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Erythromycin dose of 70 mg accelerates gastric emptying as effectively as 200 mg in the critically ill

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Abstract *Objective:* To compare the effectiveness of 70-mg and 200-mg doses of intravenous erythromycin in improving gastric emptying in critically ill patients. *Design:* Gastric emptying was measured on consecutive days; day 1 (pre-treatment), day 2 (post-treatment) after an intravenous infusion of either 70 or 200 mg erythromycin or saline placebo (0.9%), in a randomized double-blind fashion. *Setting:* Mixed medical/surgical intensive care unit, tertiary referral. *Patients and participants:* Thirty-five randomly selected, mechanically ventilated, enterally fed critically ill patients (median APACHE II score 19 on admission). *Interventions:* On day 2 either 70 or 200 mg erythromycin or saline was administered intravenously over 20 min. *Measurements and results:* Gastric emptying was measured using the [^{13}C]octanoic acid breath test. The gastric emptying coefficient (GEC) and half-emptying time ($t_{1/2}$) were calculated from the area under the $^{13}CO_2$-recovery curve. Pre-treatment gastric emptying measurements were similar in all three patient groups. Treatment with both doses of erythromycin significantly reduced the gastric $t_{1/2}$: 70 mg, 98 min (IQR 88–112); 200 mg, 86 min (75–104); vs. placebo, 122 min (102–190) ($p<0.05$). The GEC was higher with both doses of erythromycin: 70 mg, 3.8 (3.3–4.0); 200 mg, 4.0 (3.6–4.2); vs. placebo, 2.9 (2.5–3.7) ($p<0.05$). There was no difference in gastric emptying post-treatment between the two doses of erythromycin. The effect of erythromycin was greatest in patients with delayed gastric emptying. *Conclusions:* Treatment with 70 and 200 mg intravenous erythromycin are equally effective in accelerating gastric emptying in the critically ill

Keywords Critical illness · Erythromycin · Gastric emptying · Enteral feeding · Nutrition · Breath test

Introduction

Poor nutrition is associated with increased morbidity and mortality in the intensive care unit (ICU) [1, 2, 3]. Nasogastric nutrition, however, is frequently unsuccessful in the critically ill [4, 5], and the most common reason for this is gastric stasis [5]. Slow gastric emptying has a prevalence of 30–50% in mechanically ventilated critically ill patients [6, 7]. A variety of prokinetic drugs have subsequently been used to enhance transpyloric flow.

Erythromycin is a macrolide antibiotic with motilin agonist activity and has been successfully used as a prokinetic [8]. In critically ill patients intravenous erythromycin accelerates gastric motility and emptying and improves the success of enteral feeding [9, 10]. The optimal dose for erythromycin is unknown. For acute treatment most investigators have administered 200 mg erythromycin intravenously over 20–30 min [8, 9, 10]. Reports in healthy volunteers, however, suggest that a dose as low as 50 mg may improve gastric emptying [11].

Very low doses (40 mg) of erythromycin have different effects on motility than low doses (200 mg). Low doses stimulate strong antral contractions but very low doses induce distally migrating antral activity, which is likely to accelerate gastric emptying in a very efficient way [12]. Furthermore, a reduction in side effects has been reported with the lower dose [11]. For the purpose of this study we compared an erythromycin dose of 70 mg (approx. 1 mg/kg) to the standard dose of 200 mg (approx. 3 mg/kg).

The [^{13}C]octanoic acid breath test [13] is a noninvasive method for the measurement of gastric emptying. The test is a simple and useful bedside technique for measuring gastric emptying in patient groups [14, 15] and has been reported to be an excellent tool for pharmacological studies with high intraindividual reproducibility [16, 17]. Using this technique, the current study assessed the effect of two different doses of erythromycin on gastric emptying, in a placebo controlled double-blind randomized trial.

Materials and methods

Subjects

We enrolled 44 mechanically ventilated patients in a combined medical and surgical ICU into the study. Nine patients were excluded due to factors unrelated to the study (extubation, vomiting, technical difficulty with sample collection, two each; surgery, elevated liver enzyme results, death, one each). The 35 who completed the study included 25 men and 10 women (median age 48 years, range 18–79; body mass index range 18–53). No patient had a history of gastrointestinal disease, previous abdominal surgery or received prokinetic drugs such as cisapride, metoclopramide or domperidone within the 72 h before the study. No patient was receiving concurrent administration of disopyramide, bromocriptine, ergot derivatives, terfenadine, astemizole or lovastatin. Patients who had received erythromycin during the 2 weeks before the study or had a known allergy to erythromycin were excluded. Fifteen patients (four on placebo; six on 70 mg erythromycin; five on 200 mg erythromycin) received morphine (standard solution of 60 mg in 60 ml) at a rate of 7–20 ml/h. The median Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission was 19 (range 8–36) [18]. The primary diagnoses of patients were surgical (n=6), medical (n=12), neurological (n=8), trauma (excluding head injury; n=7) and burns (n=2). At the time of enrolment all patients had liver enzyme values less than three times the upper limit of normal. The median duration of stay in the ICU before the study was 6 days (range 2–40 days). Relatives of each patient gave written informed consent prior to commencement of the study, which was approved by the Research Ethics Committee of the Royal Adelaide Hospital.

Test meal

Gastric emptying was assessed using the [^{13}C]octanoic acid breath test [13]. The test meal consisted of 100 ml of a mixed nutrient liquid (13% protein, 64% carbohydrate, 21% fat, and caloric content of 1 kcal/ml; Ensure, Abbott, Kurnell, Australia) mixed with 100 µl [^{13}C]octanoic acid (Cambridge Isotope Laboratories, Andover, Mass., USA).

