects, it is not scientifically valid to assume that this is always the case. For instance, it was necessary to withdraw cerivastatin from the market because of a greater frequency of rhabdomyolysis, which was detected only during post-marketing surveillance,[40] and it has recently been suggested that the effect of ramipril on mortality in heart failure might be greater than that of other ACE inhibitors.[41] Scientifically valid conclusions

should be based on head-to-head comparative trials between the various drugs. However, as the demonstration of differences may be quite expensive (long-term trials with large study populations), smaller studies are usually carried out, the clinical relevance of which is quite debatable. Even more to the point: all too often, equivalence studies are accepted as valid while being methodologically clearly inadequate.[42]

In the case of the PPIs, the concept of bioequivalence is important because, as has already been pointed out, these drugs are highly labile in an acid environment and are rapidly degraded if released in the stomach. Thus the effect of a given preparation depends, not only on the amount of the active molecule contained in the capsule or tablet, but at least as much on the quality and stability of the enteric coating protecting the active molecule. In the particular case of the PPIs, there are studies that suggest that the quality of the enteric coating may have a considerable effect on the bioavailability of the PPI in question.[43] It is for this reason sometimes reasonable, before changing the dose, to switch to a formulation supported by adequate bioequivalence studies comparing it with the reference drug or drugs, which are those with which the clinical trials have been performed that provided the scientific evidence quoted. The potency of these bioequivalence studies is all too often debatable.[42]

Two particular differences between the available PPIs may have clinical relevance: their efficacy and the possibility of interactions.

9.1.1 Efficacy

As regards efficacy, which correlates with potency of inhibition of gastric acid secretion (Chapter 3), the available studies suggest that omeprazole 20mg, lansoprazole 30mg, rabeprazole 20mg and pantoprazole 40mg are equivalent in terms of healing rate and of control of the symptoms of the disease, and that the intermediate doses are also equivalent in maintenance treatment.[1,30] Differences are observed in some studies, but they are not consistent and they do not warrant the conclusion that a true difference exists. Esomeprazole 40mg is, in most studies, slightly more effective in terms of healing rate.[30] However, the therapeutic gain is not great, and large studies (involving thousands of patients) have been required for its demonstration. The clinical relevance of this difference is probably small in most patients, and particularly in those with uncomplicated GORD. However, it is plausible that, in refractory ulcer or in 'difficult' GORD – because of the extent of the lesion or of the presence of Barrett's oesophagus – a daily dose of esomeprazole 40mg may constitute a rational option, as it is more efficacious than the standard doses of other PPIs. Very limited data even suggest that esomeprazole 40mg could be as efficacious as doubling standard doses[44] of other PPIs, and it has been suggested to improve compliance, but this should be confirmed in good-quality equivalence trials before clinical practice is changed.

9.1.2 Interactions

It has been suggested that, because of their metabolic pathways, rabeprazole – and especially pantoprazole – present a lesser risk of interaction with other drugs. Because of the very large therapeutic margin of most drugs and of the rather mild effect of the PPIs, the clinical relevance of these differences is probably minimal. However, the number of patients receiving several medications increases continually, and in some series it has been reported that up to 30% of the patients taking PPIs are receiving other potentially interactive drugs.[45] Furthermore, in some particular cases (e.g. oral anticoagulants), dose adjustment is particularly important and the clinical consequences may be relevant. Even though it has been suggested that, in some patients, pantoprazole might be preferable to other PPIs, the scant data in the literature do not reveal clear differences, and suggest that the rate of relevant interactions is similar for all PPIs.[46]

9.2 When Should the PPI be Given?

In view of data presented above, the PPI should be given with the patient fasting and before a meal,

so that by the time the peak plasma concentration is achieved there will also be a peak number of proton pumps activated – that is, secreting acid. In fact, both omeprazole and lansoprazole are more effective when they are given before a meal than when given without a following meal.[47] A PPI given in the morning reduces acid secretion more effectively than one given in the evening, at the expense of reducing daytime acid secretion, but without affecting that at night.[48-50] Conversely, administration before the mid-day meal achieves a more effective inhibition of nocturnal secretion than when the PPI is given before breakfast.[51]

