Evidence-based medicine as it applies to acid suppression in the hospitalized patient

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An evidence-based—medicine approach may be applied to studies in the medical literature to help physicians make sound judgments about efficacy and safety data and to improve clinical decision making. To assess the role of gastric acid suppression in the prevention of stress ulcer bleeding and in the management of upper gastrointestinal bleeding after successful hemostasis of bleeding peptic ulcer disease, the following questions should be addressed: Is it possible to identify risk factors for clinically important bleeding in critically ill patients? Can intravenous acid suppression prevent stress ulcer-related bleeding or prevent rebleeding in peptic ulcers after successful hemostasis? What is the most effective method of acid suppression for these disorders? An evidence-based—medicine review of published trials yields sufficient evidence to support the use of prophylactic acid suppression in critically ill patients with coagulopathy or in those who are receiving prolonged mechanical ventilation. Not enough data have accumulated to prove the superiority of intravenous proton pump inhibitors to intravenous histamine-2—receptor antagonists for prophylaxis of clinically important stress ulcer bleeding. With respect to acute gastrointestinal bleeding, however, two well-conducted trials indicate that an intravenous proton pump inhibitor is significantly more effective than an intravenous histamine-2—receptor antagonist or placebo in reducing the rate of rebleeding after hemostasis in patients with bleeding peptic ulcer. Analysis of the data from both trials shows that only five to six patients would need to receive an intravenous proton pump inhibitor to avoid one episode of rebleeding. (Crit Care Med 2002; 30[Suppl.]:S373–S378)

KEY WORDS: evidence-based medicine; randomized controlled trials; stress ulcer bleeding; peptic ulcer rebleeding; upper gastrointestinal bleeding; prevention; treatment; gastric acid suppression; intravenous; proton pump inhibitors; pantoprazole; histamine-2—receptor antagonists

The publication of an article, even in a prestigious peer-reviewed medical journal, does not mean necessarily that the trial results are meaningful or valid. Evidence-based medicine was developed to help physicians understand which criteria of design and execution should be present in a well-controlled clinical trial. Before accepting the results of a trial and applying the findings to clinical practice, it is important that the clinician evaluate the validity of a given trial’s methods and results. Evidence-based medicine is defined as the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients (1). “Conscientious use” implies that clinical research will be reviewed and applied to the management of patients. “Current best evidence from clinical research” means that the study design and results will be systematically appraised. “Judicious use” means that clinicians ultimately use their judgment to determine whether the research can be applied to an individual patient.

The magnitude of the treatment effect also can be estimated. The most commonly used measures to do this are relative risk reduction (RRR), absolute risk reduction (ARR), and the number of patients needed to treat (NNT) (2). The RRR compares the risk of a bad outcome in a treatment group with the risk of a bad outcome in a placebo group. Of more interest to patients is the ARR, the actual reduction in the risk of a bad outcome for an individual patient in the treatment group. Another important concept used to determine the clinical relevance of the reduced risk is the NNT, the number of patients who need to be treated to prevent one additional adverse outcome. The practical importance of using these statistical concepts will be explained more fully during an analysis of two clinical trials (3, 4) that evaluate the ability of intravenous proton pump inhibitor (PPI) therapy to prevent rebleeding in patients with bleeding peptic ulcer disease.

This article will demonstrate how evidence-based medicine can affect individual management decisions. Two clinical scenarios will be presented that illustrate the process of employing evidence-based medicine to make clinical decisions regarding acid suppression in hospital patients.

The first scenario concerns a hypothetical patient, a 75-yr-old man admitted to the coronary care unit after a myocardial infarction. His condition has gradually deteriorated, and he now requires vasopressor support and mechanical ventilation. The coronary care unit staff asks if the patient is at risk for significant gastrointestinal bleeding and whether he should be placed on a prophylactic regimen. Two key questions arise: 1) How can risk factors for clinically significant gastrointestinal hemorrhage in critically ill patients be identified? 2) What prophylactic strategies, if any, will reduce the likelihood of clinically significant gastrointestinal hemorrhage in such patients?

