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Incidence of Infectious Complications Associated With the Use of Histamine$_2$-Receptor Antagonists in Critically Ill Trauma Patients

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Objective
To determine the impact of histamine$_2$ (H_2)-receptor antagonist use on the occurrence of infectious complications in severely injured patients.

Summary Background Data
Some previous studies suggest an increased risk of nosocomial pneumonia associated with the use of H_2-receptor blockade in critically ill patients, but other investigations suggest an immune-enhancing effect of H_2-receptor antagonists. The purpose of this study was to determine whether H_2-receptor antagonist use affects the overall incidence of infectious complications.

Methods
Patients enrolled in a randomized trial comparing ranitidine with sucralfate for gastritis prophylaxis were examined for all infectious complications during their hospitalization. Data on the occurrence of pneumonia were prospectively collected, and other infectious complications were retrospectively obtained from the medical record. The relative risk of infectious complications associated with ranitidine use and total infectious complications were analyzed.

Results
Of 98 patients included, the charts of 96 were available for review. Sucralfate was given to 47, and 49 received ranitidine. Demographic factors were similar between the groups. Ranitidine use was associated with a 1.5-fold increased risk of developing any infectious complication (37 of 47 *vs.* 26 of 47; 95% confidence interval, 1.04 to 2.28). Infectious complications totaled 128 in the ranitidine-treated group and 50 in the sucralfate-treated group ($p = 0.0014$). These differences remained after excluding catheter-related infections ($p = 0.0042$) and secondary bacteremia ($p = 0.0046$).

Conclusions
Ranitidine use in severely injured patients is associated with a statistically significant increase in overall infectious complications when compared with sucralfate. These results indicate that ranitidine should be avoided where possible in the prophylaxis of stress gastritis.

Prophylaxis for stress ulceration remains an important part of the management of critically ill patients. Recent data have helped identify the patients at highest risk for hemorrhage from stress ulceration, allowing a more focused approach to therapy. The clinical factors most strongly associated with hemorrhage from stress ulceration in critically ill patients are respiratory failure and coagulopathy, which are associated with a 3.7% incidence of stress ulcer bleeding.[1] In the absence of these risk factors, bleeding has a frequency of 0.1%, suggesting that stress ulcer prophylaxis can be safely withheld from patients without respiratory failure or coagulopathy.[1]

However, controversy remains regarding the optimal regimen to use when prophylaxis is indicated. Available options include antacids, various histamine$_2$ (H_2)-receptor antagonists, prostaglandins, proton pump inhibitors, and sucralfate. In addition to concerns regarding their relative efficacy in preventing stress ulcer hemorrhage, interest has been directed toward the consequences of gastric acid neutralization—namely, bacterial overgrowth and the subsequent development of nosocomial pneumonia. It has been suggested that increasing the intragastric pH with any of the acid-reducing agents supports bacterial overgrowth and predisposes to nosocomial pneumonia, and that any impact on infectious complications is caused by the local effect of artificially elevating the intragastric pH.[1]

Of the available options for the prophylaxis of stress ulceration, sucralfate presents a theoretically advantageous profile. This aluminum salt of sulfated sucrose is active locally, augmenting gastric mucosal protection and healing without affecting gastric pH. Sucralfate binds to areas of mucosal breakdown and also to pepsins and bile acids, potentially reducing their injurious effects. Sucralfate is minimally absorbed through the gastrointestinal mucosa, with <5% appearing in the urine.

Of the receptors on the acid-secreting gastric parietal cells, those for histamine play an important role in acid secretion. Histamine functions as an important cofactor for gastrin- and acetylcholine-induced acid secretion, and blockade of these histamine receptors results in a large reduction in acid secretion. Because H_2-receptor antagonists reduce [H^+] secretion, they cause a potentially profound increase in gastric pH. These contrasting features of H_2-receptor antagonists (such as ranitidine) and sucralfate have provided the major stimulus to clinical investigation of stress gastritis prophylaxis and the occurrence of nosocomial pneumonia.

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Both intravenous and oral delivery of H_2 antagonists such as ranitidine lead to measurable systemic levels. Given the presence of H_2 receptors at numerous sites, including leukocytes, more recent studies have addressed the potential immunologic actions of several of these agents.[2–4] Thus, the impact of H_2 antagonism on infectious complications may be caused by modulation of the immune system rather than by a reduction in gastric acidity. Unfortunately, the immunologic effects of H_2 antagonism identified in laboratory and clinical studies have ranged from marked suppression to marked augmentation, leading to uncertainty regarding the relevant clinical impact.[2–4]

The purpose of this study was to determine whether the immunosuppressive effects of H_2-receptor antagonism with ranitidine, suggested in basic laboratory investigations, led to clinically relevant alterations in the immune system of severely injured patients. Our hypothesis was that H_2-receptor blockade with ranitidine would result in an increased incidence of infectious complications, supporting an immunosuppressive effect of the agent.

