Published in final edited form as:

World J Surg. 1993 ; 17(4): 468–480. doi:10.1007/bf01655106.

Control of Gastric Acid Hypersecretion in the Management of Patients with Zollinger-Ellison Syndrome

David C. Metz, M.D., Joseph R. Pisegna, M.D., Vitaly A. Fishbeyn, M.D., Richard V. Benya, M.D., Robert T. Jensen, M.D.

Digestive Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, U.S.A.

Abstract

During the last 5 years important advances have occurred in the control of gastric acid hypersecretion in Zollinger-Ellison syndrome (ZES). The increased availability of potent gastric acid antiseecretory agents such as histamine H_2 -receptor antagonists and more recently the H^+K^+ -ATPase inhibitors such as omeprazole and lansoprazole have made it possible to medically control acid secretion in all patients. Increased understanding of the variation in antiseecretory drug dosage between individual patients has led to identification of criteria to ensure effective antisecretory control and to the recognition of subgroups of patients who require special monitoring. Effective regimens for parenteral antisecretory control during surgery have been established. The importance of parathyroidectomy in patients with multiple endocrine neoplasia type I with ZES and the possible usefulness of highly selective vagotomy have been investigated. We review here the new data that led to increased understanding in each of these areas from our studies and studies by others.

Résumé

D'importants progrès ont été réalisées dans ces 5 dernières années en ce qui concerne le contrôle de l'hypersécrétion acide du syndrome de Zollinger Ellison (SZE). La disponibilité d'agents antisécrétoires puissants comme les anti H_2 , et plus récemment les inhibiteurs de la pompe à protons (oméprazole et lansoprazole), offre une solution de contrôle médical chez tous les patients. Une meilleure compréhension de la variabilité de la réponse antisécrétoire des individus a amené à identifier des critères d'efficacité thérapeutique antisécrétoire et de reconnaître un sous-groupe de patients qui nécessite une surveillance spécifique. Des modèles thérapeutiques antisécrétoires efficaces ont été établis pour pallier certains actes chirurgicaux. L'importance d'envisager une hypérparathyroïdectomie chez la patient ayant un SZE/MEN –I et l'utilité d'y associer une vagotomie hyperselective est en cours d'étude. Dans cet article, les données récentes qui ont contribué à augmenter nos connaissances dans ce domaine sont passées en revue.

Resumen

Importantes avances en el control de la hipersecreción ácida del estómago en el síndrome de Zollinger-Ellison (SZE) han sido logrados en los últimos cinco años.

La creciente disponibilidad de potentes agentes que bloquean la secreción gástrica ácida, tales como antagonistas de los receptores histamínicos H₂ y más recientemente los inhibidores de la H⁺-Na⁺ ATPasa como el omeprazol y el lansoprazol, han hecho posible el control médico de la secreción ácida en todos los pacientes. Un mayor conocimiento de la variable dosificación entre pacientes individuales ha llevado a la identificación de criterios que aseguren el eficaz control antisecretorio y al reconocimiento de subgrupos de pacientes que requieren monitoría especial. Se han establecido regímenes eficaces para el control antisecretorio parenteral en el curso de la cirugía. La importancia de la paratiroidectomía en pacientes con SNEM-1 y SZE y la posible utilidad de una vagotomía altamente selectiva han sido investigadas. En el presente artículo se revisa la nueva información, proveniente de nuestros propios estudios y de los de otros autores, que ha llevado al mejor conocimiento sobre cada una de estas áreas.

In 1955 Zollinger and Ellison first described a syndrome characterized by fulminant peptic ulcer disease, marked hypersecretion of gastric acid, and non-beta islet cell tumors of the pancreas [1, 2]. In later years it was shown that these non-beta islet cell tumors were gastrinomas [3–5], and the severe gastric acid hypersecretion and resultant acid-peptic disease were a consequence of autonomous secretion of gastrin by these tumors [3, 6, 7]. Historically, most patients with the ZollingerEllison syndrome (ZES) presented late in the course of their disease, commonly with widespread liver metastases and severe, often fatal peptic ulceration [2, 8]. Total gastrectomy was the only effective form of therapy for the control of gastric acid hypersecretion [1, 8, 9], and it was often performed in an emergency setting with considerable perioperative mortality [10].

Whereas surgical management is still indicated for treatment of the gastrinoma itself [11–16], in recent years medical management of gastric acid hypersecretion in patients with ZES has become increasingly successful and important, with the result that it is currently recommended that surgical therapy to control gastric acid hypersecretion is indicated only in certain specific situations, which are discussed below [11, 15].

The increasing use of medical management came about as a result of a number of factors. The development of potent histamine H₂receptor antagonists and later H⁺ K⁺-ATPase inhibitors made it possible to effectively control gastric acid output in the acute setting as well as during long-term follow-up in most patients with ZES [16–21]. Because of a greater awareness of the disease and the development of reliable radioimmunoassays for serum gastrin determination, ZES is increasingly being diagnosed earlier in healthier patients prior to the development of metastases [11, 12]. Therefore increasing numbers of patients could benefit from possible curative resection of the gastrinoma. With the ability to control gastric acid secretion medically, detailed preoperative imaging studies could be done to attempt to localize the tumor. Furthermore, metabolic abnormalities and nutrition could be corrected prior to surgery, so surgery could be done electively under optimal conditions and directed at the tumor itself. In recent reviews tumor localization, the surgical approach to the tumor, and therapy of metastatic disease have been covered [11–16]. This review focuses on the recent advances in the medical and surgical management of gastric acid hypersecretion in patients with ZES.

Medical Management of Gastric Acid Hypersecretion

The histamine H₂-receptor antagonist metiamide and later cimetidine became available during the mid-1970s, and medical control of gastric acid secretion in patients with ZES was shown to be feasible soon afterward [17–22]. Since then, both short and long-term control of gastric acid hypersecretion with histamine H₂-receptor antagonists has been shown to be effective (Table 1) [18, 20, 21, 23]. However, a number of reports have described failures of histamine H₂-receptor antagonists in up to 50% of patients treated [23–27] (Tables 1 and 2).

It was not recognized initially that patients with ZES frequently require more than twice the daily dose of histamine H₂-receptor antagonists needed for the treatment of idiopathic peptic ulcer disease, and some require more than five times the usual dose [12, 15, 19, 40]. Only by establishing a reliable criterion of acid control and providing sufficient antisecretory medication to achieve this degree of suppression could longterm medical therapy be successful in all patients [19]. Twentyfour hour pH profiles, resolution of symptoms, and reduction of gastric hypersecretion to less than 10 mEq/hr for the hour prior to the next oral dose of antisecretory medication have been proposed as satisfactory criteria to determine adequate acid suppression [11, 12, 17, 28, 40, 41, 43] (Table 2). Most investigators have found that the relief of symptoms is an unreliable guide to the effectiveness of therapy [12, 19, 26, 27, 42]. At present, the criterion of an acid output of less than 10 mEq/hr for the hour prior to the next dose of antisecretory medication in patients without previous gastric surgery or esophageal disease is used almost universally [15, 43]. With an H⁺ K⁺-ATPase inhibitor such as omeprazole, as well as with all histamine H₂-receptor antagonists, this measurement has been shown to be a simple, safe, effective criterion [15, 36, 43, 49]. It not only allows healing of acute mucosal disease, it prevents the recurrence of mucosal abnormalities [12, 42]. To achieve this degree of control with histamine H₂-receptor antagonists, large doses are required and most patients have to take medication at 4- to 8-hour intervals [11, 12].

The single most important determinant of treatment failure is the lack of adequate suppression of acid secretion to an acceptable level because of an inadequate dose of antisecretory agent [19] (Table 2). With the availability of long-acting antisecretory agents such as the H⁺K⁺-ATPase inhibitor omeprazole, medical management of gastric acid hypersecretion has become greatly simplified. Whether a histamine H₂-receptor antagonist or, more recently, omeprazole is used, it has become clear that acid output can be safely and effectively controlled in virtually every patient, provided that sufficient medication is prescribed [12, 19, 36, 43]. Medical therapy is now the primary mode of treatment for gastric acid hypersecretion in patients with ZES [12, 40, 50]. Only in the rare patient who cannot or will not take oral antisecretory medication is a total gastrectomy necessary [15, 50] (Table 2). Recent studies have demonstrated that patients with ZES with multiple endocrine neoplasia type I (MEN-I), esophageal disease, or partial gastric resection are more resistant to therapy and are discussed below.

