Clinical Outcome Using Lansoprazole in Acid Hypersecretors With and Without Zollinger-Ellison Syndrome: A 13-Year Prospective Study

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Background & Aims: Unremitting gastric acid and pepsin hypersecretion causes serious persistent and relapsing lesions, but the natural history with medical treatment alone has not been well-defined. The aims of this study were to heal and prevent relapse of acid/peptic lesions during acid suppression and to analyze benefits and risks during long-term lansoprazole treatment. Methods: Sixty-seven patients (49 with Zollinger-Ellison syndrome [ZES], 18 without), with basal acid output (BAO) >15 mmol/h or >5 mmol/h if post-antrectomy (n = 9, all ZES), were treated with individually optimized doses of lansoprazole (7.5–450 mg/day; median, 75 mg/day) to reduce BAO to <5 mmol/h or <1 mmol/h post-antrectomy and underwent endoscopy every 3–6 months for up to 13 years (median, 6.25 years). Results: Before treatment, 94% had duodenal ulcer, 64% had esophagitis, 60% had 1 or more bleeding episodes, 13% had perforated ulcers, 90% had pain, 60% had heartburn, and 40%–48% had diarrhea, vomiting, and/or weight loss. Forty-seven patients (70%) remained symptom- and lesion-free, whereas 13 (20%) had mild, transient relapses, and 7 (10%) had more complicated relapses. Overall, symptoms were reduced 90%; ulcer or esophagitis relapsed in 4.8% of patients/year, unrelated to Helicobacter pylori, whereas complications declined to <2%/y. Post-antrectomy ZES patients had 3.6-fold higher relapse rates than unoperated ZES patients (67% vs 18%, respectively). With BAO >5 mmol/h in intact patients, relative risk of relapse was 4.1, confidence interval 2.1–8.1, P < .001. Twenty patients died, 3 as a result of ZES (2 metastatic gastrinomas). Conclusions: With individually optimized medical suppression of acid secretion, 90% of patients had good to excellent long-term outcomes without surgery, with an annualized total relapse rate of <5%.

Hypersecretion of acid (basal acid output [BAO], >15 mmol/h) and pepsin secretion, whether or not caused by gastrinoma (Zollinger-Ellison syndrome [ZES] or idiopathic [non-ZES]), causes severe and often life-threatening lesions of the esophagus, duodenum, and proximal small bowel, but, surprisingly, not stomach, with debilitating symptoms. The only therapeutic option for this condition is the proper control of acid (and pepsin) secretion, although the actual clinical outcome or the most desirable level of acid required to heal and prevent relapse of acid/peptic lesions has not been critically examined since more potent treatment with proton pump inhibitor (PPIs) has become standard.

Despite extensive and important data in the literature on survival of patients with ZES, there have been no good long-term data on clinical outcome (healing and recurrence of acid-related symptoms, lesions, or complications), either with PPI or after gastrinoma surgery.

As a follow-up to our initial reports, we present an additional 9 years of observation with double the number of hypersecretor patients, 49 with gastrinoma (ZES) and 18 without, in an open label prospective study currently in its 14th year, describing the favorable clinical outcome of effective, individually optimized acid suppression with lansoprazole in the long-term nonsurgical management of acid/peptic lesions in acid hypersecretors with and without gastrinoma.

The premise that ZES treatment could be entirely medical was examined critically in this study.

Methods

Sixty-seven patients with basal acid hypersecretion were recruited and gave written consent for inclusion in this institutional review board–approved protocol using lansoprazole. Acid hypersecretion was defined as BAO >15 mmol/h in patients without prior antrectomy (40 intact ZES and 18 non-ZES hypersecretors) or >5 mmol/h after antrectomy (n = 9, all ZES). ZES

Abbreviations used in this paper: BAO, basal acid output; B-I, Billroth I; B-II, Billroth II; BMI, body mass index; BPO, basal pepsin output; CI, confidence interval; DU, duodenal ulcer; H2RA, histamine 2 receptor antagonist; JU, jejunal ulcer; LESP, lower esophageal sphincter pressure; MU, marginal ulcer; PAO, peak acid output; PPI, proton pump inhibitor; PPO, peak pepsin output; SE, standard error; ZES, Zollinger-Ellison syndrome.