To obtain the best possible answers, the first step is to perform a MEDLINE search. The studies should be fairly recent; no data before 1989 was used in this search. Employing paired medical subject headings (MeSH) terms for key and text word searching, one should search for...
the following terms: hemorrhage (gastrointestinal) and critical care, hemorrhage (gastrointestinal) and clinical trials and critical care, hemorrhage (gastrointestinal) and clinical trials, hemorrhage (gastrointestinal) and risk factors and critical care. The desired study selection criteria include trials that are randomized and prospective with double-blinding, the population should be comprised of critically ill patients, the outcome should be gastrointestinal hemorrhage, the trials should have an adequate sample size, and the allocation of subjects into each study arm should be randomized. The MEDLINE search revealed that the most relevant study to answer question 1 (How can risk factors for gastrointestinal hemorrhage in critically ill patients be identified?) is a prospective, multicenter, cohort study by Cook et al. (5) involving 2252 patients at four university-affiliated, medical-surgical intensive care units. These authors determined risk factors associated with clinically important gastrointestinal bleeding and their prevalence in a heterogeneous group of critically ill patients. Subjects included in the trial were consecutive patients >16 yrs of age who had been admitted to medical-surgical intensive care units. Subjects were excluded if they had experienced gastrointestinal bleeding within 48 hrs after admission or within 24 hrs after admission to the hospital if they had had a previous total gastrectomy, facial trauma, or epistaxis; if they had experienced brain death or if they had a hopeless prognosis. The patients in the bleeding and nonbleeding groups were well matched according to age, gender, and Acute Physiology and Chronic Health Evaluation (APACHE) score.

Investigators encouraged the attending physicians in the medical-surgical intensive care units to avoid all stress ulcer prophylaxis, except in the cases of those patients with head injuries, burns on ≥30% of the body surface area, organ transplants, or an endoscopic or radiographic diagnosis of a peptic ulcer or gastritis within the previous 6 wks (5). Prophylaxis was defined as the administration of two or more doses of histamine-2–receptor antagonists (H2RAs), antacids, sucralfate, prostaglandin analogues, or a PPI. The first of two clinical end points was overt bleeding, defined as hematemesis, gross blood or coffee grounds in nasogastric aspirate, hematochezia, or melena. The second, more relevant outcome was clinically important bleeding, defined as overt bleeding complicated by any one of the following within 24 hrs: 1) a spontaneous decrease in systolic blood pressure of ≥20 mm Hg, 2) an increase in heart rate of ≥20 beats/min, 3) a decrease of ≥10 mm Hg of systolic blood pressure on sitting up, or 4) a decrease in the hemoglobin level of ≥2 g/dL, and 5) transfusion without an appropriate increase in hemoglobin level.

In evaluating the method of a study, it is imperative to establish that the end point criteria are applied objectively. In this trial, that goal was accomplished by appointing three blinded adjudicators. Disagreements were resolved by means of repeated review or by a fourth adjudicator. Of the 2252 patients enrolled in the study, 674 received prophylaxis for various reasons. The most common prophylaxis used was H2RA therapy. The investigators (5) found that 4.4% (100 patients) of the 2252 patients (95% confidence interval [CI], 3.6% to 5.6%) had overt bleeding. Of the 100 patients, 87 (87%) were receiving prophylaxis. Clinically important bleeding occurred in 33 (1.5%) of the 2252 patients (95% CI, 1.0% to 2.1%) and 23 (69.7%) of these 33 patients were receiving prophylactic therapy. Adjudicator agreement classifying bleeding as overt or clinically important was present 81% of the time after one review and 100% of the time after a second review.

Of the 33 patients who had clinically important bleeding (on the basis of an endoscopic or surgical diagnosis), potential bleeding sources were identified in 22. In some patients, more than one cause of bleeding was identified. Of the 31 identifiable potential sources of bleeding, 27 occurred in patients with gastric (n = 9) or duodenal (n = 7) ulcer and gastric (n = 8) or esophageal (n = 3) erosions (5).

