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REVIEW ARTICLE

Appropriate Use of Intravenous Proton Pump Inhibitors in the Management of Bleeding Peptic Ulcer

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Rebleeding from peptic ulcers is a major unsolved problem in the management of acute upper gastrointestinal bleeding. Our goal was to review what is known and what remains to be learned about the effectiveness of antisecretory therapy for acute upper gastrointestinal bleeding. We reviewed the data regarding the effectiveness of endoscopic therapy, the prediction of those at increased risk for rebleeding, and the effectiveness of antisecretory drug therapy in preventing rebleeding with or without endoscopic hemostasis. Proton pump inhibitor therapy without endoscopic hemostasis is ineffective clinically for stopping bleeding or preventing rebleeding. Endoscopic hemostasis remains the cornerstone of therapy. The data are consistent with the notion that reliable maintenance of the intragastric pH at $\geq$6 after endoscopic hemostasis is associated with the lowest rebleeding rates. H_2-receptor antagonists are ineffective for achieving this goal. Intermittent bolus and oral administration of proton pump inhibitors are equivalent and fail to achieve this goal, which can only be accomplished by bolus administration of a proton pump inhibitor (e.g., 80 mg) followed by a constant infusion (e.g., 8 mg/hr). Whether the combination of endoscopic hemostasis and pH control is equal or superior to selected second-look endoscopy is unknown. A treatment algorithm is suggested.

KEY WORDS: peptic ulcer; hemorrhage; hemostasis; pH; proton pump inhibitor; H_2-receptor antagonists; second look; rebleeding; therapy; review.

Acute upper gastrointestinal bleeding continues to be a common problem. The management goals for acute bleeding peptic ulcers include resuscitation, identification of the bleeding site, cessation of active bleeding, and prevention of recurrence of the bleeding episode. Upper gastrointestinal endoscopy has become the standard of care in such cases, as it reliably establishes the etiology of bleeding and allows for active hemostatic therapy for any lesion identified. Although endoscopic hemostasis is successful in more than 90% of cases of bleeding peptic ulcer, rebleeding occurs within 72 hr in up to 25% of cases (1), such that rebleeding following successful hemostasis has become the major unsolved problem in the management of acute upper gastrointestinal bleeding. While there are a number of endoscopic markers useful to predict the risk of rebleeding (e.g., visible vessel), successful endoscopic treatment destroys the lesion and eliminates any risks associated with it (2). One approach after initial endoscopic hemostasis has been to attempt to focus therapy on those at increased risk of rebleeding. Scoring systems have been proposed so that high-risk patients may receive special care such as second-look endoscopy (3–5). However, while second-look endoscopy largely prevents clinically significant rebleeding, the practice is expensive and not completely without hazard (5). An alternate approach is to use pharmacologic methods to improve clot stability. For example, tranexamic acid and sucralfate have been

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shown in vitro to impair plasmin-mediated fibrinolysis by gastric juice (6). Acid and pepsin impair normal hemostasis and also directly promote clot breakdown. Detailed studies in vitro have shown that at a pH of <6 the extrinsic and intrinsic coagulation cascades are impaired, and platelet aggregation is virtually abolished (7). At low pH, acid-pepsin actually digests clots. Although the findings were obtained from studies in vitro, the overall clinical experience is consistent with the notion that better outcomes are associated with better pH control.

The purpose of this article is to review what is known and what remains to be learned about the effectiveness of antisecretory therapy for acute upper gastrointestinal bleeding, as well as to address common misconceptions regarding the effectiveness of current pharmacologic therapy.

THE CHALLENGE

Maintenance of the intragastric pH at ≥6 or greater requires almost-complete inhibition of acid secretion. Parietal cells secrete acid with a pH of <1 (i.e., at an H^+ concentration of 140 to 160 mmol/L). However, gastric juice represents a mixture of secretions including both parietal-cell and non-parietal-cell secretions. The factors responsible for the actual intragastric pH include the number of parietal cells present, the proportion actually secreting acid, and the amount of acid neutralized by non-parietal-cell alkaline secretion from the surface cells in the stomach, swallowed saliva, intestinal contents entering retrograde into the stomach, and, in those infected with *H. pylori*, the ammonia produced from the hydrolysis of urea.

