Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness*

Nam Q. Nguyen, MBBS (Hons), FRACP; Marianne J. Chapman, BMBS, FANZCA, FJFICM; Robert J. Fraser, MBBS, FRACP, PhD; Laura K. Bryant, BHSc; Richard H. Holloway, MBBS, FRACP, MD

Objective: **This study aimed to a) compare the efficacy of metoclopramide and erythromycin in the treatment of feed intolerance in critical illness; and b) determine the effectiveness of "rescue" combination therapy in patients who fail monotherapy.**

Design: **Randomized controlled trial.**

Setting: **Level III mixed medical and surgical intensive care unit.**

Patients: **Ninety mechanically ventilated, medical patients with feed-intolerance (gastric residual volume ≥250 mL).**

Interventions: **Patients received either metoclopramide 10 mg intravenously four times daily (n = 45) or erythromycin 200 mg intravenously twice a day (n = 45) in a double-blind, randomized fashion. After the first dose, nasogastric feeding was commenced and 6-hourly nasogastric aspirates were performed. If a gastric residual volume ≥250 mL recurred on treatment, open-label, combination therapy was given. Patients were studied for 7 days. Successful feeding was defined as 6-hourly gastric residual volume <250 mL with a feeding rate ≥40 mL/hr.**

Measurements and Main Results: **Demographic data, blood glucose levels, and use of inotropes, opioids, and benzodiazepines were similar between the two groups. After 24 hrs of treatment, both monotherapies reduced the mean gastric residual volume (metoclopramide, 830 ± 32 mL to 435 ± 30 mL, $p < .0001$; erythromycin, 798 ± 33 mL to 201 ± 19 mL, $p < .0001$) and improved the proportion of patients with successful feeding (metoclopramide = 62% and erythromycin = 87%). Treatment with erythromycin was more effective than metoclopramide, but the effectiveness of both treatments declined rapidly over time. In patients who failed monotherapy, rescue combination therapy was highly effective (day 1 = 92%) and maintained its effectiveness for the study duration (day 6 = 67%). High pretreatment gastric residual volume was associated with poor response to prokinetic therapy.**

Conclusions: **In critical illness, erythromycin is more effective than metoclopramide in treating feed intolerance, but the rapid decline in effectiveness renders both treatments suboptimal. Rescue combination therapy is highly effective, and further study is required to examine its role as the first-line therapy. (Crit Care Med 2007; 35:483–489)**

KEY WORDS: erythromycin; metoclopramide; prokinetic therapy; feed intolerance; critical illness

Adequate nutritional support is important in critical illness. The enteral route has become the preferred method of nutrient delivery, particularly in patients with prolonged intensive care admissions, as it is cheaper, has less septic complications, and is associated with better gut mucosal barrier function than the parenteral route (1–6). However, slow gastric emptying leading to intolerance of nasogastric (NG) feeding occurs in 40–50% of critically ill patients (1–3). This not only results in inadequate nutritional support but also constitutes a major risk factor for gastroesophageal reflux and aspiration (3–6), with potential adverse effects on both morbidity and mortality (4–7).

Currently available therapeutic options for the management of delayed gastric emptying and feed intolerance in critically ill patients are prokinetic therapy, postpyloric feeding, or total parenteral nutrition (8–10). Of these, treatment with prokinetic agents is usually regarded as first-line therapy (10–12). Despite its prominence in clinical practice, data supporting the effectiveness of prolonged prokinetic therapy in feed intolerant critically ill patients are limited. This reflects the lack of large randomized control trials with a primary end point of successful feeding, as most studies have examined either the effectiveness of a single-dose therapy on gastric emptying or NG tube migration in a limited number of unselected critically ill patients (13–19). In addition, the probable development of tachyphylaxis with prokinetic agents raises further questions about their long-term effectiveness (20–22).