On further analysis, the investigators were able to identify two independent risk factors predictive of clinically important bleeding (Table 1). Prolonged mechanical ventilation and coagulopathy were both associated with a higher prevalence of gastrointestinal bleeding in critically ill patients. Prolonged mechanical ventilation was associated with an odds ratio of 15.6 (p < 0.001), whereas the odds ratio for coagulopathy was 4.3 (p < 0.001). A total of 3.7% (31 of 847; 95% CI, 2.5% to 5.2%) of patients with either respiratory failure or coagulopathy developed clinically important bleeding. Only 0.1% (2 of 1405 patients; 95% CI, 0.002% to 0.5%) without respiratory failure or coagulopathy had clinically important bleeding.

Another MEDLINE search was undertaken to determine the best method of prophylaxis for gastrointestinal hemorrhage in high risk, critically ill patients. Because this search yielded >60 trials with discordant methods, results, and small sample sizes, it is difficult to reach a conclusion regarding the best prophylaxis. In such a situation, it may be useful to refine the search criteria for meta-analyses. This statistical method pools the results of multiple studies, which individually may have little significance, to increase their statistical power and thus to reach a conclusion regarding a particular clinical question. As with single trials of a diagnostic or therapeutic intervention, meta-analyses may be scrutinized via well-defined criteria, allowing the informed clinician to determine their validity and applicability (6).

A MEDLINE search for meta-analyses on prophylaxis dating back to 1989 yielded six articles (7–12). The most promising of these was by Cook et al (12). This study pooled the results of 57 randomized controlled trials, involving 7218 patients, in an attempt to resolve the conflicting results of previous studies. In this analysis, the ability of H2RAs to reduce the prevalence of overt and clinically important bleeding was compared with that of antacids or placebo. The pooled comparative data indicated that acid suppression with H2RAs provided a significant clinical benefit with regard to overt bleeding. However, the prevalence of overt bleeding has little clinical relevance (12). Far more relevant is the finding that the prevalence of clinically important bleeding in patients receiving H2RAs is significantly less than that in patients taking placebo or antacids. The pooled data shows that the prevalence of clinically important bleeding in patients given H2RAs has an odds ratio of 0.44 (95% CI, 0.212–0.88) vs. placebo or no therapy and an odds ratio of 0.86 (95% CI, 0.46–1.59) vs. antacids (Table 2). The findings of this study are promising. However, further meta-analyses are needed to validate this finding. In the meantime, the clinician may feel more comfortable utilizing H2RAs for prophylaxis in critically ill patients with a high risk of gastrointestinal bleeding.

Mechanical ventilation for >48 hrs
OR, 15.6 (p < 0.001)
Coagulopathy
OR, 4.3 (p < 0.001)

OR, odds ratio. Adapted with permission from Cook et al (5).

Table 1. Independent risk factors predictive of clinically important bleeding
meta-analysis (12), which uses an evidence-based approach, suggest that acid suppression with H2RAs reduces the likelihood of clinically important bleeding in the critical care setting by 50%.

It is clear from studies in patients with moderate to severe gastroesophageal reflux disease that the oral and intravenous PPIs are more potent acid suppressants than the H2RAs (13). Compared with the latter agents, PPIs raise the intragastric pH higher and maintain the elevated pH for longer periods of time (14–16). Although a search of the medical literature revealed no randomized, double-blind controlled studies of PPIs for stress ulcer prophylaxis, three studies were found that investigated use of a PPI in patients at risk for stress ulcer bleeding. Phillips et al. (17) and Lasky et al. (18) carried out open-label, prospective studies in 60 and 75 mechanically ventilated patients, respectively. In both of these trials, a simplified omeprazole suspension was administered through a nasogastric tube; all study subjects received two 40-mg doses 6 to 8 hrs apart for 1 day, followed by a single daily maintenance dose of 20 mg. The primary outcome measure was clinically significant gastrointestinal bleeding. Clinically significant bleeding did not occur in any omeprazole-treated patient in these two trials (17, 18). During these two trials, omeprazole increased the mean intragastric pH from 3.3 and 3.5 to 5.6 (17) and 6.7 (18), respectively. Although the data in these two trials suggest that omeprazole prevented clinically significant bleeding, the results must be interpreted with caution because of the lack of a comparison group, use of an open-label trial design, and the small sample size. Compared with the large study by Cook et al. (19) who found approximately a 3% rate of clinically important gastrointestinal bleeding among 1200 mechanically ventilated patients, it is not surprising that no bleeding was found in studies investigating <80 patients (17, 18).

