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# Healing of Oesophagitis

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## Abstract

The reflux oesophagitis treatment aims to achieve a rapid and sustained symptom relief and a high percentage of lesion healing, apart from preventing the relapses and complications of the disease. For that purpose it is essential to maintain the oesophagic pH above 4 for as long as possible during the day and the night. All these objectives are achieved with the use of the proton pump inhibitors (PPI), which constitute the most effective drug group — being superior to the rest of the antisecretory drugs, such as anti-$H_2$, which are no longer in use in this treatment.

In moderate grades (grades A and B), all the PPIs used at their usual dosages show a similar treatment efficacy within 8 weeks. In severe cases (grades C and D), as well as those complicated with digestive haemorrhagia or Barrett's oesophagus, esomeprazole shows a higher treatment efficacy than the rest of the PPIs and is therefore the drug of choice. Furthermore, esomeprazole, an active isomer of omeprazole, shows other properties such as a higher rate of action, a lower interindividual variation and a more prolonged mode of action, which all translate into additional advantages in comparison with the rest of the PPIs.

## 1. Introduction

The therapeutic aims in patients with erosive oesophagitis secondary to gastro-oesophageal reflux disease (GORD) are as follows:

1. To achieve healing of the oesophageal lesions in the highest proportion of cases.
2. To achieve symptoms palliation, in the shortest possible time.
3. To prevent relapses of the illness.
4. To carry out prophylaxis of associated complications.

All these aims may at present be achieved because we have highly effective medical therapies available, which shall herein be reviewed. We shall, however, as an operative introduction, discuss some pathophysiological aspects that will be useful in understanding the mechanism of action of such therapies.

## 2. Relationship between Inhibition of Gastric Acid Secretion and Oesophagitis Healing

Oesophageal exposure to acid is normally less than 4% (over 24 h) to a pH level $< 4$. Any increase of exposure exceeding 4% is considered abnormal and indicative of an abnormal gastro-oesophageal reflux in 24-h pH-metry studies.

Although there is no strict direct relationship between pH-metry results and the degree or grade of oesophagitis, a series of studies have demonstrated an association between the duration of acid exposure of the oesophageal mucosa and the severity of the observed oesophageal lesions.[1–3]

The action of acid upon the oesophageal mucosa is at present considered to be the major pathogenetic factor involved in the occurrence and maintenance of oesophagitis. A number of studies

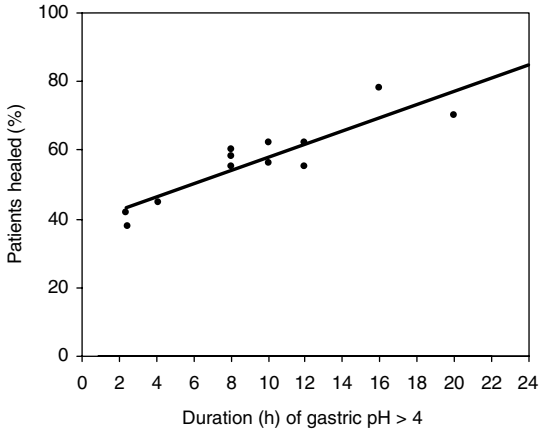


**Fig. 1.** Relationship between gastric acid secretion inhibition and oesophagitis healing.[22]

have confirmed that there is a positive linear correlation between the degree of gastric acid secretion inhibition and the healing rate of oesophageal lesions in GORD (figure 1).

This evidence all leads to the deduction that the most effective and efficacious therapy for achieving healing of oesophagitis is the use of acid-secretion-inhibiting drugs, which, besides rapidly controlling symptoms, void and counter the harmful effects of acid and pepsin on the oesophageal mucosa.

Furthermore, the anti-secretory drugs have an added positive effect, because they at the same time decrease the volume of gastric secretion and reduce the quantity of fluid refluxed from the stomach into the oesophageal lumen.

## 3. Histamine $H_2$ Receptor Antagonists

The $H_2$ receptor antagonists, have been widely used in the past, mainly during the 1980s, for the management of GORD. However, their use has by now been completely abandoned, because of their lesser anti-secretory potency as compared with drugs that have been later introduced into the therapeutic armamentarium, namely the proton pump inhibitors (PPIs).

The $H_2$ receptor antagonists (cimetidine, ranitidine, famotidine, roxatidine and nizatidine) inhibit gastric secretion only partially, as they block the $H_2$ histamine receptors on the basal membrane of the parietal cell; they thus reduce gastric secretion by some 50–70%.

Their anti-secretory effect may be physiologically countered through simultaneous stimulation of the gastrinergic and cholinergic receptors during the postprandial period, which is when the GORD symptoms are most frequent. Furthermore, continued therapy with $H_2$ receptor antagonists may induce both tolerance and a rebound effect after their withdrawal. A further consideration never to be forgotten, is their possible interference on the cytochrome P-450 system.