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1542-3565/05/$30.00
PII: 10.1053/S1542-3565(04)00606-8
was diagnosed by fasting and secretin-stimulated serum gastrin levels and/or by histologic identification of a gastrinoma.\textsuperscript{1,16} Forty-six of these patients had been treated for 17 ± 3 months with omeprazole (median, 40 mg/day) before entering this study.

Gastric analysis measuring basal and maximal pentagastrin-stimulated acid and pepsin secretion\textsuperscript{1,2,14,17–19} was performed at entry and at regular intervals (see below). Before gastric analysis, PPI treatment was suspended for at least 7 days and replaced by high dose histamine 2 receptor antagonist (H2RA), which in turn was withheld for 36 hours.

Starting with 60 mg/day, lansoprazole doses were individually adjusted in each patient to maintain BAO at <5 mmol/h, a benchmark based on upper limit for healthy control subjects,\textsuperscript{17,19} or <1 mmol/h post-antrectomy and contrary to the generally recommended 10 mmol/h.\textsuperscript{4,12,13,20–25} Optimal doses of lansoprazole in each patient were established in the first 3 weeks\textsuperscript{1} and periodically adjusted as detailed before.\textsuperscript{1} Patients were studied every 3 months for 1 year and then every 6 months with history, physical examination, endoscopy, and gastric biopsies,\textsuperscript{1,16,26} gastric analysis,\textsuperscript{1,17} serum gastrin, and routine laboratory studies. Compliance was based on self-reporting and verified by pill counts. Unexpected increases in BAO suggested noncompliance. Patients were also seen and examined as necessary between scheduled visits for any significant symptoms or evidence of relapse. All patients were interviewed, examined, and underwent endoscopy by the same nurse (J.M.) and physician (B.I.H.) throughout the study.

Esophageal manometry\textsuperscript{27} was performed in 46 of the patients during treatment.

**Dropouts**

Twelve patients dropped out of the study for various reasons after 32 ± 15 months, mainly for other disabilities, relocation, dislike of procedures, and in 1 case because of pregnancy. Seven of these patients were followed outside the study without regular endoscopy or gastric analysis. Four patients during treatment.

**Statistics**

The baseline data were analyzed with Fisher exact, Wilcoxon, and \( t \) tests. The appropriate univariate test, \( t \) test (paired and unpaired comparisons) or Wilcoxon signed rank test, and step-wise multivariate logistic regression was done with SAS (SAS Institute, Inc, Cary, NC) software. Means are expressed ± standard error of the mean. \( P \) value < .05 is considered significant. Intent-to-treat analysis was applied to include dropouts and cases with either high secretion or a relapse resulting from noncompliance.

**Results**

**Pre-entry**

**Lesions and complications before lansoprazole treatment.** A history of aggressive acid/peptic disease was present in all 67 patients. Before diagnosis and treatment, 63 (94%) of the 67 patients had had endoscopically diagnosed duodenal ulcer (DU), 43 (64%) had grade 2 or worse esophagitis, and 39 of these 43 patients had a DU or jejunal ulcer (JU) as well (Table 1). There was a high rate of complications and symptoms (Table 1). Because the intact ZES and non-ZES patients had a very similar incidence of lesions and complications due to hypersecretion as previously reported,\textsuperscript{27} they were combined.

Nine ZES patients had undergone a partial gastrec-
tomy for DU, and 5 of these underwent more than 1 operation, with presurgical and postsurgical recurrent bleeding in 7 of 9 and perforation in 3, one with a jejunoileocolonic fistula. All had active DUs (Billroth I [B-I]) or JUs (Billroth II [B-II]); 5 of 9 also had esophagitis (Table 1). Although clinically comparable to the intact patients, the patients who had undergone antrectomy were older, had significantly lower gastric secretions and body mass index (BMI), and had a worse outcome.

**Treatment**

Lansoprazole was given for 3–156 months, median 75 months, representing a total of 419 patient-years of treatment. Acid (and pepsin) output was controlled to target levels by lansoprazole in 64 of the 67 (96%) patients within 3 weeks after entry into the study.1 Later, as previously described in detail,1 lansoprazole doses were further adjusted for optimal acid control in half the patients either for elevated BAO or for dose reduction for presumed excessive suppression. Individual optimal effective doses of lansoprazole varied from 15 mg every other day to 450 mg/day, median 75 mg/day.