The third trial was a prospective randomized trial (14) that compared the prophylactic efficacy of intravenous ranitidine with that of enteral omeprazole in 77 patients being mechanically ventilated. Intravenous ranitidine, 50 mg, was administered every 8 hrs; a 40-mg dose of omeprazole was administered orally once daily or by nasogastric tube if necessary (14). Eleven of the 35 patients (31%) who received ranitidine developed clinically important bleeding, as compared with only 2 of 32 (6%) who received omeprazole (p < .05). The ARR was 25%, favoring omeprazole (p < .05), and the NNT was 4. However, as in the two reports discussed above (17, 18), this study had several limitations. The sample size was small, and the study was not blinded. The final data analysis evaluated only 63 of the 77 patients who were enrolled in the study. A difference in the number of risk factors for stress ulcer bleeding may have contributed to the greater beneficial effect of the PPI on bleeding. Patients given ranitidine had 2.7 risk factors compared with 1.5 for patients treated with omeprazole. Another limitation was the high rate of clinically important bleeding occurring in patients given the H2RA; it was significantly higher than historical controls (12). A major problem with the three trials (14, 17, 18) was the use of a different definition of clinically important bleeding than that in the benchmark studies by Cook et al. (5, 19).

### APPLYING THE RESULTS

Prophylaxis with acid-suppressing medications such as H2RAs does not seem to be warranted in patients at low risk for clinically important bleeding (i.e., patients not receiving mechanical ventilation or without significant coagulopathy) because prophylaxis would need to be given to >900 such patients to prevent a single episode of bleeding. In contrast, prophylaxis with H2RAs in high-risk patients receiving prolonged mechanical ventilation or with significant coagulopathy would need to be given to only 30 patients to prevent one episode of bleeding. This suggests that prophylaxis with acid suppression is clinically meaningful, is a reasonable approach in high-risk patients, and should be used for the hypothetical patient in scenario 1, above.

**Scenario** 2: A 68-yr-old woman with a 1-day history of melena is admitted to the intensive care unit. An endoscopy reveals a 1-cm ulcer in the duodenal bulb with a visible vessel. The lesion is treated endoscopically with an epinephrine injection and bipolar electrocoagulation therapy. The intensive care unit staff asks what, if any, acid suppression should now be started on this patient. This scenario gives rise to two questions: 1) Does acid suppression prevent rebleeding in patients with peptic ulcer disease after endoscopic therapy? and 2) If the answer to the first question is affirmative, what is the best acid-suppressive regimen?

There has been a longstanding controversy as to whether acid suppression plays a role in limiting or preventing peptic ulcer bleeding. In 1985, Collins and Langman (20) examined the clinical benefits of H2RAs for the treatment of upper gastrointestinal hemorrhage. At the time of this study, H2RAs were widely used (as they are currently), despite the dearth of convincing supporting evidence. The investigators examined the data of 27 randomized trials involving >2500 patients treated with H2RAs. Because endoscopic data were not included, the study is not relevant to the hypothetical case presented earlier; nonetheless, the study suggested that H2RAs offered clinical benefit to patients with bleeding gastric ulcer disease. Despite this weak evidence and the failure of any well-designed trials to demonstrate the effectiveness of H2RAs in controlling acute bleeding (21), the findings of the Collins and Langman study were instrumental in establishing the convention of using intravenous H2RAs for upper gastrointestinal bleeding.