Many studies carried out with these drugs in GORD have demonstrated its lower efficacy as compared with PPIs, both in achieving symptomatic improvement and in healing of oesophagitis, even when they are used at high dosages.[4,5] Thus, in one controlled study[6] in which cimetidine was given at a dose of 800 mg b.i.d. for 12 weeks, the healing of oesophagitis was achieved in only 67% of the patients so treated, *versus* 36% in the placebo group. In another similar study using famotidine (40 mg b.i.d.) in patients with moderate oesophagitis, the results were quite similar.[7]

It may thus be concluded that, in patients with mild oesophagitis (grades I and II of the Savary–Miller classification), the effectiveness of $H_2$ receptor antagonists is about 70%, while it drops to 35–40% in severe oesophagitis (grades III and IV of the same classification).

## 4. Proton Pump Inhibitors

The efficacy of omeprazole in the management of erosive oesophagitis secondary to GORD has been clearly demonstrated in a number of studies. For this reason, omeprazole has been used as the reference or comparator drug (the so-called 'gold standard') for other drugs of later introduction (level of evidence 1A; degree of recommendation A).

In a recent meta-analysis performed by Sharma et al.,[8] the efficacy of omeprazole 20 mg/day was

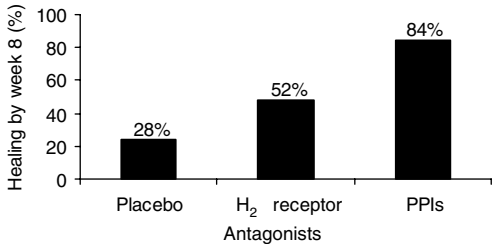


**Fig. 2.** Comparative efficacies of placebo, $H_2$ receptor antagonists and proton pump inhibitors (PPIs) in the healing of oesophagitis after 8 weeks.[9]

compared with that of lansoprazole 30 mg/day in the treatment of erosive oesophagitis. The healing rate after 4 weeks was 74.7% in the omeprazole-treated group as opposed to 77.7% in the lansoprazole-treated group. After 8 weeks the healing rates achieved were 81.3% and 83.3%, respectively, with no significant difference between the two treatment groups.

The superiority of PPIs as compared with $H_2$ receptor antagonists, and the other drugs hitherto used in the management of reflux oesophagitis, was already documented in 1997 in a meta-analysis made by Chiba et al.[9] that analysed the results of 43 published trials and clearly and definitively showed that PPIs are superior to all other treatments used regardless of the dose and the duration of therapy (figure 2) (level of evidence 1A; degree of recommendation A).

PPIs furthermore achieve greater symptomatic improvement (average 77% *vs* 47% with $H_2$ receptor antagonists), and have thus since that time been the therapeutic group of first choice in the management of oesophagitis secondary to GORD.

The mean time elapsed for heartburn disappearance, which is the most prevalent symptom of the disease, is about 2 weeks with a PPI, but may last up to 8 weeks on average with an $H_2$ receptor antagonist.[10]

The therapeutic efficacy of the first PPIs to be introduced at the doses habitually used — omeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day — is quite similar and shows no differences between the various drugs either in the healing rates achieved or in the symptomatic improvement[11] (level of evidence 1A; degree of recommendation A).

## 5. New PPIs

Rabeprazole achieves rapid and effective symptomatic improvement in patients with erosive oesophagitis. Thus, in a recent study including a total of 2579 patients treated with rabeprazole (20 mg/day for 8 weeks), palliation of heartburn was achieved in 64% on day 1 and in 81% on day 7, with a mean time to improvement of 2 days for all patients[12] (figure 3).

The symptomatic improvement achieved with rabeprazole 20 mg/day is greater than that achieved with omeprazole 40 mg/day. This effect is apparently related to a greater rapidity of onset of action of the anti-secretory effect.

Esomeprazole is the S-isomer of omeprazole. The pharmacokinetic and pharmacodynamic studies carried out with esomeprazole show that this isomer experiences less first-pass hepatic metabolism and has a lower plasma clearance than omeprazole. It has been also demonstrated that the area under the plasma concentration over time curve for esomeprazole 20 mg is about two-fold greater than that for omeprazole 20 mg, while for esomeprazole 40 mg it is about five-fold that of omeprazole 20 mg, with less between-patient variability. These data

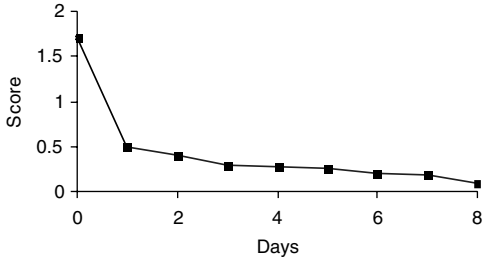


**Fig. 3.** Effects of rabeprazole on heartburn palliation. The data represent days (mean) since the institution of therapy.[12]

are indicative of more potent and uniform acid suppression by the isomer.[13]