Metoclopramide (a dopamine agonist) and low-dose erythromycin (a motilin agonist) are the two most widely used prokinetic agents in critically ill patients. A single intravenous dose of metoclopramide has been reported in several studies to improve gastric emptying in critically ill patients (13–15), but its effect on the success of feeding is unknown. In contrast, 3 mg/kg of erythromycin is associated with both increased gastric emptying and improved feeding success in previously feed-intolerant critically ill patients (16–19). Many critical care units now initiate either metoclopramide or erythromycin to treat feed intolerance, and therapy is often continued until enteral feeding is ceased. If monotherapy fails, a

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From the Department of Gastroenterology, Hepatology and General Medicine (NQN, RHH) and Department of Intensive Care (MJC), Royal Adelaide Hospital, South Australia; University Department of Medicine, University of Adelaide, South Australia (RJF); and Investigation and Procedures Unit, Repatriation General Hospital, South Australia (LKB).

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combined administration of erythromycin and metoclopramide may be effective. Other approaches include total parenteral nutrition and placement of a postpyloric feeding tube. Combination therapy is the preferred treatment due to its ease of use; however, its effectiveness in managing feed intolerance in critically ill patients has not been formally assessed.

As there are limited data on the longer term effectiveness of erythromycin, metoclopramide, or combination therapy in the management of feed intolerance in critically ill patients, the aims of the current study were a) to compare chronic administration of metoclopramide and erythromycin in the management of feed intolerance; and b) to determine the effectiveness of "rescue" combination therapy in patients who fail monotherapy.

MATERIALS AND METHODS

Study Design. The study was conducted as a two-way randomized, double-blind, parallel-group study comparing the 7-day effectiveness of metoclopramide (10 mg intravenously four times per day) and erythromycin (200 mg intravenously twice per day) in improving the success of NG feeding in feed-intolerant intensive care unit patients.

Subjects. One-hundred and seven consecutive mechanically ventilated patients who failed NG feeding were enrolled into the study over a 12-month period (August 2004 to August 2005). Failure of feeding was defined clinically as a 6-hourly gastric residual volume (GRV) ≥250 mL (5, 7, 16) ≥6 hrs after commencing enteral feeding (Nutrison Standard: Gluten- and lactose-free feed; 100 kcal, 4 g of protein, 12.3 g of carbohydrate, 3.9 g of fat per 100 mL; Nutricia N.V., Zoetermeer, The Netherlands) at a rate ≥40 mL/hr. The cutoff GRV of 250 mL is a clinical marker of feed intolerance in our unit and has been previously used by other studies that examined the issue of feed intolerance (14–16). A 12-Fr or larger NG tube was placed in the stomach before the study, with the distal tip 10 cm below the gastroesophageal junction and clearly visible in the stomach on plain abdominal radiograph.

Exclusion criteria included a) administration of prokinetic drugs (metoclopramide, cisapride, or erythromycin) within the previous 24 hrs; b) known allergy to a macrolide antibiotic or metoclopramide; c) administration of drugs known to interact with erythromycin (carbamazepine, cyclosporine, theophylline, aminophylline, digoxin, oral anticoagulants); d) recent major abdominal surgery (within 6 wks) or past history of esophagectomy or partial/total gastrectomy; e) suspected bowel obstruction or perforation; f) myasthenia gravis; or g) evidence of liver dysfunction (i.e., more than three times elevation above the upper end of normal range of bilirubin, γ-glutamyl transferase, aspartate transaminase, alanine transaminase, or lactate dehydrogenase). Patients were excluded from the data analysis if their participation in the trial was <7 days.

The Human Research Ethics Committee of the Royal Adelaide Hospital approved the study, and written informed consent was obtained from the patients' next of kin before enrollment. The study was performed according to the Australian National Health and Medical Research Committee Guidelines for the conduct of research on unconscious patients.

Protocol. At enrollment, enteral feeding was temporarily stopped and the stomach was aspirated to remove all gastric contents. The GRV aspirated via the NG tube over the previous 24 hrs was documented. Patients were then given either erythromycin or metoclopramide in a randomized, double-blind fashion. After the first dose of study medication, NG feeding was recommenced at a rate of 40 mL/hr. The study drug was administered as a slow intravenous bolus over 10 mins at 4 am, 10 am, 4 pm, and 10 pm.

