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Sequential single doses of cisapride, erythromycin, and metoclopramide in critically ill patients intolerant to enteral nutrition: A randomized, placebo-controlled, crossover study

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Sequential single doses of cisapride, erythromycin, and metoclopramide in critically ill patients intolerant to enteral nutrition: A randomized, placebo-controlled, crossover study

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Abstract

Objective: To evaluate the comparative efficacy of enteral cisapride, metoclopramide, erythromycin, and placebo for promoting gastric emptying in critically ill patients with intolerance to gastric enteral nutrition (EN).

Design: A randomized, crossover study.

Setting: Adult medical intensive care unit at a university-affiliated private hospital and trauma intensive care unit at a university teaching hospital.

Patients: Ten adult, critically ill, mechanically ventilated patients not tolerating a fiber-containing EN product defined as a single aspirated gastric residual volume >150 mL or two aspirated gastric residual volumes >120 mL during a 12-hr period.

Interventions: Patients received 10 mg of cisapride, 200 mg of erythromycin ethylsuccinate, 10 mg of metoclopramide, and placebo as 20 mL of sterile water every 12 hrs over 48 hrs. Acetaminophen solution (1000 mg) was administered concurrently. Gastric residual volumes were assessed, and plasma acetaminophen concentrations were serially determined by TDx between 0 and 12 hrs to evaluate gastric emptying.

Measurements and Main Results: Gastric residual volumes during the study were not significantly different between agents. No differences in area under the concentration vs. time curve or elimination rate constant were identified between agents. Metoclopramide and cisapride had a significantly shorter mean residence time of absorption than erythromycin (6.3 ± 4.5 [SEM] mins and 10.9 ± 5.8 vs. 30.1 ± 4.5 mins, respectively [$p < .05$]). Metoclopramide (9.7 ± 15.3 mins) had a significantly shorter time to peak concentration compared with erythromycin and placebo (60.7 ± 8.1 and 50.9 ± 13.5 mins, respectively [$p < .05$]). The time to onset of absorption was significantly shorter for metoclopramide vs. cisapride (5.7 ± 4.5 vs. 22.9 ± 5.7 mins [$p < .05$]).

Conclusion: In critically ill patients intolerant to EN, single enteral doses of metoclopramide or cisapride are effective for promoting gastric emptying in critically ill patients with gastric motility dysfunction. Additionally, metoclopramide may provide a quicker onset than cisapride.

Clinical practice favors early administration of enteral nutrition (EN) in critically ill patients,¹⁻⁵ because EN decreases the frequency rate of septic complications⁶⁻⁸ and reduces gastrointestinal mucosa permeability compared with parenteral nutrition.⁹ Unfortunately, gastrointestinal motility is frequently impaired in critically ill patients.¹⁰ This may result in intolerance to EN,¹¹⁻¹⁴ delayed absorption of enterally administered medications, gastric colonization with Gram-negative bacteria,^{15,16} and an increased risk of nosocomial pneumonia.¹⁷⁻²⁰

Gastrointestinal motility dysfunction most commonly manifests as large volumes of aspirated gastric residuals or vomiting.¹¹⁻¹⁴ Prokinetic agents such as cisapride, erythromycin, and metoclopramide are often utilized to promote gastric emptying in critically ill patients who are intolerant to gastric EN.²¹ The results of studies comparing individual agents with placebo have demonstrated these agents to be effective in increasing gastric emptying, with minimal adverse effects.²²⁻²⁵ Unfortunately, these studies were not selective for patients with proven intolerance to EN.

Although these agents may be effective for facilitating gastric emptying, they possess different pharmacologic properties and may not be equally efficacious. Cisapride acts by selectively enhancing cholinergic motor activity throughout the gastrointestinal tract. Erythromycin acts locally to enhance motilin release from the enterochromaffin cells of the duodenum. Motilin, a 22-amino acid peptide, is responsible for enhancing contractile activity of the gastric antrum and duodenum. Metoclopramide acts as a selective dopamine-2 receptor antagonist to enhance cholinergic-induced peristaltic contractility of the esophagus, gastric antrum, duodenum, and jejunum. No studies directly compare the relative efficacy of these agents for promoting gastric emptying in critically ill patients. The purpose of this study was to evaluate the comparative efficacy of these three prokinetic agents and placebo for promoting gastric emptying in critically ill patients with an intolerance to gastric EN.