pH is measured as a logarithmic scale such that each increase or decrease of 1 pH unit reflects a 10-fold change in acid concentration. As such, an intragastric pH of 5 represents an extremely low concentration of acid (i.e., H^+ concentration of 0.01 mmol/L). The fasting volume of intragastric fluid is typically 50 to 80 mL. It follows that only 3 μL of parietal cell secretion is required to drop the pH of 50 mL of basal gastric contents from 7 to 5, and only 30 μL of secretion would drop the pH from 7 to 4. In order to maintain an intragastric pH of ≥6 without the use of added alkali, essentially every parietal cell must be continuously inhibited. Maintenance of a pH ≥6 is even more difficult in the presence of food, the best physiologic stimulus of acid secretion by parietal cells. The fasting versus fed state and other factors such as sex, ethnicity, and underlying disease with high or low parietal-cell masses (e.g., duodenal or gastric ulcer, respectively) must be considered when one is viewing data concerning the relative effectiveness of acid suppression or the effects of a particular regimen on preventing rebleeding.

Histamine$_2$ (H_2)-Receptor Antagonists for Acid Suppression

H_2-receptor antagonists are not capable of completely inhibiting acid secretion even when given at a high dose by constant infusion, in part because H_2-receptor antagonists are subject to tolerance (defined as waning of effectiveness) (8). H_2-receptor antagonists have proven in clinical use to be unreliable in maintaining the intragastric pH at ≥6 for more than 24 hr, irrespective of the route of administration (9). A meta-analysis of the use of H_2-receptor antagonists in acute upper gastrointestinal bleeding suggested at most a modest benefit in reducing the rates of rebleeding, surgery, and death (10). This analysis was hampered by heterogeneity among trials with regard to patient population, doses of antisecretory drug, and outcome measures. One of the largest studies was a randomized, prospective trial of continuous intravenous famotidine (10-mg bolus followed by 3.2 mg/hr) given for 72 hr in 1005 patients with peptic ulcers bearing stigmata of bleeding (11). The study did not demonstrate a significant benefit of famotidine over placebo with regard to rebleeding, surgery, and death. Although endoscopic therapy was not rendered, intragastric pH was not monitored, and fasting–fed status of the patients was not mentioned, the authors concluded that gastric acid suppression alone was inadequate to manage acute peptic ulcer bleeding.

Proton Pump Inhibitors for Acid Suppression

Attention has shifted away from H_2-receptor antagonists and toward the use of proton pump inhibitors in the management of bleeding peptic ulcer. Proton pump inhibitors are not subject to tolerance (12–16). They inhibit acid secretion directly by covalently and irreversibly binding to the H^+/K^+ adenosine triphosphatase "proton pumps" present in the secretory canaliculi of parietal cells (17) and thus have the highest likelihood of maintaining the intragastric pH at ≥6 (16). Omeprazole has been available for some time in many countries in an intravenously administered form. An intravenous administrable form of pantoprazole has recently been introduced in the United States and become widely used, even to the point of producing a shortage of the drug for several months. Intravenous formulations of esomeprazole and lansoprazole are expected shortly.

The switch from intravenously administered H_2-receptor antagonists to proton pump inhibitors in the United States reflected dissatisfaction with the H_2-receptor antagonists, but it may also reflect marketing,

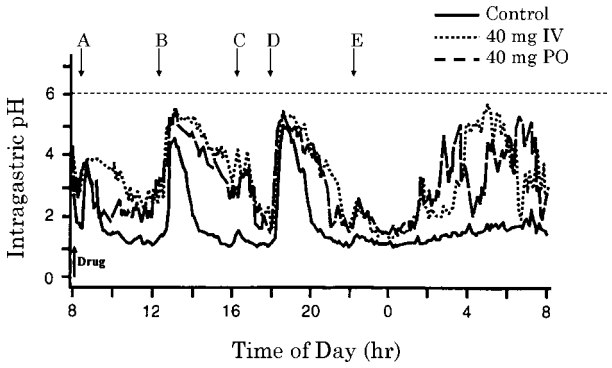

Fig 1. Comparison of orally and intravenously administered proton pump inhibitor (40 mg of pantoprazole) with placebo in 20 hrealthy volunteers. The median 24-hr pH profiles are shown. The times of (A) breakfast, (B) lunch, (C) tea, (D) dinner, and (E) snack. Adapted from Ref. 18 with permission.