Acute Management

Patients with ZES who present with severe electrolyte disturbances, gastrointestinal bleeding, or a surgical emergency require intravenous medication to rapidly reduce acid output to within safe limits. Studies show that intravenous cimetidine or ranitidine or, if

available, intravenous omeprazole can control acid hypersecretion satisfactorily [45, 46, 51, 52], but only if the appropriate dose is determined. One regimen that has been shown to be effective [51] is a bolus injection of 150 mg of cimetidine followed by a continuous infusion of cimetidine in 5% dextrose (Table 3). It is not possible to predict the correct dose for an individual patient unless the previously effective oral dose of histamine H₂-receptor antagonist is known; thus the appropriate dose must be determined by measuring acid output [45, 51, 54]. A typical starting dose of cimetidine is 3 mg/kg/hr (4050 mg/day for a 70-kg man) [51, 54]. A few hours after giving a bolus of 150 mg of intravenous cimetidine and starting the continuous intravenous cimetidine infusion at 3 mg/kg/hr, acid output should be checked; if it is more than 10 mEq/hr, the dose of cimetidine should be increased to 4 mg/kg/hr [51]. Acid output should be rechecked on the new dose and the dose then increased or decreased, depending on acid output (Fig. 1, top). The dose may have to be increased to up to 7 mg/kg/hr in an occasional patient (Fig. 2, top). If acid output is still more than 10 mEq/hr, an anticholinergic agent such as propantheline should be given subcutaneously or intramuscularly every 6 hours [51, 53, 54]. Ranitidine is also effective [45, 52]; if it is used instead of cimetidine, the starting dose should be 1 mg/kg/hr with the dose increased in 0.5-mg steps to 2 mg/kg/hr [45, 51, 53] (Table 3). It has been shown that acid output in patients with ZES can be safely and effectively controlled using a continuous intravenous ranitidine infusion of 0.5 to 0.9 mg/kg/hr in 36% of patients, 1.0 to 1.4 mg/kg/hr in another 48%, and 1.5 to 2.5 mg/kg/hr in the remaining 16% for up to 11 days of treatment [45]. Intravenous antiseecretory medication should be continued until oral antiseecretory drug can be resumed. Intravenous omeprazole has been studied in ZES patients going to surgery and requiring parenteral antiseecretory drug, and it was found to be effective [46] (Fig. 2, bottom).

Long-Term Medical Management of Gastric Acid Hypersecretion

Histamine H₂-Receptor Antagonists.—Long-term control of acid output has been well studied and shown to be possible with the three oral histamine H₂-receptor antagonists: cimetidine, ranitidine and famotidine [20] (Fig. 1, bottom; Table 1). On a weight basis, famotidine is approximately ninefold more potent than ranitidine and 32-fold more potent than cimetidine in patients with ZES [20, 21]. As the tablet content of famotidine (20 mg) is one-eighth that of ranitidine (150 mg) and one-fifteenth that of cimetidine (300 mg), this increased potency is not a major advantage in terms of the number of tablets a given patient may be required to take per day to control acid secretion. However, the greater potency of famotidine allows some patients to stop taking an anticholinergic agent they required while taking cimetidine or ranitidine [21]. Furthermore, famotidine has a duration of action 1.3 times greater than that of cimetidine or ranitidine (Fig. 3, top) [20] and allows some patients who required 4-hourly dosing of other histamine H₂-receptor antagonists to switch to 6-hourly dosing, and other patients to switch from 6-hourly to 8-hourly dosing [21]. Ranitidine or famotidine is preferable to cimetidine in men because the large doses of cimetidine required in some patients (>4.8 g/day) can have antiandrogen effects, leading to breast tenderness, gynecomastia, or impotence [12, 40, 55]. Furthermore, cimetidine, unlike ranitidine or famotidine, interferes with the metabolism of drugs by the hepatic mixed-function oxidase system; thus there is a greater possibility of significant drug interactions with cimetidine than with either of the other two histamine H₂-receptor antagonists.

In studies at the National Institutes of Health (NIH), the mean daily dose of cimetidine required to control gastric acid hypersecretion was 3.6 g, that of ranitidine 1.2 g, and that of famotidine 0.25 g [15, 20]. To establish the effective oral dose of histamine H₂-receptor antagonist, patients should be started on 300 mg of oral cimetidine 6-hourly, 150 mg of ranitidine 6-hourly, or 40 mg of famotidine 6-hourly (Table 3). If gastric acid output is more than 10 mEq/hr during the last hour before the next dose of drug (>5 mEq/hr in patients with previous gastric surgery), the 6-hourly dose of drug should be increased (Fig. 1, bottom). If acid output is still more than 10 mEq/hr, the dose of drug should be increased further. Patients with ZES have been treated safely with doses of cimetidine as high as 12 g/day, ranitidine as high as 9 g/day, and famotidine as high as 800 mg/day for many months [21, 23]. Use of these drugs has not been associated with evidence of drug-related hematologic, hepatic, renal, central nervous system (CNS), or other toxicity. The reasons for patients with ZES requiring large doses of histamine H₂-receptor antagonists are multiple and not entirely clear [56]. Studies have reported that some patients with ZES have altered bioavailability of cimetidine [57] or parietal cell resistance to histamine H₂-receptor antagonists [57, 58]. In a recent prospective study of 9 patients with ZES, 80% of the patients had abnormal cimetidine pharmacokinetics, with 30% having a decreased sensitivity of the acid secretory process to drug (i.e., parietal cell resistance), and in 50% there was delayed or decreased absorption of drug. No patients had evidence of increased drug elimination. In 20% no abnormality could be detected, suggesting that altered metabolism, tachyphylaxis, or increased basal acid output per se could be contributing to the increased dose requirements in some patients [56]. After controlling gastric acid hypersecretion initially, patients should have control of gastric acid hypersecretion checked at least yearly or if any new peptic symptoms develop because the dose requirement slowly increases with time. On average, one dose increase per year is required [12, 36].

Anticholinergic Agents.—Although anticholinergic drugs such as propantheline or isopropamide have only a small effect on gastric acid secretion when used alone in patients with ZES, when used with histamine H₂-receptor antagonists potentiation is observed [59, 60]. Typically, the use of an anticholinergic agent alone reduces basal acid output by 15% to 25% [59]. However, when used with histamine H₂-receptor antagonists, anticholinergic agents not only potentiate the action by increasing the extent of suppression of gastric acid secretion, they increase the duration of the effect of histamine H₂-receptor antagonists [59, 60]. Thus whenever a patient required a large dose of histamine H₂-receptor antagonist, an anticholinergic agent was frequently added prior to the availability of omeprazole [12, 40, 59, 60].

Anticholinergic agents do have certain disadvantages. They require 3 days of administration to have their full effect, and they cause side effects, including dry mouth, constipation, and visual changes. Anticholinergic agents should be used with caution in patients with prostatism, glaucoma, partial gastric outlet obstruction, or severe esophageal disease. Because of their side effects, low efficacy, and the availability of omeprazole, anticholinergic agents are now rarely used.

H⁺ K⁺-ATPase Inhibitors.—Omeprazole is the first widely used member of a new class of antisecretory drugs, the substituted benzimidazoles [61, 62]. These agents have a mechanism of action different from that of the histamine H₂-receptor antagonists; they act by binding to a unique enzyme at the luminal aspect of the gastric parietal cell, the H⁺K⁺-ATPase [62].

Omeprazole has a much longer duration of action than histamine H₂-receptor antagonists (Table 3; Fig. 3, bottom) [30, 61]. In patients with ZES the effects of omeprazole are observed within 4 hours and last in excess of 48 hours [30]. Most patients with ZES who require histamine H₂-receptor antagonists every 4 to 8 hours can be treated effectively with a single daily dose of omeprazole, although about 10% to 25% of patients require omeprazole every 12 hours [33, 36, 47]. In most studies gastric acid hypersecretion is controlled with less than 80 mg of omeprazole per day, but occasional patients require more than 200 mg/day [29, 31, 32, 34–37, 47].

Omeprazole has been given to patients with ZES for more than 4 years [33, 36, 47]. No significant drug-related hepatic, renal, hematologic, or other toxicity has been observed, nor have any clinically significant drug interactions been noted [33, 36, 47]. Omeprazole is now the drug of choice for treating patients with ZES because of its potency, long duration of action, and ease of use [43, 47]. Patients with ZES must continue to take omeprazole indefinitely unless cured surgically. The long-term use of omeprazole has led to concern because in animal toxicity studies rats given omeprazole for 2 years developed a proliferation of enterochromaffin-like (ECL) cells and carcinoid tumors of the stomach [63]. Mice, however, did not develop such tumors [63]. Further studies with rats suggested that the tumors were not due to a direct effect of omeprazole but were due to drug-induced hypergastrinemia [64]. In the rat, omeprazole induces achlorhydria, which in turn causes hypergastrinemia [64]. Indeed powerful histamine H₂-receptor antagonists are also capable of producing gastric tumors in rats, presumably through the same mechanism [64]. Fundectomy, partial corpectomy, and long-term infusion of gastrin 17 also increase the numbers of ECL cells; and fundectomy has been shown to result in the development of gastric carcinoid tumors [65–67]. Hypergastrinemic states in humans, such as in patients with ZES or pernicious anemia, are associated with an increased risk of gastric carcinoids [67]. If the dose of omeprazole is properly titrated to avoid achlorhydria, patients with ZES do not develop additional increases in serum concentrations of gastrin during omeprazole therapy [31, 33, 36, 47].