Materials and Methods

The protocol was reviewed and approved by the Ethical/Research Committees of Baptist Memorial Hospital and the University of Tennessee, Memphis, TN. The study was conducted between January 1997 and April 1997 in the medical and surgical intensive care units at Baptist Memorial Hospital and in the trauma intensive care unit at the Regional Medical Center at Memphis. Written informed consent was obtained from each patient or closest relative.

Critically ill, mechanically ventilated patients between the ages of 18 and 75 yrs who are not tolerating a fiber-containing EN product (Glucerna and Jevity, Ross Laboratories, Columbus, OH; Isosource VHN, Sandoz Nutrition, Minneapolis, MN) by nasogastric or orogastric administration were eligible for the study. Intolerance to EN was defined as a single aspirated gastric residual volume >150 mL or two aspirated gastric residual volumes >120 mL during a 12-hr period. Volumes measured within 1 hr of enteral administration of medications or free water were not assessed as intolerance.

Patients were not eligible for enrollment if any of the following conditions were present: known allergy or severe adverse reaction to any study medication; concurrent administration of astemizole, terfenadine, cyclosporine, theophylline, warfarin, or a monoamine oxidase inhibitor; administration of any study medication within 24 hrs of enrollment; gastrointestinal bleeding within 72 hrs of eligibility; bowel obstruction or perforation; history of gastrointestinal malabsorptive disease (short-bowel syndrome or Crohn's disease); hepatic cirrhosis or abnormal liver function defined by the presence of two of the following: transaminases more than three times the upper limit of normal, prothrombin time ratio more than two times the upper limit of normal, or total bilirubin more than three times the upper limit of normal; burn injuries; hemodynamic instability defined as a mean atrial pressure of <70 mm Hg despite fluid resuscitation or the administration of intravenous infusions of >5 mg/kg/min dopamine, norepinephrine, or phenylephrine to maintain a mean arterial pressure of >70 mm Hg; pregnancy; diabetes mellitus; or morbid obesity defined by actual body weight \geq 150% of ideal body weight. Acute Physiology and Chronic Health Evaluation (APACHE) III was assessed for the 24-hr period before enrollment and for the 24-hr period at study completion.

All patients received three prokinetic regimens and a single placebo regimen 12 hrs apart in a randomized, crossover manner over 48 hrs. These regimens were enterally administered through the gastric feeding tube in equal volumes and consisted of 10 mg of cisapride (Propulsid, Janssen Pharmaceutical, Titusville, NJ) as 10 mL of suspension (1 mg/1 mL), followed by 10 mL of sterile water and 200 mg of erythromycin ethylsuccinate (Abbott Laboratories, North Chicago, IL) as 5 mL of suspension (200 mg/5 mL), followed by 15 mL of sterile water and 10 mg of metoclopramide (Reglan, A.H. Robins Company, Richmond, VA) as 10 mL of syrup (1 mg/mL), followed by 10 mL of water and placebo as 20 mL of sterile water. These doses were chosen because they represent the doses used in other studies and are frequently used clinically. Although other studies have frequently used intravenous metoclopramide and erythromycin, enteral delivery was chosen for all products to standardize the effect of delayed absorption for each agent.

To assess the possible impact of prokinetic agents on gastric emptying, gastric residual volumes were aspirated, measured, and replaced at baseline and at 180, 360, and 720 mins of each study regimen. Correct antral placement of the gastric feeding tube was assessed radiographically on a daily basis and confirmed before each regimen by auscultating over the stomach while injecting air. EN was administered during the study at a constant rate that did not exceed 50 mL/hr.

Gastric emptying was assessed by the acetaminophen absorption model.²⁶⁻²⁹ Immediately before administering each study drug or the placebo, 1000 mg of enteral acetaminophen (Zenith Goldline Laboratories, Ft. Lauderdale, FL) as 31.25 mL of solution (32 mg/mL) was administered followed by 10 mL of sterile water. Arterial blood samples of 3 mL were taken from an indwelling catheter at baseline and seven additional times between 30 mins and 720 mins to determine serum acetaminophen concentrations. Blood samples were collected in test tubes without heparin, transported on ice, and centrifuged for 15 mins at 3000 rpm. Sera were

separated and stored at -70°F (-60.1°F) until acetaminophen concentrations were measured using a fluorescence polarization assay (TDxFLx, Abbott Diagnostics, Chicago, IL).