On the basis of the more complete acid suppression achieved with PPIs, it is reasonable to investigate the possible effectiveness of PPIs for peptic ulcer bleeding. A MEDLINE search from 1985 to the present revealed eight studies of acid suppression with PPIs for bleeding peptic ulcer disease (3, 4, 22–27) (Table 3). Only two of these eight PPI trials were applicable to the clinical scenario presented above (3, 4). Again, the evidence-based medicine criteria for a treatment trial stipulate that they ideally be randomized, double-blinded, placebo-controlled studies, with adequate numbers of subjects and follow-up, in addition to using concealed allocation and intention-to-treat analysis data reporting. With respect to current practice and the hypothetical scenario above, applicable studies should include initial endoscopic treatment for

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Table 2. Prevention of overt and clinically important bleeding by H2 receptor antagonists

<table>
<thead>
<tr>
<th>Overt bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs. placebo or no therapy: OR, 0.58</td>
</tr>
<tr>
<td>(95% CI, 0.42–0.79)</td>
</tr>
<tr>
<td>vs. antacids: OR, 0.56 (95% CI, 0.37–0.84)</td>
</tr>
</tbody>
</table>

**Clinically important bleeding**

| vs. placebo or no therapy: OR, 0.44 |
| (95% CI, 0.22–0.88) |
| vs. antacids: OR, 0.86 (95% CI, 0.46–1.59) |

OR, odds ratio; CI, confidence interval.

Adapted with permission from Cook et al (12).
bleeding peptic ulcer disease, followed by acid suppression therapy.

The study conducted by Lin et al. (3) included 100 patients who had bleeding peptic ulcer disease or high-risk ulcer lesions. Before acid suppression therapy was initiated, ulcer hemostasis was achieved by either heater-probe thermocoagulation or multipolar electrocoagulation (3). The primary outcome measure in this trial was endoscopically confirmed rebleeding at days 3 and 14 after endoscopic hemostasis (3). Rebleeding was defined as either the presence of blood in the stomach 24 hrs after endoscopic therapy or a fresh blood clot or bleeding in the ulcer base on repeat endoscopy.

Patients were assigned randomly to one of two regimens. Fifty patients received a bolus dose of intravenous omeprazole, 40 mg, followed by a 160-mg continuous infusion daily for 3 days; after this infusion, oral omeprazole, 20 mg, was administered once daily for 2 months. The other 50 patients received a 300-mg bolus intravenous cimetidine, followed by a 1200-mg continuous infusion daily for 3 days, and then oral cimetidine, 400 mg, twice daily for 2 months. The mean intragastric pH in the omeprazole group rose to 6.0 at 1 hr after the initial bolus was administered and remained approximately the same for the rest of the 24 hrs. In the cimetidine group, the pH rose to 4.0 at 1 hr and stayed at approximately 4.5–5.5 for the rest of the 24 hrs. By the third day of the study, no patient in the omeprazole group had experienced rebleeding, as compared with eight patients in the cimetidine group (p < 0.01). By the 14th day, 12 patients in the cimetidine group and two patients in the omeprazole group had rebled (24% vs. 4%, respectively, p < 0.01) (Table 4) (3). The length of hospital stay, number of procedures performed, and mortality rates of the two groups were not statistically different (3).

The study by Lau et al. (4) was a randomized, double-blind study of 240 patients with bleeding peptic ulcer disease. The method was similar to that of Lin et al. (3). In this trial, heater-probe thermocoagulation and epinephrine injection were used successfully in all study subjects to treat actively bleeding or high-risk lesions. Subjects were then randomized to receive either placebo infusion for 3 days, followed by oral omeprazole, 20 mg/day for 2 months, or an 80-mg intravenous bolus of omeprazole, followed by 8 mg/hr continuous infusion for 3 days, and then 20-mg oral omeprazole for 2 months.

Five of 120 patients (4.2%) in the omeprazole group and 24 of 120 (20%) in the placebo group rebled within the first 3 days (p < .001). After 1 wk, 7 of 120 (5.8%) patients in the omeprazole group had rebled, as compared with 26 of 120 (21.7%) patients in the placebo group (p < .001) (Table 5) (4). Thus, the probability of not rebleeding 1 wk after endoscopic hemostasis in patients treated with intravenous omeprazole was 94.2%, as compared with 78.3% of patients receiving placebo (4). The benefit yielded by PPI administration was consistent both for actively bleeding ulcers and for those with a nonbleeding visible vessel. Statistically significant differences also were observed between the omeprazole and placebo groups in the number of days spent in the hospital (4 vs. 5 days, p < .006) and in the number of units of transfused blood required (2.7 vs. 3.5 units, p < .04). However, no statistically significant differences were noted between these two groups regarding the need for surgery or the mortality rate within 30 days.

