Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe reflux oesophagitis

R H Holloway, J Dent, F Narielvala, A M Mackinnon

Abstract
Background/aims—Reducing oesophageal acid exposure by suppressing acid secretion with omeprazole is highly effective in healing reflux oesophagitis. Some patients with severe oesophagitis, fail to heal and whether this results from inadequate acid suppression or other factors is unclear. The aim of this study, was to investigate the relation between oesophageal acid exposure and healing in patients with severe reflux oesophagitis treated with omeprazole.

Methods—Sixty one patients with grade 3 or 4 ulcerative oesophagitis were treated for eight weeks with omeprazole 20 mg every morning. Those patients unhealed at eight weeks were treated with 40 mg every morning for a further eight weeks. Endoscopy and 24 hour oesophageal pH monitoring were performed before treatment and at the end of each treatment phase while receiving treatment.

Results—Thirty per cent of patients failed to heal with the 20 mg dose. Unhealed patients had greater total 24 hour oesophageal acid exposure before treatment, and while receiving treatment also had greater acid exposure and a smaller reduction in acid exposure than did patients who healed. Forty seven per cent of the unhealed patients also failed to heal with the 40 mg dose. These patients had similar levels of acid exposure before treatment to those who healed, but had greater acid exposure while receiving treatment, particularly at night when supine.

Conclusions—Patients with severe ulcerative oesophagitis who are refractory to omeprazole have greater oesophageal acid exposure while receiving treatment than responding patients. This is due to a reduced responsiveness to acid suppression, and is likely to be an important factor underlying the failure of the oesophagitis to heal.

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Keywords: gastro-oesophageal reflux, pH monitoring, gastric acid secretion, oesophagus

The duration of oesophageal acid exposure is the most important factor determining the severity of reflux symptoms and the degree of oesophagitis. Sustained high level acid suppression with the potent acid pump inhibitor, omeprazole, has proved an extremely effective treatment for reflux oesophagitis. Complete healing has been reported in 70% to 90% of patients even in patients who were refractory to H2 receptor antagonists. Healing rates, however, in the most severely affected patients with endoscopic grades 3 and 4 are substantially less, only 58%, with doses up to 40 mg per day. The reasons for this failure are not clear. A direct relation exists between healing rate and the degree of acid suppression over 24 hours, and inadequate acid suppression appears to be an important factor underlying the failure to heal with H2 receptor antagonists. A recent study in patients with severe reflux oesophagitis that was refractory to omeprazole showed that such patients had persistent pathological reflux, particularly at night. However, the relation between oesophageal acid exposure and healing of oesophagitis with omeprazole has not been formally studied in a prospective manner. The aim of this study, therefore, was to investigate the relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe oesophagitis.

Methods

Patients
Sixty one outpatients (49 M, 12 F age range 23–86 years, mean 63) with severe reflux oesophagitis, endoscopic grade 3 or 4 were recruited at three Adelaide university teaching hospitals: Royal Adelaide Hospital (22 patients), Repatriation General Hospital (21 patients), and Flinders Medical Centre (17 patients). Patients were excluded if aged under 18 years. Other reasons for exclusion were previous oesophageal gastric or duodenal surgery except for simple closure of a perforation or dilatation, presence of strictures (other than mild) requiring dilatation, oesophagitis due to systemic disease, infection, intubation or other mechanical trauma, caustic or other burns, irradiation or physical deformity, concurrent gastric or duodenal ulcer or oesophageal...
Oesophageal pH monitoring

Twenty four hour ambulatory oesophageal pH monitoring was performed using an antimony pH electrode (Synectics) positioned 5 cm above the manometrically determined lower oesophageal sphincter and connected to a portable digital recorder (Synectics Digitrapper Mark II 6100). Patients were requested to avoid drinking coffee, cordials, and fruit juices during the recording period. Omeprazole treatment was continued but patients were not allowed to take any antacid.

Clinical and laboratory assessment

Symptoms were assessed by interview at entry and at four weekly intervals during the study. Heartburn, (day and night scored separately), regurgitation and dysphagia were graded as: 0 – none, 1 – mild, not interfering with usual activity; 2 – moderate, interfering with usual activity; and 3 – severe, incapacitating and preventing usual activity. Patients were specifically questioned about the occurrence of adverse events or symptoms. Compliance, assessed at each visit by capsule counts, was judged to be adequate only if at least 75% of the capsules had been consumed. Blood samples were taken for haematological and biochemical testing.