Pharmacokinetic Analysis. Compartmental modeling of acetaminophen concentrations was used to assess gastric emptying. Acetaminophen serum concentrations (C) as a function of time (t) were fitted by the computer program NONLIN³⁰ using the following equation:

$$C = \frac{ka F_{Dose}}{V(ka - K)} (e^{-K(t-t_{lag})} - e^{-ka(t-t_{lag})}) + C_R e^{-K(t-t_{lag})}$$

where ka and K are the first-order rate constants describing absorption and elimination, respectively, F is the bioavailability, V is the volume of distribution, t_{lag} is the time elapsed between administration and onset of absorption, and C_R is the acetaminophen serum concentration at the time the dose is administered. The computer program provides the least square estimates of the variables: F/V, ka, K, and t_{lag}. The area under the acetaminophen serum concentration vs. time curve (AUC) was determined by:

$$AUC = \frac{F_{Dose}}{V_K}$$

The mean residence time for absorption (MRT_{ABS})³¹ was determined by:

$$MRT_{ABS} = \frac{1}{ka}$$

Time required to achieve peak serum concentrations of acetaminophen (t_p) was determined by:

$$t_p = \frac{\ln \left[\frac{ka}{K} \right]}{ka - K}$$

An absorption phase was not evident in several patients; consequently, their serum concentration vs. time data were fitted using the following equation:

$$C = \frac{F_{Dose}}{V} e^{-Kt} + C_R e^{-Kt}$$

The AUC in these patients was calculated using the second equation, and MRT_{ABS} was 0.

Table 1. Patient characteristics

Patient	Age (Yrs)	Gender/Race	Clinical Diagnosis	Regimen Order
1	26	M/B	MVA/subdural hematoma	PLA, CIS, MET, ERY
2	49	M/B	Spontaneous subarachnoid hemorrhage	CIS, ERY, PLA, MET
3	70	F/W	Pneumonia/acute renal failure	ERY, CIS, MET, PLA
4	27	F/W	MVA/subarachnoid hemorrhage	CIS, MET, ERY, PLA
5	55	M/B	Spontaneous subarachnoid hemorrhage	ERY, PLA, MET, CIS
6	43	F/W	Pneumonia/sepsis	CIS, MET, PLA, ERY
7	75	M/W	Pneumonia/sepsis/ARDS	MET, ERY, PLA, CIS
8	60	M/B	Spontaneous subarachnoid hemorrhage	MET, PLA, ERY, CIS
9	70	F/B	Respiratory arrest	PLA, CIS, MET, ERY
10	75	M/W	Carotid artery stenosis/sepsis	PLA, MET, CIS, ERY

M, male; F, female; W, white; B, black; MVA, motor vehicle accident; ARDS, acute respiratory distress syndrome; PLA, placebo; CIS, cisapride; MET, metoclopramide; ERY, erythromycin.

For a power of 0.8 and a significance level of 0.05, it was originally calculated that ten patients were required to demonstrate a difference of 120 mins in total time to peak serum acetaminophen concentration ($t_{Lag} + t_p$). Unlike previous studies, the present study was designed to identify specific components of acetaminophen absorption (t_{Lag} , t_p , MRT_{ABS}) to allow for less variability than that used in the original power calculations. Two-way analysis of variance (ANOVA) with Fisher's Least-Significant-Difference test was used to assess differences between the individual study regimens. A three-way ANOVA (main effect of administration order added) with Fisher's least significant difference test was used to assess the impact of either repeated doses of prokinetic agents or patient improvement during the 48-hr study period. Statistical significance was defined as $p < .05$.