1. Metoclopramide: Patients received four time-labeled syringes containing 10 mg of metoclopramide in 10-mL volume.
2. Erythromycin: Patients received two "active-drug" syringes containing 200 mg of erythromycin (at 10 am and 10 pm) and two "placebo" (0.9% saline) syringes (at 4 am and 4 pm), all of 10 mL volume.

Manual aspiration of the gastric contents using a 60-mL syringe was performed 2 hrs after administration of the first dose of the study drug and then 6-hourly over the following 7 days. The GRVs obtained were recorded. If the initial 6-hourly GRV was <250 mL, the feeding rate was increased by 20 mL/hr every 6 hrs up to the patient's predicted requirement rate, which was determined independently by a dietitian and was based on the patient's body mass index (60–100 mL/hr). In patients who were feed-tolerant (i.e., GRV continuously <250 mL), the assigned therapy was continued for 7 days or until discharge. At all time points, successful feeding was defined as a GRV <250 mL with a feeding rate ≥40 mL/hr.

Failure with either erythromycin or metoclopramide was defined as a) two or more high GRVs (i.e., ≥250 mL) within the first 24 hrs; or b) any 6-hourly GRV ≥250 mL thereafter. All patients who failed monotherapy and required further enteral feeding were given open-label rescue combination therapy of intravenous metoclopramide (10 mg four times daily) and intravenous erythromycin (200 mg twice daily). Combination therapy was continued for ≥6 days and only ceased if enteral feeding was no longer required as judged by the treating intensive care specialist. For patients who continued to have a high GRV despite combination therapy, all prokinetic agents were discontinued and a postpyloric feeding tube was placed endoscopically to allow delivery of nutrition.

Statistical Analysis. The study code was not broken until completion of the study. *A priori*, the number of patients enrolled was determined using power calculations to show a 20% significant difference in the rate of successful feeding between the different arms of therapy, with a p value <.05. Statistical analysis was performed independently by a statistician in the Department of Public Health at the Royal Adelaide Hospital.

Differences in demographic characteristics between critically ill patients treated with erythromycin and metoclopramide were assessed using the unpaired Student's t-test for continuous data and chi-square test for categorical data. Differences in the success of feeding between the treatment groups over time were assessed using Kaplan-Meier survival curves with a log-rank test. Differences in the time to develop feed intolerance while on therapy between the two treatment groups were expressed as median and interquartile range and were compared using Mann-Whitney U test. Risk factors (demographic data, duration in intensive care unit, Acute Physiology and Chronic Health Evaluation II score, pretreatment GRV, diagnosis, blood glucose level, biochemistry, medications, and mode of ventilation) for poor response to prokinetic therapy were assessed by logistic regression and the Cox proportional hazards model. All data are mean ± SEM. A p value of <.05 was considered statistically significant.

RESULTS

Of 107 enrolled patients, 17 (nine on metoclopramide and eight on erythromycin) were excluded from the analysis because their participation in the trial was <7 days. Reasons for withdrawal from the trial included early recovery and ability to have oral intake (n = 9), death from withdrawal of medical therapy (n = 7), and massive gastrointestinal bleeding (n = 1). One patient with myasthenia gravis was withdrawn from the trial after the first dose, as erythromycin has been reported to exacerbate myasthenia gravis crisis (23).

Ninety patients completed the study, of whom 45 were treated with erythromycin (31 males, 52 ± 2 yrs) and 45 with metoclopramide (35 males, 46 ± 2 yrs). The demographic characteristics (Acute Physiology and Chronic Health Evaluation II, duration and type of mechanical ventilation before study, pretreatment 24-hr GRV, sedation regimen, and admission diagnosis) and mean blood glucose concentrations were similar between the two treatment groups (Table 1). The feeding rate achieved before the development of feed intolerance was similar between the 2 groups (erythromycin, 47 ± 2 vs. metoclopramide, 43 ± 2 mL/hr). The

Table 1. Demographic characteristics of critically ill patients who were treated with erythromycin or metoclopramide: Gastric residual volume (GRV) is the total over the previous 24-hr period

