Misoprostol *Versus* Antacid Titration for Preventing Stress Ulcers in Postoperative Surgical ICU Patients

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Bleeding from gastroduodenal lesions is a potentially life-threatening complication in patients subjected to overwhelming physiologic stress. Titration of gastric contents with antacid was the first prophylactic treatment regimen proved to decrease the incidence of bleeding and remains the standard by which other methods are compared. We designed a prospective double-blind, double-placebo study comparing the effectiveness of antacid titration with fixed doses of a synthetic prostaglandin E_1 analog (misoprostol) for preventing stress gastritis and bleeding. To assess the success of each treatment regimen, we did endoscopic examinations before operation, 72 hours after operation, and after the patient had completed the study. A total of 281 patients entered the study (140 misoprostol, 141 antacid). The two groups were comparable with respect to preoperative parameters and type of operation. We found no statistically significant differences between the two treatment groups concerning upper gastrointestinal tract lesions or serious adverse effects. No clinically evident upper gastrointestinal hemorrhage occurred in either group. Mean gastric pH, measured at two-hour intervals during the initial 72 hours, was maintained at 4.0 or higher in both groups. We conclude that fixed-dose misoprostol is as effective as intensive antacid titration in preventing stress ulcers and bleeding in surgical ICU patients.

NEARLY ALL UNTREATED patients in intensive care units develop either endoscopically proved gastroduodenitis or stress ulcers unless prophylaxis is instituted.[1-3] Without preventive treatment, stress bleeding will occur in 6% to 25% of patients, and in this group the mortality rate approached 80%.[2] Respiratory failure, sepsis, trauma, heart failure, peritonitis, and renal failure are associated with higher rates of stress ulcers and bleeding.[2,4,5] Currently the most effective prophylaxis is hourly titration of gastric pH to approximately 4.0 with antacid.[6] While antacid treatment has proved efficacy, it is very labor intensive.

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An alternative to antacids are H-2 blockers; the best studied is cimetidine. However cimetidine may not be as effective as antacids for preventing stress-induced lesions and bleeding. Some reports claim that they are equally effective,[6] while others suggest that fixed-dose cimetidine does not consistently maintain gastric pH higher than 3.5.[7] Failure of cimetidine to control acidity in stressed surgical ICU patients ranges from 15% to 35% and is associated with upper gastrointestinal bleeding, especially in patients with high stress-severity indexes and sepsis.[7,8]

A new alternative to cimetidine and antacids is misoprostol, a prostaglandin E_1 analog that has cytoprotective properties and diminishes gastric acid secretion. It is thus potentially useful for preventing stress ulcers.[2,9] In animals it has been shown to protect the gastric mucosa against salicylate injury and ulcer formation.[10] In man misoprostol inhibits basal and stimulated gastric acid secretion and protects the gastric and duodenal mucosa against a variety of injurious substances.[11] We designed this study to compare the efficacy of misoprostol with antacid titration of gastric pH for preventing stress ulcers and bleeding in postoperative surgical ICU patients.

Materials and Methods

Fifteen physician-investigators at 16 university-associated medical centers enrolled 371 patients scheduled to undergo major surgical procedures. The patients were expected to require at least 48 hours of postoperative monitoring in an ICU. Subjects with additional risk factors

such as sepsis, trauma, electrolyte imbalance, diabetes, major burns, respiratory failure requiring ventilator assistance, congestive heart failure, arrhythmias requiring medication, or a need for steroids were included. Major exclusion criteria were active peptic ulcer disease, esophageal, gastric, or duodenal malignancies, esophageal varices, gastric outlet obstruction, acute renal failure, concurrent therapy with salicylates, nonsteroidal anti-inflammatory drugs, anti-ulcer therapy, or anti-neoplastic agents. The Institutional Review Board at each of the study sites approved the protocol. Each patient gave written informed consent.

Before randomization each patient underwent an endoscopic examination of the upper gastrointestinal tract to exclude pre-existing lesions. The appearance of the gastric and duodenal mucosa was rated according to a standard grading scale (Table 1). Endoscopic examinations were repeated after 72 hours of drug administration and at completion of the study.

Acceptable candidates were randomly assigned to each group and they received either tablets containing 200 mcg of misoprostol (Searle Inc., Skokie, IL) every four hours plus placebo liquid antacid every two hours, or placebo tablets every four hours plus magnesium-aluminum hydroxide liquid antacid (Maalox TC, Rohrer Pharmaceuticals, Fort Washington, PA) every two hours.