Results

Ten patients were enrolled. Table 1 summarizes the patient characteristics and order of study regimen administration. Two patients (Nos. 3 and 6) were excluded from analysis because of their complete intolerance of EN with residuals >250 mL requiring discontinuation of enteral feedings. Two additional patients (Nos. 9 and 10) were excluded from analysis for the cisapride regimen because their serum concentration vs. time profiles could not be reliably fitted. This left a total of 30 study regimens to be evaluated in eight patients. Of the patients included in the final analysis, none received continuous infusion of dopamine or norepinephrine. All received histamine-2 receptor antagonists, and four patients received intermittent opioid bolus doses (>2 doses/12-hr study regimen). The APACHE III scores for patients included in the final analysis were 60 ± 25 and 64 ± 26 before and after the study, respectively. The mean aspirated gastric residual volume for enrollment was 211 ± 103 mL, at which time the mean EN rate was 51 ± 16.6 mL/hr.

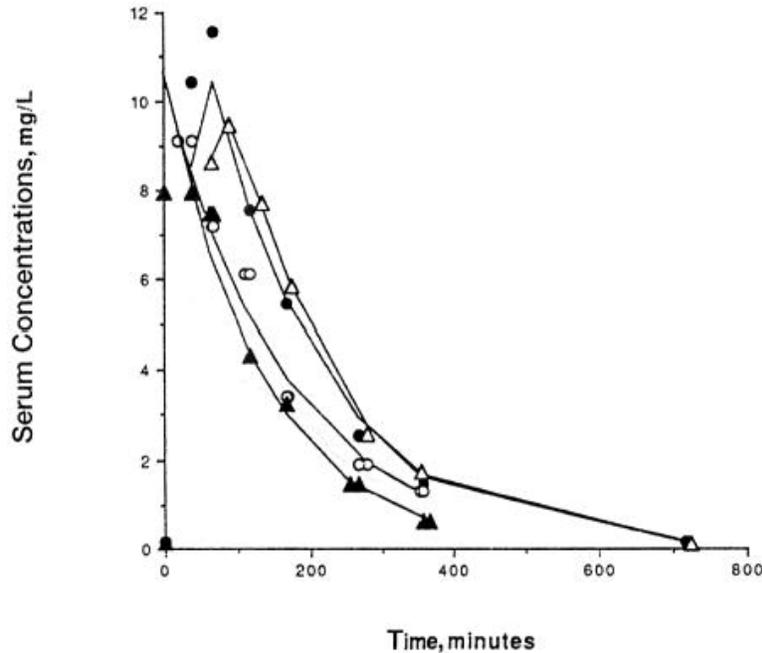


Figure 1. Effect of prokinetic drugs on the pharmacokinetics of acetaminophen. Serum concentrations (*ordinate*) vs. time (*abscissa*) after the oral administration of 1 g of acetaminophen given with cisapride (*filled triangles*), metoclopramide (*open triangles*), erythromycin (*filled circles*), and placebo (*open circles*). The *symbols* are experimental observations, and the *lines* are computer fitted by first or fifth equation in the text.

A one-compartment open pharmacokinetic model fit the acetaminophen serum concentration vs. time data well (Fig. 1). Values for the coefficient of correlation (r^2) of the fit varied between .84 and 1.0; 90% of the computer fit had r^2 values of $>.9$. The pharmacokinetic variables are summarized in Table 2. Cisapride and metoclopramide significantly shortened the MRT_{ABS} compared with erythromycin (6.5 ± 6.1 mins and 8.6 ± 5.1 vs. 28.1 ± 5.1 mins, respectively; $p < .05$), but only cisapride tended to shorten MRT_{ABS} compared with placebo (6.5 ± 6.1 vs. 20.5 ± 5.1 mins; $p = .09$). No significant differences were observed for time to onset of absorption (t_{Lag}). Both cisapride and metoclopramide tended to accelerate absorption once it had started to occur (t_p) compared with erythromycin (27.3 ± 13.3 mins and 33.8 ± 14.5 vs. 63.8 ± 10.1 mins, respectively; $p = .097$), but only metoclopramide tended to accelerate t_p compared with placebo (33.8 ± 14.5 vs. 65.1 ± 11.7 mins; $p = .08$). No significant difference in AUC or k values was observed, suggesting that the clearance and/or bioavailability of acetaminophen were not affected by coadministration of prokinetic drugs.

Table 3 summarizes the cumulative EN volume and aspirated gastric residual volumes. The volume of EN administered and aspirated gastric residual during the 12-hr study period did not differ between the study regimens. The order of administration did not affect the volume of aspirated gastric residuals ($p = .81$) during the study period.