Data analysis

The pH data were analysed by computer (Synectics, Esophogram) for the duration pH<4 and the number of reflux episodes. Acid clearance time was calculated by dividing the duration pH<4 by the number of reflux episodes. Values were determined separately for the total 24 hours, and upright, supine, and three hour postprandial periods. Data for healed and unhealed patients were compared using the Mann-Whitney U test and are expressed in the text as median (interquartile range).

Results

Pre-treatment

Sixty patients entered the study of which 59 received medication; one patient withdrew

<table>
<thead>
<tr>
<th>TABLE 1 Clinical and endoscopic data at entry into the study</th>
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<tbody>
<tr>
<td><strong>Omeprazole (20 mg)</strong></td>
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<tr>
<td><strong>Omeprazole (40 mg)</strong></td>
</tr>
<tr>
<td>Number entered</td>
</tr>
<tr>
<td>Male:Female</td>
</tr>
<tr>
<td>Mean age (range) (y)</td>
</tr>
<tr>
<td>Symptom duration &lt;1 Year</td>
</tr>
<tr>
<td>1–5 Years</td>
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<tr>
<td>&gt;5 Years</td>
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<tr>
<td>Cigarette smokers</td>
</tr>
<tr>
<td>Recent NSAID use</td>
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<tr>
<td>Recent aspirin use</td>
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<tr>
<td>Recent H2 receptor antagonists</td>
</tr>
<tr>
<td>Oesophagitis at entry</td>
</tr>
<tr>
<td>Grade 3</td>
</tr>
<tr>
<td>Grade 4</td>
</tr>
<tr>
<td>Columnar mucosa</td>
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<tr>
<td>Deep ulcer</td>
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<td>Stricture</td>
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</table>

NSAID, non-steroidal anti-inflammatory drug.
before receiving medication. Four patients were withdrawn from the study. Reasons for withdrawal were: nausea that occurred within 24 hours of starting omeprazole (one patient), failure to comply (one patient), loss to follow up (three patients) thus leaving 55 patients available for analysis. Table I summarises the demographic, clinical and endoscopic data on entry into the trial.

Pre-treatment total 24 hour oesophageal acid exposure in the patients who did not heal with omeprazole 20 mg was significantly greater than that in the patients who healed (Fig 1). Ten of 17 (59%) unhealed patients had received H₂ antagonists before the study compared with 16 of 38 (42%) patients who healed. Total 24 hour acid exposure in the unhealed patients who had taken H₂ antagonists (28.8%, 22.6–34.2%) was significantly greater than in those who had not taken H₂ antagonists (17.0%, 11.1–19.8%, p<0.03). Previous use of H₂ antagonists, however, did not affect acid exposure in the patients who healed (19.8%, 14.6–19.8% v 20.2%, 16.5–20.2%).

Values for pre-treatment upright, supine, and postprandial acid exposure, however, were similar in the two groups (Table II). Pre-treatment acid clearance times were also similar in the two groups (healed: 1.7 min, 0.6–3.0 min; unhealed: 3.5 min, 2.6–5.1 min).

For patients who remained unhealed on 20 mg omeprazole and subsequently received the 40 mg dose, pre-treatment total, upright, supine, and postprandial oesophageal acid exposures were similar in those who eventually healed and those who remained unhealed (Table III, Fig 2). Oesophageal acid clearance time before treatment was also similar in the healed patients (3.1 min, 2.6–6.2 min) to that in the unhealed patients (3.9 min, 3.5–5.9 min).

**Phase 1: omeprazole 20 mg**

Seventeen patients failed to heal their oesophagitis after eight weeks’ treatment with omeprazole 20 mg every morning. Total 24 hour oesophageal acid exposure while receiving treatment was significantly greater in those patients who failed to heal than in those who healed (Fig 1), and significantly fewer unhealed patients fell within the normal range of <5% (4 of 17 patients v 27 of 38 patients, p<0.005). The mean percentage fall in total acid exposure with treatment in the unhealed patients (45%) was significantly less than that in the healed patients (82%), p<0.02. Unhealed patients also had greater levels of upright, supine, and postprandial reflux during treatment than did those who healed (Table II).

Most patients (47 of 55) were rendered symptom free after eight weeks of treatment. The prevalence of complete symptom relief in the patients who did not heal (15 of 17 patients) was similar to that in those who healed (32 of 38 patients). The use of histamine H₂ receptor antagonists before entry into the trial (healed – 42%, unhealed – 58%), non-steroidal anti-inflammatory agents (healed – 45%, unhealed – 29%), and smoking (healed – four of 38, unhealed – one of 16) were not statistically different in the two groups.