Studies demonstrate that hyperplasia of gastric endocrine cells occurs in patients with ZES, and gastric ECL cells are increased approximately twofold independent of any antisecretory agent [37, 67–72]. In two studies with prolonged omeprazole treatment for up to 4 years, there was no further statistical increase in ECL cells [37, 68]. Gastric carcinoid tumors have been reported in patients with ZES [37, 47, 73–75], some of whom were being treated with omeprazole [37, 76]. A recent review pointed out that in 15 of the 16 cases of gastric carcinoids reported in patients with ZES, there were sufficient data to determine whether the patients had MEN-I in addition to ZES [47]. In these 15 cases of ZES, 14 had MEN-I [47]. Because ZES with MEN-I comprises only 20% of all cases, these data suggest that gastric carcinoid tumors are much more common in patients with MEN-I. Of the 16 patients with

gastric carcinoids, 14 had never taken omeprazole, whereas 2 patients had and both had MEN-I. These data suggest that the presence of MEN-I rather than omeprazole may be the important determinant of the development of gastric carcinoids in patients with ZES [47].

Long-term treatment with omeprazole of patients with ZES has demonstrated no drug-related side effects [36, 47]. Furthermore, in one-third of patients the dose has had to be increased, it was decreased in one-third, and it has remained stable in one-third [47]. These results demonstrate that long-term tachyphylaxis does not occur, and in general the dose is increased less frequently with omeprazole than with histamine H₂-receptor antagonists.

Lansoprazole, a new substituted benzimidazole that, unlike omeprazole, contains a fluorinated side chain [77], is not yet available for general use in patients with ZES. A report comparing the use of lansoprazole and omeprazole in short-term control of gastric acid hypersecretion in 4 patients with ZES demonstrated similar efficacy and safety for both drugs, although lansoprazole possibly had a slightly shorter duration of action [38]. Ongoing studies at the NIH suggest that lansoprazole is both safe and effective for the long-term control of gastric acid hypersecretory states. Recent studies [39, 99] show that the potency, duration of action, efficacy, and safety profile of lansoprazole in patients with ZES is similar to those of omeprazole.

Prostaglandins, Somatostatin, and Other Antisecretory Agents.—Prostaglandin analogs such as 16,16-dimethylprostaglandin E₂ have been used to treat ZES [78, 79]. Although these agents have antisecretory activity, their low potency and dose-related side effects (i.e., diarrhea) limit their usefulness in ZES [78].

The long-acting somatostatin analog octreotide inhibits gastric acid secretion by a direct effect and by lowering serum gastrin levels [78, 80]. In patients with ZES, octreotide effectively controls gastric acid hypersecretion [43, 78] and lowers serum gastrin levels, with a decrease into the normal range in about 30% of patients. Parenteral octreotide has also been used to control gastric acid hypersecretion in patients with ZES during surgery [81]. Two theoretic advantages of octreotide over other antisecretory medications make it potentially useful in patients with ZES. Octreotide may have an antitumor effect [78], and by lowering serum gastrin it may also reverse the trophic effects of long-standing hypergastrinemia [78]. However, neither of these potential advantages are proved. The need for subcutaneous administration two to three times daily and the potential side effects of long-term use (gallstones, steatorrhea, abdominal discomfort) make its use for the control of gastric acid hypersecretion in ZES less attractive when compared with easily administered, well tolerated, oral alternatives [78]. Furthermore, because octreotide has an inhibitory effect on gastrointestinal motility, using it to control gastric acid hypersecretion during the perioperative period when patients cannot take oral medications may complicate postoperative management [78].

In theory, gastrin receptor antagonists would be the ideal agents for control of gastric acid hypersecretion in patients with ZES. The ideal agent would have high affinity and specificity for the gastrin receptor, would be well absorbed after oral administration, and would have a

long duration of action. Proglumide, a weak gastrin receptor antagonist, has been shown to be insufficiently potent for clinical use [78].

Antacids are not useful for controlling gastric acid hypersecretion in patients with ZES. They cannot be given in sufficient quantities to neutralize the high output of hydrogen ions by gastric parietal cells in ZES [78]. Mucosal protectants such as sucralfate have not been proved to be effective in patients with ZES.

Control of Acid Hypersecretion in Special Circumstances

Patients With a Previous Partial Gastrectomy.—Patients with ZES who have had a previous Billroth I or II gastrectomy require gastric acid secretion to be reduced to lower values than do patients with normal gastric anatomy (Table 2) [44]. When gastric acid secretion is lowered to less than 10 mEq/hr during the last hour before the next dose of drug in patients with a Billroth I or II gastrectomy with ZES, many still have evidence of mucosal disease, especially at the gastrojejunal anastomosis [44]. Some patients develop significant complications of ulcer disease despite acid outputs being less than 10 mEq/hr [44]. Only when antisecretory medication is increased so that acid output is less than 5 mEq/hr, and in some cases less than 1 mEq/hr, does all mucosal disease heal and is recurrence prevented [44]. In some of these patients omeprazole is the only drug capable of healing the mucosa completely [44, 78]. The reasons for the increased sensitivity of the operated stomach to acid are not known, but it may be that acid output is consistently underestimated in these patients. Nevertheless, patients who have had a partial gastrectomy with a Billroth I or II anastomosis should have gastric acid outputs lowered to less than 5 mEq/hr and then endoscopy to check for mucosal healing. If the mucosa is not normal, the dose of antisecretory medication should be increased and the adequacy of the drug dose checked by repeat endoscopy [44].

Patients With Severe Esophageal Disease.—Esophageal symptoms occur in 33% to 61% of patients with ZES in different series [48, 78]. In one large series 42% of the patients with ZES had esophageal abnormalities at endoscopy, and 8% of patients with ZES had severe esophageal disease with stricture formation (Table 2) [48]. When these patients were given sufficient antisecretory medication to lower gastric acid output to less than 10 mEq/hr, the strictures healed in about half the patients and the need for repeated esophageal dilation declined markedly or was abolished (Fig. 4) [48]. However, the other 50% of patients with strictures continued to form strictures and required repeated dilations despite acid output being less than 10 mEq/hr [48]. When such patients are given sufficient medication to reduce acid output to less than 1 mEq/hr (which means prescribing omeprazole, as only high doses of histamine H₂-receptor antagonists are capable of reducing acid output to such levels), all these patients improved markedly, reducing their need for dilation from once every 2 to 4 weeks to once every 3 to 6 months (Fig. 4) [48]. These results demonstrate that esophageal disease can be difficult to treat in patients with ZES, and only with omeprazole can it be controlled in many patients.

Patients Requiring Surgery.—Many patients with ZES require surgery at some time, whether it be for exploratory laparotomy for tumor resection, a highly selective vagotomy, a parathyroidectomy (see below), or an incidental surgical procedure. These patients require

intravenous antisecretory medication during and after the procedure while they are unable to take oral medication. Prior to surgery all patients should be given a continuous intravenous infusion of cimetidine or ranitidine, and gastric acid output should be measured (Table 3; Fig. 2) [45, 51, 52]. For patients in whom the oral dose of histamine H₂-receptor antagonist that reduces acid output to less than 10 mEq/hr during the last hour before the next dose of drug is known, the approximate intravenous dose can be calculated by multiplying the total oral daily dose by 0.7 and administering that quantity of intravenous drug as a continuous infusion over 24 hours [51]. The adequacy of this dose, however, should be checked by measuring acid output after a few hours to ensure that the output is less than 10 mEq/hr. If acid output is more than 10 mEq/hr, the dose of drug should be increased. Acid output should be rechecked during the early postoperative period, as in some patients drug requirements increase after surgery [51].

It should be realized that relatively high doses of intravenous cimetidine or ranitidine are required by many patients (Fig. 2, top) [45, 51, 52]. The mean intravenous cimetidine dose required in one study [51] was 2.9 mg/kg/hr, but there was a wide range, from 0.5 to 7.0 mg/kg/hr. The minimal effective intravenous dose correlated closely with the previous oral dose of cimetidine ($r = 0.96$, $p < 0.001$), ranitidine, or famotidine ($r = 0.95$, $p < 0.001$) [51]. The regression equation of this correlation was intravenous cimetidine dose = 0.7 oral dose; therefore approximately 1.4 times the daily intravenous dose is required orally. In this study [51] patients were treated for up to 83 days with these intravenous doses without side effects or loss of efficacy. Another study demonstrated that a continuous intravenous infusion of ranitidine at 100% of the previously effective oral equivalent dose effectively controls gastric acid output in 95% of patients with ZES, thereby limiting the need for repeated dose adjustments and gastric output assessment in patients who require parenteral therapy [45].