Tablets were dissolved in 20 mL of water and administered six times daily through a nasogastric tube, or were given orally if no tube was in place. Antacid or placebo liquid was administered every two hours at a dose of 10, 20, 40, or 80 mL, increasing the dose upward as necessary during the first 72 hours to maintain gastric pH at 4.0 or higher. Samples were aspirated through the nasogastric tube every two hours and gastric pH was measured using litmus paper. After 72 hours repeat endoscopic examinations were done and the liquid antacid or placebo was titrated downward to 20 mL every four hours. Study patients were treated for a maximum of 14 days or until they were able to take 1500 calories orally for at least one day. All patients entered into the protocol were evaluated for safety. Patients who met the following four criteria were evaluated for outcome: (1) completed at least three days in the study; (2) took at least 80% of the assigned medication; (3) did not withdraw from the study except for side effects of the medication; (4) had sufficient follow-up endoscopy information to permit outcome evaluation.

TABLE 1. *Endoscopic Evaluation of Gastroduodenal Mucosa*

Grade	Description
0	Normal Mucosa
1	Slight diffuse mucosal hyperemic changes
2	A single hemorrhagic lesion or one area of marked patchy erythema
3	2–5 hemorrhagic lesions
4	6–10 hemorrhagic lesions partially confluent or connected with areas of patchy erythema
5	Large area of confluent hemorrhagic lesions
6	Erosions with white bases surrounded by erythematous edges
7	Well-defined ulcer craters

Therapeutic success required absence of clinically evident upper gastrointestinal bleeding and satisfactory prevention of endoscopically proved gastrointestinal lesions during the treatment period. We defined clinically significant bleeding as hematemesis, melena, hematochezia, or red blood through the nasogastric tube that did not immediately clear after a 500-mL normal saline lavage; or a drop in hemoglobin of 2 g/% or more for which other causes of bleeding had been ruled out. The cause of any significant postoperative bleeding was investigated endoscopically.

Endoscopic scores were used in two ways to evaluate therapeutic success. In the first case, we used a strict criterion and defined successful prophylaxis as no increase from the initial preoperative endoscopic score. In the second case, we used a looser criterion and considered prophylaxis successful if the gastric or duodenal lesion score did not increase to 5 or more (erosions or ulcer craters).

Statistical Analysis

The results from all 16 study sites were pooled. The principal objective was to compare the efficacy of misoprostol and antacid in preventing peptic stress bleeding and ulcers in surgical ICU patients. Because this was a multicenter trial, the analysis tested for consistency of results among investigators using log-linear analysis with a model that included investigator, treatment group, outcome, and interactions factors. To assess whether the randomization was successful, the two treatment groups were compared with respect to sex, race, and age using the Pearson chi square test. Outcome assessment was based on gastrointestinal lesion scores or upper gastrointestinal bleeding and required that the patient complete the study. The ratio of patients satisfying the four criteria described above for successful prophylaxis were compared for both groups. In addition the ratio of patients in each group with initial endoscopic scores of 0 or 1 and follow-up scores of less than 2 (lesion prevention) or less than 5 (prevention of clinically significant lesions) was compared. These comparisons were made using Pearson's chi square test or Fisher's exact test. The distribution of initial lesion scores in both treatment groups was tested using a Wilcoxon two-sample test. The proportions of patients in the two treatment groups experiencing diarrhea were compared using log-linear analysis. Differences between the two groups with respect to laboratory values were compared using analysis of variance. The protocol was de-

signed to require a minimum of 270 fully evaluable patients to complete the study (135 in each group). This sample size is sufficient to detect differences of 20% or more between two treatment groups ($p = 0.05$; power = 0.90) with two-sided tests of significance. That is, this study size should detect a clinically significant difference between misoprostol and antacid that is greater than 20%.

Results

A total of 371 subjects were enrolled; 187 patients received misoprostol and 184 received antacids titrated to maintain gastric pH at or above 4.0. The study population included the following operative categories: trauma 72 (19.4%); emergency general surgery 95 (26.6%); elective general surgery 93 (25.1%); elective cardiothoracic surgery 10 (2.6%); elective vascular surgery 87 (23.5%); and renal transplant 14 (3.8%).

There were no statistical differences between the two treatment groups with respect to age, sex, or race (Table 2). They were also comparable in mean height, weight, and vital signs on admission, and these did not differ with respect to study site. Initial gastric lesion scores were 0 or 1 in 88% of the patients, and initial duodenal lesion scores were 0 or 1 in 96% of the patients, with no significant differences between the two treatment groups ($p = 0.141$ and 0.848, respectively).