**Outcomes During Treatment**

**Initial healing.** Symptoms cleared rapidly, and most patients soon regained lost weight. By 3 months after starting therapy all ulcers had healed, but 5 patients had unhealed esophagitis or residual esophageal stricture that eventually resolved within 3–14 months.

**Symptoms.** Marked reduction in symptoms reflected the major reduction in disease. Forty-six (70%) of the patients reported no significant symptoms. The number of visits in which, on systematic questioning, patients reported 1 or more moderate or severe symptoms since the prior visit as a proportion of 1050 follow-up visits was pain, 7.4%; heartburn, 2.7%; vomiting, 3.3%, and diarrhea, 4.1%. (Figure 1A). However, there was poor correlation between symptoms and lesion relapse; 89% of heartburn reports were not associated with esophagitis relapses, and 86% of visits in which patients reported pain were unrelated to relapse of either ulcer or esophagitis (Table 2). In half of those with pain unrelated to ulcer or esophagitis, pain was related to other known gastrointestinal pathology such as gallstones, irritable bowel, pancreatitis, or cancer. Conversely, there were no symptoms associated with 21 of 28 (75%) episodes of ulcer and 18 of 25 (72%) episodes of esophagitis (Table 2), suggesting that the pain of ulcer or esophagitis, or heartburn, normally acid related, is absent because of low acid. In 6 symptomatic relapse episodes, patients used supplemental antacids.

**Lesions.** Frequency, severity, and complications of acid/peptic disease manifestations were dramatically reduced by treatment. On lansoprazole, 47 (70%) of the 67 patients were stable without relapse or symptoms during a median period of 84 months. These comprised 76% of the 58 intact patients (33/40 [82%] ZES and 11/18 [61%] non-ZES) who had no relapses of ulcer or esophagitis after first healing with lansoprazole, but only 3 of 9 (33%, \( P < .03 \)) antrectomized ZES patients were free of relapse (Figure 2). In the 20 patients who experienced relapse, 13 had a mild relapse and 7 had more complicated or multiple relapses (see below).

During a period of 6.3 ± 0.5 years (median, 6.25 years), which includes the patients who experienced relapse, 20 patients (30% of all patients or 4.8%/y) had relapses either of ulcer (n = 8) or esophagitis, at least grade 2 (n = 8), or both ulcer and esophagitis, not necessarily concurrently (n = 4) (Figure 1B). Fourteen (24%) of the intact patients (7 ZES and 7 non-ZES) had
1 or more relapses, 14 of ulcer and 20 of esophagitis, for an annual rate of 3.9%. Time to first relapse of ulcer was 4–43 months (mean, 20.7 months), and for esophagitis it was 5–56 months (mean, 17 months). The 9 antrectomized ZES patients had a 3.6-fold higher rate of relapse than the unoperated ZES patients (67% [8.7%/y] vs 18% [2.4%/y], $P < .01$), with 5 of the 6 having 14 episodes of ulcer relapse with 7 episodes in 1 patient. Another of these patients had 4 relapses of esophagitis with stricture as well as a DU (Table 3). Mean time to first relapse in these 6 antrectomized patients was 23.5 months versus 20.1 months in intact patients.

Because some patients had more than 1 relapse, outcome might also be expressed as an annual rate of relapse episodes, counting all episodes regardless of multiple recurrences in some patients. Altogether there were 53 acid/peptic-related relapse episodes in these 20 patients, 28 of ulcer and 25 of esophagitis. Assuming that before treatment ulcers relapsed at least annually, if they healed at all, then by this measure, the ulcer attack rate fell more than 10-fold, from 94% to 6.7% per year, and esophagitis from 64% to 5.8% per year ($P < .001$). The rate of ulcer complications during treatment also fell steeply, bleeding to 1.2% per year and perforation to 0.5% per year (Figure 1, B).

### Severity of the relapses.

**Mild relapses.** In 13 of the 20 patients relapses were mild; 10 patients had only a single relapse of ulcer (3 patients) or of esophagitis (7 patients), all of which healed rapidly. These 10 patients remained relapse-free up to the time of this analysis for another 3–89 months (mean, 40 months). Of the remaining three, 2 patients each had 2 relapses of ulcer that healed quickly with no further relapse for 27 and 72 months, respectively, on continuing treatment. One intact patient had one grade 1 and two grade 2 esophagitis relapses that healed rapidly, with no further relapse for 24 months.