Table 1 outlines the order of administration with respect to the study regimens. Several pharmacokinetic variables were affected by the order of administration. The fourth study dose

Table 2. Pharmacokinetic variables for study regimens

Regimen (No.)	t_{Lag}	MRT_{ABS}	t_p	k (L/min $\times 10^{-3}$)	AUC (mg/min/L)
CIS (6)	18.3 \pm 6.2	6.5 \pm 6.1 ^{a,b}	27.3 \pm 13.3 ^{c,d}	8.2 \pm 2.1	2270 \pm 236
ERY (8)	13.1 \pm 5.2	28.1 \pm 5.1	63.8 \pm 10.1	8.6 \pm 1.7	2306 \pm 196
MET (8)	7.9 \pm 5.2	8.6 \pm 5.1 ^a	33.8 \pm 14.5 ^{c,e}	8.5 \pm 1.7	2254 \pm 196
PLA (8)	12.5 \pm 5.2	20.5 \pm 5.1	65.1 \pm 11.7	6.0 \pm 1.7	2581 \pm 196

Data are reported as mean \pm SEM; No., number of patients; t_{Lag} , time to onset of absorption; MRT_{ABS} , time of absorption; t_p , time to peak concentration; k , elimination rate constant; AUC, area under the concentration-time curve; CIS, cisapride; ERY, erythromycin; MET, metoclopramide; PLA, placebo.

^a $p < .05$ vs. ERY; ^b $p < .05$ vs. PLA; ^c $p < .09$ vs. ERY; ^d $p < .11$ vs. PLA; ^e $p < .10$ vs. PLA.

Table 3. Volume of enteral nutrition and gastric residuals for study regimens

Regimen (No.)	12-Hr EN Intake (mL)	Baseline Residual (mL)	180-min Residual (mL)	360-min Residual (mL)	720-min Residual (mL)	Total Residual (mL)
CIS (8)	448 \pm 208	49 \pm 84	25 \pm 32	32 \pm 48	35 \pm 61	142 \pm 146
ERY (8)	455 \pm 144	16 \pm 17	19 \pm 22	13 \pm 26	22 \pm 27	69 \pm 25
MET (8)	448 \pm 220	28 \pm 36	30 \pm 66	27 \pm 42	40 \pm 84	125 \pm 164
PLA (8)	395 \pm 131	27 \pm 25	27 \pm 37	59 \pm 79	14 \pm 10	127 \pm 115

Data are reported as mean SEM; No., number of patients; EN intake, volume of enteral nutrition received (12 hrs); CIS, cisapride; ERY, erythromycin; MET, metoclopramide; PLA, placebo.

Table 4. Pharmacokinetic variables for study regimens accounting for order of administration

Regimen (No.)	t_{Lag}	MRT_{ABS}	k (L/min $\times 10^{-3}$)	AUC (mg/min/L)
CIS (6)	22.9 \pm 5.7	10.9 \pm 5.8 ^a	7.2 \pm 2.1	2312 \pm 269
ERY (8)	15.5 \pm 4.5	30.1 \pm 4.5	8.0 \pm 1.6	2329 \pm 209
MET (8)	5.7 \pm 4.5 ^b	6.3 \pm 4.5 ^{a,c}	8.9 \pm 1.6	2244 \pm 210
PLA (8)	10.1 \pm 4.5	18.5 \pm 4.5	6.7 \pm 1.6	2559 \pm 209

Data are reported as mean \pm SEM; No., number of patients; t_{Lag} , time to onset of absorption; MRT_{ABS} , time of absorption; k , elimination rate constant; AUC, area under the concentration-time curve; CIS, cisapride; ERY, erythromycin; MET, metoclopramide; PLA, placebo.