	Metoclopramide (n = 45)	Erythromycin (n = 45)
Age, yrs	46 ± 2	52 ± 2
Gender, male/female	35:10	31:14
Body mass index, kg/m^2	26.3 ± 0.4	27.4 ± 0.4
Days in ICU before study	6.1 ± 0.6	6.4 ± 0.7
APACHE II score		
Admission	24.3 ± 0.5	26.2 ± 0.6
Study day	21.4 ± 0.5	22.2 ± 0.7
Pretreatment 24-hr GRV, mL	722 ± 27	680 ± 22
Diagnosis, % (n)[a]		
Sepsis	47 (21)	71 (32)
Respiratory failure	71 (32)	82 (37)
Trauma	38 (17)	18 (8)
Renal failure	24 (11)	29 (13)
Head injury	29 (13)	14 (6)
Burns	9 (4)	11 (5)
Diabetes mellitus	9 (4)	11 (5)
Blood glucose level, mmol/L	7.3 ± 0.2	7.8 ± 0.2
Serum creatinine, mmol/L	0.120 ± 0.01	0.110 ± 0.006
Medications, % (n)		
Opioid + benzodiazepine	71 (32)	84 (38)
Propofol	36 (16)	38 (17)
Inotropes	44 (20)	47 (21)
Insulin (actrapid-infusion)	64 (29)	64 (29)
Mode of ventilation		
SIMV, % (n)	51 (23)	51 (23)
Pressure support, % (n)	49 (22)	49 (22)
Positive end expiratory pressure, cm H_2O	8.1 ± 0.4	8.7 ± 0.4
Positive inspiratory pressure, cm H_2O	20 ± 1	21 ± 1

ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SIMV, synchronized, intermittent, mandatory ventilation.

[a]More than one diagnosis possible in any patient.

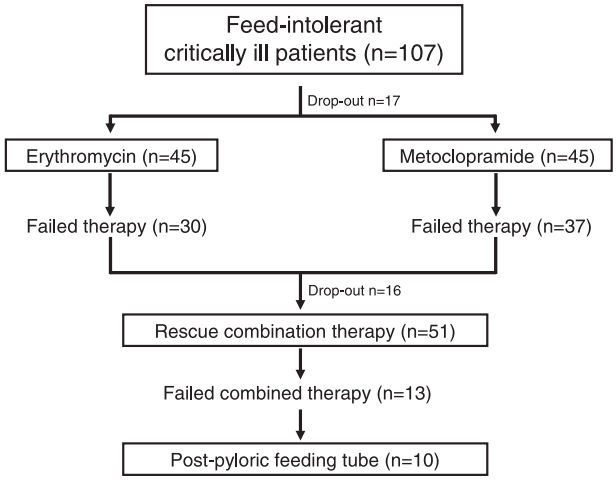

Figure 1. Schematic outline of the overall study results.

overall results of the study are shown in Figure 1.

Effects of Erythromycin and Metoclopramide on the Total 24-Hr Gastric Residual Volume on Day 1. After 24 hrs of treatment with either metoclopramide or erythromycin, the total GRV in both groups was significantly smaller than during the 24 hrs before therapy ($p < .0001$; Fig. 2). Treatment with erythromycin produced a greater reduction in the GRV than metoclopramide (59 ± 4 vs. 35 ± 6%, respectively; $p < .001$; Fig. 2).

Effects of Erythromycin and Metoclopramide on the Success of Gastric Feeding Over 7 Days. By 24 hrs, successful enteral feeding was achieved in 87% of erythromycin-treated patients and 62% of patients treated with metoclopramide. Thereafter, both treatments became significantly less effective (erythromycin, day 3 = 47% and day 7 = 31%, $p = .02$; metoclopramide, day 3 = 27% and day 7 = 16%, $p = .02$). Erythromycin was associated with more successful feeding than metoclopramide at all time points ($p = .02$; Fig. 3*a*). Patients treated with metoclopramide became feed-intolerant earlier than those treated with erythromycin (median [interquartile range], 2 [1–4] days vs. 3 [2–8] days; respectively; $p = .002$). On intention-to-treat analysis, a similar pattern in the effectiveness of both therapies was observed over the 7 days, with erythromycin associated with greater feeding success than metoclopramide at all time points ($p = .005$; Fig. 3*b*).