**Serious, multiple, or complicated relapses.** However, 7 (10%) of the patients, including 3 of the 9 antrectomized ZES patients, had more serious or complicated relapses (Table 3). The majority of the episodes in these patients occurred with BAO in the target range, but in 2 of the 7 patients, relapses were related to 1 or more spikes of high acid output because of lapses in treatment. Most of the 7 patients also had concurrent problems that might have contributed to the poor responses to treatment including NSAIDs (patient 1), severe diabetes (patient

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### Table 2. Relation Between Relapse and Symptoms in Hypersecretors Treated With Lansoprazole (1050 Return Visits)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of patients</th>
<th>No. of visits</th>
<th>Ulcer</th>
<th>Esophagitis</th>
<th>With no lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visits with symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>28</td>
<td>78</td>
<td>7</td>
<td>4</td>
<td>67 (86%)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>18</td>
<td>28</td>
<td>0</td>
<td>3</td>
<td>25 (89%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22</td>
<td>37</td>
<td>1</td>
<td>4</td>
<td>32 (86%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23</td>
<td>43</td>
<td>2</td>
<td>1</td>
<td>40 (93%)</td>
</tr>
<tr>
<td>None</td>
<td>46</td>
<td>910</td>
<td>22</td>
<td>18</td>
<td>870 (96%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion</th>
<th>No. of patients</th>
<th>No. of visits</th>
<th>Pain</th>
<th>Heartburn</th>
<th>Without symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer</td>
<td>12 (b)</td>
<td>28</td>
<td>7</td>
<td>0</td>
<td>21 (75%)</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>12 (b)</td>
<td>25</td>
<td>7</td>
<td>4</td>
<td>18 (72%)</td>
</tr>
</tbody>
</table>

Note. Top, frequency of moderate or severe symptoms reported during 1050 return visits and their relation to lesion relapses. Bottom, frequency of lesion relapses and associated symptoms.

*Half these patients had other causes for pain.

*Four patients in each group had both.

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![Figure 2](image.png)  
**Figure 2.** The percent distribution of intact and post-antrectomy patients, respectively, with no relapse, mild relapses, and more complicated or serious relapses.
Complications.

Eleven complications of ulcers occurred in 8 patients. Perforation of a JU occurred in 1 noncompliant intact ZES patient and 1 post-antrectomy ZES patient; the latter was fatal. Five (7.5%) of the 67 patients bled from ulcer, 3 bled twice, and 2 other patients bled from a Mallory-Weiss esophageal tear. Pyloric (stomal) stenosis in 1 patient with a gastroduodenostomy (B-I) required surgery.

Of esophagitis. The principal complication of esophagitis relapse was stubborn stricture, which recurred in 5 of the 10 patients who had strictures before treatment. In 4 of these 5 patients the stricture was associated with a circumscribed ulcer, and in 3 of these, a mid-esophageal location suggested a pill-related cause for the ulcer/stricture.

Risk factors.

Pretreatment predictors of relapse. By univariate analysis, those with peptic ulcer relapses were younger (30 vs 43 y, \(P < .01\)) and had a lower BMI (23.1 vs 27.7, \(P < .001\)), but there were no other differences from the nonrelapsers with respect to demographics, prior symptoms, type and severity of lesions or complications, acid and pepsin output, serum gastrin, family history of ulcer or Helicobacter pylori (data not presented), or in duration of follow-up.

For esophagitis relapses, univariate analysis with the additional variables of severity of prior esophagitis and hiatal hernia at entry showed that only severity, ie, grade 3 or 4 esophageal disease before treatment (37% relapsed

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Table 3. Complicated or Multiple Relapses