^a $p < .05$ vs. ERY; ^b $p < .05$ vs. CIS; ^c $p < .07$ vs. PLA.

was associated with a significantly accelerated time-to-absorption onset (t_{Lag}) compared with the first, second, and third doses ($p < .03$) and a significantly shortened time of absorption (MRT_{ABS}) compared with the first and third doses ($p < .03$). Table 4 summarizes the pharmacokinetic variables for each study regimen accounting for the impact of order of administration (three-way ANOVA). No significant difference in AUC or k values was observed, suggesting that the clearance and/or bioavailability of acetaminophen were not changed over time. Similar to the comparison of study regimens without regard to order of administration, cisapride and metoclopramide significantly shortened the absorption time (MRT_{ABS}) compared with erythromycin (10.9 \pm 5.8 and 6.3 \pm 4.5 mins vs. 30.1 \pm 4.5 mins, respectively; $p < .05$). Unlike the previous comparison, cisapride did not tend to shorten MRT_{ABS} compared with placebo. However, metoclopramide did tend to shorten MRT_{ABS} compared with placebo (6.3 \pm 4.5 vs. 18.5 \pm 4.5 mins; $p = .07$). Moreover, metoclopramide significantly accelerated the onset of absorption (t_{Lag}) compared with cisapride (5.7 \pm 4.5 vs. 22.9 \pm 5.7 mins; $p < .05$). Effect of order of administration on time to peak (t_p) could not be assessed because of the limited sample size.

Discussion

Early administration of EN to critically ill patients is important because it stimulates gastrointestinal motility,^{9,12} blunts gut lumen atrophy, and may prevent mucosal attachment of bacteria³²⁻³⁶ and bacterial translocation by maintaining the integrity of the mucosal membrane.⁹ Randomized studies^{6,7} and a subsequent meta-analysis⁸ have demonstrated that the frequency rate of septic complications is significantly reduced with EN compared with parenteral nutrition. However, intolerance to EN is a risk factor for morbidity and mortality rates in critically ill patients.¹¹ This is of concern because the reported frequency rate of intolerance is 48%-52% with the development of elevated volumes of aspirated gastric residuals representing the primary reason for discontinuing EN.¹¹⁻¹⁴ Gastroduodenal reflux in critically ill patients is likely the result of deficiencies of phase 3 contractions in the gastric antrum to produce dyskinetic propagation of hypokinetic contractions.¹⁰ These irregularities may be related to dysfunction of the interstitial cells of Cajal that are concentrated in the gastric antrum and act as the "pacemaker" of gastrointestinal motility.³⁷ Although these mechanisms were postulated, other factors may be involved and may differ based on the cause of the delayed gastric emptying. Further studies must be conducted to further define these mechanisms and to identify differences between individual patient subsets in the ICU.

Cisapride, metoclopramide, and erythromycin are often used in clinical practice to promote gastric motility and possibly facilitate tolerance to EN.²¹ The purpose of our study was to compare directly the efficacy of one dose of these agents with placebo in patients with intolerance to EN. No study compared these agents for this indication. In fact, studies in critically ill patients conducted to date have not enrolled patients with documented EN intolerance. The current study was designed to administer all three agents by the enteral route to avoid differences in effect that might be seen by administering metoclopramide and erythromycin intravenously and cisapride enterally. Although previous differences between enteral and intravenous erythromycin are seen in diabetic gastroparesis,³⁸ single-dose enteral erythromycin has been shown to be effective.³⁹

We evaluated gastric emptying with the acetaminophen absorption model. Studies in healthy,^{26,40} diabetic,²⁷ hospitalized,²⁸ and critically ill²⁹ subjects have demonstrated that acetaminophen absorption is significantly correlated with gastric emptying. This model has been used in other studies to assess gastric emptying in subsets of critically ill patients^{41,42} and studies evaluating prokinetic agents.^{23-25,43,44}

Most studies to date have used non-compartmental or graphic methods to estimate AUC during a defined period of time (usually the first 60 mins after acetaminophen administration), peak concentration of acetaminophen, and the time at which the peak concentration was observed. However, several limitations exist with using these noncompartmental or graphic methods to evaluate gastric emptying. AUC is determined by clearance and bioavailability and has nothing to do with absorption rate. Using peak concentrations is confounded by other factors that can obscure the effects of prokinetic drugs on the absorption rate of acetaminophen. Peak

concentrations are not only determined by the absorption rate but also by bioavailability, clearance, volume of distribution, lag time and the timing of blood samples. Moreover, the time at which peak concentrations are observed is determined by the elimination rate constant, lag time, and timing of blood samples. The modeling approach used in the present study allowed us to compare the effects of prokinetic drugs on the absorption rate of acetaminophen, as determined by MRT_{ABS} , and to avoid the effects of other pharmacokinetic variables, lag time, and timing of blood samples, which can obscure the effects of prokinetic drugs on the absorption rate of acetaminophen. We believe that compartmental analysis of acetaminophen serum concentration vs. time data is superior to other methods of assessing gastric emptying in patients.

