

# Efficiency of Potent Gastric Acid Inhibition

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## Abstract

The evidence regarding the efficiency of potent gastric acid inhibition is exposed after a systematic search and a critical evaluation of its quality, using a specific score. The aim was to review alternative options, in economic terms, especially related with gastro-oesophageal reflux disease. The results show that the superiority of the proton pump inhibitors over the histamine H<sub>2</sub> receptor antagonist is clear in moderate and severe oesophagitis and in patients with persistent or severe symptoms. This evidence is clearly related with the intensity of the gastric inhibition. An associated benefit is the improvement of the quality of life obtained with this potent gastric acid inhibition profile.

## 1. Economical Evaluation and Gastric Acid Inhibition

This issue analyses the effects of potent gastric acid secretion inhibition in various diseases and clinical situations. The foregoing articles have established the pharmacological bases of gastric acid inhibition and the concept of 'potent acid inhibition' (PAI), and have addressed some of the major indications in which PAI is mandatory, with particular emphasis on gastro-oesophageal reflux disease (GORD) and *Helicobacter pylori* eradication. The aspect addressed by the present article, within the nosological framework of this issue, is whether this therapeutic strategy is worthwhile in economical terms.

The economic analysis of therapeutic decisions is thus much more convenient the higher the prevalence of the diseases considered and the higher the cost of the available therapies. The medical treatment of GORD and that for *H. pylori* infection eradication represent a very frequent assignation of resources with drugs of proven efficacy and effectiveness, particularly when PAI is to be

achieved, but also one with non-negligible cost; it is therefore usual that those who pay for those resources focus their attention repeatedly on this subject. One starting problem affecting this type of analysis is that it is not at all the same to make a therapeutic decision regarding one precise and concrete patient or to decide on generic recommendations from the perspective of the Health Care System. In either case, the therapeutic alternatives considered must have been validated; that is, they must be efficacious. Also in either case, that which has been validated must show itself to be applicable under the conditions of everyday clinical practise; that is, it must be effective. Once these preconditions have been fulfilled, which may not be at all easy, the concrete preferences of the patient have to be most firmly borne in mind at the time of making a decision for the individual patient; the patient would thus make his/her choice between validated alternatives.

The limitations of such a procedure are only those of rationing (or resource assignation) if the 'payer' is not the patient himself/herself, or the acquisitive capacity of the patient if he/she is the

'payer'. In the case of a generic recommendation aimed at resource optimisation within a health care system, the scenario is one in which the main payer for the various alternatives is the system itself, which at least in theory acts in the name of society. In this situation, and besides the assessment and judgement of efficacy and effectiveness, a further required condition is rationality, defined as that strategy which allows achieving the proposed objective with the least possible resources consumption; this is, in turn, a definition for efficiency, which is the subject of this article. It is precisely in the context of recommendations for patient groups where the elements of economic consideration and reflection are most necessary. Equity demands that which has been validated as efficacious to also be accessible to the population, and particularly so if also demonstrated to be effective. Economic analysis serves equity only if it helps make more efficient decisions, but equity, similar to efficacy and effectiveness, is a matter of principle that must precede the true economic analysis, even though it may be highly related to and conditioning for the latter. Stated in other words, one may non-spuriously address oneself to the economic assessment only if and when both efficacy and effectiveness are clear and, besides, if and when one pursues equity. As the present article quite clearly and extensively states the evidence supporting the efficacy and the effectiveness of PAI, the only remaining positioning would be one in terms of equity; this, in turn, demands that some concepts on economic assessment be explained.

The cost-effectiveness analysis is the most interesting analysis from the clinical point of view. This type of evaluation measures the net cost of providing a service as well as the outcomes obtained. Outcomes are reported in a single unit of measurement, typically as years of life gained. The comparison is made between the benefits achieved per unit cost, or alternatively between the costs incurred for each benefit unit gained. The cost-effectiveness analysis thus requires a definition of the 'units of result', which must be common to all alternatives, in which the benefit is to be measured.

When it is not possible to ensure equivalence between the results, or those results cannot be measured in the same units, the best option is to carry out a cost-benefit study. In this type of study, all the effects are transformed in monetary units. The advantage of this type of analysis is that it offers information on the absolute value of the programmes.

The cost-utility analyses also do not demand equivalence of effectiveness between the alternative options. What is now of interest is to measure the effects according to criteria of utility attributed from an individual or a social perspective. A typical unit of measurement in this type of assessment is that of quality-adjusted years of life.