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Onset age (y)</th>
<th>Esophagitis grade</th>
<th>Ulcer</th>
<th>BAO Ulcer</th>
<th>Esophagitis</th>
<th>Month of relapse</th>
<th>H pylori</th>
<th>BAO at relapse (mmol/h)</th>
<th>Follow-up after last lesion (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>M</td>
<td>19</td>
<td>–</td>
<td>DU</td>
<td>15.5</td>
<td>DU (x2)(^a)</td>
<td>–</td>
<td>25, 31</td>
<td>0, 0</td>
<td>0.6, 7.6</td>
</tr>
<tr>
<td>45</td>
<td>M</td>
<td>41</td>
<td>2</td>
<td>DU(^b)</td>
<td>1.5</td>
<td>DU (x3)(^p)</td>
<td>–</td>
<td>4, 53, 73</td>
<td>0, 0, 4.7</td>
<td>0, 0.1, 0.4</td>
</tr>
<tr>
<td>34</td>
<td>M</td>
<td>31</td>
<td>4(^c,d)</td>
<td>DU(^p)</td>
<td>17.8</td>
<td>DU</td>
<td>–</td>
<td>47, 12</td>
<td>1.2</td>
<td>36, 0.1</td>
</tr>
<tr>
<td>35</td>
<td>M</td>
<td>10</td>
<td>3</td>
<td>JU(^b,f)</td>
<td>37.1</td>
<td>JU (x3)(^p)</td>
<td>–</td>
<td>15, 20, 27</td>
<td>14.6, 0, 0</td>
<td>0, 0.4, 4.7</td>
</tr>
<tr>
<td>52, B-II</td>
<td>M</td>
<td>37</td>
<td>–</td>
<td>DU→JU(^b)</td>
<td>8.3</td>
<td>MU</td>
<td>–</td>
<td>43, 15</td>
<td>0, 0.8</td>
<td>0, 0.4, 4.7</td>
</tr>
<tr>
<td>59, B-II</td>
<td>F</td>
<td>41</td>
<td>–</td>
<td>DU(^p)→JU(^f)</td>
<td>16.9</td>
<td>MU</td>
<td>–</td>
<td>52, 15</td>
<td>Unknown</td>
<td>0, 0.4, 4.7</td>
</tr>
<tr>
<td>59, B-I</td>
<td>M</td>
<td>53</td>
<td>4(^b,c,e)</td>
<td>DU→JU(^b)</td>
<td>15</td>
<td>DU</td>
<td>+(^c,d,e)</td>
<td>8, 24–34</td>
<td>24–34</td>
<td>0, 0.4, 4.7</td>
</tr>
</tbody>
</table>

Note. Details of pretreatment status and relapses in 7 patients with multiple or complicated relapses.

\(^a\)no. of episodes.

\(^b\)Bleed.

\(^c\)Esophageal stricture.

\(^d\)Barrett’s esophagus.

\(^e\)Esophageal ulcer.

\(^f\)Perforation.

\(^g\)Total gastrectomy.

2), vascular disease (patients 4 and 5), alcohol abuse (patients 3, 5, and 6), lung cancer (patient 3), poor compliance (patients 2, 3, 4, and 7), and pill-related mid-esophageal ulcer (patients 2, 3, and 7).

**Complications.**

*Of peptic ulcer.* Eleven complications of ulcers occurred in 8 patients. Perforation of a JU occurred in 1 noncompliant intact ZES patient and 1 post-antrectomy ZES patient; the latter was fatal. Five (7.5%) of the 67 patients bled from ulcer, 3 bled twice, and 2 other patients bled from a Mallory-Weiss esophageal tear. Pyloric (stomal) stenosis in 1 patient with a gastroduodenostomy (B-I) required surgery.

*Of esophagitis.* The principal complication of esophagitis relapse was stubborn stricture, which recurred in 5 of the 10 patients who had strictures before treatment. In 4 of these 5 patients the stricture was associated with a circumscribed ulcer, and in 3 of these, a mid-esophageal location suggested a pill-related cause for the ulcer/stricture.

**Risk factors.**

**Pretreatment predictors of relapse.** By univariate analysis, those with peptic ulcer relapses were younger (30 vs 43 y, \(P < .01\)) and had a lower BMI (23.1 vs 27.7, \(P < .001\)), but there were no other differences from the nonrelapsers with respect to demographics, prior symptoms, type and severity of lesions or complications, acid and pepsin output, serum gastrin, family history of ulcer or Helicobacter pylori (data not presented), or in duration of follow-up.