All 371 patients were evaluated for safety of the prophylaxis regimen. Of these, 141 receiving misoprostol and 140 receiving antacid met the four criteria for evaluation of primary outcome.

TABLE 2. *Characteristics of Study Population*

Treatment Group	Misoprostol	Antacid	p value
Total number with complete information	187	181	
Age (years)			0.686*
<30	25	24	
30–39	13	17	
40–49	19	19	
50–59	38	46	
60–69	60	51	
>70	32	24	
Sex			0.638†
Male	152	153	
Female	35	24	
Race			0.146‡
Caucasian	100	99	
Negro	62	72	
Hispanic	18	8	
Other	7	4	

* Wilcoxon Rank-Sum.
† Chi square, 1 d.f.
‡ Chi square, 3 d.f.

TABLE 3. *Patients with Follow-up Endoscopic Scores Less than 2*

Treatment Group	Misoprostol*	Antacid*	p value†
72-hour gastric Endoscopy	56/147 (38.1%)	53/142 (37.3%)	0.892
72-hour duodenal Endoscopy	143/156 (91.7%)	150/159 (94.3%)	0.352
Final gastric Endoscopy	61/120 (50.8%)	63/123 (51.2%)	0.952
Final duodenal Endoscopy	117/124 (94.4%)	126/136 (92.6%)	0.578

* All enrolled patients with initial endoscopic scores of 0 or 1.
† Chi square comparison.

Evaluation of Efficacy

The proportion of patients satisfying the strict criteria of therapeutic success (no change in lesion score) was slightly higher in the antacid group (31.4% antacid *vs.* 26.2% misoprostol), but the difference was not statistically significant ($p = 0.337$). Using the looser criteria (mucosal scores remaining less than 5), the overall success rates were also similar (69.2% antacid *vs.* 70.5% misoprostol; $p = 0.820$). No clinically evident bleeding occurred among the patients of either treatment group. Comparable numbers of patients completed the 14 days of treatment or were released earlier, having met the dietary requirement. By the eighth day, only 16% of the misoprostol group and 21% of the antacid group remained in the ICU (p = ns). Total time of nasogastric medication administration was also somewhat shorter in the misoprostol group (655 patient days *vs.* 731 patient days in the antacid group), but again these differences were not statistically significant.

Follow-up lesion scores were compared for all patients enrolled in the two groups with initial endoscopic scores of 0 or 1 and follow-up scores of less than 2. Results for the 72-hour and final gastric follow-ups and for the 72-hour and final duodenal follow-ups were comparable between treatments, with no statistically significant differences (Table 3). When follow-up lesion scores of less than 5 were counted as successful prevention of clinically significant lesions (Table 4), the numbers and proportions of successes were greater in both treatment groups, but there were no statistically significant differences between groups. We repeated these analyses, stratifying by the number of risk factors present (all patients, 2 or more factors, 3 or more factors) to determine if there were subgroups in whom one of the treatments may have been more effective but we found no significant differences between the treatment groups.

Analysis of pH

The initial pH measurements were similar in the two groups. On the first postoperative day, pH was higher in

TABLE 4. *Patients with Follow-up Endoscopic Scores Less than 5*

Treatment Group	Misoprostol*	Antacid*	p value†
72-hour gastric Endoscopy	121/147 (82.3%)	115/142 (81.0%)	0.771
72-hour duodenal Endoscopy	153/156 (98.1%)	158/159 (99.4%)	0.305
Final gastric Endoscopy	108/120 (90.0%)	108/123 (87.8%)	0.586
Final duodenal Endoscopy	120/124 (96.8%)	134/136 (98.5%)	0.346

* All enrolled patients with initial endoscopic scores of 0 or 1.
† Chi-square comparison.

both groups, probably reflecting the stress and trauma of anesthesia and operations on acid secretion. Thereafter pH levels fell in both groups, but remained consistently higher in the antacid group. Mean pH levels in the misoprostol group were always at or above 4.0 (Fig. 1), reflecting the antisecretory properties of misoprostol in doses greater than 100 μg.[12] In both groups there were statistically significant inverse correlations between follow-up lesion scores and average pH levels in individual patients.

Safety

Fifteen patients in the misoprostol group and 13 in the antacid group died during the study or shortly thereafter due to underlying disease states or surgical complications. All deaths and serious complications were reviewed by the Institutional Review Boards of each respective medical center and none of these deaths were attributed to study medications.