**Phase 2: omeprazole 40 mg**

Sixteen of 17 patients who failed to heal with omeprazole 20 mg received eight weeks treatment with omeprazole 40 mg every morning; one patient withdrew at week 8 for social reasons. Two other patients refused to undergo further pH monitoring leaving 14 patients available for analysis. Eight of 15 patients who underwent endoscopy healed their oesophagitis with the larger dose. All patients who healed

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**TABLE II Oesophageal acid exposure with omeprazole 20 mg every morning**

<table>
<thead>
<tr>
<th>Oesophageal acid exposure</th>
<th>Pre-treatment</th>
<th>Omeprazole 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (%)</td>
<td>Upright (%)</td>
</tr>
<tr>
<td></td>
<td>Supine (%)</td>
<td>Postprandial (%)</td>
</tr>
<tr>
<td></td>
<td>Total (%)</td>
<td>Upright (%)</td>
</tr>
<tr>
<td></td>
<td>Supine (%)</td>
<td>Postprandial (%)</td>
</tr>
<tr>
<td>Healed</td>
<td>16-0 (8-4-20.3)</td>
<td>14-5 (9-3-21.9)</td>
</tr>
<tr>
<td>Unhealed</td>
<td>21-3 (16-2-28.8)</td>
<td>23-3 (16-6-26.3)</td>
</tr>
</tbody>
</table>

Median (interquartile range), *p<0.03, †p<0.01, v healed.
and four of six unhealed patients were rendered asymptomatic; two unhealed patients had residual mild heartburn (grade 1).

During treatment total oesophageal acid exposure was significantly greater in those patients who failed to heal than in those who healed (Fig 2), and all unhealed patients had acid exposures above 5% (range 10.3–21.8%) compared with only one of eight healed patients. Upright acid exposure was similar in the healed and unhealed patients while receiving 20 mg omeprazole but was significantly greater in the unhealed patients with the 40 mg dose (Table III). Supine acid exposure, however, was significantly greater in the unhealed patients during treatment with both the 20 mg dose and 40 mg dose. Postprandial acid exposure was similar in the healed and unhealed patients with both the 20 mg and 40 mg doses.

### Discussion

In this study we evaluated prospectively the relation between oesophageal acid exposure and healing of oesophagitis in patients with severe reflux oesophagitis treated with omeprazole. Our data show that failure of oesophagitis to heal is associated with a higher level of oesophageal acid exposure before treatment, and higher levels of acid exposure while receiving omeprazole because of a smaller reduction in acid exposure, particularly at night. These findings are consistent with the hypothesis that failure of oesophagitis to heal with omeprazole is due to inadequate acid suppression.

Severity of oesophagitis as judged by endoscopy before treatment is the most important factor determining the response to treatment with acid suppressant drugs. We selected patients with severe reflux oesophagitis as we have shown previously that such patients are more refractory to omeprazole than patients with lesser degrees of oesophagitis. Most of the patients had proved refractory to H₂ receptor antagonists. The healing rate with the 20 mg dose in this study (69%) is comparable to that seen previously, and illustrates the difficulty in treating patients with severe oesophagitis even with potent acid suppressants. In contrast with earlier studies, however, which reported similar healing rates with 20 mg and 40 mg doses, doubling the dose of omeprazole from 20 mg to 40 mg in this study was associated with healing of the oesophagitis in an additional 15% of the patients. This increase in healing rate may have been a result of a longer duration of treatment in the patients who received the 40 mg dose as these patients had already received eight weeks’ treatment with the 20 mg dose; in the previous studies, patients received only eight weeks’ treatment overall.

The important finding from this study was that failure of oesophagitis to heal was associated with higher levels of acid exposure on treatment. There are two main explanations for this finding. Firstly, patients that remained unhealed on the 20 mg dose had higher levels of acid exposure before treatment. Previous findings on the relation between pre-treatment oesophageal acid exposure and response to acid suppression have been conflicting. Some studies have shown no relation, and a direct relation has been reported, however, in patients refractory to H₂ antagonists and may be a consequence of more defective gastro-oesophageal competence or more severely impaired oesophageal acid clearance or both in the refractory patients. It has also been suggested that higher pre-treatment acid exposure is related to gastric acid hypersecretion.