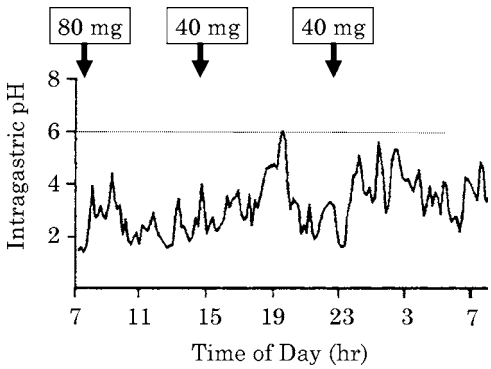

Fig 2. Median pH profiles after an initial bolus of 80 mg of pantoprazole followed by 40-mg boluses every 8 hr in six healthy volunteers showing that intermittent bolus administration of a proton pump inhibitor is ineffective in maintaining the pH in the ≥6 range. Adapted from Ref. 19 with permission.

which in turn may have led to some unrealistic expectations of the effectiveness of proton pump inhibitors in raising the intragastric pH. Because oral and intravenous intermittent boluses of a proton pump inhibitor have essentially identical effects with regard to pH control and duration of action, there is little to be gained in choosing the intravenous over the oral route of administration of routine doses (Figure 1) (18). The main advantage of the intravenously administered formulations is that the drug can reliably and safely be given to patients who cannot take medications by mouth. However, neither oral nor intravenous proton pump inhibitors given as intermittent bolus therapy (irrespective of the dose given) will reliably maintain the intragastric pH at ≥6. The problem is that the half-life of current proton pump inhibitors is short (ranging from 40 to 50 min), and the drug can inhibit only stimulated parietal cells. Unstimulated parietal cells, in which inactive proton pumps are present in smooth membrane vesicles of the cytoplasm and not in canalicular membranes, are thus "protected" from the drug and escape inhibition until after the drug has left the body. Complete inhibition of acid secretion therefore requires a steady state in which sufficient drug has accumulated in the secretory canaliculi to inactivate and deplete proton pump reserves as they are recruited to the canaliculi by a cascade of stimuli such as food, gastrin, and histamine. In addition, new proton pumps are constantly being synthesized and must also be inhibited. The implication is that at least in the first 24 hr of therapy intermittent boluses of proton pump inhibitors cannot provide sufficient drug to inhibit continuously regenerated proton pumps and suppress the minute amount of acid secretion required to drop the intragastric pH below 6 (19). Administration every 2 to 3 hr to overcome the short half-life would perhaps be effective but probably impractical clinically. The only reliable way to ensure near-complete, continuous suppression of acid secretion is to give a bolus injection followed by continuous intravenous infusion of proton pump inhibitor. A comparison of continuous intravenous omeprazole (80-mg loading dose, then 8 mg /hr), intermittent bolus intravenous omeprazole (80-mg bolus, then 40 mg every 6 hr), continuous intravenous ranitidine (50-mg loading dose, then 0.25 mg/kg per hour), or intermittent bolus intravenous ranitidine (100 mg every 6 hr) in healthy volunteers (13) showed that all regimens increased intragastric pH above 6 within an average of 60 min of initiation. However, continuous omeprazole infusion was superior to the other regimens with respect to the percentage of time above intragastric pH 6. This difference in effectiveness between continuous infusion and intermittent bolus injections was also shown with pantoprazole (19). When fasting volunteers received intermittent bolus injections of 40 mg every 8 hr, the intragastric pH was above 6 for only about 1% of the 48-hr period (Figure 2), compared to 84% with continuous infusion at 8 mg/hr after an 80-mg loading dose over 2 min (Figure 3A). Administering the 80-mg loading dose over 2 hr rather than 2 min was markedly less effective in maintaining the pH at 6 (Figure 3B). Overall, the results with omeprazole and pantoprazole have been similar in that reliable pH control has only been achieved with an intravenous bolus of 80 mg given over 2 min, followed by a continuous infusion of 8 mg/hr.