Two patients were excluded from analysis for all study regimens. These two patients continued to have elevated volumes of aspirated gastric residuals throughout the entire study period. Analysis of serum concentration vs. time did not reveal substantial absorption, and thus, the pharmacokinetic variables were indeterminate. Two additional patients were excluded from analysis for the cisapride regimen because we were unable to perform compartmental pharmacokinetic modeling with the data. Analysis of concentration vs. time for these two regimens demonstrated two peak serum concentrations. Despite exclusion of these subjects from the final analysis, sufficient differences were detected to identify statistically significant differences ($p < .05$) between the agents.

Pharmacokinetic analysis without respect to the order of study regimen administration (Table 2) showed that cisapride and metoclopramide significantly accelerated gastric emptying compared with erythromycin, and they tended to accelerate gastric emptying compared with placebo. Taking into account the order of study regimen administration (Table 4), cisapride and metoclopramide maintained significance for gastric emptying compared with erythromycin. In contrast, metoclopramide and erythromycin administration for 3 wks was equally effective for promoting gastric emptying in a randomized, crossover study involving 13 patients with diabetic gastroparesis.⁴⁵ With respect to order of administration, cisapride lost any trend toward significance compared with placebo but metoclopramide demonstrated significance compared with placebo. Moreover, metoclopramide significantly accelerated the onset of absorption compared with cisapride. This is in contrast to studies in healthy adults⁴⁶ and patients with morphine-induced gastric motility dysfunction⁴⁷ or diabetic gastroparesis⁴⁸ that have shown cisapride to significantly improve gastric emptying compared with metoclopramide.

The changes in pharmacokinetic variables that occurred with analysis of administration order may be attributable to the fact that three of the six patients included in the final analysis for cisapride regimen received cisapride as the fourth dose (Table 1). For all study regimens combined, the fourth dose significantly shortened t_{Lag} compared with all other doses and significantly accelerated MRT_{ABS} compared with the third and first dose. Therefore, our results can be interpreted only after order of administration is included in the analysis. The lack of benefit with erythromycin is likely not related to administration order because three of the eight patients in the final analysis received erythromycin as the fourth dose.

Two factors may explain the effect of order identified in the current study. An improvement in physiologic status could account for an increase in gastric emptying. Another explanation could be the effect of cumulative doses of prokinetic agents in promoting gastric emptying. In our study, the mean APACHE III score did not change with time and no patient demonstrated a substantial improvement in APACHE III score during the study period. The 12-hr interval between the study regimens was chosen to allow for adequate clearance of the prokinetic agents to minimize any carryover effect while allowing the study to be completed in a time frame (48 hrs) that would minimize any effects related to physiologic changes. No studies to date have evaluated the effects of repeated prokinetic administration compared with single-dose regimens.

Of the eight patients included in the final analysis, five received Jevity, two received Isosource VHN, and one received Glucerna. These patients were able to maintain EN throughout the entire study. To limit the effect that EN volume may have on gastric emptying, nutrition was maintained at a constant rate of <50 mL/hr for the 48-hr crossover study period. The mean volume of aspirated gastric residuals did not change over time for a particular study regimen nor did they differ between study regimens (Table 3). This lack of difference may be the result of the large amount of variability seen in measured residuals. Because aspirated gastric residual volumes are the only objective clinical measurement of tolerance, residual assessment is advocated;⁴⁹⁻⁵² however, the volume of aspirated gastric residuals that defines intolerance is controversial.^{53,54}