METHODS

Patients enrolled in a randomized trial comparing ranitidine with sucralfate for stress gastritis prophylaxis were reviewed for all infectious complications. The results of this study with regard to the occurrence of stress ulceration hemorrhage and pneumonia incidence were previously reported.[5] Data on the occurrence of pneumonia were prospectively collected; other infectious complications were retrospectively obtained from the medical record. All infectious complications were defined according to previously determined criteria. Pneumonia was defined by the presence of a white blood cell count >12,000/mL, a new or changing infiltrate on chest radiography, temperature >38.5 C or <36.5 C, and positive sputum and Gram stain for specific pathogen(s). Intravascular line infections were diagnosed by the presence of >15 colonies of a single pathogen by semiquantitative culture of the intracutaneous segment of an intravascular catheter and a temperature of >38.5 C or <36.5 C. Bacteremia required the presence of a positive blood culture. Empyema was diagnosed by the presence of a fluid collection identified by radiologic studies and the presence of a pathogen(s) grown from pleural fluid. A diagnosis of intraabdominal abscess was based on the presence of an intraabdominal fluid collection that required percutaneous or surgical drainage, with pathogens(s) identified on Gram stain or culture. Wound infections were defined by the presence of a positive culture of wound drainage and the presence of a local inflammatory response. Sinus infections were indicated by opacified nasal sinuses, identified by computed tomography, and purulent aspirate from a nasal sinus. Urine cultures growing >100,000 organisms/mL

Table 1. BASELINE DEMOGRAPHIC INFORMATION

	Ranitidine	Sucralfate	Total	p Value‖
Number of patients	49	47	96	
Age*	34.3	34.2	34.3	0.56
Gender (male)†	35 (71.4)	39 (83.0)	74 (77.1)	0.17
ISS‡	28.1 (9–56)	29.0 (8–50)	28.7 (8–56)	0.71
Admission GCS*	6.5	6.6	6.6	0.82
Severe head injuries†,§	30 (61.1)	32 (68)	62 (64.6)	0.48
Severe chest injuries†,§	33 (67.3)	26 (55.3)	59 (61.5)	0.27
Severe abdominal injuries†,§	16 (32.6)	32 (27.7)	29 (30.2)	0.56
Intensive care length of stay*	15.0	9.8	12.4	0.02
Hospital length of stay*	26.3	20.8	23.6	0.16
Mortality†	11 (22.4)	6 (12.8)	17 (17.7)	0.21

* Indicates mean value for each treatment group and for total study sample.
† Indicates number in each group, percentages in parentheses.
‡ Injury severity score (ISS) presented as mean for treatment group; range presented in parentheses.
§ Severe injury defined as abbreviated injury scale score of greater than or equal to 3.
‖ Pearson chi square for categorical data and Mann-Whitney U test for continuous data.

defined urinary tract infections. Other infectious complications required the presence of a culture growing pathogen(s) from a normally sterile space (*e.g.*, the central nervous system).

The retrospective assignment of infectious complications was performed by a reviewer (GEO) blinded to the stress gastritis prophylaxis regimen used. For individual patients, each positive catheter culture was counted as a separate complication, as were repeat positive cultures after an appropriate course of antibiotic treatment for bacteremia. Repeat episodes of pneumonia were defined by the presence of new pathogen(s) on sputum culture in conjunction with the other defining criteria.

Demographic data included age, gender, mechanism of injury, and measures of injury severity, including the injury severity score and individual abbreviated injury scale scores (AIS) for each body region. Severe injuries for AIS body regions are defined by an AIS score of 3 or more. Data on hospital length of stay, intensive care unit (ICU) length of stay, and mortality were collected. Patients randomized to ranitidine received an initial loading dose of 0.5 mg/kg, followed by a continuous infusion of 0.25 mg/kg • hour. Patients randomized to sucralfate received the drug as a slurry by nasogastric tube (1 g every 6 hours). All patients received standard care provided by the admitting surgical service, and all were mechanically ventilated and had gastric (oral or nasal) drainage tubes in place. No oral prophylactic antibiotics were used in study subjects. Prophylactic intravenous antibiotics were used only for open fractures and gastrointestinal injuries and were continued for 24 hours after injury.