CLINICAL OUTCOMES WITH PROTON PUMP INHIBITORS IN BLEEDING PEPTIC ULCER

Theoretically, maintenance of the intragastric pH at ≥6 in patients with bleeding peptic ulcer should result in better

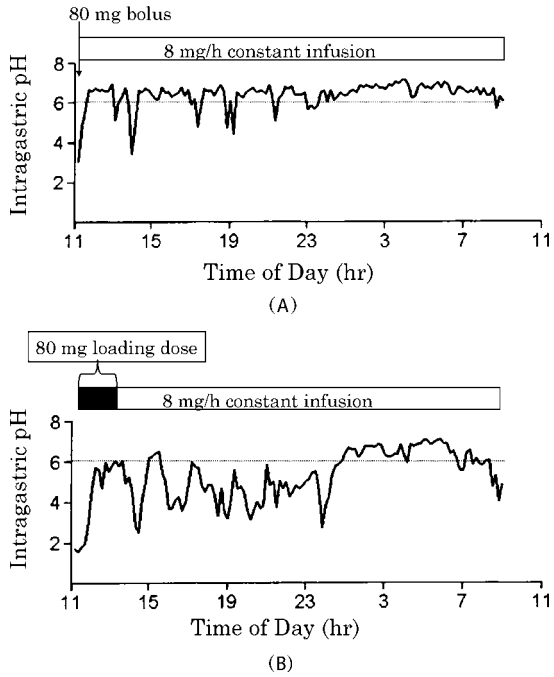

Fig 3. Median pH profiles in eight healthy subjects after receiving an intravenous infusion of 80 mg of pantoprazole followed by 8 mg/hr as a constant infusion. (A) The effect of administration of the 80-mg bolus over a 2-min period. (B) When the initial bolus was administered over 2 hrs, the overall effectiveness was markedly diminished. Adapted from Ref. 19 with permission.

clinical outcomes such as a reduction in the rate of rebleeding, surgery, or death. Prospective outcomes studies employing proton pump inhibitors have been variable with regard to the use of endoscopic therapy, route of administration (intravenous versus oral), and nature of the control group (placebo versus H_2-receptor antagonists), as well as the dose and frequency (intermittent bolus injections versus continuous infusion) of administration (Table 1). Not unexpectedly these studies have produced conflicting results, albeit for plausible reasons.

Comparison to Placebo Without Endoscopic Therapy

Khuroo *et al.* gave oral omeprazole at a dose of 40 mg twice daily for 5 days or placebo to 220 patients with endoscopically identified ulcers with stigmata of bleeding (20). No endoscopic therapy was rendered. Overall, the use of omeprazole significantly reduced the rate of continued bleeding or rebleeding (10.9%) compared to placebo (36%) ($P < 0.001$). Analysis of small subgrouPps showed that the reduction was statistically significant in those ulcers with visible vessels (omeprazole, 11.8% [2/17], versus placebo, 55.6% [10/18]; $P = 0.018$) or with adherent clots (omeprazole, 0% [0/64], versus placebo, 21.3% [13/61]; $P < 0.001$). There was no benefit among those ulcers with arterial spurting (omeprazole, 72.7% [9/12], versus placebo, 92.9% [13/14]; $P = 0.92$)