Intravenous omeprazole is not licensed in most countries, although a recent study demonstrated that it may be useful in patients with ZES who require parenteral antisecretory agents such as at the time of surgery [46]. In this study [46] 60 mg of omeprazole given by intravenous bolus every 12 hours controlled gastric acid secretion in 19 of 20 patients with ZES; one patient required 100 mg every 12 hours (Fig. 2, bottom). No patient developed clinical, hematologic, or biochemical toxicity related to omeprazole even with treatment up to 15 days, and the drug remained effective [46]. Because of the ease of administration and its potency, intravenous omeprazole during surgery will likely become the drug of choice.

Patients Receiving Chemotherapy.—Patients with metastatic disease who require chemotherapy often develop chemotherapy-induced vomiting, which may interfere with the effectiveness of their antisecretory medication and lead to uncontrolled gastric acid output [82]. Such patients may require a continuous intravenous infusion of cimetidine or ranitidine to cover the period of vomiting. An alternative is for the patient to take oral omeprazole a few hours prior to beginning chemotherapy, which because of its long duration of action is able to control the acid hypersecretion during the period of vomiting.

Patients After Curative Gastrinoma Resection.—A recent large prospective study demonstrated that successful gastrinoma resection, defined as a normal fasting serum gastrin, negative provocative testing, and negative abdominal imaging, is possible in up to

50% of patients with sporadic ZES who undergo surgery [83]. Controversy exists regarding the chances for long-term cure, the selection of patients in whom to attempt curative resection, and the technicalities of the operation itself [16, 83–87]. These issues are beyond the scope of this review. The same study [83] demonstrated that long-term cure is possible in selected patients, and ongoing studies at the NIH suggest that 25% to 30% of patients remain cured 5 years after surgery.

At present controversy also exists regarding the need for antisecretory medication postoperatively in patients who appear to be cured surgically [52, 86–89], as it is unknown whether curative surgery also reverses the trophic effects of chronic hypergastrinemia. The trophic effects of chronic hypergastrinemia in patients with ZES include a markedly increased parietal cell mass [90, 91]; thus the reversal of the gastric trophic effect can be assessed by measuring the maximal acid secretory function in patients with ZES after curative resection. Gastric acid secretion and antisecretory drug requirements were recently analyzed in 20 patients who underwent curative gastrinoma resection (Fig. 5) [88]. After curative resection, the maximal acid output (MAO) level, a measure of parietal cell mass, decreased 50%, although it remained mildly elevated in 33% of patients at 3 to 6 months, 23% at 1 year, 45% at 2 years, and 0% at 3 and 4 years, respectively [88]. Although basal acid output decreased rapidly and stabilized within 6 months in all patients, more than 60% of patients remained low level gastric acid hypersecretors for up to 4 years after surgery (Fig. 5) [88]. The mean daily ranitidine dose markedly decreased in patients after curative resection (from 1500 mg/day preoperatively to 300 mg/day 1–4 years postoperatively). Forty percent of patients required no antisecretory drug, and 60% required small doses of antisecretory medication to effectively control gastric acid output (Fig. 5) [88]. It appears that the trophic effects of chronic hypergastrinemia on the gastric mucosa are reversed relatively rapidly after curative gastrinoma resection; but in a significant proportion of patients, mild basal gastric acid hypersecretion continues [88]. Patients who are apparently cured of ZES by surgical resection should therefore be carefully monitored and may require small doses of antisecretory medication, as guided by acid secretory studies [88].

Surgical Management of Gastric Acid Hypersecretion

Prior to the advent of histamine H₂-receptor antagonists, total gastrectomy was the only way to safely control gastric acid hypersecretion [1, 8, 9]. Even if a tumor was found at surgery and removed, surgeons were not confident leaving the stomach in place and thus performed a total gastrectomy [2, 10, 78]. Furthermore, any procedure less than a total gastrectomy led to increased mortality because of recurrent peptic ulceration [2, 10, 78]. Now that increasingly effective medical therapy is available, it is generally recommended that surgical management of acid hypersecretion be limited to a few special circumstances [15].

Highly Selective Vagotomy

In patients with ZES, highly selective vagotomy has been recommended [86]. In 22 patients with ZES, highly selective vagotomy produced a mean fall in basal acid output of 41%, and drug requirements were reduced by a mean of 38% [86], although no patient was able to stop medication completely. Highly selective vagotomy augmented the inhibitory effect of

histamine H₂-receptor antagonists on acid secretion. In all but one patient gastric acid hypersecretion was satisfactorily controlled with no more than 2.4 g of cimetidine per day [86]. On the basis of these results it seems that highly selective vagotomy could reduce the cost of medical therapy but cannot replace it. However, follow-up in this study was relatively short, 6 weeks to 6 years with a median of 2 years, and the long-term effects of a highly selective vagotomy are therefore difficult to assess. In addition, it has been suggested that highly selective vagotomy may make subsequent total gastrectomy more difficult and increase esophageal reflux [15]. Therefore it is currently recommended that this procedure not be used routinely [15] and be reserved for the occasional patient who at laparotomy has an unresectable tumor or no tumor but has a very high antisecretory drug requirement (i.e., >4.8 g of cimetidine per day) [12, 15].

Parathyroidectomy in Patients with MEN-I

In patients with MEN-I, hyperparathyroidism exacerbates the symptoms of gastric acid hypersecretion from ZES. Most studies, but not all, show that a successful parathyroidectomy can ameliorate the manifestations of ZES [93–96]. In a study of 10 patients with MEN-I who had hyperparathyroidism and ZES, fasting serum concentrations of gastrin, serum gastrin response to secretin provocation, basal and maximal gastric acid outputs, and drug requirements before and after parathyroidectomy were measured [93]. In the 9 patients who were rendered normocalcemic by surgery, basal acid output decreased in all 9; and in 4 patients it fell to less than 10 mEq/hr (Fig. 6, left). Serum gastrin concentrations also fell (Fig. 6, middle). The control of the hypercalcemia increased the sensitivity of acid secretion to the effects of histamine H₂-receptor antagonists such that a given dose of antisecretory medication became more effective (Fig. 6, right) [93]. In fact, after successful parathyroidectomy, 2 of the patients had no evidence of ZES, with normal fasting serum gastrin, a negative secretin provocative test, and acid output in the normal range. The 1 patient who remained hypercalcemic after surgery had no change in acid output, serum gastrin, or antisecretory drug requirement [93]. The results of this study suggest that in patients with MEN-I, hyperparathyroidism, and ZES, parathyroidectomy should be performed not only in those with symptomatic hypercalcemia but also in patients with high antisecretory drug requirements (i.e., >4.8 g cimetidine per day) [15, 84, 93]. Because patients with MEN-I have hyperplasia of all four parathyroids, if relatively rapid postoperative recurrence of hyperparathyroidism is to be avoided, these patients should have either a 3.5-gland parathyroidectomy, or all four glands should be removed and an implant placed in the forearm—even if at surgery only one gland is enlarged and the other three are of normal size [84].

Total Gastrectomy

Total gastrectomy should be reserved for those occasional patients who will not or cannot take oral medication [15, 50]. In the original studies where patients were frequently dehydrated and in electrolyte imbalance, the mortality with total gastrectomy was high (i.e., 15%) [10]. With the availability of histamine H₂-receptor antagonists, total gastrectomy in patients with ZES is now relatively safe. In 248 patients reported since 1980 overall operative mortality was 5.6%, and mortality after elective operations was 2.4% [97]. However, after total gastrectomy the degree of postoperative morbidity including weight

loss, strictures, inability to eat normal-sized meals, and cramping abdominal pain with nausea or vomiting is unclear. Whereas one study [97] reported no long-term morbidity, another reported that all 18 patients with ZES experienced one or several side effects including symptoms of esophageal reflux, early satiety, cramping, or diarrhea [28]. In 50% of the patients these side effects were moderate to severe, and in 3 patients (17% of the total series) additional complications developed including esophageal stenosis of the esophagogastric junction in 2 patients and severe, recurrent vomiting in 1 patient [28]. Thus the true morbidity associated with total gastrectomy may be significant and is probably underestimated in many series.

