The Effect of Duodenojejunal Alimentation on Gastric pH and Hormones in Intensive Care Unit Patients*

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We evaluated effects of duodenojejunal (DJ) feeding on gastric pH and selected gastrointestinal hormones in 13 randomly selected patients in an intensive care unit (ICU). To obtain baseline values for gastric pH, a nasogastric (NG) tube was placed in each patient and gastric pH was measured every 30 minutes for 2 hours. To obtain control values, a Dobbhoff tube was placed fluoroscopically and 0.45 percent saline solution (NaCl), 75 ml, was infused for 1 hour and gastric pH was measured again; the previously placed NG tube was left in position. Then, by randomization, either 0.45 percent NaCl (pH = 5) was continued (n = 6) or a high-nitrogen, isotonic, enteral feeding solution (Osmolite HN, pH = 6.4) (n = 7) was infused, both at 75 ml/h. Gastric pH was noted hourly for 96 hours; antacid (Maalox TC, 15-ml aliquots) was given by NG tube when the pH was 4 or less. After 96 hours, the infusion was stopped and gastric pH was noted for 4 additional hours. Before and during initial saline solution infusion; after 24, 48, 72, and 96 hours of continuous infusion; and 4 hours after stopping the infusion, peripheral venous blood was obtained for measurement of plasma gastric inhibitory polypeptide (GIP) and serum gastrin. Data were analyzed by ANOVA (RMD), Fishers' exact test, and the unpaired t-test. Groups did not differ demographically. Throughout the infusion, gastric pH tended to be higher with the enteral feeding solution than with saline solution, but this was significant only at 24 hours. Less antacid was required with the enteral feeding solution at 24 and 48 hours than with saline solution. Plasma GIP levels were significantly higher with the enteral feeding solution than with saline solution during most of the infusion. Serum gastrin levels did not differ between the groups. In this cohort, infusion of the enteral feeding solution tended to maintain a gastric pH of more than 4 and was associated with increased plasma GIP levels, which may inhibit gastric acid secretion. Early enteral feeding may benefit certain ICU patients.

(S) Sixty to 100 percent of patients admitted to the intensive care unit (ICU) have been found to have stress-related gastric mucosal damage; significant gastrointestinal hemorrhage may occur in 5 to 20 percent of patients.3 A Antacids or type-2-histamine (H2) receptor antagonists significantly reduce the incidence of stress ulcera-

© One group has suggested that direct substrate absorption by gastric mucosal cells was of primary importance in the prevention of stress ulceration in rats when solution was infused into their stomachs.4 Other data suggest that gastric or duodenal infusion decreases gastric acid secretion, perhaps by variation in blood level of gastrointestinal regulatory peptides, including gastric inhibitory polypeptide (GIP), gastrin, or both.5,6 We hypothesized that duodenojejunal (DJ) infusion would increase blood levels of GIP and decrease those of gastrin which, in turn, would decrease the number of times per day that gastric pH would decrease to 4 or less, and, thus, reduce the amount of antacid required to maintain an intraluminal gastric pH of more than 4. We tested this hypothesis in a group of ICU patients.

**METHODS**

Following approval by the institutional review board, 13 consenting ICU patients were randomly selected for this nonblinded, noncrossover, placebo-controlled study. Patients with clotting abnormalities or a history of peptic ulcer disease, those unable to use their small bowel, or those who were taking H2-receptor antagonists

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DJ = duodenojejunal; ICU = intensive care unit; NG = nasogastric; GIP = gastric inhibitory polypeptide; RMD = repeated measures design; ANOVA = analysis of variance; CHI = closed head injury; COPD = chronic obstructive pulmonary disease
Table 1—Demographic Data for Patients Who Received Duodenojejunal Alimentation with 0.45 Percent NaCl or Enteral Feeding Solution*

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>0.45% NaCl</th>
<th>Enteral Feeding Solution</th>
<th>p</th>
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<tr>
<td>55.7±20.2</td>
<td>48.1±20.1</td>
<td>NS</td>
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</table>

Sex, M/F

Mechanically ventilated, %

APACHE II

24 h | 11.2±2.5 | 12.6±4.2 | NS |

96 h | 10.5±3.2 | 10.3±3.6 | NS |

Race, %

White | 83 | 86 | NS |

Black | 17 | 14 | NS |

Steroids, n

100 | 100 | — |

*Values are means ± SD when not otherwise specified. NS = not significant.