The only way to achieve total inhibition of acid secretion is to block the proton pumps as they become activated. For this reason, only continuous, high-dose PPI infusion, continuously maintaining high plasma concentrations of the active drug, can achieve the extreme degree of inhibition required for the treatment of upper gastrointestinal bleeding.[52] For this reason also, administration in divided doses seems to be more effective than a single daily dose. Thus one study has shown that the same daily dose of omeprazole, administered in two divided doses (2 × 20mg), achieves a slightly better control of acid secretion than is obtained with single-dose administration (1 × 40mg).[53] However, therapeutic compliance will be much more difficult to achieve in the case of divided dosage, and there are no comparative clinical studies that may allow conclusions as to whether the difference in control of gastric secretion is really relevant with respect to the therapeutic effect.

Thus if single daily-dose administration is chosen, the most reasonable option is to give the PPI with the patient fasting, before breakfast or before the mid-day meal. If there is no response, divided-dose administration may be tried, although it is probably more reasonable to increase the dose of the PPI (see below).

9.3 What Dose?

The actual dose of PPI to be administered should be tailored to the individual, depending on the therapeutic response; the symptoms may often be a reasonable guide. However, it is sometimes necessary to check the mucosal healing response. As already pointed out, up to 20% of patients with GORD exhibit an inadequate antisecretory response to omeprazole 20mg twice daily. Higher doses of omeprazole (80 mg/day) achieve reduction of the acid secretion in these patients.[29] It is therefore reasonable to escalate the dose of omeprazole to at least 80 mg/day (or the equivalent doses of rabeprazole 80 mg/day, lansoprazole 120 mg/day, or pantoprazole 160 mg/day) if the standard dose does not achieve the desired response. Besides direct evidence, experience gained in the treatment of Zollinger-Ellison syndrome suggests that this strategy is effective.[5] Esomeprazole 40mg twice daily would achieve a response even greater than that to omeprazole 80 mg/day, and would be a practical option for excluding the possibility that the lack of symptomatic response is caused by an insufficient effect of the PPI in patients refractory to conventional treatment. The therapeutic advantage of esomeprazole, which might be less relevant in the overall population, might be of more interest in this refractory one. For example, it has been reported that, in a group of patients with symptoms that persisted during treatment with lansoprazole 30 mg/day, switching to esomeprazole 40 mg/day was as effective as increasing the dose of lansoprazole to 30mg twice daily.[44]

It has also been suggested that gastric pH monitoring during treatment might identify those patients with PPI failure, and this would make it possible to increase the dose until correct control – defined as pH greater than 4 for 16 h or longer – is achieved; however, this option is not easily applicable to the conditions of daily clinical practice. It has even been suggested that this objective should be targeted in patients with Barrett's oesophagus, in order to reduce the rate of replication of the mucosa.[54] However, the scientific evidence supporting this approach remains rather weak.

9.4 For How Long?

The administration of a PPI will be effective for as long as it is maintained: the therapeutic

management of GORD should continue for an indefinite period of time, although in some patients it is acceptable to use it on demand.[1] In the case of peptic ulcer, the recommendations of 4 and 8 weeks of treatment for duodenal and gastric ulcer, respectively, are still sufficient in most patients, although the duration of treatment and the doses of the drugs should be increased in refractory ulcers. In any case, improvement under antisecretory treatment should never obviate the need to investigate and eventually treat *H. pylori* infection.[2] In the particular case of gastroprotection, treatment should continue for as long as the patient requires NSAIDs or acetylsalicylic acid.[19,21]

10. What About the Future?

The advent of the PPIs represented a veritable revolution in the management of acid-related diseases. And yet, almost 15 years later, many questions remain unanswered. It is quite surprising that, apart from the abundant small-sized studies that have addressed aspects of theoretical interest, there is still a worrying dearth of clinical trials providing really relevant information. Can it perhaps be necessary to inhibit acid even more profoundly in order to reduce the risk of malignancies of the oesophagus and cardias?[55] Alternatively, would a more controlled inhibition be more prudent? Are there really relevant differences between the various PPIs? Is it better to divide the dose? Is it at all useful to perform pH monitoring during treatment? These and other questions require answers based on the findings of clinical trials, and these trials should be long-term ones, as they concern chronic diseases.

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