Critical examination of these two trials reveals that they meet most established validity criteria. Both were randomized, used concealed allocation, reported an intention to treat analysis, and achieved excellent rates of patient follow-up (Table 6). Lau et al. (4) was a double-blind trial, but the Lin et al. trial (3) was not. Thus, it seems that on the basis of a critical appraisal of the clinical care literature, the most appropriate course of action for the patient in scenario 2 would be initiation of an intravenous PPI for 72 hrs, followed by 2 months of oral PPI maintenance therapy.

Table 3. Acid suppression with proton pump inhibitors (PPIs) for treatment of upper gastrointestinal bleeding: MEDLINE search results

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Omeprazole (n = 50)</th>
<th>Cimetidine (n = 50)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding at day 3</td>
<td>0</td>
<td>8 (16%)</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>Rebleeding at day 14</td>
<td>2 (4%)</td>
<td>12 (24%)</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

Adapted with permission from Lin et al (3).

Table 4. Comparative effects of a proton pump inhibitor and a H₂ receptor antagonist to prevent peptic ulcer rebleeding after successful endoscopic hemostasis of the initial bleed

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Omeprazole (n = 50)</th>
<th>Cimetidine (n = 50)</th>
<th>p Value</th>
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Determination of Risk in Evidence-Based Medicine: Is the Level of Risk Reduction Clinically Meaningful?

The RRR can be impressively high even when a bad outcome is extremely uncommon. Conversely, the ARR considers the baseline risk of a bad outcome and offers an estimate of the actual risk reduction for an individual patient in the treatment group (2). Determination of the NNT provides information regarding the practical value of an intervention. For example, an NNT of 300 for a specific therapy may reduce the likelihood that a physician would use that intervention in a patient because 300 patients would need to be treated to prevent a single additional adverse outcome. Thus, NNT ultimately becomes a value judgment on the basis of the potential benefits, harms, and costs.

The data in the trials by Lin et al. (3) and Lau et al. (4) may be analyzed to determine the RRR, ARR, and NNT. As previously stated, at day 14 of the Lin et al. (3) trial, endoscopically confirmed rebleeding occurred in fewer patients who had received intravenous omeprazole.
21.7% of patients who had received placebo (5.8% in the PPI group compared with an intravenous H2RA). Moreover, the PPI treatment with an intravenous PPI seems to have a similar ability to raise gastric acid above 6 on an almost continuous basis for 24 hrs and maintain effective clotting (28).

Table 5. Effect of omeprazole on rebleeding of peptic ulcer after hemostasis

<table>
<thead>
<tr>
<th>Outcome: Omeprazole</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent Bleeding</td>
<td>Group</td>
<td>Group</td>
<td></td>
</tr>
<tr>
<td>By day 3</td>
<td>(n = 120)</td>
<td>(n = 120)</td>
<td></td>
</tr>
<tr>
<td>By day 7</td>
<td>24 (20)</td>
<td>26 (21.7)</td>
<td>3.71 (1.68-8.23)</td>
</tr>
<tr>
<td>By day 30</td>
<td>27* (22.5)</td>
<td>3.38 (1.60-7.13)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

CI, confidence interval. Adapted with permission from Lau et al. (4).

*Total number of patients in the treatment or placebo group who had recurrent bleeding within 30 days after treatment.