For esophagitis relapses, univariate analysis with the additional variables of severity of prior esophagitis and hiatal hernia at entry showed that only severity, ie, grade 3 or 4 esophageal disease before treatment (37% relapsed
compared with 6% of those with lesser or no esophagitis, 
\( P < .03 \), lower esophageal sphincter pressure (LESP) <16 mm Hg (\( P < .03 \)), and smoking (\( P < .04 \)) were more common in those who experienced relapse.

By multivariate analysis of all 67 patients, or of only the 58 intact patients, for ulcer and esophagitis relapse, lower BMI and earlier age at onset were the only significant contributors to outcome. The clinical significance of these findings is uncertain.

**Predictors during treatment.**

**Acid and pepsin.** One might expect that the most significant factor in relapses of ulcer or esophagitis would be gastric secretion. In the 20 patients during relapse episodes, both basal and peak acid and pepsin outputs were higher than in those 47 patients who never had a relapse (\( A \) vs \( C \), Figure 3). There were no significant differences in secretion within the relapse group between periods of relapse and remission (\( A \) vs \( B \), Figure 3).

**Basal acid output as a risk factor.** Gastric secretion was measured at the time of relapse in 50 of the 53 episodes in the 20 patients who experienced relapse. Figure 4A (intact) and Figure 4B (post-antrectomy) show individual episodes of esophagitis and ulcer relapse-related BAO during treatment as well as the mean BAO (±3 standard errors [SEs]) derived from the median value for each patient who never experienced relapse.

In 58 intact patients, 14 of 33 (42%) relapses occurred at BAO >5 mmol/h (Figure 4A) and in the post-antrectomy patients (Figure 4B), 33% at BAO >1 mmol/h. In the intact patients the relative risk of a relapse episode (33 relapses) of ulcer or esophagitis at BAO >5 mmol/h was 4.08, confidence interval [CI], 2.05–8.1, \( P < .001 \). Overall, about half the relapses occurred with BAO <1 mmol/h, although not all patients with low BAO were as suppressed as might appear at first glance. Of 21 episodes of relapse with BAO <1 mmol/h, 8 (38%) responded to pentagastrin with PAO 5–50 mmol/h. Of the remaining 14 instances with PAO responding to \( <2 \) mmol/h, 7 occurred in 1 (antrectomized) patient (Table 3).

**Other risk factors.**

**Helicobacter pylori.** \( H \) pylori was present in 26 (39%) of the 67 patients at entry and for at least part of the treatment period.\(^{15,26}\) \( H \) pylori was present in 10 (34%) of 29 ulcer relapse episodes and in 20 (36%) of the 55 patients who did not have an ulcer relapse. Six of the
12 patients with ulcer relapse were \textit{H pylori} positive, and 3 of these 6 relapsed again after clearing \textit{H pylori}.

\textbf{Risk factors for esophagitis.} In 10 of 14 relapses, LESP was below 16 mm Hg\textsuperscript{27} compared to 12 of 32 nonrelapsers ($P < .03$), whereas BAO and hiatal hernia appeared unrelated (Figure 5). \textit{H pylori} was present in 3 of 12 patients with and in 21 of the 55 patients without esophagitis relapse (NS).

\textbf{Other outcomes.}

\textbf{Deaths.} During this study, 17 of the 49 ZES patients (35\%) died, from 6–50 years after the onset of symptoms (Table 4), whereas only 3 (6\%) of total ZES patients died directly as a result of ZES, and of these, 2 (4\%) died of metastatic gastrinoma already present in the liver at the start of treatment, and 1 patient, an antrectomized ZES, B-II, died after perforation of a JU. Five patients died of other malignancies; 4 died of cardiovascular disease, 4 of chronic renal failure, and 1 died at age 100 years, with a 50-year ulcer history that included 2 gastrectomies, coincident esophagitis, a mastectomy, and 13 years of lansoprazole therapy without further relapse. Two of the 18 non-ZES hypersecretor patients died of malignancy and the other of cystic fibrosis at age 41 years, 28 years after onset of ulcer symptoms (Table 4).

\textbf{Malignancy.} Among the ZES patients 3 had hepatic gastrinoma metastases at entry. Two died of this malignancy, but 1 ZES patient, with onset of ulcer symptoms at age 31 years, had known liver metastases that remained stable for 30 years, including 12 years in remission on H2RAs and 16 years on PPI treatment. He died of cardiac disease at age 73 years. Two other patients first developed evidence of liver metastases 40 and 15 years after onset of ZES symptoms, 8 and 14 years, respectively, after start of PPI treatment. One progressed slowly over 7 years, whereas the other has been stable for at least 4 years. All 5 patients with hepatic metastases progressively developed very high levels of serum gastrin (8000–80,000 pg/mL).