Factors that were associated with a poor response to either prokinetic monotherapy are summarized in Table 2. Taking into account the treatment effects, only high pretreatment GRV was found to be a significant predictor of poor response to prokinetic monotherapy ($p = .01$; hazard ratio, 1.128; confidence interval, 1.028, 1.237).

Effectiveness of Rescue Combination Therapy on the Success of Gastric Feeding in Patients Who Failed Monotherapy. Fifty-seven of the 67 patients who failed monotherapy were enrolled into open-label combination therapy. Six of the 57 enrolled patients were excluded from the final analysis due to their short participation in this phase of the study (<48 hrs), because of early recovery and resumption of oral intake (n = 4), or because of death (n = 2). The mean duration of combination therapy was 4.8 ± 0.2 days. The demographic characteristics of patients who received rescue combination therapy are summarized in Table 3.

After 24 hrs of combination therapy, successful enteral feeding was achieved in 92% of the patients who had failed monotherapy. Successful feeding was maintained for the first 5 days (day 3, 89%; day 5, 71%; $p > .05$), but therapy was marginally less effective on day 6 (67%, $p = .03$; Fig. 4). Ten of the 13 patients who failed monotherapy eventually required insertion of a postpyloric feeding tube for ongoing nutritional support. There were no factors associated with a poor response to rescue combination therapy identified on Cox regression analysis.

DISCUSSION

There are limited data on the effectiveness and application of prokinetic agents

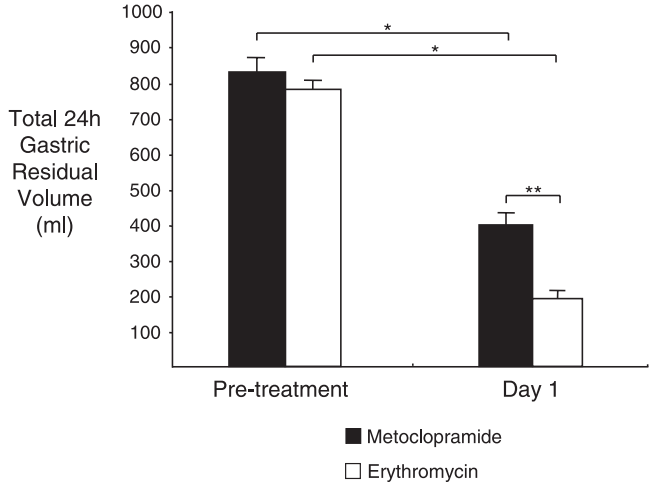

Figure 2. The effect of erythromycin and metoclopramide treatment on the total 24-hr gastric residual volume. *$p < .0001$; **$p < .001$.