The two groups were compared for the presence of any infectious complication using chi square analysis. The estimated relative risk for the development of an infectious complication with ranitidine treatment with the associated 95% confidence interval was determined. Total infectious complications were compared using the Mann-Whitney test, and to control for the effect of potential confounding variables, analysis of variance was carried out. To exclude any potential bias associated with increased catheter manipulations in the ranitidine-treated patients, analyses excluding catheter-related infections were also carried out. This study was approved by the University of Washington Institutional Review Board.

RESULTS

Of the 96 patients, 47 received sucralfate and 49 ranitidine (Table 1). Age averaged 34.3 years, 77.1% were male, and 17.7% of the patients died. The injury severity score averaged 28.6. Head injuries occurred in 78.1% of patients, followed in frequency by extremity (70.8%) and chest (68.7%) injuries. Severe head injuries were slightly more common in the sucralfate group, severe chest and abdominal injuries slightly more common in the ranitidine group.

In the patients receiving ranitidine, mortality was greater (22.4% *vs.* 12.8%; $p = 0.21$) and both ICU length of stay (15 *vs.* 9.8 days; $p = 0.02$) and hospital length of stay (26.3 *vs.* 20.8 days; $p = 0.16$) were longer. Analysis of variance was performed to determine whether this prolonged ICU stay in the ranitidine group was a function of other factors. After controlling for the effects of age and body region AIS scores (other variables were found to be unimportant), treatment with ranitidine still remained associated with a prolonged ICU stay ($F = 4.22$, $p = 0.042$).

Sixty-three patients (65.6%) developed at least one infectious complication. The number of infectious complications per patient ranged from 1 to 12, with an overall

Table 2. TOTAL INFECTIOUS COMPLICATIONS ACCORDING TO SITE AND TREATMENT GROUP

Infection Site	Ranitidine	Sucralfate
Abdominal abscess	3	0
Vascular catheter	20	6
Bacteremia	55	19
Pneumonia	26	14
Wound infection	6	3
Central nervous system	1	0
Nasal sinus	3	1
Pleural	2	2
Urine	12	5
Total	128	50

total of 178 infectious complications. Total infections according to site for the two treatment groups are presented in Table 2. Bacteremia was the most common, occurring in 46.9% of patients, followed in frequency by pneumonia (25%) and catheter-related infections (19.8%). Gram-positive bacteria accounted for 60.7% of the infections and gram-negative bacteria for 38.8%, with 1 fungal infection (0.6%). The proportion of gram-positive to gram-negative infections was similar in the two treatment groups. In patients receiving ranitidine, 82 of 130 infections (63.1%) were caused by gram-positive organisms; similarly, in patients receiving sucralfate, 26 of 47 infections (55.3%) were caused by gram-positive organisms (chi square = 0.87, p = 0.35).

Patients receiving ranitidine were more likely to develop an infectious complication (37 of 49 *vs.* 26 of 47; relative risk, 1.5; 95% confidence interval, 1.04 to 2.28). The total number of infectious complications per patient was greater in the ranitidine group than the sucralfate group (p = 0.0014) (Table 3). After excluding catheter-related infections, patients receiving ranitidine still developed more infections per patient (p = 0.0046). Similarly, after excluding positive blood cultures, which potentially reflected other infectious sites, there remained more infections in the ranitidine group (p = 0.0042). Of the 49 patients who received ranitidine, 14 developed 26 separate episodes of pneumonia; of the 47 patients who received sucralfate, 10 developed 14 episodes of pneumonia.

Because survival and duration of stay can affect risk of nosocomial infections, analysis of covariance was carried out to control for the effects of survival, ICU length of stay, and total hospital length of stay. After controlling for these factors, treatment with ranitidine remained associated with higher total infectious complications (F = 5.28, p = 0.024).

DISCUSSION

In recent years, clinically relevant hemorrhage from stress gastritis has decreased in frequency in critically ill patients,[6–8] probably because of improvements in general supportive care. This fact, in addition to knowledge of specific risk factors for stress ulcer hemorrhage, suggests that a more focused approach to prophylaxis could be used in which only patients at highest risk would receive prophylaxis. Critically ill patients with coagulopathy or respiratory failure requiring mechanical ventilation for >48 hours appear to be at greatest risk for stress ulcer hemorrhage, and limiting prophylaxis to these patients would reduce the number receiving prophylaxis while addressing the overwhelming majority of those at risk for hemorrhage from stress ulceration.[1]

However, the appropriate regimen remains to be established. H_2-receptor antagonists remain the most frequently used form of prophylaxis for this condition, but questions remain regarding the consequences of the resultant gastric acid neutralization. Data are conflicting, but overall they indicate that prophylaxis with H_2-receptor antagonists is associated with an increase in the incidence of pneumonia as compared with placebo treatment.[5,9] However, this increased risk is not consistent across studies.[9]