The clinical efficacy of esomeprazole in the acute therapy of erosive oesophagitis has been assessed in clinical trials of 4–8 weeks' duration (the usual duration in this type of study). The largest of such studies to date, coordinated by Castell et al.,[14] involved 5241 patients in a randomised, double-blind multicentre design; this trial compared the efficacy of esomeprazole 40 mg/day *versus* that of lansoprazole 30 mg/day. Greater healing rates of oesophagitis were achieved by week 8 in the esomeprazole 40 mg/day-treated group (92.6%) than in the lansoprazole 30 mg/day-treated group (88.8%) ($p = 0.0001$), together with an improvement in the resolution of both day-time and night-time heartburn and with a shorter elapsed time, until achieving a sustained resolution of the clinical symptomatology.

In a further controlled study, also regarding the acute treatment of erosive oesophagitis, carried out by Kahrilas et al.[15] on 1960 patients, the efficacy of omeprazole 20 mg/day was compared with that of two different esomeprazole dosages (20 and 40 mg/day). At week 8, the healing rate achieved was greater with esomeprazole 40 mg/day (94.1%) and with esomeprazole 20 mg/day (89.9%) than with omeprazole 20 mg/day (86.9%), with significant differences in both cases ($p < 0.05$) in the intention-to-treat analysis.

Finally, in another large American study directed by Richter et al.[16] that included 2425 patients, a greater efficacy was also demonstrated in the resolution of endoscopic lesions after 8 weeks of therapy with esomeprazole 40 mg/day as compared with omeprazole 20 mg/day (93.7% *vs* 84.2%, $p < 0.001$). The tolerability and safety of the drugs in the last three studies mentioned was similar.

Esomeprazole was also superior to the comparator drugs in the achievement of clinical improvement. Thus, remission of heartburn under esomeprazole was significantly more rapid than under omeprazole or lansoprazole, and the mean time elapsed until complete resolution of the symptoms was shorter with esomeprazole 40 mg/day as compared with omeprazole 20 mg/day ($p < 0.001$) (table I).

The therapeutic gain using esomeprazole in healing oesophagitis as compared with omeprazole was 10.2%, and in absolute terms was 8.7%; thus, in order to avoid one treatment failure it would be necessary to treat 11 patients with esomeprazole 40 mg/daily *versus* one patient with omeprazole 20 mg/day.[14–16]

**Table I.** Summary of three large-scale clinical trials comparing the clinical and endoscopic efficacy of esomeprazole, lansoprazole and omeprazole in erosive oesophagitis patients

| Reference | Number of patients | Therapy | Oesophagitis healing (%) | Days without heartburn (mean, %) | Nights without heartburn (mean, %) | Days until remission of heartburn (median) |
|---|---|---|---|---|---|---|
| Castell et al.[14] | 2264 | Esomeprazole 40 mg/day | 92.6*** | 72.5 | 87.1* | 7** |
| | 2617 | Lansoprazole 30 mg/day | 88.8 | 70.9 | 85.8 | 8 |
| Kahrilas et al.[15] | 656 | Esomeprazole 20 mg/day | 89.9† | 69.3 | 83.6† | 8 |
| | 654 | Esomeprazole 40 mg/day | 94.1†† | 72.7†† | 84.7†† | 5†† |
| | 650 | Omeprazole 20 mg/day | 86.9 | 67.1 | 80.1 | 9 |
| Richter et al.[16] | 1216 | Esomeprazole 40 mg/day | 93.7*** | 74.9*** | 90.8*** | 5*** |
| | 1209 | Omeprazole 20 mg/day | 84.2 | 69.7 | 87.9 | 8 |

*$p < 0.05$,
**$p < 0.01$,
***$p < 0.001$ *versus* comparator drug.
†$p < 0.05$,
††$p < 0.01$ *versus* omeprazole.

## 6. Treatment Response in Relation to Grade of Oesophagitis

The greater response rate to therapy with esomeprazole occurred in all categories of erosive oesophagitis as graded using the Los Angeles endoscopic classification, both at week 4 and at week 8, in the various previously described controlled studies.[14–16]

The pooled clinical and endoscopic data of 6708 patients participating in a number of multicentre, randomised, double-blind studies carried out in the USA confirmed these results.[16]

In the largest study yet published,[14] involving over 5000 patients, the oesophagitis healing was achieved with esomeprazole 40 mg/day after 8 weeks of therapy in 97%, 92%, 88% and 81% of patients with grades A, B, C and D of oesophagitis, respectively, while in the lansoprazole 30 mg/day-treated group the healing rate decreased more markedly with increasing grades of oesophagitis (97%, 91%, 77% and 64%, respectively, for grades A, B, C and D of the Los Angeles classification) ($p < 0.01$) (figure 4).