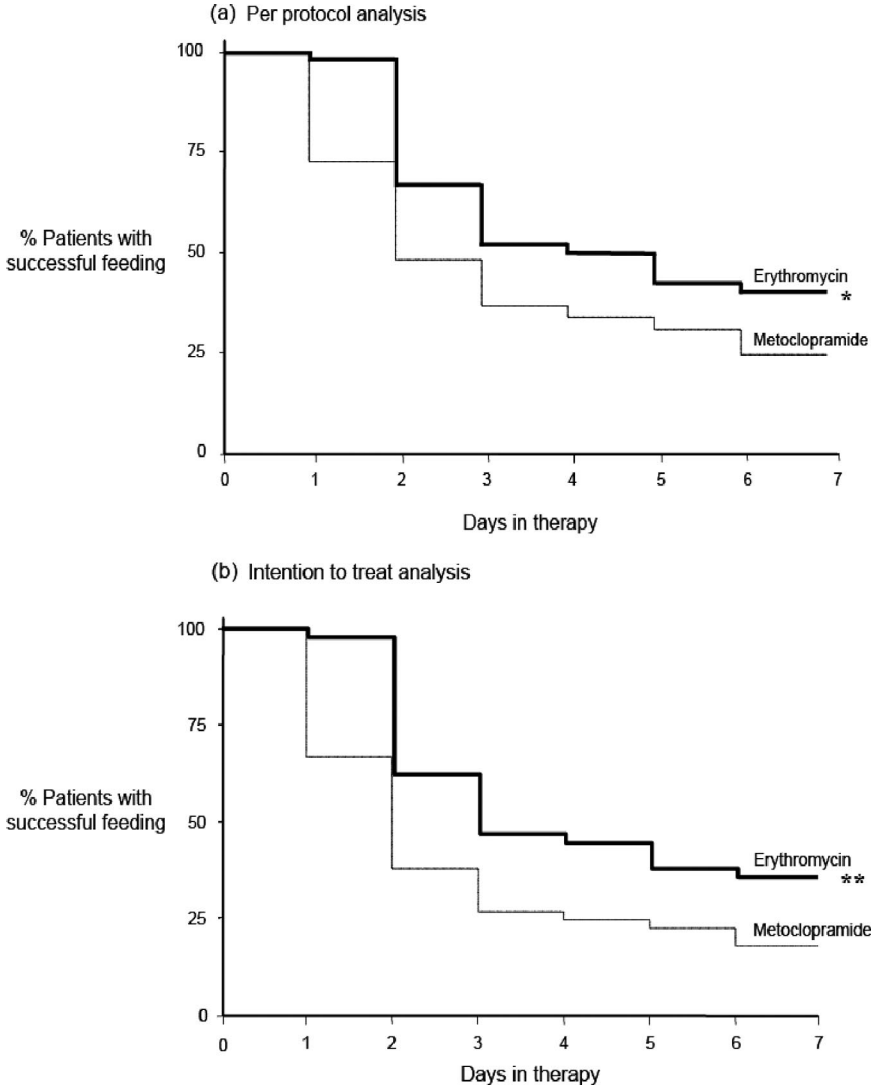

Figure 3. The effectiveness of erythromycin and metoclopramide on the success of feeding over the 7 days, based on (*a*) per protocol analysis and (*b*) intention to treat analysis. *$p < .05$; **$p < .01$; vs. metoclopramide.

in critically ill patients. Two recent systematic reviews of evidence on prokinetic therapy in critical illness over the last 2 decades failed to reach any strong treatment recommendations (24, 25). This study is the first prospective, double-blind, randomized controlled trial comparing erythromycin and metoclopramide in the management of feed intolerance in critically ill patients. The main findings show that a) erythromycin is significantly more effective than metoclopramide in the short-term treatment of feed intolerance; b) tachyphylaxis develops rapidly with the use of both drugs; and c) combination therapy is highly effective in patients who have failed monotherapy.

Given the potential problems associated with other prokinetic drugs (26–28), metoclopramide has been the recommended prokinetic agent for the treatment of feed intolerance in critical illness (24–25). Metoclopramide has multiple effects on gastrointestinal motor function (29–31), although its precise mechanism of action on the gastrointestinal tract is still unclear in humans. However, the beneficial effects of metoclopramide on gastric emptying in critically ill patients remain controversial (13, 15, 32), and there are no data on the effectiveness of metoclopramide in improving the success of feeding in patients with feed intolerance. Our findings suggest that metoclopramide is a weak prokinetic agent in the critically ill and appears to work only in the first 48 hrs of therapy.

In contrast, consistent with previous findings (13–18), erythromycin was highly effective as initial therapy. Furthermore, critically ill patients who were treated with erythromycin remained tolerant to NG feeding longer than patients who were treated with metoclopramide (3 vs. 2 days). This greater efficacy of erythromycin has also been observed in diabetic patients with gastroparesis (33). The greater efficacy of erythromycin over metoclopramide in the current study suggests that it should be the preferred prokinetic agent in the treatment of feed intolerance.