The most common adverse event was diarrhea, defined as three or more watery stools within a 24-hour period, representing a clinically significant change from the patient's normal habits. We found this in 25.3% of the misoprostol group and in 22.8% of the antacid group, an insignificant difference ($p = 0.58$). This difference was similar to those found in other studies.[13] Statistically significant differences between the two groups were observed in some laboratory tests, namely serum bicarbonate and serum phosphorus levels. An average increase of 1.75 mEq/l in serum bicarbonate concentration occurred in the antacid treated group compared to a decline of 0.23 mEq/L in those treated with misoprostol. While this difference is statistically significant ($p = 0.001$) it is of questionable clinical significance. Of 163 patients treated with antacid, 33 (20%) developed final serum bicarbonate concentration elevated to 30 mEq/L. Among misoprostol recipients only 16 of 175 (9%) had similar elevations ($p = 0.004$).

Phosphorus concentrations fell 0.38 mg/dL in the antacid group, but rose by a similar amount in misoprostol recipients ($p = 0.003$). Of 132 patients treated with antacid, 32 (24%) developed final inorganic phosphorus concentrations of less than 2.5 mg/dL. Only 21 of 144 patients

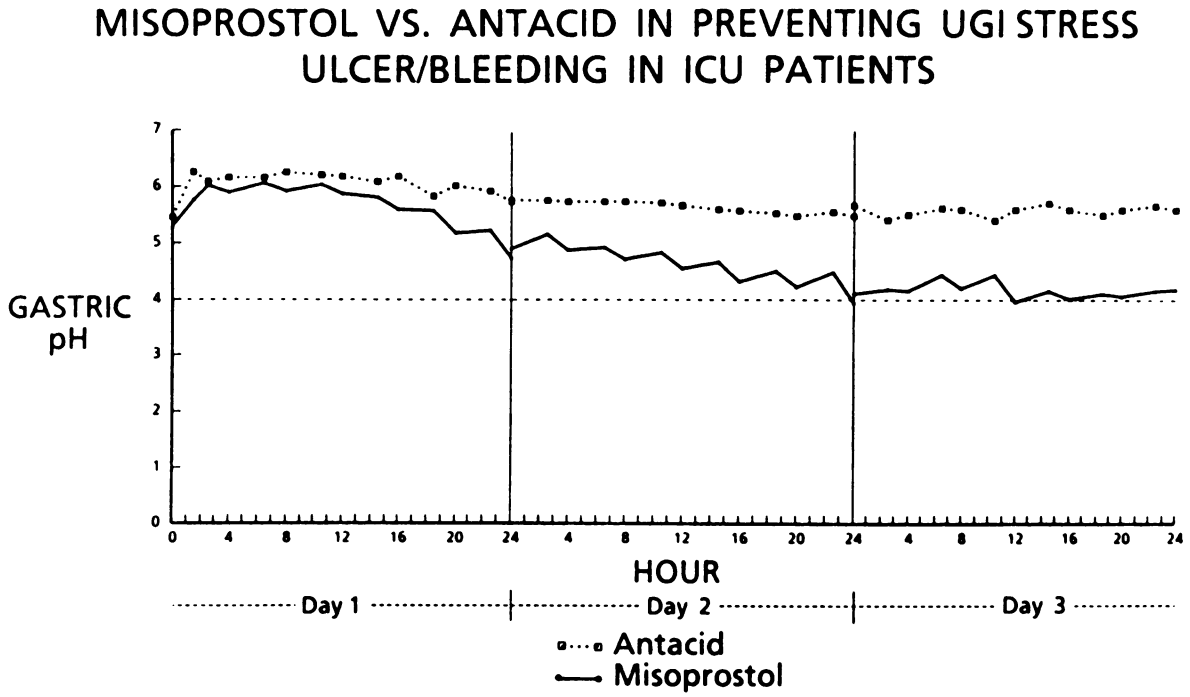

FIG. 1. Graph showing the pooled values for pH at 1-hour intervals. The gastric pH levels fell in both groups but were consistently higher in the antacid group. The average pH in both groups remained greater than 4.0.

(15%) in the misoprostol group had phosphorus levels of less than 2.5 ($p = 0.042$).