After the last measurement, enteral infusion of the isotonic feeding solution was administered to all subjects. During the study, occurrences of occult bleeding (naso-gastric aspirate that was guaiac positive) or gastrointestinal hemorrhage, defined as visibly bloody naso-gastric aspirate or hematemesis, were noted.

**Measurements of GIP and Gastrin**

Venous blood was collected in chilled tubes containing 1,000 kallikrein inactivator units aprotinin (Trasylol, Bayer, Leverkusen, West Germany). Samples were centrifuged at 1,000 × g at 4°C, and then stored at −20°C. Venous blood for gastrin determination was collected in sterile glass tubes, allowed to clot, and then centrifuged at 1,000 × g at 4°C. Serum was stored at −20°C. Radioimmunoassays were performed as detailed previously.11 All samples were analyzed at the same time to eliminate interassay variation.

**pH Paper Accuracy**

As a control experiment, paper pH was determined in triplicate and compared with pH obtained by a calibrated pH glass-electrode (Fischer Scientific, Springfield, NJ). In a blinded manner, solutions of known pH (pH 1 to 8, Certified Buffer Solutions, Fischer Scientific, Springfield, NJ) were evaluated by three different persons; after their evaluations were transcribed, the true pH of each solution was determined with a pH electrode and the data were compared.

**Statistical Analysis**

All data were analyzed by using the repeated measures design (RMD) of the analysis of variance (ANOVA) except demographic variables, which were evaluated by the unpaired t test and Fisher's exact test. The data on pH accuracy were evaluated by regression analysis techniques. Statistical significance was taken as p<0.05. Proof of the null hypothesis would result in no difference between test patients and control with regard to the number of times per day that the intraluminal gastric pH was 4 or less.

**RESULTS**

The patients in each group did not differ significantly by age, sex, race, or ventilatory status (Table 1). Patients who received 0.45 percent NaCl had subarachnoid hemorrhage (n = 4), peripheral vascular disease and chronic bronchitis/emphysema (n = 1), and closed head injury (CHI) from a motor vehicle accident (n = 1); those who received enteral feeding solution had subarachnoid hemorrhage (n = 3), CHI from motor...
vehicle accident (n = 2), and internal carotid artery aneurysm or pituitary tumor (n = 1 each). All patients received glucocorticoids throughout the study period. Severity of the underlying disease, as determined by the APACHE II scores, which were measured at 24 and 96 hours, did not differ between the two groups.

To determine the accuracy of pH paper measurements, regression analysis techniques were used, the best fit of the data was via a linear model (Fig 2). The equation describing data points is as follows: 

\[ Y = AX + B, \] 

where \( Y \) = paper pH determination, \( A \) = slope (1.07), \( B \) = intercept (−0.51), and \( X \) = glass electrode pH determination. The \( r^2 \) for this relationship is 0.98.

Gastric pH in the enteral feeding solution group tended to be higher than in the 0.45 percent NaCl group throughout the study, except after infusion (Fig 3); however, the difference was statistically significant only at 24 hours (p = 0.014). Overall there were more occurrences of gastric pH of 4.0 or less with 0.45 percent NaCl than with enteral feeding solution (p ≤ 0.035). When data at each time point were evaluated, pH of 4 or less occurred significantly more often during the first 24 hours of infusion in the saline solution infusion group than in the enteral feeding solution group (p = 0.0086) (Fig 4).

The dose of antacid was titrated to maintain a gastric pH of more than 4; during the first 24 hours of infusion, this required 84 ml of antacid in those receiving enteral feeding solution and 233 ml in those receiving 0.45 percent NaCl (p = 0.017). The antacid requirement remained significantly lower with enteral feeding than with 0.45 percent NaCl at 48 hours (54 ml compared with 138 ml, respectively, p = 0.008). Although the amount of antacid required in the subsequent periods remained lower with the enteral feeding solution than with the 0.45 percent NaCl, the two groups did not differ statistically at 72 and 96 hours (Fig 5). The amount of antacid required each hour

**Figure 2.** Regression analysis plot of electrode pH vs paper pH measurements of solutions of known pH. Dashed lines represent 95 percent confidence intervals.