Two other interesting findings from the current study were a) the speed in which tachyphylaxis developed and rendered monotherapy with either drug relatively ineffective after only 3 days of therapy; and b) the sustained effectiveness of treatment with combination therapy in patients who failed monotherapy. Tachyphylaxis has been reported 2 wks after commencing oral metoclopramide

Table 2. Factors associated with a poor response to erythromycin or metoclopramide therapy

	Global, p Value	Control for Treatment Effects, p Value; Hazard Ratio (CI)
High pretreatment GRV	.006	.01; 1.13 (1.03–1.24)
On inotropic therapy	.03	.08; 1.53 (0.94–2.51)
High blood glucose level	.04	.16; 0.9 (0.77–1.04)
On insulin therapy	.04	.12; 1.51 (0.9–2.5)
Higher degree of hypoalbuminemia	.02	.08; 1.03 (0.99–1.07)
High APACHE II score on admission	.05	.19; 1.03 (0.99–1.07)

CI, confidence interval; GRV, gastric residual volume; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 3. Demographic characteristics of critically ill patients treated with "rescue" combination therapy

	Rescue Combination Therapy (n = 51)
Age, yrs	49 ± 3
Gender, male/female	34:17
Body mass index, kg/m^2	27.2 ± 0.5
Days in ICU prior to study	5.6 ± 0.7
APACHE II score	
Admission	25.0 ± 0.9
Study day	21.8 ± 0.9
Pretreatment 24-hr GRV, mL	723 ± 35
Diagnosis, % (n)[a]	
Sepsis	51 (26)
Respiratory failure	80 (41)
Trauma	33 (17)
Renal failure	23 (12)
Head injury	23 (12)
Burns	12 (6)
Diabetes mellitus	12 (6)
Blood glucose level, mmol/L	7.3 ± 0.2
Serum creatinine, mmol/L	0.123 ± 0.01
Medications, % (n)	
Opioid + benzodiazepine	78 (40)
Propofol	35 (18)
Inotropes	57 (29)
Insulin (actrapid-infusion)	69 (35)
Mode of ventilation	
SIMV, % (n)	51 (29)
Pressure support, % (n)	49 (22)
Positive end expiratory pressure, cm H_2O	8.5 ± 0.6
Positive inspiratory pressure, cm H_2O	21.7 ± 1.5

ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; GRV, gastric residual volume; SIMV, synchronized, intermittent, mandatory ventilation.

[a]More than one diagnosis possible in any patient.

(34) and 3 wks after commencing oral erythromycin (22) in the treatment of diabetic gastroparesis. Although a decline in the effectiveness of erythromycin has been reported in critically ill patients (18, 35), the rapid development of tachyphylaxis within the first 3 days of therapy in the current study was unexpected. The mechanisms underlying this rapid loss of effectiveness of erythromycin and metoclopramide are unclear but may relate to the down-regulation, desensitization, and endocytosis of neurohumoral receptors (36, 37).

The sustained effect of combination therapy in patients who failed enteral feeding on two occasions was also unexpected. The control of gastric emptying is complex and highly regulated by multiple neurohumoral pathways (38). The redundancies of these control mechanisms and the multiple actions of combination therapy are likely to contribute to the diminished tachyphylaxis that was observed in the combination-treated group. A well-recognized technique to prevent the development of drug resistance or tachyphylaxis in the treatment of infection and neoplasia is the use of a combination of drugs with different modes of action (39, 40). In the current study, the combination of metoclopramide and erythromycin was highly successful in preventing tachyphylaxis. Although the treatment was open-labeled, the highly sustained response to combination therapy suggests that this approach should be considered for feed-intolerant patients who fail monotherapy. Our findings suggest a potential role for combination therapy as the first-line therapy for feed intolerance in critical illness, which should be further investigated. In addition, they may indicate a strategy for developing pharmacotherapeutic agents in the future.