In actual practise these types of studies, and those on the present subject, are no exception, are frequently overlapping in design and are even clearly biased according to the point of view from which the analysis is carried out. For this reason it is fundamental to assess their validity, so as to thereafter estimate their applicability. An interesting approach to these validity and applicability assessments is that provided by the *Critical Appraisal Skills Programme España* with its questionnaire for the critical reading of this type of study,<sup>[1]</sup> which is briefly presented in table I.

The objective of the present article is to review the available scientific information on the comparison, in economic terms, of alternative options in which at least one of the arms is constituted by PAI models, and this fundamentally as related to GORD, although the discussion will also address aspects of *H. pylori* eradication. Other relevant indications for PAI such as the therapeutic management of upper digestive tract bleeding or of its recurrences, gastroprotection in association with non-steroidal anti-inflammatory drug medication, prophylaxis of upper digestive tract bleeding in the critically ill patient or prophylaxis of acid bronchoaspiration have not been considered, as in the present article the evidence for efficacy and effectiveness regarding these aspects has not been presented.

**Table I.** Eleven questions for giving sense to an economic assessment, proposed by the *Critical Appraisal Skills Programme España* within its critical reading programme<sup>[1]</sup>

A. Is this assessment valid?	1. Is the question or objective of the assessment well defined?
Elimination questions	2. Is there a sufficient description of all the possible alternatives and of their consequences?
How are the costs and consequences assessed?	3. Does proof of the effectiveness of the assessed intervention or programme exist?
	4. Are the effects of the intervention(s) adequately identified, measured and assessed or considered?
	5. Are the costs incurred because of the intervention(s) adequately identified, measured and assessed?
	6. Are discount rates applied to the costs of the interventions? And to the effects?
B. What are the results?	7. What are the results of the assessment?
	8. Was an adequate sensitivity analysis carried out?
C. Will the results aid in the acquisition or implantation of services for our population or our patients?	9. Would the programme be equally effective in your own environment?
	10. Would the costs be transferable to your own environment?
	11. Is it worthwhile to apply them to your environment?

## 2. How Can We Obtain the Evidence and Judge its Quality?

The source of information was a computerised search for the original articles and systematic reviews published on the economic assessment in GORD and *H. pylori* eradication. This search was performed in the Cochrane Library and in the Medline database. The key words used were the combination of the terms *gastroesophageal reflux*, *GORD* and *GERD*, *proton pump inhibitors* (PPIs), *H. pylori*, *acid suppression* and *acid inhibition* with the terms *economics*, *guidelines*, *systematic review*, *clinical trial*, *therapeutic* and *quality of life*. The originals thus identified were considered only if

they passed a pertinence and quality assessment. Pertinence was directly assessed after reading, based on whether the paper considered actually dealt with the economic comparison between the alternatives considered in the objective. The quality criteria were defined with the help of an *ad hoc* scoring scale ranging from 0 to 10 points (table II) that had been previously constructed and used by the author.<sup>[2]</sup> Studies scoring 5 or higher were accepted for inclusion.

## 3. What is the Well-qualified Evidence?

It will be noted that most of the studies comparing PPIs and histamine H<sub>2</sub> receptor antagonists

**Table II.** Quality criteria established for the inclusion of originals<sup>[2]</sup>

Question	Score	
	Yes	No
Was the population of interest clearly defined?	1	0
Were the alternatives to be compared adequately defined?	1	0
Was the point of view from which the analysis was performed clearly established?	1	0
Were all the clinically important results described?	1	0
Is the chosen type of economic analysis design adequate for the proposed objectives?	3	0
Are the assigned probabilities credible?	1	0
Are the assigned costs and benefits, or alternatively the utilities, credible?	1	0
Was a sensitivity analysis performed?	1	0

