EDITORIAL

The improbability of an insignificant 'P' value?

STUART M. HAMILTON, MD, FRCSC, ALAN B.R. THOMSON, MD, PhD, FRCPC, FACP

GRAM-NEGATIVE NOSOCOMIAL PNEUMONIA MAY RESULT from retrograde colonization of the pharynx from the stomach, and this may be more likely when the gastric pH is relatively high. Driks and colleagues (1) concluded that "in patients receiving mechanical ventilation, the use of a prophylactic agent against stress-ulcer bleeding that preserves the natural gastric acid barrier against bacterial overgrowth may be preferable to antacids and H₂ blockers".

The possibility of using sucralfate for prophylactic treatment of stress ulcers has called forth the battle cry 'first do no harm' in a signed editorial in *The Canadian Journal of Surgery*. Indeed, Dr MacLean suggests that "the results to date strongly suggest that this breakthrough will have wide application in the treatment of seriously ill patients" (2). What, then, is the improbability of an insignificant P value?

Hospital acquired pneumonia is frequently caused by Gram-negative bacilli and usually results from aspiration of bacteria from the oropharynx arising during acute or chronic illnesses, previous use of antibiotics, endotracheal intubation or retrograde pharyngeal colonization by organisms from the stomach. Antacids or H₂ receptor antagonists are often used in an intensive care unit setting for the trauma or multiple system disease patient to reduce the risk of upper gastrointestinal tract hemorrhage. These agents raise the intragastric pH and may be associated with an increase in Gram-negative bacilli in the gastric contents and thereby, at least on a theoretical basis, increase the risk of nosocomial pneumonia as a result of retrograde colonization of the pharynx.

In the study of Driks and co-workers (1), patients admitted to the surgical, medical or coronary intensive care units who had been intubated within the previous 24 h, were receiving mechanical ventilation and had a nasogastric tube in place, were eligible for study. Patients were excluded if they had active upper gastrointestinal tract hemorrhage, had received antacids, H₂ blockers or sucralfate within the previous 48 h, or had not received mechanical ventilation for more than 24 h. Patients were randomly assigned to prophylaxis with sucralfate 1 g every 6 h suspended in 20 mL of sterile water administered by nasogastric tube, or to conventional therapy with antacids, H₂ blockers or both antacids and H₂ blockers. The dose of these was not specified although standard regimens of various antacid preparations were administered. Similarly, standard doses of intravenous cimetidine or ranitidine were prescribed. It is presumed that these were given by bolus rather than by the more optimal route of continuous intravenous infusion (1).

Nasogastric aspirates were examined for bright red blood, 'coffee grounds' material or occult blood as detected by the guaiac test. Ventilator associated pneumonia was diagnosed if a chest film showed a new and persistent infiltrate that was consistent with pneumonia for at least three of the following findings: purulent sputum that showed more than 25 leukocytes on Gram staining, less than 10 squamous epithelial cells per low power field, and numerous bacteria per oil immersion field; an important respiratory or nosocomial pathogen isolated from culture of a tracheal aspirate; peripheral leukocytosis of more than 10,000 cells/mm³; and fever (temperature above 38°C).

Sputum samples and gastric aspirates were collected according to standard procedures, samples of gastric aspirates were tested with pH paper and aerobic bacteria were identified

Departments of Surgery and Medicine, University of Alberta, Edmonton, Alberta

Correspondence and reprints: Dr A.B.R. Thomson, 519 Robert Newton Research Building, University of Alberta, Edmonton, Alberta T6G 2C2

according to routine methods. In some patients, quantitative and qualitative analysis of aerobic bacteria present in the stomach, pharynx and trachea were undertaken. Isolates were characterized by results of Gram staining and colony morphologic studies and quantitative analysis was performed for Gram-negative bacilli only. The characteristics of the two treatment groups were compared by means of Student's *t* test for continuous variables with Fisher's exact test (two-tailed) for categorical variables. Quantitative levels of gastric, pharyngeal and tracheal colonization were compared with use of the Wilcoxon rank sum test adjusted for ties. Rates of pneumonia and mortality in the two groups were compared in terms of relative risks with 95% confidence intervals.

The two treatment groups were similar in terms of demographic characteristics and severity of illness on admission to the study. Of the 130 study patients, 61 received sucralfate and 69 received antacids or H_2 blockers. In all, 39 patients received antacids, 17 received H_2 blockers (cimetidine or ranitidine) and 13 received both an H_2 blocker and antacids.

The distribution of underlying diseases, indications for intubation and surgical procedures according to site were similar in the two groups. Two patients in the sucralfate group and one patient in the antacid- H_2 group had evidence of bright red blood in the nasogastric aspirate. One of the sucralfate treated patients died from massive gastrointestinal bleeding despite numerous transfusions and despite later use of ranitidine. The other patient in the sucralfate group, who had a small amount of bright red blood in the nasogastric aspirate, was switched to intravenous ranitidine with no further bleeding. The one patient treated with ranitidine who developed bright red blood did well with the bleeding subsiding after antacids were added.

Endoscopy was not performed in the patients so that the adequacy of sucralfate versus antacid- H_2 for the prevention of gastric stress erosions could not be assessed. However, 16.4% of the sucralfate patients had occult blood in the nasogastric aspirate compared with 34.8% in the antacid- H_2 group, yet 6.6% of the sucralfate group had 'coffee grounds' and 3.3% had bright red blood; figures for the antacid- H_2 group were 1.4% and 1.4%, respectively.