Thus, the healing rate in erosive oesophagitis under esomeprazole treatment was 11% greater than with lansoprazole in grade C patients, and up to 17% greater in grade D patients.[16]

Esomeprazole is therefore the agent of first choice for the treatment of severe oesophagitis, corresponding to grades C and D of the Los Angeles endoscopic classification (level of evidence 1A; degree of recommendation A).[17]

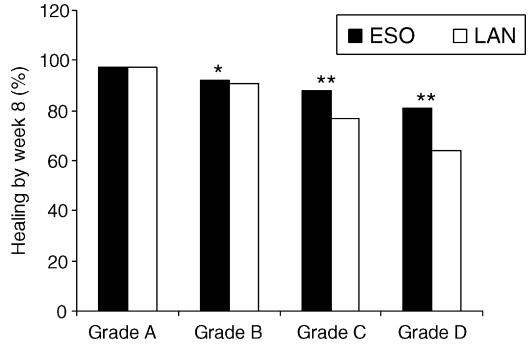


**Fig. 4.** Comparative efficacies of esomeprazole (ESO) and lansoprazole (LAN) as related to the grade of oesophagitis (Los Angeles classification[14–16]). $^{*}p < 0.05$; $^{**}p < 0.01$.

In mild to moderate oesophagitis (grades A and B), no significant differences between drugs were observed, either in the healing rate or in the symptomatic improvement, between esomeprazole and the remainder of the PPIs.[18]

## 7. Double-dose PPI Therapy

The available studies on this subject show that increasing the dose of omeprazole to 40 mg/day (double the standard dose) does not overall improve the results achieved with the standard 20 mg/day dose. The magnitude of the difference in efficacy between meprazole 20 mg/day and omeprazole 40 mg/day in the treatment of reflux oesophagitis is insufficient for recommending the routine use of the latter dose, in patients requiring more than 4 weeks of therapy. The omeprazole 40 mg/day dose only achieves a somewhat more rapid healing of the oesophageal lesions than the omeprazole 20 mg/day dose, and the initial grade of endoscopic involvement also has a slight prognostic value[19] (level of evidence 2C; degree of recommendation B).

Furthermore, the omeprazole 40 mg/day dose evidences the same clinical and lesion healing efficacy as lansoprazole 30 mg/day for all grades of oesophagitis, as demonstrated in a large-scale multicentre Netherlands study.[20]

## 8. Control of Acidity with the Various PPIs

Miner et al.,[21] in a recently published study, compared the pharmacodynamics of gastric acid suppression with the standard doses of the five PPIs presently marketed (omeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day, rabeprazole 20 mg/day and esomeprazole 40 mg/day) using an open, randomised and sequential design in 34 patients. All patients took each drug for five consecutive days, followed by a 10-day washout period before switching to the next one. The assessment criterion was 24-h pH-metry.

On day 5 the gastric pH remained above 4 for a mean of 14 h with esomeprazole, 12.1 h with rabeprazole, 11.8 h with omeprazole, 11.5 h with lansoprazole and 10.1 h with pantoprazole ($p < 0.001$ for esomeprazole as compared with the other drugs).

This greater duration of acid secretion inhibition is, beyond doubt, the main factor responsible for the increased therapeutic potency of the S-isomer of omeprazole, as compared with the remainder of the PPIs.

## 9. Systematic Review of PPIs and the Healing of Oesophagitis

A recently published meta-analysis[11] confirms that the oesophagitis healing rates after 4 and 8 weeks are greater with the use of esomeprazole as compared with omeprazole. The remainder of the PPIs (lansoprazole, pantoprazole and rabeprazole) did not achieve greater response rates.

## 10. Summary and Conclusions

The therapy of choice in the acute phase of reflux oesophagitis consists of the use of the PPIs, which are the drugs that have evidenced the greatest effectiveness, both in the healing of the lesions and in achieving symptomatic relief for the patients.

All currently available PPIs show a similar efficacy in the management of patients with mild to moderate oesophagitis (grades A and B of the Los Angeles classification of oesophagitis).

In patients with moderate to severe oesophagitis, as well as in those with associated complications (grades C and D of the Los Angeles classification of oesophagitis), esomeprazole is the agent of first choice as it shows an evident therapeutic benefit in these patients as compared with the remainder of the PPIs.

The slight difference observed in clinical and endoscopic efficacy between the 20 mg/day and 40 mg/day doses of omeprazole is not sufficient for recommending the use of double doses of this agent in patients requiring more than 4 weeks of therapy, as the results achieved after 8 weeks show no differences between the two dosages.

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