In this study, however, the higher pre-treatment acid exposure may have been related to prior use of H₂ antagonists. Cessation of these drugs is associated with rebound gastric hypersecretion. Pre-treatment acid exposure was higher only in patients who did not heal and who had been taking H₂ antagonists before entering the study; acid exposure was similar in healed and unhealed patients who had not taken H₂ antagonists. Interestingly, previous use of H₂ antagonists did not affect pre-treatment acid exposure in patients who healed with the 20 mg omeprazole dose suggesting

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**Table III: Oesophageal acid exposure with omeprazole 40 mg every morning**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Pre-treatment</th>
<th>Omeprazole (20 mg)</th>
<th>Omeprazole (40 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (%)</td>
<td>Upright (%)</td>
<td>Supine (%)</td>
</tr>
<tr>
<td>Healed</td>
<td>20.8 (25.3)</td>
<td>14.7 (20.8)</td>
<td>17.7 (24.4)</td>
</tr>
<tr>
<td>Unhealed</td>
<td>28.4 (34.2)</td>
<td>21.5 (29.9)</td>
<td>30.4 (36.6)</td>
</tr>
</tbody>
</table>

Median (interquartile range), *p<0.05, t<0.05 v healed.
that patients who did not heal may have different patterns of acid secretion. Despite the con-
founding factor of H2 antagonists, however, differences in reflux patterns cannot account for the failure of patients to respond to the higher dose of omeprazole as the pre-treatment oesophageal acid exposure levels in these patients were no different from those in the patients who healed with this dose.

Secondly, and more importantly, our data suggest that failure of oesophagitis to heal is associated with lower degrees of acid suppression. Patients who did not heal with the 20 mg dose not only had higher levels of acid exposure while receiving treatment but also had a significantly smaller reduction in acid exposure. Additionally, patients that remained unhealed with the 40 mg dose had substantially higher levels of acid exposure on treatment despite similar pretreatment levels of acid exposure to those in patients who healed. Although we did not measure gastric acid secretion, these findings are best explained by a relative refractoriness to acid suppression with omeprazole in a subgroup of patients with severe oesophagitis. The reasons for this are not clear. Possibilities include: gastric hyper-secretion, a decreased response of the parietal cell, perhaps related to increased drive for acid secretion, poor absorption, and changed pharmacokinetics with increased metabolic rate or elimination.25 Whether or not reflux disease in general26-28 or that refractory to acid suppressant treatment18 29 is associated with acid hypersecretion is controversial. Patients with duodenal ulcer exhibit substantial variability in acid suppression with low (10 mg) doses of omeprazole, which becomes less noticeable with higher doses.30

While oesophageal acid exposure was higher overall in unhealed patients, the important component was a higher level of supine and therefore nocturnal reflux. Indeed, the 40 mg dose had virtually no impact on supine reflux in the patients who failed to heal. These findings confirm previous reports of persistently increased supine and nocturnal oesophageal acid exposure in patients with reflux oesophagitis resistant to omeprazole.5 17 In part this is probably a result of refractoriness of nocturnal acid secretion. Omeprazole in doses of 20 mg or greater virtually ablates daytime acid secretion, whereas partial breakthrough occurs at night.31-33 Whether nocturnal breakthrough is more noticeable in patients with refractory reflux disease, however, awaits specific study. While persistence of nocturnal oesophageal acid exposure could also result from more adequate acid clearance, this hypothesis is not supported by our finding that acid clearance times before treatment were similar in healed and unhealed patients for both the 20 mg and 40 mg doses.

Oesophageal acid exposure was not the only determinant of healing. Some patients healed despite continuing high levels of acid exposure, and some patients failed to heal despite reduction of acid exposure to below normal levels. Aspirin use has been implicated as a significant factor in the resistance of oesophagitis treatment.34 As with other studies, however,6 8 smoking or the use of non-steroidal anti-inflammatory drugs including aspirin did not affect the rate of healing. Increased exposure to bile salts has been reported in patients with severe reflux disease.35 Whether patients who are refractory to omeprazole have greater oesophageal exposure to these agents, however, remains to be determined.

In summary we have shown that failure of severe oesophagitis to heal with omeprazole is associated with persistence of a high level of oesophageal acid exposure that is most consistent with inadequate suppression of acid secretion. The mechanisms underlying this apparent refractoriness require further investigation. Our findings also underline the need in patients with severe reflux disease to titrate the dose of omeprazole to achieve adequate acid suppression, and that oesophageal pH monitoring is a useful guide for this approach. The apparent breakthrough of nocturnal acid secretion in refractory patients may be just related to dose. Whether or not night time compared with morning dosing,30 or dividing the single 40 mg dose into twice daily 20 mg doses would achieve better healing awaits further study.

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