Significantly more patients in the antacid- H_2 group had colonization with Gram-negative bacilli from the gastric aspirate, pharyngeal swab and tracheal aspirate. What was the clinical importance of the greater percentage of Gram-negative bacilli colonization of these aspirates? The rate of development of pneumonia in all patients was significantly lower in those treated with sucralfate than with antacid (seven of 61 patients [11.5%] versus 16 of 69 patients [23.2%], $P = 0.11$), and there was a lower mortality rate in the sucralfate treated patients (18 of 61 patients, [29.5] versus 32 of 69 patients [46.4%], sucralfate versus antacid- H_2 group, $P = 0.07$).

However, while this analysis was performed on 'intention to treat' principle, in which all comers were analyzed, there were two patients in whom pneumonia developed three and eight days after their treatment with sucralfate. These subjects were subsequently switched to antacids. If the data are examined, excluding these crossover patients (ie, patients

treated with sucralfate and subsequently treated with antacids) then the differences between the sucralfate and the antacid- H_2 group for development of pneumonia and for mortality rates became statistically significant. The results of comparing sucralfate versus the antacid- H_2 group for development of pneumonia is as follows: 9.1% versus 23.2%, respectively, $P = 0.05$; for mortality the results are 23.6% versus 46.4%, $P < 0.05$ (1). Other workers have also demonstrated much lower rates of development of nosocomial pneumonia in patients receiving mechanical ventilation assigned to sucralfate rather than to antacids (3).

If our perspective is one of 'first do no harm', then one must ask the question of whether antacids or H_2 receptor antagonists are useful in preventing stress ulceration. The routine use of antacids or H_2 blockers in the intensive care unit is based on a number of excellent studies (4,5), and antacids and cimetidine appear to be equally effective in reducing the incidence of bleeding and the requirement for transfusion (6).

Sucralfate has been studied for the prevention of stress ulceration (3,7-9). In one study six patients in the sucralfate group developed coffee grounds or bright red blood and one patient died, whereas only two patients in the antacid- H_2 group had coffee grounds or bright red blood and there was no evidence of upper gastrointestinal bleeding (9). These differences are not statistically significant. One cannot make the judgement, therefore, that the sucralfate group is comparable to the antacid- H_2 group for the prevention of stress ulcers because endoscopies were not performed to determine whether, in fact, stress ulcers developed; no placebo group was included so that the sucralfate group may be as good or as bad as the antacid- H_2 group; the antacid- H_2 group was clearly a heterogeneous population.

This heterogeneous population comprised 69 patients, 39 receiving antacids, not all of whom were pH monitored to ensure that the intragastric pH was at least 4; 17 receiving H_2 blockers (cimetidine or ranitidine), although the dose or the numbers of patients in each of the two different H_2 receptor antagonist groups is unknown; and finally 13 patients receiving both an H_2 blocker and antacids.

Thus, it is unclear whether sucralfate prevented stress ulcers in this study, and the study was not properly designed to determine whether the prevalence of clinically important bleeding episodes was different between sucralfate and either antacid or a single H_2 receptor antagonist. Furthermore, it has been demonstrated that infusion of H_2 receptor is superior to bolus injection for the prevention of stress ulcers and bleeding, so that the optimal dose and route of administration of H_2 blockers was not achieved. Therefore, while one heartily agrees with the concept of doing no harm, one also wishes to do some good!

It is accepted that the rates of pneumonia and mortality among patients treated with sucralfate were lower than in the antacid- H_2 group. The authors correctly point out that, with the data available, it is difficult to isolate the effects of pneumonia from factors such as the patient's medical condition and underlying disease (9). Furthermore, the percentage rate

of pneumonia development in patients treated with either sucralfate or antacid- H_2 blocker was much lower in this group than in previous studies published by these authors. They considered that this "most likely reflects selection of patients with less acute illness who did not require the addition of antacid to elevate gastric pH" (9). Enteral feeding also increases gastric pH and may increase the risk of nosocomial pneumonia (10). The number of patients receiving enteral feeding is not stated in the article although it was noted that one patient in the sucralfate group had pneumonia during tube feeding and also had an elevated gastric pH.

I would certainly agree with the reviewer's suggestion that a randomized study would be needed to assess accurately the risk associated with different regimens for prophylaxis against stress ulcers.

In summary, while these two prospective randomized trials on the use of sucralfate in the intensive care unit have suggested the inferiority of antacids, with or without added H_2 blockers, it is not yet possible to conclude that agents that maintain the natural gastric acid barrier, such as sucralfate,

are superior to H_2 blockers in the development of stress lesions. It is also impossible to conclude that the risk of Gram-negative colonization in the development of pneumonia is higher. Studies need to be performed on larger numbers of patients and examination of the efficacy of treatment against elevated stress ulcers and clinically significant bleeding also need to be carried out. Control for the use of enteral feeding, the use of 'standard' doses of H_2 blockers, and the use of infusion rather than bolus injection of these H_2 -receptor antagonists are also necessary for a successful study.

Finally, what was the impact of the presence of a nasogastric tube? A nasogastric tube was needed to administer the sucralfate and antacid. Did the presence of the nasogastric tube contribute to the occult blood present in the gastric aspirate of some patients, and did the presence of the nasogastric tube itself contribute to the colonization of the pharynx, sputum and stomach? First do no harm, but even before that, ensure that the agent selected for use is in fact effective and that the method of its delivery is itself doing no harm.

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