Discussion

Because acute gastrointestinal bleeding from stress ulceration can be life-threatening in postoperative ICU patients,[1–3] some form of preventive medication is usually given. Maintaining the gastric pH of 4.0 or greater by titrating with antacids is the most effective prevention of stress ulcer bleeding, although it is time-consuming.[5,8] In their prospective controlled trial of this regimen, Hastings et al.[14] reduced bleeding rates in ICU patients from 25% in a placebo group to 4% in a group receiving antacid.

A fixed-dose drug regimen that does not require pH monitoring and is as effective as antacid titration, would be an important advance in ICU care, allowing more efficient use of nursing staff. Initially H-2 blockers seemed promising. However several studies have shown that cimetidine is not as effective as antacid in preventing stress-induced bleeding and is most likely to fail in patients with multiple risk factors or sepsis.[7,8] The association between successful prophylaxis of stress bleeding by antacid and the maintenance of pH level at 4.0 or greater has been described repeatedly in the literature. In Hastings' study,[14] gastric pH in the antacid group stayed between 7.0 and 8.0, but in untreated controls it varied widely (from 1.0 to 8.0). Zinner et al.[8] found that antacids consistently kept the pH at 4.0 or greater, cimetidine was less reliable than antacids, and untreated patients had a mean pH value of 3.0. In a placebo-controlled trial of cimetidine for preventing upper gastrointestinal bleeding in medical ICU ventilator-dependent patients, mean pH during cimetidine treatment was 4.8, compared to 3.1 in patients give a placebo.[15] An explanation of the disparate results of studies of H-2 blockers is suggested by Martin et al.[7] and may reflect the incidence of sepsis in the various study populations. They found that cimetidine was most likely to fail to maintain gastric pH greater than 4.0 in patients with sepsis as a risk factor. However stratifying the groups with respect to the number of risk factors did not produce data supporting the use of either treatment in our study.

Mean pH levels were consistently higher in the antacid group, an expected result of periodic antacid titration. In the misoprostol group, the mean pH level was consistently greater than 4.0. This pH level can probably be attributed to the acid antisecretory effect of misoprostol in doses greater than 100 μg as were given in this study.[12,16]

A unique feature of this study was routine postoperative evaluation of the upper gastrointestinal tract by endoscopy. Previous prospective trials used bleeding as the dependent variable. However we did not believe that this variable was sensitive enough to determine the condition of the mucosa. We wanted to learn whether effective treatment prevents stress ulcers as well as decreases the rate of upper gastrointestinal tract bleeding. We found that misoprostol and antacid were equally effective in preventing upper gastrointestinal lesions, success being defined as no increase in gastric or duodenal lesion scores at 72 hours. Misoprostol had a success rate of 39.4% and the antacid success rate was 39.3% ($p = 0.991$), that is, approximately 60% of patients developed some increase in gastric lesion score, and the increases were equal in the two groups.

With respect to side effects, the two medications were similar. Both misoprostol and antacids have been reported to produce diarrhea. In this study both treatment groups experienced a similar incidence of diarrhea (misoprostol, 23%; antacid, 25%) in rates similar to previous trials.[13] There were statistically significant differences in some laboratory studies between the two groups that we believe were probably not clinically significant. Patients receiving antacids developed a significant increase in serum CO_2, while patients receiving misoprostol did not. The slight difference in serum CO_2 levels is probably not clinically significant, although in individual patients hypercarbia associated with metabolic alkalosis can impair the weaning of patients from ventilators. The decrease in serum phosphate levels seen in the antacid group could be due to binding of phosphate to antacid in the gastrointestinal tract.

Essentially we could find no important differences with respect to safety and efficacy between fixed-dose misoprostol and antacid titration of gastric acidity with a magnesium aluminum hydroxide antacid in a randomized group of 281 patients. Thus the appropriate choice of a drug for stress ulcer prophylaxis must rest on other factors such as price and convenience. To date no price has been determined for misoprostol. However it is probably fair to say that it will be more expensive than antacids. If fixed-dose misoprostol is to be compared with antacids for stress ulcer prophylaxis, the additional time and equipment required for nurses to titrate gastric acid to levels greater than 4.0 with antacids should also be considered. We expect that this cost is considerable.

We conclude that fixed-dose misoprostol and antacid titration are similarly effective in preventing clinically evident upper gastrointestinal tract hemorrhage and the development of endoscopically proved stress lesions. Although at this time the cost of treatment with misoprostol is not known, it will probably be more expensive than antacids. However misoprostol has advantages over antacid titration in ease of administration and should significantly reduce the amount of nursing time required for stress ulcer prophylaxis.

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