Besides the 5 fatal cancers, one ZES patient had metastatic gallbladder cancer, and 3 others had nonfatal surgically cured malignancies of lung, breast, and palate, respectively. One non-ZES patient had a squamous cell cancer of the back.

\textbf{Laboratory studies.} There were no indications to stop medication for abnormal laboratory values, and none were ascribed to lansoprazole. Interestingly, urine pH, which ranged from 6.8–7.0 before acid suppression, declined to 5.7–6.4 ($P < .01$) after acid suppression.

\textbf{Discussion}

The annualized rate of acid-related mucosal lesions in hypersecretors approaches 100\% in the untreated state. Our study population had classic severe symptomatic acid/peptic disease, almost all with recurrent DU, and two thirds with esophagitis as well. Complications were common, including bleeding, perforation, or stricture, and all had multiple symptoms.

In sharp contrast to the focus during the last 25 years\textsuperscript{28–31} on healing and prevention of relapse in the medical treatment of conventional peptic ulcer and esophagitis, most articles dealing with medical\textsuperscript{4,23,24,32–34}
or surgical treatment of ZES, the archetypical class of acid hypersecretor, describe effects on gastric acid secretion,21–25 and safety, including possible adverse effects of acid suppression,25,33,34 and on mortality, but they have not dealt specifically with long-term clinical outcome with respect to acid/peptic lesions. However, as in conventional acid/peptic diseases, the object of treatment should be not only initial healing of lesions and control of symptoms, but also the prevention of recurrent lesions and complications.

In this study, symptoms were controlled within 1–4 weeks. All ulcers had healed by the first repeat endoscopy at 3 months, as had esophagitis in 38 of 43 patients, with healing in the next 3–14 months of the 5 unhealed patients. Long-term outcome was equally gratifying, because 70% of the patients (76% of intact patients) had no relapse of any acid/peptic lesions, ulcer and/or esophagitis, or symptoms in up to 13 years (median, 7 years) of treatment, and another 20% of patients had only 1 or 2 readily treatable mild relapses in a follow-up of 419 patient-years. There were 1 or more moderate or severe symptoms reported at fewer than 7.5% of 1050 return visits, representing 90% reduction from pretreatment prevalence. Thus approximately 90% of all patients were completely or very well controlled, with an annual rate of relapse of ulcer or esophagitis of 4.8% of all patients per year and complications of <2%. For intact ZES patients the rate was 2.4%/y, but for antrectomized ZES patients, it was 8.7%/y. There was an interesting disconnect between symptoms and relapses, because lesions were associated with symptoms in fewer than 25% of cases, presumably because of low acid, similar to the transient symptom relief by antacids. Conversely, up to 90% of symptoms were apparently unrelated to endoscopically demonstrated relapses. A similar paucity of symptoms with relapses of ulcer or esophagitis was reported by Metz et al.12 Such silent lesions might pose additional risks because they are unsuspected but are still potentially subject to complications.

Table 4. Causes of Death

<table>
<thead>
<tr>
<th>Cause</th>
<th>n</th>
<th>Age onset (ZES) or ulcer (y)</th>
<th>Age at death (y)</th>
<th>Total PPI treatment (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant ZES 1</td>
<td>1</td>
<td>61</td>
<td>68</td>
<td>28</td>
</tr>
<tr>
<td>Malignant ZES 1</td>
<td>1</td>
<td>52</td>
<td>63</td>
<td>47</td>
</tr>
<tr>
<td>ZES perforated JU (B-II) 1</td>
<td>1</td>
<td>37</td>
<td>57</td>
<td>97</td>
</tr>
<tr>
<td>Renal failure (mean ± SE) 4</td>
<td>4</td>
<td>51 ± 1</td>
<td>63 ± 3</td>
<td>32 ± 10</td>
</tr>
<tr>
<td>Cardiovascular (mean ± SE) 4</td>
<td>4</td>
<td>40 ± 14</td>
<td>66 ± 10</td>
<td>71 ± 32</td>
</tr>
<tr>
<td>Cancera (mean ± SE) 5</td>
<td>5</td>
<td>38 ± 6.5</td>
<td>66 ± 5</td>
<td>94 ± 24</td>
</tr>
<tr>
<td>Age (100 y) 1</td>
<td>1</td>
<td>50</td>
<td>100</td>
<td>136</td>
</tr>
<tr>
<td>Non-ZES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancerb 2</td>
<td>49, 56</td>
<td>51, 59</td>
<td>25, 31</td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis 1</td>
<td>13</td>
<td>41</td>
<td>125</td>
<td></td>
</tr>
</tbody>
</table>