TABLE 1. SUMMARY OF STUDIES USING PROTON PUMP INHIBITORS IN BLEEDING ULCERS

Reference	N	*PPI*	*Dose*	*Route*	*Control*	*Endoscopic therapy*	*Rebleed rate*		P *value*
							PPI	*Control*	
					No endoscopic therapy				
20	220	Ome	40 mg/12 hr	po	Placebo	No	10.9%	36%	<0.001
21	503	Ome	80 mg + 40 mg/8hr*	iv	Placebo	Mostly no†	24%	27%	NS
22	322	Ome	80 mg + 8 mg/hr	iv	Placebo	Mostly no‡	3.1%§	2.5%§	NS
					Endoscopic therapy				
23	156	Ome	80 mg + 8 mg/hr	iv	PPI alone (iv)	Yes/no¶	1.1%	11.6%	0.009
24	88	Ome	40 mg + 40 mg/6hr	iv	None	Yes	4.8%	20%**	0.03
25	166	Ome	40 mg/12 hr	po	Placebo	Yes	7%	21%	0.02
26	149	Ome	20 mg/6 hr	po	Placebo	Yes	12%	26%	0.022
27	240	Ome	80 mg + 8 mg/hr	iv	Placebo	Yes	6.7%	22.5%	<0.001
28	265	Ome	80 mg + 8 mg/hr	iv	Placebo	Mostly yes††	7.1%§	12.4%§	NS
29	168	Pan	40 mg + 8 mg/hr	iv	Pan 40 mg/24 hr (iv)	Yes	13%	12%	NS
30	142	Ome	80 mg + 8 mg/hr	iv	Ome 20 mg/24 hr (iv)	Mostly yes‡‡	8.2%	11.6%	NS
					Vs HR_2-receptor antagonists				
16	100	Ome	40 mg + 6.7 mg/hr	iv	Cimetidine 300 mg + 50 mg/hr	Yes	4%	24%	0.004
32	51	Ome	80 mg + 40 mg/12 hr	iv	Ranitidine 50 mg/4 hr (iv)	No	21.4%	39.1%	NS
33	86	Ome	80 mg + 40 mg/8 hr	iv	Ranitidine 50 mg/6 hr (iv)	Yes	26%	24%	NS
34	232	Ome	80 mg + 40 mg/8 hr	iv	Ranitidine 0.125 mg/kg per hr (iv)	Yes	19.8%	17.5%	NS

Note. PPI, proton pump inhribitor; ome, omeprazole; pan, pantoprazole; HR_2, histamine$_2$; po, per os; iv, intravenous; NS, not significant.
*Forty milligrams every 12 hr after 24 hr.
†Fifteen underwent endsocopic therapy.
‡Twenty underwent endoscopic therapy.
§Days 4–21.
¶No endoscopic therapy in control group.
**"Control" refers to patients with intragastric pH <6 on omeprazole.
††One hundred ninety-two underwent endoscopic therapy.
‡‡One hundred two underwent endoscopic therapy.

or with oozing (omeprazole, 11.1% [2/18], versus placebo, 18.8% [3/16]; $P = 0.65$). A significant reduction in surgery was also achieved (7.3 versus 23.6%) ($P < 0.001$), but mortality was unchanged. Interestingly, the group reported that the oral twice-daily omeprazole regimen maintained intragastric pH between 5.9 and 7.2 in patients with duodenal ulcers who were not actively bleeding.

Daneshmend *et al.* studied intermittent bolus injection of intravenous omeprazole (80 mg initially, then three doses of 40 mg every 8 hr, followed by 40 mg every 12 hr, for a total of 4 days) compared to placebo in a large prospective study of 503 patients with bleeding peptic ulcer (21). Only 15 of the patients underwent endoscopic therapy involving injection therapy, electrocoagulation, or thermocoagulation. There was no significant beneficial effect from the use of intravenous omeprazole compared to placebo in reducing the rate of rebleeding (24 versus 27%, respectively; $P = 0.40$) or surgery (18.3 versus 19.5%; $P = 0.83$). The number of deaths in the intravenous omeprazole was higher than placebo (9.3 versus 5%, respectively; $P = 0.90$). Notably, inclusion criteria included both ulcers with stigmata suggestive of a high rebleeding risk (i.e., active spurting, oozing, nonbleeding visible vessel, or adherent clot) and low-risk lesions for which rebleeding was expected to be uncommon.

Hasselgren *et al.* reported 322 patients with bleeding peptic ulcers associated with high-risk stigmata (22). They gave continuous intravenous omeprazole at an 80-mg bolus followed by 8 mg/hr for 72 hr. Only 20 of the 322 patients received unspecified endoscopic therapy for actively spurting ulcers. There was an improvement in "overall outcome," defined as a composite endpoint weighted toward death, surgery, and necessity for endoscopic treatment, but no reduction in the rebleeding rate (3.1% with omeprazole versus 2.5% with placebo; $P = 0.97$). The rebleeding rate in the placebo group was uncommonly low, complicating interpretation of the study.