confirm the better cost-effectiveness ratio of the former over the latter in GORD. Only one, already rather old, paper<sup>[3]</sup> dissents by pointing out as more cost-effective the strategy that begins with the administration of prokinetics or histamine H<sub>2</sub> receptor antagonist, provided that the GORD is mild, then passing on to the indication of PPIs in case of therapeutic failure. However, in this paper the cost difference between the histamine H<sub>2</sub> receptor antagonist and omeprazole was only £177 *versus* £189. The Canadian Coordinating Office for Health Technology Assessment had already taken up this aspect of the higher cost of omeprazole as compared with histamine H<sub>2</sub> receptor antagonist in continuous maintenance therapy,<sup>[4]</sup> but it made clear that the cost saving of US\$348 per patient per year was achieved at the price of 6.22 weeks longer with symptoms among those treated with histamine H<sub>2</sub> receptor antagonist than among those given the PPI. Furthermore, when intermittent omeprazole therapy was compared with continuous ranitidine the results showed cost-effectiveness superiority for omeprazole, at such a level that this option became the dominant strategy. When only patients with more severe disease are considered, in whom the symptoms are persistent, moderate or severe, all studies are consistent as regards greater cost-effectiveness for the PPIs.<sup>[5]</sup> Hillman and coworkers report cost savings of US\$1800 over 7 months of therapy with omeprazole *versus* ranitidine, with the added benefit of improved symptom control.<sup>[6,7]</sup> This same criterion of frank superiority of PPIs over histamine H<sub>2</sub> receptor antagonist in the long-term therapy of oesophagitis was confirmed in another study in which the ranitidine strategy was the least cost-effective over 1 year.<sup>[8]</sup> The authors report that the administration of the standard dose of the histamine H<sub>2</sub> receptor antagonist involves an additional cost per prevented recurrence of between US\$52 and US\$688, depending on the acquisition price of the drug. This criterion of cost-effectiveness in favour of omeprazole is maintained in the sensitivity study provided there is at least a 9% gain in quality of life. Another European study carried out from the social perspective reports the same trend of superiority of

the PPIs over ranitidine.<sup>[9]</sup> An analytic decision model published by Holzer et al. confirms the effectiveness of therapy with omeprazole over ranitidine, once more especially in the more severe forms of oesophagitis.<sup>[10]</sup> The better cost-effectiveness ratio of the PPIs is still maintained in other studies when concrete clinical events within the context of GORD are considered, such as dysphagia<sup>[11]</sup> or peptic stenosis.<sup>[12]</sup> Gerson et al. again arrive at the conclusion of a better cost-effectiveness ratio for omeprazole as initial therapy, followed by on-demand therapy for 8 weeks in symptomatic recurrence, if no more than three courses per year were needed.<sup>[13]</sup> In the study by Kaplan-Machlis et al. there are no significant differences between the 6-month therapy costs for omeprazole and ranitidine (US\$1198 for omeprazole and US\$1158 for ranitidine), without differences in symptom control, so they also conclude on the superiority of PPIs.<sup>[14]</sup> The comparison of rabeprazole and ranitidine is also favourable as regards cost-effectiveness with that PPI, as pointed out by Dean et al.<sup>[15]</sup> The cost of preventing one additional episode of symptom recurrence was US\$313 higher with ranitidine than with rabeprazole.

A recent study shows that the mean total cost of a physician-controlled intermittent therapy strategy with esomeprazole 40 mg is higher than that of a patient-controlled therapy with a 20 mg dose, but the difference disappeared when only the direct medical costs were considered.<sup>[16]</sup> In this same line of comparison of the profiles of the more potent PPIs (such as esomeprazole) *versus* the racemic PPIs, one study comparing lansoprazole and esomeprazole concludes that the greater efficacy of esomeprazole in healing and symptom control, with no differences as regards tolerability and safety, also translates into a better cost-effectiveness ratio for esomeprazole.<sup>[17]</sup> Similarly contingent are the results reported by Wahlqvist et al., demonstrating that continuous on-demand therapy with esomeprazole 40 mg or esomeprazole 20 mg is more cost-effective than the administration of various continuous or intermittent strategies with omeprazole.<sup>[18,19]</sup> As for rabeprazole, another study

similarly concludes a better cost-effectiveness ratio of this PPI as compared with lansoprazole or omeprazole.<sup>[15]</sup>