Studies comparing individual agents with placebo have demonstrated prokinetic agents to be effective for promoting gastric emptying in critically ill patients.²²⁻²⁵ In a randomized, controlled study of 21 critically ill patients, Spapen et al.²² showed that cisapride promotes gastric emptying as assessed by the volume of gastric residuals and bedside scintigraphy compared with placebo. During the 7-day study period, the mean gastric residual volume was significantly higher and gastric emptying significantly slower in the placebo group than in the cisapride group ($p < .005$). In a randomized, double-blind study, Heyland et al.²³ compared cisapride with placebo using an acetaminophen absorption model in 72 critically ill patients not receiving EN support. Compared with placebo, cisapride significantly decreased the time to peak plasma acetaminophen concentration ($p = .02$) and significantly elevated the maximum plasma acetaminophen concentration ($p < .05$). In a randomized, placebo-controlled, double-blind study, Goldhill et al.²⁴ compared rectal cisapride with placebo in 23 critically ill patients not receiving EN. Although the authors concluded no differences between cisapride and placebo, the area under the concentration vs. time curve for the first 60 mins tended to be higher with cisapride than placebo ($p < .08$).

Our methodology differed from other studies that utilized the acetaminophen absorption model because we administered acetaminophen and the prokinetic regimens simultaneously, whereas other studies in critically ill patients administered acetaminophen 60-120 mins after cisapride, thus allowing the absorption of cisapride to occur before acetaminophen administration. We did not demonstrate cisapride to be significantly better than placebo for promoting gastric emptying. These findings are similar to the randomized, double-blind, placebo-controlled study by

Rowbotham et al.⁴³ involving 12 healthy adults. They demonstrated that oral cisapride did not accelerate gastric emptying compared with placebo when acetaminophen is administered simultaneous with the study drug.

Simultaneous administration provided comparison of first-dose efficacies between prokinetic agents because absorption of the prokinetic agent constitutes a component of single-dose efficacy. Our results may differ from other studies because the absorption of cisapride may be delayed to prolong the effect. This may explain why metoclopramide significantly shortened the time to onset of acetaminophen absorption compared with cisapride without shortening the time to peak absorption once absorption was initiated. Moreover, the dual serum peak concentrations for two of the cisapride regimens may be explained by a change in the absorption rate of acetaminophen once cisapride was absorbed. The lack of statistical improvement over placebo could also be the result of the limited sample size in the cisapride group ($n = 6$) because MRT_{ABS} was >40% shorter with cisapride compared with placebo.

In a randomized, double-blind, placebo-controlled, crossover study of ten critically ill patients, Dive et al.²⁵ demonstrated the erythromycin enhances antral motility and accelerates gastric emptying compared with placebo. The mean number and amplitude of contractions and motility index were increased significantly during the first hour after erythromycin infusion ($p < .005$). Additionally, the time to reach peak plasma acetaminophen concentration was shorter, and the maximum plasma acetaminophen concentration and AUC during the first 60 mins were increased over placebo ($p < .007$). We did not demonstrate erythromycin to be effective for promoting gastric emptying compared with placebo or other prokinetic agents. However, our methodology differed because we administered acetaminophen simultaneously with enteral erythromycin; whereas Dive et al.²⁵ administered acetaminophen 60 mins after intravenous erythromycin. Single^{38,39,55,56} and repeated doses^{38,57-60} of erythromycin have significantly enhanced gastric emptying compared with placebo in studies involving healthy adults^{39,55,56} and patients with diabetic gastroparesis^{38,57,58} or bowel resection^{59,60}; however, these studies did not utilize the acetaminophen absorption model to assess gastric motility.

Although no study has directly compared the effectiveness of metoclopramide with placebo for the promotion of gastric emptying in adult critically ill patients, this agent is commonly used for this clinical indication and several studies have demonstrated metoclopramide to be effective for facilitating immediate placement of transpyloric feeding tubes.⁶¹⁻⁶³ Moreover, intravenous administration of metoclopramide was more effective than placebo for enhancing gastric emptying in patients with morphine-induced gastric dysfunction,^{44,64} head injury,⁶⁵ diabetic gastroparesis,²⁷ and preterm infants;⁶⁶ however, only two of these studies^{27,44} utilized the acetaminophen absorption model to assess gastric motility.

In summary, our study is the first to compare prokinetic agents and the first to enroll patients with EN intolerance. We conclude that single enteral doses of metoclopramide or cisapride are effective for promoting gastric emptying in critically ill patients with gastric motility dysfunction. Metoclopramide may provide a quicker onset than cisapride. Future studies are

needed to compare multiple doses of prokinetic agents and intravenous administration with enteral administration.

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