References

1. Zollinger RM, Ellison EH: Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. *Ann. Surg* 142:709, 1955 [PubMed: 13259432]
2. Ellison EH, Wilson SD: The Zollinger-Ellison syndrome: re-appraisal and evaluation of 260 registered cases. *Ann. Surg* 160:512, 1964 [PubMed: 14206854]
3. Gregory RA, Tracy HJ, French JM, Sircus W: Extraction of a gastrin-like substance from a pancreatic tumor in a case of Zollinger-Ellison syndrome. *Lancet* 1:1045, 1960 [PubMed: 13851712]
4. Gregory RA, Grossman MI, Tracy HJ, Bentley PH: Nature of the gastric secretagogue in Zollinger-Ellison tumors. *Lancet* 2:543, 1967 [PubMed: 4166897]
5. Gregory RA, Tracy HJ, Agarwal KL: Amino acid constitution of two gastrins isolated from Zollinger-Ellison tumor tissue. *Gut* 10:603, 1969 [PubMed: 5822140]
6. McGuigan JE, Trudeau WL: Immunochemical measurement of elevated levels of gastrin in the serum of patients with pancreatic tumors of the Zollinger-Ellison variety. *N. Engl. J. Med* 278:1308, 1968 [PubMed: 5648596]
7. Walsh JH, Grossman MI.: Gastrin. *N. Engl. J. Med* 292:1324, 1377, 1975 [PubMed: 236515]
8. Zollinger RM, Ellison EC, O'Dorisio TM, Sparks J: Thirty years experience with gastrinoma. *World J. Surg* 8:427, 1984 [PubMed: 6148806]
9. Zollinger RM, Ellison EC, Fabri PJ, Johnson J, Sparks J, Carey LC: Primary peptic ulceration of the jejunum associated with islet cell tumors: twenty-five year appraisal. *Ann. Surg* 192:422, 1980 [PubMed: 6251758]
10. Fox PS, Hofmann JW, Wilson SD, DeCosse JJ: Surgical management of the Zollinger-Ellison syndrome. *Surg. Clin. North Am* 54:395, 1974 [PubMed: 4361607]
11. Jensen RT, Gardner JD, Raufman JP, Pandol SJ, Doppman JL, Collen MJ: Zollinger-Ellison syndrome: NIH combined clinical staff conference (R.T. Jensen, moderator). *Ann. Intern. Med* 98:59, 1983 [PubMed: 6336642]
12. Jensen RT, Doppman JL, Gardner JD: Gastrinoma. In *The Pancreas: Biology, Pathobiology and Disease*, Go VLW, DiMagno EP, Gardner JD, Lebenthal E, Reber H, Scheele GA, editors, second edition. New York, Raven Press, 1993, pp. 931–978
13. Harmon JW, Norton JA, Collen MJ, et al.: Removal of gastrinoma for control of the Zollinger-Ellison syndrome. *Ann. Surg* 200:396, 1984 [PubMed: 6148919]
14. Stabile BE, Passaro E: Benign and malignant gastrinoma. *Am. J. Surg* 149:144, 1985 [PubMed: 2857072]
15. Wolfe MM, Jensen RT: Zollinger-Ellison syndrome. *N. Engl. J. Med* 317:1200, 1987 [PubMed: 3309661]
16. Jensen RT, Gardner JD: Zollinger-Ellison syndrome: clinical presentation, pathology, diagnosis and treatment. In *Peptic Ulcer and Other Acid-Related Diseases*, Dannenberg A, Zakim D, editors. New York, Spectrum, 1991, pp. 117–212
17. McCarthy DM: Report on the United States experience with cimetidine in Zollinger-Ellison syndrome and other hypersecretory states. *Gastroenterology* 74:453, 1978 [PubMed: 620913]

18. Collen MJ, Howard JM, McArthur KE, et al.: Comparison of ranitidine and cimetidine in the treatment of gastric hypersecretion. *Ann. Intern. Med* 100:52, 1984 [PubMed: 6318628]
19. Jensen RT: Basis for failure of cimetidine in patients with Zollinger-Ellison syndrome. *Dig. Dis. Sci* 29:363, 1984 [PubMed: 6705649]
20. Howard JM, Chremos AN, Collen MJ, et al.: Famotidine, a new potent long acting histamine H₂-receptor antagonist: comparison with cimetidine and ranitidine in the treatment of Zollinger-Ellison syndrome. *Gastroenterology* 88:1026, 1985 [PubMed: 2857672]
21. Vinayek R, Howard JM, Maton PN, et al.: Famotidine in the therapy of gastric hypersecretory states. *Am. J. Med* 81(Suppl. 4B):49, 1986
22. McCarthy DM, Olinger EJ, May RJ, Long BW, Gardner JD: H₂-histamine receptor blocking agents in the Zollinger-Ellison syndrome. *Ann. Intern. Med* 87:668, 1977 [PubMed: 22304]
23. Jensen RT, Collen MJ, McArthur KE, et al.: Comparison of the effectiveness of ranitidine and cimetidine in inhibiting acid secretion in patients with gastric hypersecretory states. *Am. J. Med* 77(Suppl. B):90, 1984
24. Stadil F, Stage JG: Cimetidine and the Zollinger-Ellison (Z-E) syndrome. In *Cimetidine: The Westminster Hospital Symposium*, Wastell C, Lance P, editors. London, Churchill Livingstone, 1978, pp. 91–104
25. Bonfils S, Mignon M, Gratten J: Cimetidine treatment of acute and chronic Zollinger-Ellison syndrome. *World J. Surg* 3:597, 1979 [PubMed: 516777]
26. Deveney CW, Stein S, Way LW: Cimetidine in the treatment of Zollinger-Ellison syndrome. *Am. J. Surg* 146: 116, 1983 [PubMed: 6869669]
27. Stabile BE, Ippoliti AF, Walsh JA, Passaro E Jr.: Failure of histamine H₂-receptor antagonist therapy in Zollinger-Ellison syndrome. *Am. J. Surg* 145:17, 1983 [PubMed: 6129812]
28. Malagelada JR, Edis AJ, Adson MA, Von Heerden JA, Go VLW: Medical and surgical options in the management of patients with gastrinoma. *Gastroenterology* 84:1524, 1983 [PubMed: 6840481]
29. Lamers CDHW, Lind T, Moberg S, Jansen JBMJ, Olbe L: Omeprazole in Zollinger-Ellison syndrome: effects of a single dose and of long term treatment in patients resistant to histamine H₂-receptor antagonists. *N. Engl. J. Med* 310:758, 1984 [PubMed: 6142418]
30. McArthur KE, Collen MJ, Maton PN, et al.: Omeprazole: effective convenient therapy for Zollinger-Ellison syndrome. *Gastroenterology* 88:939, 1985 [PubMed: 3972233]
31. Delchier JC, Soule JC, Mignon M, et al.: Effectiveness of omeprazole in seven patients with Zollinger-Ellison syndrome resistant to histamine H₂-receptor antagonists. *Dig. Dis. Sci* 31:693, 1986 [PubMed: 2873001]
32. Bardram L, Stadil F: Omeprazole in the Zollinger-Ellison syndrome. *Scand. J. Gastroenterol* 21:374, 1986 [PubMed: 3715402]
33. Lloyd-Davies KA, Rutgersson K, Solvell L: Omeprazole in Zollinger-Ellison syndrome: four-year international study. *Aliment. Pharmacol. Ther* 2: 13, 1988 [PubMed: 2979229]
34. Corleto J, Puoti M, Annibale B, et al.: Loss of efficacy of famotidine (FMT) in the control of gastric acid secretion in patients with Zollinger-Ellison syndrome (ZES) reversed by omeprazole [abstract]. *Gastroenterology* 94:A79, 1988
35. Hirschowitz BI, Denen J, Raufman JP, LaMont B, Berman R, Humphries T: A multicenter U.S. study of omeprazole treatment of Zollinger-Ellison syndrome [abstract]. *Gastroenterology* 94:A188, 1988
36. Maton PN, Vinayek R, Frucht H, et al.: Long term efficacy and safety of omeprazole in patients with Zollinger-Ellison syndrome: a prospective study. *Gastroenterology* 97:827, 1989 [PubMed: 2777040]
37. Lehy T, Mignon M, Cadiot G, et al.: Gastric endocrine cell behavior in Zollinger-Ellison patients upon long-term patient antsecretory treatment. *Gastroenterology* 96: 1029, 1989 [PubMed: 2925050]
38. Hochlaf S, Vatie J, Ruszniewski PH, Poiterin CH, Lewin MJM, Mignon M: Is lansoprazole as effective as omeprazole in patients with Zollinger-Ellison syndrome (ZES)? [abstract]. *Gastroenterology* 100:A84, 1991
39. Metz DC, Pisegna JR, Ringham GL, et al.: Prospective study of efficacy and safety of lansoprazole in Zollinger-Ellison syndrome. *Dig. Dis. Sci* 38:245, 1993 [PubMed: 8425437]