The Importance of Endoscopic Hemostasis

Sung *et al.* tested the hypothesis that endoscopic hemostasis would enhance any benefit obtained from the continuous infusion of an intravenous proton pump inhibitor in reducing rebleeding (23). They studied 156 patients with ulcers with nonbleeding visible vessels or adherent clots. Patients were randomized to endoscopic injection therapy and thermocoagulation together with intravenous omeprazole (80-mg bolus followed by 8 mg/hr for 72 hr) or intravenous omeprazole alone. Rebleeding occurred in 1.1% of those receiving combined therapy, compared to 11.6% of those receiving omeprazole alone ($P = 0.009$). While this study did not use a placebo, it suggested that intravenously administered proton pump inhibitor therapy with endoscopic hemostasis was likely superior to antisecretory drug therapy alone.

The Importance of Effective pH Control

Hsieh *et al.* assessed whether the incidence of peptic ulcer rebleeding is influenced by failure to maintain the intragastric pH at ≥ 6 (24). After endoscopic injection therapy, thermocoagulation, or electrocoagulation, 88 patients with ulcers with active bleeding or nonbleeding visible vessels were given a 40-mg bolus of intravenous omeprazole followed by 40 mg every 6 hr for 3 days. Intragastric pH was measured during the first 24 hr. At 3 days the rebleeding rate was significantly lower in the group whose mean intragastric pH was ≥ 6 (4.8%) than in the group whose mean pH was <6 (20%; $P = 0.03$).

Comparison to Placebo After Endoscopic Therapy

Javid *et al.* reported 166 patients with bleeding peptic ulcers receiving either 40 mg twice daily of omeprazole orally for 5 days or placebo (25). Endoscopic injection therapy was employed in all patients. They found a significant reduction in rebleeding rate with the use of omeprazole (7%) compared to placebo (21%; $P = 0.02$). The reduction in rebleeding was evident but not significant when ulcers were divided into small subgroups of bleeding stigmata, such as spurting (3 of 13 [23.1%] with omeprazole versus 8 of 13 [61.5%] with placebo [$P = 0.112$]), oozing (1 of 20 [5%] versus 2 of 21 [9.5%; P=1.0], or visible vessels (2 of 17 [11.8%] versus 4 of 20 [20%; $P = 0.667$]). Patients with ulcers with adherent clots did have a significant reduction in rebleeding from the use of omeprazole: 0 of 32 (0%) versus 4 of 30 (13.3%; $P = 0.05$). Kaviani *et al.* corroborated these findings using oral omeprazole (20 mg every 6 hr) compared to placebo in 149 patients with peptic ulcers with arterial spurting, oozing, or nonbleeding visible vessels after endoscopic injection therapy (26). They also reported a significant reduction in rebleeding rate: 12% with omeprazole versus 26% with placebo ($P = 0.022$).

Lau *et al.* studied 240 patients with bleeding peptic ulcers with high-risk stigmata, (i.e., spurting, oozing, or nonbleeding visible vessels) (27). All had endoscopic hemostasis with injection therapy and thermocoagulation. The patients who received continuous intravenous omeprazole (80-mg bolus followed by 8 mg/hr for 72 hr) had less rebleeding (6.7%) than those receiving placebo (22.5%; $P < 0.001$). There was also a trend toward a reduction in the rates of surgery and death. This study suggests that an intravenous proton pump inhibitor, at

continuous high doses during the 72-hr high-risk period of rebleeding, may reduce the risk of rebleeding among those who have had endoscopic hemostasis. In contrast, Schaffalitzky de Muckadell *et al.* reported 265 patients with bleeding peptic ulcers associated with high-risk stigmata receiving either a continuous intravenous dose of omeprazole (80-mg bolus followed by 8 mg/hr for 72 hr) or placebo (28). Of these patients, 192 received endoscopy therapy with injection therapy, electrocoagulation, or thermocoagulation. The reduction in rebleeding rate with the use of intravenous omeprazole versus placebo was not significant (7.1 versus 12.4%, respectively).