Factors that were associated with a poor response to prokinetic therapy from this study are consistent with previous findings (3, 7, 12, 30, 41–43). The severity of the patient's critical illness, reflected by a high Acute Physiology and Chronic Health Evaluation II score and requirement for inotropic support, has been reported to correlate with the severity of disturbed gastrointestinal motility and feed intolerance (3, 7, 12, 30, 41). Furthermore, inotropic medications are well known to inhibit gastric motility and emptying (41, 42). In this study, high pretreatment GRV was a significant predictor of poor response to therapy, as it reflects the severity of gastroparesis in these patients. As hyperglycemia can attenuate the promotility effects of erythromycin (43), it is plausible that patients with hyperglycemia, and thus requiring insulin therapy, may respond poorly to prokinetic therapy. Finally, a higher degree of hypoalbuminemia, a marker of stress and severe illness, was associated with a better response to therapy. It is possible that the greater degree of hypoalbuminemia may have reduced drug-albumin binding and allowed more unbound active drug to exert the prokinetic effect.

Clinically, the use of erythromycin as a routine prokinetic agent has been restricted by its potential cardiac toxicity (26) and the concern of bacterial resistance (27). Although subinhibitory concentrations of antibiotics can exert selective pressure on bacteria for resistance development (27), there are currently no data to support the clinical relevance of this concern regarding a short course of low-dose erythromycin. Furthermore, treatment options for feed intolerance, a common problem that is associated with significant complications (3–7), are lim-

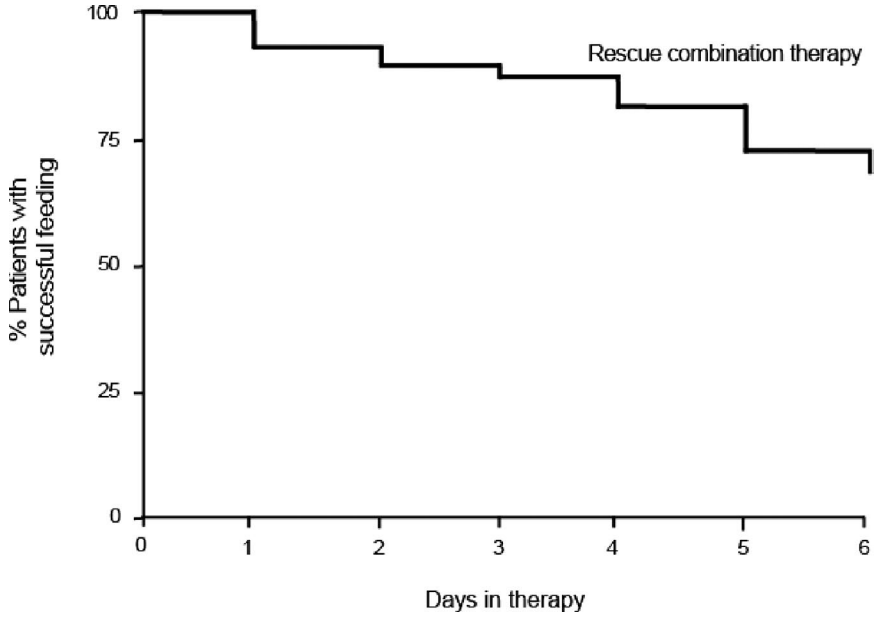

Figure 4. The effectiveness of rescue combination therapy on the success of feeding in patients who failed monotherapy.

ited. Cisapride is effective but is severely restricted due to its cardiac toxicity (28). Although motilin derivatives were specifically developed to avoid bacterial resistance, their effectiveness is poor due to the rapid development of tachyphylaxis (36). Whereas agents such as tegaserod (44) and loxiglumide (45, 46) have been demonstrated to accelerate gastric emptying in humans, their role in the treatment of feed intolerance in critically ill patients requires further investigation. Thus, until a new, safe, and effective prokinetic agent becomes available, the short-term use of low-dose erythromycin is a reasonable approach for the treatment of feed intolerance in critical illness.

CONCLUSIONS

Although erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness, the effectiveness of both drugs diminishes rapidly over time. In patients who fail to respond to these agents, combination therapy is highly effective, and its efficacy is sustained for ≥5 days. The role of combination therapy as a first-line therapy should be further investigated.

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