40. Jensen RT, Maton PN, Gardner JD: Current management of Zollinger-Ellison syndrome. *Drugs* 32: 188, 1986 [PubMed: 2874977]
41. Vallot T, Mignon M, Mazure R, Bonfils S: Evaluation of antisecretory drug therapy of Zollinger-Ellison syndrome (ZES) using 24-hour pH monitoring. *Dig. Dis. Sci* 28:577, 1983 [PubMed: 6305607]
42. Raufman JP, Collins SM, Pandol S, et al.: Reliability of symptoms in assessing control of gastric acid secretion in patients with Zollinger-Ellison syndrome. *Gastroenterology* 84: 108, 1983 [PubMed: 6128284]
43. Maton PN, Gardner JD, Jensen RT: Recent advances in the management of gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. *Med. Clin. North Am* 18:847, 1989
44. Maton PN, Frucht H, Vinayek R, Wank SA, Gardner JD, Jensen RT: Medical management of patients with Zollinger-Ellison syndrome who have had previous gastric surgery: a prospective study. *Gastroenterology* 94:294, 1988 [PubMed: 3335308]
45. Vinayek RV, Hahne WF, Euler A, Norton JA, Jensen RT: Parenteral control of gastric hypersecretion in patients with Zollinger-Ellison syndrome. *Dig. Dis. Sci* (in press)
46. Vinayek R, Frucht H, London JF, et al.: Intravenous omeprazole in patients with Zollinger-Ellison syndrome undergoing surgery. *Gastroenterology* 99:10, 1990 [PubMed: 1971604]
47. Frucht H, Maton P, Jensen RT: The use of omeprazole in patients with Zollinger-Ellison syndrome. *Dig. Dis. Sci* 36:394, 1991 [PubMed: 2007355]
48. Miller LS, Vinayek R, Frucht H, Gardner JD, Jensen RT, Maton PN: Reflux esophagitis in patients with Zollinger-Ellison syndrome. *Gastroenterology* 98: 341, 1990 [PubMed: 1967239]
49. Vinayek R, Frucht H, Chiang HCV, Maton PN, Gardner JD, Jensen RT: Zollinger-Ellison syndrome: recent advances in the management of the gastrinoma. *Gastroenterol. Clin. North Am* 19: 197, 1990 [PubMed: 2184129]
50. Bonfils S, Jensen RT, Malagelada J, Stadil F: Zollinger-Ellison syndrome management: a protocol for strategy. *Gastroenterol. Int* 2:9, 1989
51. Saeed ZA, Norton JA, Frank WO, et al.: Parenteral antisecretory drug therapy in patients with Zollinger-Ellison syndrome. *Gastroenterology* 96: 1393, 1989 [PubMed: 2565842]
52. Fraker D, Norton J, Saeed Z, Maton P, Gardner JD, Jensen RT: A prospective study of pre- and postoperative control of acid hypersecretion in patients with Zollinger-Ellison syndrome. *Surgery* 104: 1054, 1988 [PubMed: 2904182]
53. London J, Frucht H, Doppman JL, Maton PN, Gardner JD, Jensen RT: Zollinger-Ellison syndrome in the acute care setting. *J. Intens. Care Med* 4:272, 1989
54. Jensen RT, Gardner JD: Gastrinoma. In *Current Therapy in Gastroenterology and Liver Disease*, Bayless TM, editor. Philadelphia, B.C. Decker, 1986, p. 77
55. Jensen RT, Collen MJ, Allende HD, et al.: Cimetidine induced impotence and breast changes in patients with gastric hypersecretory states. *N. Engl. J. Med* 308:883, 1983 [PubMed: 6835285]
56. McArthur KE, Raufman JP, Seaman JJ, et al.: Cimetidine pharmacodynamics in patients with Zollinger-Ellison syndrome. *Gastroenterology* 93:69, 1987 [PubMed: 3582917]
57. Zemniak JA, Madura M, Adamonis AJ, Olinger EJ, Dreyer M, Schentag JJ: Failure of cimetidine in Zollinger-Ellison syndrome. *Dig. Dis. Sci* 28:976, 1983 [PubMed: 6628158]
58. Andersen BN, Larsen NE, Rune SJ, Worning H: Development of cimetidine resistance in Zollinger-Ellison syndrome. *Gut* 26: 1263, 1985 [PubMed: 4065699]
59. McCarthy DM, Hyman PE: Effect of isopropamide on response to oral cimetidine in patients with Zollinger-Ellison syndrome. *Dig. Dis. Sci* 27:353, 1982 [PubMed: 6121690]
60. Richardson CT, Walsh JH: The value of histamine H₂-receptor antagonists in management of patients with Zollinger-Ellison syndrome. *N. Engl. J. Med* 294:133, 1976 [PubMed: 616]
61. Clissold SP, Campoli-Richards DM: Omeprazole. *Drugs* 32:15, 1986
62. Fellenius E, Berglindh T, Sachs G, et al.: Substituted benzimidazoles inhibit acid secretion by blocking H⁺/K⁺ ATPase. *Nature* 290: 159, 1981 [PubMed: 6259537]
63. Ekman L, Hansson E, Havu N, Carlsson E, Lundberg C: Toxicological studies on omeprazole. *Scand. J. Gastroenterol* 20(Suppl. 108):53, 1985

64. Larson H, Carlsson E, Mattsson H, et al.: Plasma gastrin and gastric enterochromaffin cell activation and proliferation—studies with omeprazole and ranitidine in intact and antrectomized rats. *Gastroenterology* 90:391, 1986 [PubMed: 3510144]
65. Mattsson H, Ryberg B, Hakanson R, Lundell L, Sundler F: Correlation between plasma gastrin and gastric mucosa! ECL-cell density in rat after acid inhibition, partial fundectomy and gastrin-17 infusion, Presented at the International Symposium on Omeprazole in Monte Carlo, Monaco, Nov. 11–12, 1988
66. Mattsson H, Havu N, Brautigam J, Carlsson K, Lundell L, Carlsson E: Partial gastric corpectomy results in hypergastrinemia and development of gastric enterochromaffin-like cell carcinoids in the rat. *Gastroenterology* 100:311, 1991 [PubMed: 1985029]
67. Hakanson R, Sundler F: Mechanisms for the development of gastric carcinoids. *Digestion* 35(Suppl. 1):1, 1986
68. Maton PN, Lack EE, Collen MJ, et al.: The effect of Zollinger-Ellison syndrome and omeprazole therapy on gastric endocrine cells. *Gastroenterology* 99:943, 1990 [PubMed: 1697548]
69. D'Adda T, Corleto V, Pilato FP, et al.: Quantitative ultrastructure of endocrine cells of oxyntic mucosa in Zollinger-Ellison syndrome. *Gastroenterology* 99:17, 1990 [PubMed: 2344924]
70. Lamberts R, Creutzfeldt W, Stockmann F, Jacobaschke U, Maas S, Brunner G: Long term omeprazole treatment in man: effects on gastric endocrine cell populations. *Digestion* 39: 126, 1988 [PubMed: 3410169]
71. Helander H: Oxyntic mucosa histology in omeprazole treated patients suffering from duodenal ulcer or Zollinger-Ellison syndrome. *Digestion* 35(Suppl. 1):123, 1986 [PubMed: 3792669]
72. Bardram L, Thomsen P, Stadil F: Gastric endocrine cells in omeprazole treated and untreated patients with Zollinger-Ellison syndrome. *Digestion* 35(Suppl. 1):116, 1986 [PubMed: 3792668]
73. Solcia E, Capella C, Sessa G, Cornaggi M, Riva C, Villani L: Gastric carcinoid and related endocrine growths. *Digestion* 35(Suppl. 1):3, 1986 [PubMed: 3539679]
74. Solcia E, Bordi E, Creutzfeldt W, et al.: Histopathological classification of nonantral gastric endocrine growths in man. *Digestion* 41: 185, 1988 [PubMed: 3072229]
75. Camey JA, Go VLW, Fairbanks JF, Moore SB, Alport EC, Nora EE: The syndrome of gastric argyophil carcinoid tumors and nonantral gastric atrophy. *Ann. Intern. Med* 99:761, 1983 [PubMed: 6197001]
76. Goldfain D, LeBodic MF, Lavergne A, Gallan A, Modigliani R: Gastric carcinoid tumors in patients with Zollinger-Ellison syndrome on longterm omeprazole. *Lancet* 1:776, 1989
77. Kubo K, Oda K, Kaneko T, Satoh H, Nohara A: Synthesis of 2-[(4-fluoroalkoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazoles as antiulcer agents. *Chem. Pharm. Bull. (Tokyo)* 38:2853, 1990 [PubMed: 2076571]
78. Jensen RT, Maton PN: Zollinger-Ellison syndrome. In *The Stomach*, Gustavsson S, Kumar D, Graham DY, editors. London, Churchill-Livingstone, 1991, pp. 341–374
79. Ippoliti AF, Isenberg JI, Hagie L: The effect of oral and intravenous 16,16-dimethyl prostaglandin E2 in duodenal ulcer and Zollinger-Ellison syndrome. *Gastroenterology* 80:55, 1980
80. Ellison EC, O'Dorisio TM, Woltering EA, et al.: Suppression of gastrin and gastric acid secretion in the Zollinger-Ellison syndrome by long-acting somatostatin. *Scand. J. Gastroenterol* 21 :206, 1986
81. Klingsworth AN, Gould DA, Rodgers B: Pretreatment with octreotide as an adjuvant to surgical resection in patients with Zollinger-Ellison syndrome. *Br. J. Surg* 76:75, 1989 [PubMed: 2917265]
82. Von Schrenck T, Howard JM, Doppman JL, et al.: Prospective study of chemotherapy in patients with metastatic gastrinoma. *Gastroenterology* 94: 1326, 1988 [PubMed: 2966088]
83. Norton JA, Doppman JL, Jensen RT: Curative resection in Zollinger-Ellison syndrome: results of a ten year prospective study. *Ann. Surg* 215:8, 1992 [PubMed: 1531004]
84. Norton JA, Doppman JD, Jensen RT: Cancer of the endocrine system. In *Principles and Practice of Oncology*, 3rd ed., DeVita VT, Helman S, Rosenberg SA, editors. Philadelphia, Lippincott, 1989, pp. 1269–1344
85. McCarthy DM: The place of surgery in the Zollinger-Ellison syndrome. *N. Engl. J. Med* 302:1844, 1980