Despite the theoretical advantage of continuous infusion of a proton pump inhibitor and the experimental support provided by various outcomes studies, two others offer caution. Published in abstract form, one was a study of 168 patients who received endoscopic injection therapy and an intermittent bolus of intravenous pantoprazole 40 mg once daily for 3 days, compared to a continuous infusion of a 40-mg loading dose followed by 8 mg/hr for 3 days (29). The rebleeding rates were high: 12% using intermittent injection versus 13% using continuous infusion ($P = 0.90$). The second study evaluated 142 patients, 102 of whom underwent endoscopic injection therapy and/or thermocoagulation. Intravenous omeprazole at 20 mg once daily for 3 days was compared to a continuous infusion of an 80-mg bolus followed by 8 mg/hr for 3 days (30). The rebleeding rate was 8.2% with intermittent injection versus 11.6% with continuous infusion ($P = 0.70$).

Comparison of Proton Pump Inhibitors to H_2-Receptor Antagonists

A number of prospective, randomized, comparative trials have evaluated whether proton pump inhibitors are more effective than H_2-receptor antagonists in the management of bleeding peptic ulcer. The studies are heterogeneous with respect to sample sizes, doses, inclusion of actively bleeding ulcers, and application of endoscopic therapy. A meta-analysis conducted by Gisbert *et al.* involving 1239 patients demonstrated that proton pump inhibitors were significantly more effective than H_2-receptor antagonists in reducing rebleeding (6.7 versus 13.4%, respectively; $P < 0.001$) (31). There were no statistically significant differences in rates of surgery or death between the two classes of drugs. The advantage of proton pump inhibitors over H_2-receptor antagonists was more marked in patients with high-risk stigmata (spurting, oozing, or nonbleeding visible vessels) and those without adjunctive endoscopic therapy.

The dose of intravenous proton pump inhibitor used may be a particularly important variable in interpreting such comparison studies. Lin *et al.* studied 100 patients with bleeding peptic ulcers with high-risk stigmata (spurting, oozing, or nonbleeding visible vessel) (16). All had endoscopic hemostasis with electrocoagulation or thermocoagulation. Rebleeding occurred in 4% of patients who received a continuous infusion of intravenous omeprazole (40-mg bolus plus 6.7 mg/hr) compared to 24% who received intravenous cimetidine (300-mg bolus plus 50 mg/hr; $P = 0.004$). Rates of surgery and death were similar between the two groups. In contrast, Lanas *et al.* (32), Villanueva *et al.* (33), and Prassler *et al.* (34) all reported no significant difference in rebleeding rate between groups receiving intermittent boluses of intravenous omeprazole (80-mg bolus plus 40 mg every 8 or 12 hr) or intravenous ranitidine, whether intermittent (50 mg every 4 or 6 hr) or continuous infusion (0.125 mg/kg per hour).

DISCUSSION

The ideal therapy in the management of bleeding peptic ulcer would be one that promotes hemostasis and prevents recurrent bleeding. The relative roles served by pharmacologic and endoscopic therapies in achieving these goals continue to be refined. Before the results of different therapies can be compared, it is important to define what outcome must be achieved to declare the result acceptable. For the purposes of this discussion, we define a rebleeding rate of 5% or less as an acceptable outcome for therapy.

Endoscopy offers both diagnostic and therapeutic possibilities for the acute bleeding episode but is expensive and not without risk. Currently, the primary question is not whether to perform endoscopy but, rather, when. There is little argument regarding the need for early endoscopy in patients with persistent bleeding, as there are sufficient studies showing that endoscopic hemostasis is the most effective approach to the management of actively bleeding ulcers (35–37). However, by the time of hospitalization and institution of resuscitative measures, most patients have stopped bleeding. One question is whether antisecretory drugs can replace early endoscopy. This question can be reframed as whether antisecretory therapy alone can effectively treat patients with peptic ulcers in whom bleeding has stopped (e.g., those with nonbleeding visible vessels). The frequency of rebleeding from nonbleeding visible vessels in patients undergoing "standard medical therapy" (i.e., intravenous H_2-receptor antagonists and later oral proton pump inhibitors) ranges from 40 to 50%, with 95% confidence intervals from pooled data ranging from 27 to 52% (1, 36, 38). As previously mentioned, Khuroo *et al.* showed in a post hoc subgroup analysis that 40 mg of oral omeprazole twice daily alone reduced the rebleeding rate of ulcers with nonbleeding visible vessels to 11.8%