**Figure 3.** pH was measured at baseline (B), during 0.45 percent NaCl infusion for 1 hour for control data (C), and during and after (PI) duodenojejunal infusion of either 0.45 percent NaCl or enteral feeding solution. Values are mean ± 1 SD. Asterisk = p < 0.05.
(mean ± 1 SD) was greater with 0.45 percent NaCl than with enteral feeding solution (6.12 ml/h ± 3.08 and 3.04 ± 1.75, respectively, p<0.045).

No massive gastrointestinal bleeding occurred in either group. Although at each time period and overall, more episodes of guaiac positivity were associated with 0.45 percent NaCl than with enteral feeding solution, this difference was not statistically significant. One patient in each group had a decreased hematocrit that required blood transfusion; the anemia was attributed to frequent blood sampling rather than upper gastrointestinal tract bleeding. Green dye was not noted in any gastric aspirate of any patient.

Plasma GIP levels increased significantly (p<0.05) in response to enteral feeding. There was no increase in plasma GIP detected with the 0.45 percent NaCl infusion. Further, in the enteral feeding solution group, plasma GIP was significantly higher at hours 24, 48, 72, and 96 than at baseline, control, or after the infusion (Table 2). Serum gastrin did not increase with the 0.45 percent NaCl infusion, nor with the enteral feeding solution. Finally, there were no differences in serum gastrin between groups or between times within groups (Table 2).

**Discussion**

Bleeding in a severely ill patient that begins as a complication of underlying illness may be the harbinger of death.7 Mortality from bleeding can exceed 50 percent.15 Conditions associated with increased in-
Table 2—Gastric Inhibitory Polypeptide and Gastrin Profiles for Patients Who Received Duodenojejunal Alimentation with 0.45 Percent NaCl or Enteral Feeding Solution*

<table>
<thead>
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<th></th>
<th>0.45% NaCl</th>
<th>Enteral Feeding Solution</th>
<th>p</th>
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<tbody>
<tr>
<td>Plasma gastric inhibitory polypeptide, pg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>543.8±117.7</td>
<td>502±144.3</td>
<td>0.607</td>
</tr>
<tr>
<td>Control</td>
<td>583.3±187.1</td>
<td>621.1±219.9</td>
<td>0.765</td>
</tr>
<tr>
<td>During alimentation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td>641.6±282.8</td>
<td>1416.1±450.3†</td>
<td>0.007</td>
</tr>
<tr>
<td>48 h</td>
<td>510.6±242.8</td>
<td>1177.6±321.1†</td>
<td>0.003</td>
</tr>
<tr>
<td>72 h</td>
<td>565.8±218.6</td>
<td>1151.8±311.8†</td>
<td>0.005</td>
</tr>
<tr>
<td>96 h</td>
<td>612.4±294.7</td>
<td>1072.3±404.8†</td>
<td>0.057</td>
</tr>
<tr>
<td>After alimentation</td>
<td>853.0±523.2</td>
<td>559.1±47.1</td>
<td>0.163</td>
</tr>
</tbody>
</table>

*Values are means ± SD.
†p<0.05 when compared with values at baseline, control, and after alimentation in the same group.

Incidence of bleeding includes sepsis,16,17 severe burns,1,18,19 central nervous system injury,4,5,20 multiple trauma,21 major surgical procedures,22,23 or either respiratory, renal, or hepatic failure.24-26 Furthermore, the risk of bleeding increases in medical ICU patients when they are mechanically ventilated or when they have an underlying coagulopathy.12,27

Because of the risks involved, the use of prophylaxis to prevent stress ulceration has become the standard of care in critically ill patients. Prophylaxis is based on three premises: the morbidity and mortality of stress ulceration are significant; the high-risk population can be identified before the event; and prophylaxis will decrease gastric acidity, may enhance gastric mucosal defense, or both and, thus, prevent mucosal injury or progression to bleeding.28 Clinical trials have shown that antacids, H2-blocker antagonists, and sucralfate reduce the frequency of stress ulcers, and compared with placebo they reduce the risk of upper gastrointestinal tract bleeding significantly.2,6,18,20,29