The prevalence of infectious complications in this study

Table 3. COMPARISON OF INFECTIOUS COMPLICATIONS BETWEEN TREATMENT GROUPS

	Ranitidine* (n = 49)	Sucralfate* (n = 47)	p Value (Mann-Whitney U test)†
Total infections	128	50	0.0014
Primarily infections‡	114	46	0.0042
Non-catheter related infections§	102	44	0.0046

* Values indicate total number of infectious complications in the treatment group.
† The Mann-Whitney U test compares total infections per patient between the two treatment groups.
‡ Excluding positive blood cultures obtained within 48 hours of a positive culture from another site with the same pathogen.
§ Excluding all positive semiquantitative catheter cultures.

is consistent with the experience of others.[10] Risk factors for ICU-acquired infections include major trauma, mechanical ventilation, pulmonary artery catheterization, central venous access, urinary bladder catheterization, and increasing length of stay.[10] These factors were frequently, if not uniformly, present in the patients in this study, placing the study patients at extremely high risk. This study identified a 25% incidence of pneumonia, consistent with other studies.[9,11,12] The risk of developing pneumonia in the ranitidine-treated patients was 1.3 times the risk in the patients receiving sucralfate, approximating relative risk estimates in the literature.[13,14]

The mechanism by which ranitidine increases overall infectious complications remains to be established. With regard to pneumonia, although gastric-to-tracheal migration of bacteria occurs, evidence suggests that the oropharynx is often the primary source and both gastric and tracheal colonization follow, suggesting that gastric bacterial overgrowth is not etiologic in all instances of ventilator-associated pneumonia.[5] Thus, the possibility remains of an alternative mechanism by which ranitidine leads to infectious complications. This study provides additional evidence favoring an adverse immunologic effect of ranitidine as a potential cause for the increase in pneumonia and other infectious complications. This immunosuppression has several possible explanations.

Myelosuppression, often presenting as thrombocytopenia, is a documented but infrequent complication of ranitidine use. Other investigators have identified a reduction in myelocyte production in persons treated with cimetidine.[15] Whether this would explain the association seen in this study between ranitidine therapy and infectious complications is unknown. It is unlikely to be a major cause, given the infrequency of documented myelosuppression associated with H_2-receptor antagonist treatment.

Identification of H_2 receptors on leukocytes and other immune cells has recently led to investigation of additional cellular effects of H_2 antagonism.[2–4,16] However, little has been accomplished in elucidating the clinical relevance of these effects. Experimental studies examining the immune effects of H_2 antagonists have suggested a variable effect on immune system function that appears to differ among drugs (*e.g.*, famotidine, cimetidine, and ranitidine).[2–4] Suppression of an overwhelming immune response, leading to increased survival in experimental septic shock, is consistent with the findings of the present study. The findings of this study may be explained by an immunosuppressive effect of ranitidine, leading to an increased susceptibility to infectious complications. However, this is in contrast to a recent investigation[16] in which ranitidine use was found to improve monocyte and neutrophil function, suggesting enhanced immune function.

In the present study, the increase in infectious complications in the patients receiving ranitidine was marked. For all sites, infectious complications occurred as often or more often in patients receiving ranitidine prophylaxis. The number of infectious complications per patient averaged 2.6 in those receiving ranitidine and 1.1 in those receiving sucralfate. Because the ranitidine-treated group may have required prolonged vascular access, it could be argued that the increase in infectious complications could be caused by catheter-related infections. However, analysis was repeated with catheter-related infections excluded, and there remained a significantly greater number of infections in the ranitidine group. In addition, after controlling for the effects of ICU length of stay on infection rate, ranitidine treatment remained associated with a higher rate of infectious complications.

This study provides evidence, based on data obtained in a randomized clinical trial, that suggests an adverse effect of ranitidine therapy on the occurrence of infectious complications, which were 1.5 times more frequent in patients receiving ranitidine. The fact that infectious complications at multiple sites were increased suggests a potential immunosuppressive effect of ranitidine. Whether these findings can be extrapolated to other H_2 antagonists remains to be established, and the exact mechanism by which immunosuppression occurs requires additional investigation. Given the present understanding of the risk factors for stress ulcer hemorrhage and the potential for adverse consequences of acid-reduction therapy with H_2-receptor antagonists, a more focused approach, involving prophylaxis with locally active agents for patients with respiratory failure or coagulopathy, provides the safest and most rational approach to this complication of critical illness and injury. The results of this study suggest that sucralfate is a more appropriate agent than the H_2 antagonist ranitidine as prophylaxis for patients at risk for hemorrhage from stress ulceration.

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