86. Richardson CT, Peters MN, Feldman M, et al.: Treatment of Zollinger-Ellison syndrome with exploratory Japarotomy, proximal gastric vagotomy, and H₂-receptor antagonists: a prospective study. *Gastroenterology* 89:357, 1985 [PubMed: 2861140]
87. Norton JA, Jensen RT: Unresolved surgical issues in the management of patients with Zollinger-Ellison syndrome. *World J. Surg* 15:151, 1990
88. Pisegna JR, Norton JA, Slimak GG, et al.: Effects of curative gastrinoma resection on gastric secretory function and antiseecretory drug requirements in patients with Zollinger-Ellison syndrome. *Gastroenterology* 102:767, 1992 [PubMed: 1537514]
89. Thompson NW: Discussion of paper by Fraker, D., Norton, J.A., Saeed, Z., Maton, P.N., Gardner, J.D., Jensen, R.T.: *Surgery* 104:1063, 1988
90. Polacek MA, Ellison EH: Parietal cell mass and gastric acid secretion in the Zollinger-Ellison syndrome. *Surgery* 60:606, 1966 [PubMed: 5913787]
91. Sum P, Perey BJ: Parietal cell mass (PCM) in a man with Zollinger-Ellison syndrome. *Can. J. Surg* 12:285, 1969 [PubMed: 5792941]
92. Feldman M: Gastric secretion. In *Gastrointestinal Disease*, 2nd ed., Sieisenger MH, Fordtran JS, editors. Philadelphia, Saunders, 1983, pp. 541–558
93. Norton JA, Cornelius MJ, Doppman JL, Maton PN, Gardner JD, Jensen RT: Effect of parathyroidectomy in patients with hyperparathyroidism and Zollinger-Ellison syndrome and multiple endocrine neoplasia type I: a prospective study. *Surgery* 102:958, 1987 [PubMed: 2891201]
94. Stevens MH, Thirlby MD, Richardson CT: Lack of effect of parathyroidectomy or calcium channel blockade on serum gastrin concentration and gastric acid secretion in a patient with hyperparathyroidism and Zollinger-Ellison syndrome. *Surgery* 101: 108, 1987 [PubMed: 3798319]
95. Gogel KH, Buckman MT, Cadieux T, McCarthy DM: Gastric secretion and hormonal interactions in multiple endocrine neoplasia type I. *Arch. Intern. Med* 145:855, 1985 [PubMed: 2859842]
96. McCarthy DM, Peikin SR, Lopatin RN: Hyperparathyroidism—a reversible cause of cimetidine-resistant gastric hypersecretion. *B.M.J* 1:765, 1979
97. Thompson JC, Lewis BG, Wiener I, Townsend CM: The role of surgery in the Zollinger-Ellison syndrome. *Ann. Surg* 197:594, 1983 [PubMed: 6847279]
98. Mignon M, Vallot T, Hervoir P, Benfredy P, Bonfils S: Ranitidine versus cimetidine in the management of Zollinger-Ellison syndrome. In *Ranitidine A.J. Riley, Salmon PR, editors. Amsterdam, Excerpta Medica*, 1982, pp. 169–177
99. Jensen RT, Metz DC, Koviack PD, Feigenbaum KM: Prospective study of the long-term efficacy and safety of lansoprazole in patients with the Zollinger-Ellison syndrome. *Aliment. Pharmacol. Ther* 7(Suppl. 1):41, 1993

Fig. 1.

Determination of the intravenous (top) and oral (bottom) antisecretory doses of histamine H₂-receptor antagonist required in two patients with ZES. **Top.** Acid secretory data from a typical patient with ZES demonstrating the method for determining the minimum intravenous cimetidine infusion dose to reduce gastric acid output to less than 10 mEq/hr, the accepted level of control (dotted line). Basal acid output (54 mEq/hr) was determined off all antisecretory medication. In this patient, cimetidine 1 mg/kg/hr IV was insufficient to reduce gastric acid output to less than 10 mEq/hr. Increasing the infusion rate to 2 mg/kg/hr was also insufficient. The minimum dose required to control gastric acid output was 3 mg/kg/hr. **Bottom.** Determination of the minimum 6-hourly dose requirement for famotidine, ranitidine, and cimetidine in a typical patient with ZES. The numbers at the top of the vertical bars indicate the dose of drug in grams per 6 hours. Gastric acid output was measured during the 6th hour after each indicated dose of drug. The dotted line represents an

output of 10 mEq/hr, the accepted level of control. In this patient the minimum 6-hourly oral dose required to control gastric acid output was 0.06 g of famotidine, 0.9 g of ranitidine, or 2.4 g of cimetidine. (**Top:** modified from ref. 51; **bottom** modified from ref. 20.)

Fig. 2. Effects of intravenous cimetidine (top) or omeprazole (bottom) on gastric acid secretion in patients with ZES. **Top:** Effect of continuous infusion of intravenous cimetidine on gastric acid secretion in 46 patients with ZES. Basal acid output was determined in all patients at a time when they were not taking any antisecretory medications. The minimum infusion dose to reduce acid output below 10 mEq/hr, the accepted level of control, in each patient is shown in parentheses. **Bottom:** Effect of an intravenous bolus dose of omeprazole on gastric acid secretion during the last hour before the next dose of drug in 20 patients with ZES. Basal acid output was determined on a previous occasion in all patients at a time when they were taking no antisecretory medications. The dotted line represents an acid output of 10 mEq/hr, the accepted level of control. (**Top:** modified from ref. 51; **bottom:** modified from ref. 46.)

Fig. 3.

Duration of action of oral histamine H_2 -receptor antagonists and omeprazole in patients with ZES. **Top:** Duration of action of equipotent doses of famotidine, ranitidine, and cimetidine in 5 patients with ZES. The minimum dose requirement for each drug to reduce gastric acid output to less than 10 mEq/hr during the 6th hour after administration was determined in each patient. Thereafter, gastric acid output was measured from the beginning of the 6th hour to the end of the 12th hour in each patient with each of the three equipotent doses for famotidine, ranitidine, and cimetidine. **Bottom:** Duration of action of omeprazole in 5 patients with ZES. The minimum dose requirement for omeprazole to reduce gastric acid output to less than 10 mEq/hr during the last hour before the next dose of drug was determined. Gastric acid output was measured every 8 hours after the last dose of omeprazole. The dotted line represents the mean BAO for the subjects being tested prior to

receiving these drugs. Results given are means from five determinations. Vertical bars represent 1 SEM. (**Top:** modified from ref. 20; **bottom:** modified from ref. 30.)

Fig. 4.

Effect of progressive reduction of acid output on gastroesophageal reflux disease (GERD) in 122 patients with ZES. Uncomplicated GERD is defined as symptoms of gastroesophageal reflux including dysphagia with or without endoscopic evidence of inflammation but without stricture formation. Complicated GERD is defined as the presence of esophageal stricture requiring dilation. **Left.** GERD was present in 74 patients (uncomplicated in 64 and complicated in 10) prior to reduction of acid to less than 10 mEq/hr. When acid output was reduced to less than 10 mEq/hr, GERD resolved completely in 54 patients (including 6 with complicated disease) but persisted in 20 patients (4 with complicated disease). **Middle.** When acid output was reduced further to less than 1 mEq/hr, in 13 of the 20 patients (including all 4 with complicated disease) who were uncontrolled with acid outputs of less than 10 mEq/hr, uncomplicated GERD resolved in all but 1 patient. Symptoms of GERD decreased in the four patients with strictures but the strictures remained. **Right.** Reduction of acid output to less than 1 mEq/hr in 4 patients with esophageal strictures reduced the required frequency of dilations from once every 2 to 4 weeks to once every 4 to 6 months. (Modified from ref. 48.) All strictures subsequently resolved with continued treatment.

Fig. 5.