The use of agents to prevent stress ulcers is not without difficulties and adverse side effects. Antacids require frequent administration and titration; in addition, diarrhea, hypophosphatemia, hypermagnesemia, metabolic alkalosis, or physiologic intolerance may develop.30,32-34 Cimetidine has been associated with occasional reversible confusion, and, rarely, reversible hepatic impairment, mild increases in serum creatinine concentration, thrombocytopenia, and significant drug interactions, especially with lidocaine, phenytoin, warfarin, and theophylline.33-34 However, all H2-blockers have side effects; it is likely that those of ranitidine, nizatidine, and famotidine will parallel the adverse effects of cimetidine as clinical use of the former compounds increases.4 Furthermore, antacids or H2-receptor antagonists have been reported to predispose patients to Gram-negative colonization and infection.44-46 Serious flaws may be found in the two studies that suggested this predisposition. One showed no differences in culture findings between the cimetidine and control groups, except that the control group had NG aspirates colonized more frequently with mixed mouth organisms than did the study group.46 The other study had no controls and inadequate distribution of patients in each study group (ie, 48 patients received antacids, three received cimetidine, nine received both antacids and cimetidine).44 Although sucralfate appears to have no serious side effects, constipation has been a problem.47-49 Interestingly, recent work that purported to show an increased incidence of Gram-negative pneumonia in patients receiving either H2-blockers or antacids, as compared with sucralfate, actually had different results. Driks and colleagues40 studied 130 intensive care patients. Sixty-one received sucralfate, 39 received antacids, 17 received H2-blockers, and 13 received both antacids and H2-blockers. When the patients were evaluated for nosocomial pneumonia, it was found in 23 (17.7 percent) of the 130 study patients—seven (11.5 percent) of the sucralfate group, nine (23.1 percent) of the antacid group, six (46.2 percent) of the antacid plus H2-blocker group, but only one (5.9 percent) of the H2-blocker alone group. Therefore, while the risk of nosocomial pneumonia may be higher when antacids and H2-blockers are used together, this does not appear to be the case when H2-blockers are used as individual agents.

There is increased interest in the use of enteral alimentation to prevent upper gastrointestinal tract bleeding in critically ill patients. Recent studies showed that gastrointestinal hemorrhage decreased significantly among mechanically ventilated patients and in patients with thermal injuries when enteral alimentation was used.7,51,52 In our study population, feeding did not have to be discontinued in any patient and, although complications are known to occur with enteral alimentation,53,54 we noted none of significance.

Our data suggest that, in mechanically ventilated, primarily neurosurgical, or neurologically injured patients receiving intravenous glucocorticoids, enteral alimentation aids in the maintenance of an intragastric pH of more than 4 when the alimeniting solution is delivered to the duodenum or jejunum. In our study, compared with 0.45 percent NaCl, the enteral feeding solution had a statistically significant effect only on the first full day of alimentation. The reason for this is...
not clear, but the first 24 hours may be more stressful than subsequent time periods. Also, the small number of patients in the study may have obscured differences after 24 hours because of β-error. Although differences in pH between the two infusions were noted only during the first 24 hours, antacid was required more often in the control group through the second day, which may imply that the saline solution control patients had more acid requiring neutralization than did the test group. The question remains whether the effect of enteral feeding on gastric pH may be dose dependent.

Entirely different findings have been reported when the H2-receptor antagonist, ranitidine, and continuous gastric alimentation were used to maintain an intragastric pH of more than 4 in patients with chronic obstructive pulmonary disease (COPD) who required mechanical ventilation. Neither ranitidine alone nor the combination of ranitidine plus continuous alimentation into the stomach had better results than placebo.50 That study also reported an increase in serum gastrin levels during gastric alimentation; maintenance of intragastric acidity may have been due to nutrient-induced gastrin secretion. In our study, in patients who underwent DJ alimentation, serum gastrin levels did not significantly change, most likely because enteral feeding would not stimulate release of gastrin from the gastric antrum.

Gastrin is recognized to play a major physiologic role in the stimulation of gastric acid secretion; however, less is known about hormones that induce physiologic down-regulation of acid secretion by the stomach. GIP and several other peptides, including secretin, vasoactive intestinal peptide, neurotensin, somatostatin, peptide YY, and oxyntomodulin, have been proposed as potential enterogastrones, that is, hormones released from the small intestine in response to lipid, which inhibit gastric acid secretion.56-61 Although named originally because of its capacity to inhibit secretion of gastric acid, the role of GIP in the physiologic regulation of gastric acid secretion, as well as the roles of other proposed enterogastrones, remains uncertain. Duodenally administered fat inhibits gastrin release, reduces gastric acid secretion by 75 percent, and does not appear to affect plasma secretin concentration in response to a protein meal, the most potent stimulus of gastrin release.9