Table 6. Comparison of evidence-based trial methods

<table>
<thead>
<tr>
<th>Lin et al. (3)</th>
<th>Lau et al. (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized:</td>
<td>Randomized:</td>
</tr>
<tr>
<td>Concealed allocation: Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Double blinded: No</td>
<td>Yes</td>
</tr>
<tr>
<td>ITT analysis: Yes</td>
<td>ITT analysis: Yes</td>
</tr>
<tr>
<td>Patient follow-up: 100%</td>
<td>Patient follow-up: 97.5%</td>
</tr>
</tbody>
</table>

ITT, intention to treat.

than in those who were treated with intravenous cimetidine (4%) vs. 24%, respectively, p < .01). Similarly, at day 7 in the Lau et al. trial (4), endoscopically confirmed rebleeding was observed in 5.8% in the PPI group compared with 21.7% of patients who had received placebo (p < .001). The RRR calculated in the trial by Lin et al. (3) was 83%; for the trial by Lau et al. (4), the RRR was 73% (Table 7). The ARR for each trial were 20% and 16%, and the NNTs were 5 and 6 patients, respectively. Thus, a physician can tell a patient that after successful endoscopic hemostasis, further treatment with an intravenous PPI seems to reduce the risk of recurrent bleeding between 73% and 83% when compared with a similar patient given either nothing or an intravenous H2RA. Moreover, the PPI would reduce that individual patient’s risk by 16% to 20%. NNT calculations indicate that for every 5 or 6 patients who fit the enrollment criteria in these trials, the use of an intravenous PPI will prevent one additional case of recurrent bleeding.

It is important for physicians to understand that the efficacy of a treatment in a given trial does not predict its usefulness to every single patient being treated for that particular disorder. Practitioners must determine whether they can apply these data to their individual patients. Other considerations in specific patients may argue for or against the use of the treatment in question (2).

Table 7. Comparison of relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT)

<table>
<thead>
<tr>
<th>Lin et al. (3)</th>
<th>Lau et al. (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRR = 83%</td>
<td>RRR = 70%</td>
</tr>
<tr>
<td>ARR = 20%</td>
<td>ARR = 15.8%</td>
</tr>
<tr>
<td>NNT = 5</td>
<td>NNT = 6.5</td>
</tr>
</tbody>
</table>

It is worth asking whether perhaps intravenous PPIs are more effective in Asians (3, 4) than they are in Europeans or in North Americans. For example, it is possible that Asians may produce less gastric acid than do white people (4). If so, white Europeans and North Americans who are treated with an intravenous PPI may not be able to maintain gastric pH above 6 on an almost continuous basis for 24 hrs and maintain effective clotting (28). Practitioners must judge for themselves if they can generalize data from Asian patients (3, 4) to white patients in North America or Europe. Moreover, these studies were done with intravenous omeprazole; would the results be the same with intravenous pantoprazole? Because both these PPIs have a similar ability to raise and to maintain intragastric pH (29, 30), it is highly likely that intravenous pantoprazole may be at least as effective as intravenous omeprazole in a similar patient population.

The results of two well-designed trials demonstrate that as compared with a placebo or cimetidine, an intravenous proton pump inhibitor can significantly reduce rebleeding from peptic ulcer disease after hemostasis.

CONCLUSION

Before applying the results of a medical trial to their practice, physicians should determine whether the trial meets established criteria for a well-conducted study. An evidence-based–medicine approach can be used to analyze published trials that have examined risk factors for clinically important bleeding, the benefits of intravenous acid suppression for the prophylaxis of clinically important stress ulcer bleeding, and the prevention of peptic ulcer rebleeding after endoscopic hemostasis. The analysis confirms the validity of a major trial that identifies mechanical ventilation and coagulopathy as major risk factors for stress ulceration and recommends limiting prophylaxis to patients with at least one of these two complications. A well-conducted meta-analysis of trials examining the role of acid suppression prophylaxis for stress ulcer gastrointestinal bleeding found that acid suppression with H2RAs significantly reduces the likelihood of clinically important bleeding in the critical care setting. Evidence regarding the use of PPIs for this indication is scarce, although extensive data indicates that acid suppression with PPIs is significantly greater than that achieved with H2RAs. The results of two well-designed trials demonstrate that as compared with a placebo or cimetidine, an intravenous PPI can significantly reduce rebleeding from peptic ulcer disease after hemostasis.

REFERENCES

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