(20), which is comparable to the rebleeding rate of 17 to 19% achieved by endoscopy alone (39, 40). Grosso *et al.* directly compared the two therapies in 42 patients with nonbleeding visible vessels in peptic ulcers randomized to endoscopic injection therapy and standard medical therapy (which included intermittent intravenous ranitidine) or intravenous omeprazole (40 mg twice daily for 2 days) followed by oral omeprazole at 40 mg daily (40). The rebleeding rate at 48 hr was 19% in both groups. The study by Sung *et al.* included ulcers with nonbleeding visible vessels or adherent clots together and showed that combination therapy with endoscopic hemostasis and continuous intravenous omeprazole produced a lower, more acceptable rebleeding rate (1.1%) than intravenous omeprazole alone (11.6%) (23). We conclude that pharmacotherapy alone cannot replace endoscopic hemostasis for patients with actively bleeding ulcers or ulcers with nonbleeding visible vessels. The available data do not address whether rebleeding is delayed such that early endoscopy could be transformed into elective endoscopy.

Whether antisecretory drug therapy alone can eliminate rebleeding from ulcers with adherent clots remains unclear. The rebleeding rate of an ulcer with an adherent clot in patients undergoing standard medical therapy is high (i.e., in the range of 20 to 35%, with 95% confidence intervals for pooled data ranging from 20 to 39%) (1, 38). Khuroo *et al.* reported a rebleeding rate of zero with oral omeprazole alone (40 mg twice daily) (20), which is comparable to the 0 to 5% rebleeding rate achieved by endoscopic therapy alone (41, 42). It is important to note that the definition of an adherent clot is not standardized (42).

Endoscopy is currently the only diagnostic tool that can identify and characterize the source of acute upper gastrointestinal bleeding. Moreover, endoscopic therapy for peptic ulcers adds little risk to the endoscopic procedure itself. Therefore, we believe there is little justification for withholding endoscopic therapy for all high-risk lesions, including ulcers with active bleeding, nonbleeding visible vessels, and adherent clots. After endoscopic therapy, the ability of endoscopic appearance to predict the rebleeding rate is eliminated, and comparisons are no longer meaningful or useful.

The problem remains that while endoscopic therapy is effective in stopping bleeding and reducing the rate of rebleeding, rebleeding still occurs in up to 25% of cases. The primary issue then becomes how best to prevent rebleeding after endoscopic therapy. Clinical scoring systems have been introduced to separate those at low from those at high risk of rebleeding (3–5). Second-look endoscopy in the high-risk group can effectively reduce the rebleeding rate but is an expensive approach that is not free of risk, especially as patients with the highest rebleeding risk are often elderly and have comorbid diseases. Studies are needed to compare second-look endoscopy with effective antisecretory drug therapy in this high-risk group identified with a bleeding score such as the Baylor Bleeding Score (2–4). The safest, most cost-effective approach to the upper gastrointestinal bleeder is then likely to consist of endoscopy at the emergency center, endoscopic hemostasis for those with high-risk lesions, and the use of a risk-of-rebleeding score to triage those needing admission from those who could be managed at home. Intravenous proton pump inhibitor therapy would be continued for those requiring admission, especially if it could be demonstrated to be as effective as second-look endoscopy. Studies are also needed to determine whether starting effective antisecretory drug therapy at entry will allow early endoscopy to be put off and replaced by elective endoscopy. Finally, studies are also needed to ask whether combination pharmacotherapy can improve the effectiveness of intravenously administered proton pump inhibitors. As noted above, the hydrogen ion concentration at pH 5 is only 0.01 mmol/L, implying that regular administration of very small amounts of an antacid (e.g., sodium bicarbonate) would greatly enhance the ability to maintain the pH at or near neutral. Used alone, fibrinolytic inhibitors such as tranexamic acid have demonstrated modest reductions in the rates of rebleeding, surgery, and death in patients with upper gastrointestinal bleeding (43). While these agents might act in synergy with intravenous proton pump inhibitors to promote clot stability, they may pose unnecessary risk if appropriate control of pH alone proves effective. Importantly, an "effective" regimen should entail more than superiority to placebo or H_2-receptor antagonists. We suggest a "hard endpoint "based on rebleeding rates.

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