Intravenous administration of GIP decreases gastrin-stimulated acid secretion by the stomach and also decreases meal-stimulated gastrin release and associated gastric acid secretion. Immuneneutralization studies with antibodies to GIP have supported a role for GIP in decreasing meal-stimulated secretion of gastric acid.59 GIP release is stimulated principally by fat and carbohydrate. Carbohydrate, a strong stimulus of GIP release and a weak stimulus of gastrin release, is the principal nutrient in Osmolite (13.7 percent w/v), which contains smaller concentrations of lipid (3.6 percent) and protein (3.5 percent). Serum gastrin may be decreased by GIP when the former hormone is increased above a basal level in response to stimulation. Somatostatin, which inhibits release of many polypeptide hormones, decreases gastric acid secretion by directly inhibiting gastric parietal cells and by inhibiting gastrin release. GIP increases somatostatin release and potentiates hydrochloric acid's action in releasing gastric somatostatin. These observations suggest that somatostatin may serve as the mediator of GIP's effects both in reducing gastrin release and in directly inhibiting gastric acid secretion. Peptide YY inhibits gastrin-stimulated secretion of gastric acid and pepsin.60 Oxyntomodulin (glicentin 33 to 69), located principally in the ileum and colon, has been shown to reduce gastrin-stimulated gastric acid secretion.61

Plasma GIP increased significantly with enteral alimentation compared with 0.45 percent NaCl infusion in our study. This suggests that a possible mechanism in stress ulcer protection during enteral alimentation may be DJ alimentation-induced GIP secretion. Since GIP was increased through day 3 (72 hours) but pH differences were noted only on day 1 (24 hours), increased plasma GIP is likely only one of several factors that decreased gastric acidity in our test patients.

One explanation of the effectiveness of enteral alimentation in preventing upper gastrointestinal tract bleeding may be that food in the stomach, or reflux of food from the duodenum, dilutes and neutralizes secreted acid and thereby increases intragastric pH.6 This effect was not observed in a study of COPD patients50 and, indeed, seems unlikely given previous quantitative pH titration studies.9 Luminal substrate may afford protection by providing nutrition needed to maintain and repair gastric and intestinal mucosa and, thereby, may allow mucosal cells to resist injury.7,9-82 Enteraly fed rats are less susceptible to stress-related mucosal damage than intravenously fed control animals.63 Thus, the flow of nutrients to ischemic mucosal cells might be interrupted with intravenous nutrition, but this would not happen if nutrition were administered directly into the stomach. Translocation of viable bacteria through the gastrointestinal tract may cause infection in critically injured patients.64 Translocation occurs when (1) indigenous microflora are disrupted, which allows bacterial overgrowth; (2) host-immune dysfunction occurs; and (3) the physical integrity of the mucosal barrier is altered.

In a population with serious thermal injury, mortality was lower in patients receiving enteral alimentation than in those receiving parenterally supplemented enteral nutrition,65 at least during the first 14 days.
after thermal injury, enteral feeding without parenteral supplementation may decrease the susceptibility to enteric bacterial translocation. These data, in conjunction with others, argue strongly for use of the gastrointestinal tract for nutritional support.

A question regarding the present study involves the use of pH paper, rather than a glass-electrode to measure gastric pH. We used the pH paper because this method is the clinical standard. Our preliminary experiment indicated a good correlation between paper and glass-electrode pH measurements (Fig 2). Recent data, however, suggest that, in other hands and with clinical samples, the correlation is weak.

In conclusion, our data show that DJ alimentation can assist in the maintenance of an intragastric pH of more than 4, can decrease antacid requirements by as much as two thirds compared with 0.45 percent NaCl, and may thus decrease the incidence of stress-related mucosal damage of the upper gastrointestinal tract. The data we have presented suggest that a humorally mediated mechanism is at least partly responsible. Elevation of plasma GIP, without any significant change in serum gastrin concentration, may lower gastric volume and acidity. While further study is required to fully evaluate the relationship between DJ alimentation and stress-related mucosal damage of the upper gastrointestinal tract, we use enteral alimentation for critically ill patients when possible. Our data and those of others in the literature support this conclusion.

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