#### 4. Comments

GORD is directly attributable to the presence of acid content in the oesophagus, regardless of whether macroscopic lesions are present and of whether the disease courses with or without extra-digestive manifestations. The aims of anti-secretory drug therapy are both the healing of the lesions and symptomatic control. This latter aspect, that of symptomatic control, is highly relevant in the case of the extra-oesophageal manifestations. An evident conclusion arising after reading this issue, including the present article, is that anti-secretory therapy achieves better results the more potent it is; non-optimal anti-secretion, such as that achieved with histamine H<sub>2</sub> receptor antagonist, can only aspire to achieve symptomatic control in mild forms of non-erosive GORD without extra-digestive manifestations, although of course this symptomatic control is also achieved, and in a more rapid and sustained fashion, with the PPIs. In those cases with severe clinical manifestations, oesophagitis, complications of GORD or its extra-digestive manifestations, effectiveness and even cost-effectiveness superiority is evident for the PPIs, and particularly high-dose PPIs or the last-generation ones such as esomeprazole. Many of the studies carried out in past years have addressed the economic analysis of various alternative therapy options only for oesophagitis — and even in oesophagitis they have focused on moderate and severe cases. However, the finding that the quality of life of the patients is also impaired in GORD without macroscopic lesions is not new.<sup>[20,21]</sup> Thus, in latter years there has been a trend to consider that achieving symptom control is a therapeutic objective of the first order. It is therefore not surprising that the systematic reviews now openly address the efficacy of anti-secretory therapies in endoscopy-negative GORD.<sup>[22]</sup>

The therapeutic options in long-term medical treatment are varied. Among them, on-demand

therapy has been shown to be effective, provided it is carried out with PPIs.<sup>[23,24]</sup> It is, however, important to stress that such therapy should be preferentially given with full doses of the drugs.<sup>[23]</sup>

The superiority of the PPIs over the histamine H<sub>2</sub> receptor antagonist is quite clear in patients with moderate or severe oesophagitis or in patients with persistent or severe symptoms.<sup>[25]</sup> When the symptoms or the oesophagitis are mild the power of the cost-effectiveness studies decreases, but in these cases the individual perspective of the patient can and should be borne in mind. The great effectiveness of PPIs in controlling the patients' symptoms demands that the information provided to the patients be loyal. Some authors even consider that this high efficacy warrants the systematic prescription of PPIs in all cases, whatever the cost-effectiveness studies may say,<sup>[26]</sup> or they contend that the apparent savings achieved with a different strategy are, in the long run, expensive.<sup>[27]</sup> Whatever the case, the patients must know that at some additional cost it is possible to achieve better relief and improved quality of life. In this context, one particularly revealing study shows that the patients are ready to incur additional cost in order to maintain their favourite medication<sup>[23]</sup> or to gain access to the diagnostic tests they prefer.<sup>[28]</sup> Nevertheless, in some of these cases it is perfectly possible to also obtain a good symptomatic control with H<sub>2</sub> receptor antagonists, an option to discuss with the patient.

As for *H. pylori* eradication, the extensive evidence accumulated from economic studies is not aimed at establishing the superiority of PAI over other strategies, but simply at corroborating the well-defined and effective path of eradication over any other strategy in the quest to prevent ulcer disease recurrences. Other economic studies, also abundant, address the consideration of which is the best eradication strategy based on the prevalence of the infection. Logically these studies deviate from the objectives of the present one, and they have therefore not been considered. Another article in this issue addresses the evidence in support of PAI as the most effective strategy, in combination with antibiotics, in achieving *H. pylori* eradication.

However, regarding this aspect — which indeed enters into the proposed objectives — there are no published well-performed economic studies. This is logical, as the great effectiveness of these strategies and the proven effectiveness in eradication obviate the need to demonstrate their cost-effectiveness as compared with less effective strategies that will unavoidably be associated with a higher rate of therapeutic failures that always involve additional costs.

In any case, and to conclude, economic analyses must be borne in mind and considered, but always with caution. In the first place, they can hardly be extrapolated because of the diversity of the local data underlying these assessments. Also, the possible approaches are diverse and as a result the heterogeneity of studies that would appear to be assessing one and the same problem is quite noteworthy, as stressed by Sadowski et al. in their review on cost-effectiveness studies.<sup>[29]</sup> In the second place, the quality of the studies is also quite different, although in the present article it has been endeavoured to obviate this factor through a previous, quality-based selection of the original sources. The third limitation is that the analyses are highly dependent on small evolutive variations in some of the critical factors involved; hence the need for sensitivity analyses. For all these reasons it is always difficult to arrive at definitive conclusions, and even more so within a market in continuous transformation. And yet, despite all this, the usefulness of economic analyses is evident, even if it were only because of their ability to render explicit the intervening variables. They therefore help in better defining the alternative options and the decision nodes, and thus contribute to a better quality of the decisions, although, in the end, such decisions may not be made based exclusively on the results of the economic analyses performed.

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