Effects of curative gastrinoma resection on basal acid output and antisecretory drug requirement. **Top.** Basal acid output was measured before and up to 4 years after curative gastrinoma resection in 17 patients with ZES. Data for men ($n = 9$) and women ($n = 8$) are shown on the left and right, respectively. Data from 3 patients with previous partial gastrectomy are excluded. The dotted line represents the upper limit of normal for men (10 mEq/hr) [92] and women (5.6 mEq/hr) [92]. **Bottom.** Antisecretory dose requirements for control of gastric acid hypersecretion before and up to 4 years after curative gastrinoma resection. Control is defined as an acid output below 10 mEq/hr during the last hour before the next dose of drug [18, 36, 43] in patients without previous partial gastrectomy ($n = 15$) and below 5 mEq/hr during the last hour before the next dose of drug [44] in patients with previous partial gastrectomy ($n = 3$). The ranitidine equivalent dose is the amount of ranitidine or after converting from famotidine or cimetidine to ranitidine equivalent dose

[20] for each patient. Two patients taking omeprazole preoperatively are excluded. The numbers in parentheses indicate the number of patients followed postoperatively for the indicated time. Each dot represents a patient who was able to discontinue antisecretory medication at the time specified. (Modified from ref. 88.)

Fig. 6.

Effect of parathyroidectomy on basal acid output (left panel), fasting serum gastrin determination (middle panel) and antisecretory drug requirements (right panel) in patients with multiple endocrine neoplasia type 1 (MEN-I), hyperparathyroidism, and ZES. **Left.** Basal acid output before and after parathyroidectomy in 10 patients. Except for patient 4, all patients were normocalcemic after surgery. **Middle.** Fasting serum gastrin concentrations before and after parathyroidectomy in 10 patients. Except for patient 4, all patients were normocalcemic after surgery. The dotted line represents the upper limit of normal for fasting serum gastrin. **Right.** Antisecretory drug requirements in 2 patients before and after parathyroidectomy. Acid output in patient 1 was suppressed for 7 hours but not for 8 hours after 150 mg ranitidine preoperatively. Postoperatively, the same dose of ranitidine caused improved suppression of acid output that persisted for at least 8 hours. Patient 2 required 160 mg of famotidine preoperatively to cause a inhibition of acid output similar to that caused by 120 mg of famotidine postoperatively at 5 hours after the last dose was administered. (Modified from ref. 93.)

Table 1.

Success of long-term medical therapy for gastric acid hypersecretion in patients with ZES.

Antisecretory drug	No. of patients	Mean duration of treatment (mo)	Mean % failure	Year	Ref.
Histamine H ₂ -receptor antagonist					
Cimetidine	14	11	0	1978	24
	13	—	61	1979	25
	17	26	65	1983	26
Cimetidine + anticholinergic agent	61	12	8	1978	17
	20	33	50	1983	27
	18	29	6	1983	28
Ranitidine	15	18 ^b	40	1982	98
Ranitidine + anticholinergic agent ^a	19	14	0	1984	23
Famotidine + anticholinergic agent ^a	32	10	0	1985	20
H ⁺ /K ⁺ -ATPase inhibitor					
Omeprazole	7	14	0	1984	29
	11	1–9 ^c	0	1985	30
	11	15	2	1986	31
	9	2–27 ^c	0	1986	32
	80	19	7.5 ^d	1988	33
	9	6–16 ^c	0	1988	34
	31	0–18 ^c	3.2	1988	35
	40	29 ^e	0	1989	36
	10	21	0	1989	37
Lansoprazole	4	<1	0	1991	38
	20	18	0	1993	39

Modified with permission of the publisher [15].

^a rsopropamide, propantheline, or pirenzepine was used in a few patients.

^b Approximate duration of treatment.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

^cMean not determined, range given.

^dSix patients underwent total gastrectomy and were listed as having had drug failures, although secretion was reported to have been controlled before surgery.

^eMedian dose reported.

Table 2.

Causes of failure to control acid output medically and methods to prevent failure.

Failure to use established criteria of efficacy

1. Symptoms, 24 hour pH monitoring, and acid output during the last hour before the next dose of medication have been proposed [11, 12, 17, 28, 40, 41].
2. Symptoms alone are unreliable to assess control of acid output [12, 26, 27, 42].
3. Most widely accepted criterion is output <10 mEq/hr during the last hour before the next dose of medication [19, 26, 36, 43]. (<5 mEq/hr if previous gastric surgery [44].

Failure to use an adequate dose of antisecretory medication

1. Maximum dose arbitrarily set too low or failure to check adequacy of dose by established criteria.
2. Patients with ZES need higher doses than patients with idiopathic peptic disease.
 - a. *Parenteral therapy:* Histamine H₂-receptor antagonists are best given by continuous infusion [51]. Mean constant infusion requirement for cimetidine = 3.5 mg/kg/hr [51]. Range of requirements for ranitidine = 0.5–2.5 mg/kg/hr [45]. Omeprazole can be given by intermittent bolus dosing of 60–100 mg q12h [46].
 - b. *Oral maintenance therapy:* Mean daily requirement for cimetidine 3600 mg [20], ranitidine 1200 mg [20], famotidine 250 mg [20], and omeprazole 82 mg [36].
3. Patients with ZES need more frequent administration of antisecretory medication than patients with idiopathic peptic disease.
 - a. Oral histamine H₂-receptor antagonists are frequently needed every 4 to 6 hours [11, 12]. Histamine H₂-receptor antagonist dose requirements require upward adjustment about once a year [12, 36].
 - b. Omeprazole has to be given every 12 hours in approximately 25% of patients [47].

Failure to recognize patient noncompliance

1. Inconvenient to take multiple doses at frequent intervals.
2. High-dose antisecretory medication is expensive. With appropriate counseling, most patients with ZES are compliant with medications.

Failure to recognize special circumstances in which very high doses are required

1. *Severe reflux esophagitis:* Gastric acid output must often be maintained <1 mEq/hr [48]. Often it can be achieved only with omeprazole [48].
 2. *Previous gastric surgery:* Gastric acid output must be maintained <5 mEq/hr followed by repeat endoscopy to confirm healing of anastomotic lesions [44].
 3. *MEN-I syndrome with hyperparathyroidism:* In the presence of hypercalcemia, acid output fluctuates and very high doses of antisecretory medications are required [11]. Best to use omeprazole 60 mg q12h.
-

Table 3.

Current recommended methodology to control gastric acid secretion in ZES.

Acute symptoms
1. Put nasogastric tube in dependent part of fundus and attach to low, continuous suction.
2. Administer IV bolus of cimetidine 150 mg or ranitidine 100 mg. ^a
3. Start continuous infusion of IV cimetidine 3 mg/kg/hr or ranitidine 1 mg/kg/hr.
4. Check gastric acid output after 4 hours (pH alone is unhelpful). a. Collect four 15-minute samples of gastric secretions. b. Measure volume of each specimen (V ₁). c. Dilute 1 ml of each specimen in 20 ml distilled water. d. Titrate to pH 7.0 with 0.01 NaOH while continuously stirring and measure the volume required (V ₂). e. Calculate the number of mEq H ⁺ per sample: (V ₁ × V ₂)/100. f. Add number of mEq H ⁺ in four 15-minute samples = gastric acid output per hour (mEq/hr).
5. Increase the infusion rate by 1 mg/kg/hr increments for cimetidine (0.5 mg/kg/hr for ranitidine) every 4 hours until gastric acid output is <10 mEq/hr. ^b
6. Add an anticholinergic agent parenterally if large doses of histamine H ₂ -receptor antagonists (e.g., cimetidine 6 mg/kg/hr) are ineffective in controlling acid output. Alternatively, add oral omeprazole 60 mg together with oral antacids.
7. Begin oral drug when patient has resumed eating and check control after 6 hours. ^c
Long-term control
1. Start with oral cimetidine 300 mg q6h, ranitidine 150 mg q6h, famotidine 40 mg q6h, or omeprazole ^d 60 mg q24h.
2. Measure gastric acid secretion 1 hour before the next medication. Increase dose until acid secretion is <10 mEq/hr. ^b
3. If uncontrolled on high-dose cimetidine (900 mg q6h), ranitidine (600 mg q6h), or famotidine (60 mg q8h), switch to omeprazole. ^e
4. If omeprazole 120 mg q24h is ineffective, split the dose to 60 mg q12h.
5. If MEN-I syndrome with hyperparathyroidism is present, consider parathyroidectomy. ^e
6. If severe reflux esophagitis is present, reduce acid output below 1 mEq/hr. ^e

Modified from references 40 and 54.

^aIntermittent bolus doses of intravenous omeprazole (not available in United States) is also effective. Start with 60 mg q12h. Some patients require 100 mg q12h.

^bLess than 5 mEq/hr if the patient has had previous gastric surgery.

^cOral 24 hour cimetidine dose = total 24-hour IV cimetidine dose × 1.4. Give cimetidine every 6 hours.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Omeprazole is the drug of choice for oral control of gastric acid hypersecretion. Administer the first dose 1 to 2 hours after an IV bolus of cimetidine 150 mg.

Suggested starting dose for patients with complicated ZES is omeprazole 60 mg q12h.