Note. Cause of death in 17 patients with ZES and 3 with non-ZES hypersecretion.

aHead & neck (2), pancreas with prior jaw (1), lung (1), colon (1).
bHead & neck, pancreas.

H pylori did not seem to be a factor in the ulcer relapses,23 but we could not rule out NSAIDs with certainty. Nocturnal acid rebound37 was ruled out by 24-hour intragastric pH measurements38 in a subset of 11 patients (data not presented). Explanations for mucosal lesions at low BAO, especially in those without prior gastric surgery, thus remain speculative, although many with BAO of 0 did indeed secrete significant amounts of acid with pentagastrin stimulation.

In keeping with prior experience,36 the highest rate of relapse and the poorest outcome were found in the post-antrectomy ZES patients, with 67% relapse or 3.6-fold greater than in unoperated ZES patients, raising the...
question whether these patients had more aggressive disease before surgery. It seems more likely, however, that aggressive disease after gastric surgery is due to the post-antrectomy anatomy, because patients who had vagotomy without resection, but presumably for the same ulcer indications, did not have a high relapse rate. Thus, timely diagnosis of ZES would avoid inadvertently exposing the patient to so much additional risk from antrectomy.

It has been reported that about 50% of ZES patients with grade 2 or worse erosive esophagitis required treatment more potent than H2RA. That finding was similar to the general experience during the last 20 years in the treatment of conventional (non-ZES related) esophagitis, in which PPIs have consistently been found to be superior to H2RA. Our results in the 43 patients with acid hypersecretion and at least grade 2 esophagitis resemble the experience with PPI treatment of conventional patients for esophagitis not caused by hypersecretion.

As others have reported for common esophagitis, with otherwise normal acid secretion, we also found in ZES that prior severe esophagitis predicts treatment difficulties and, often, relapse. Other predictors of relapse were LESP <16 mm Hg, a low BMI, and smoking.

In hypersecretors, compliance is essential, because interruption for only a few days might lead to major relapses. Even supervised dose reduction in 27 of the patients led to 7 ulcers with 4 bleeds, 3 esophagitis with 1 stricture, and 5 symptom relapses requiring reversal of reduction.

Despite clinical success of carefully supervised medical treatment in ~90% of the patients, response to treatment in 10% of cases was problematic. There were several factors that might have contributed to the poor response to therapy in the 7 difficult cases, including alcoholism in 3, severe complicated diabetes or vascular disease, NSAIDs, and poor compliance in 1 psychotic patient, ultimately requiring total gastrectomy. Two patients experienced relapse because treatment was inadvertently interrupted while in the intensive care unit for other reasons in other hospitals.

Unlike the non-ZES hypersecretors, ZES patients are at additional risk of death from metastatic gastrinoma. In this study, with an average duration of 16 years from the onset of symptoms, 5 patients (10% of ZES) had metastatic hepatic gastrinomas, although of these 5 patients only 2 (4% of 49 ZES patients), both known at entry, died of this cause.

**Conclusion**

In the long-term, 70% of the patients had neither lesion relapse nor symptoms, and another 20% had only 1 or 2 easily healed relapses. Thus 90% had excellent or very good clinical outcomes. Relapse rates in antrectomized patients were >3-fold higher than in intact patients. Although many relapses at very low BAO are unexplained, reduction of BAO to <5 mmol/h in intact patients was highly effective in greatly reducing the frequency and severity of the clinical manifestations of acid/pepsin hypersecretion (relative risk, 0.25; CI, 0.15–0.5; P < .001). The case for individually optimized long-term medical treatment without surgery, carefully monitored to rule out silent lesions, is supported by the results reported here.

**References**