Protocol

Studies were performed on two consecutive days, with patients rested in the supine position. On both study days enteral feeding was ceased 4 h before the study. On day 1 gastric emptying was measured for 4 h using the [^{13}C]octanoic acid breath test. On day 2 breath testing was repeated after a 20-min intravenous infusion of either 70 or 200 mg erythromycin or saline (0.9%) placebo, in a randomized double-blind fashion. Syringes containing 20 ml erythromycin (David Bull Laboratories, Mulgrave, Victoria, Australia) or saline were prepared by the hospital pharmacy department. The liquid meal (100 ml) was mixed with 100 µl [^{13}C]octanoic acid and infused into the stomach over 5 min. Correct positioning of the nasogastric tube was verified by the insufflation of air and radiologically via routine chest radiography. End-expiratory breath samples were collected from the ventilation tube using a T-adapter (Datex-Engstrom, Helsinki, Finland) and holder for vacutainers (Blood Needle Holder, Reko, Lisarow, Australia), containing a needle (VenoJect, Terumo Corporation, Tokyo, Japan). This technique allowed the reliable filling of collection tubes (Exetainer, Buckinghamshire, UK) during end-expiration of mechanically ventilated patients [6]. Breath samples were collected immediately before the test meal, every 5 min during the 1st h, and every 15 min thereafter for a further 3 h. Gastric content was aspirated immediately before each breath test and tested for pH using indicator paper (Whatman, Maidstone, UK). Analysis of gastric emptying was performed prior to randomization disclosure. Enteral feeding was continued as clinically indicated between the two gastric emptying tests and upon completion of the study.

Measurement of gastric aspirate

Periodic aspiration of gastric content is often used as a surrogate marker for gastric emptying for the determination of feeding success, as this is correlated reasonably well with scintigraphic measurements of gastric emptying [19]. Gastric aspirates were collected 6 hly during the 24 h before and after the study. Successful measurements were used to calculate the grand mean for each patient and treatment group.

Breath sample analysis

Collection of breath samples did not interfere with patient care. Breath samples from all 35 patients had a CO_2 level greater than 1%, indicating correct end-expiratory sampling. Breath samples were analysed for $^{13}CO_2$ concentration using an isotope ratio mass spectrometer (Europa Scientific, ABCA model 20 20, Crewe, UK). The values obtained were used to determine the percentage of ^{13}C recovered per hour, which was plotted over time. The area under the recovery curve was used to calculate the gastric emptying coefficient (GEC) and gastric half-emptying time ($t_{1/2}$) [13].

Data analysis

Differences were assessed in gastric emptying (GEC, $t_{1/2}$ and aspirate volumes) within and between patient groups before and after treatment. Pre-treatment (day 1) GEC values from the two erythromycin groups were pooled. There was a bimodal distribution of pre-treatment gastric emptying consistent with a normal (48%) and delayed (52%) emptying group. For delayed emptiers comparisons were made within and between each group.

Data were assessed for normality (Kolmogorov-Smirnov) and the results subsequently expressed as median and interquartile range (IQR). Non-parametric analysis of variance (Kruskal-Wallis) was performed prior to group comparisons (Mann-Whitney) using

Table 1 Demographic data (BMI body mass index apache II Acute Physiology and Chronic Health Evaluation II)

	Placebo (n=12)	70 mg erythromycin (n=11)	200 mg erythromycin (n=12)
Age, median (years; IQR)	59 (47–77)	32 (21–51)	46 (32–63)
BMI, median (IQR)	25 (23–31)	24 (22–28)	26 (24–31)
Gender: M/F	9/3	5/6	11/1
Admission APACHE II score, median (IQR)	20 (14–25)	19 (13–23)	19 (15–22)
Enteral feeding rate 4 h pre-study, mean (ml/h)	58±8.7	52±13.4	54±12.3
Days in ICU, median (IQR)	7 (3–8)	5 (4–7)	5 (3–12)
Patients on inotropes	2	2	5
Patients on morphine	4	6	5

Minitab 13.31 software. Differences with a p value less than 0.05 were considered statistically significant.

Results

The groups did not differ significantly in demographic data, including gender, body mass index, admission APACHE II score and time spent in intensive care before the study (Table 1); the placebo group was older than the group given 70 mg erythromycin (59 years, 47–77, vs. 32 years, 21–51).

There were no differences in pre-treatment gastric emptying measurements between the groups (Fig. 1a). Both doses of erythromycin improved gastric emptying compared to placebo. The $t_{1/2}$ value was reduced after treatment with both doses of erythromycin compared to placebo (Fig. 2b): 70 mg, 98 min (IQR 88–112); 200 mg, 86 min (75–104); placebo, 122 min (102–190; p<0.05). Similarly, GEC was higher after treatment with both doses of erythromycin compared to placebo: 70 mg, 3.8 (3.3–4.0); 200 mg, 4.0 (3.6–4.2); placebo, 2.9 (2.5–3.7; p<0.05). There were no differences in gastric emptying between the erythromycin-treated groups.

A pre-treatment GEC of 3.2 or higher was considered normal [1]. In both erythromycin-treated groups, patients with a pre-treatment GEC less than 3.2 (delayed emptying) had a significant improvement in gastric emptying following treatment (p<0.05; Fig. 2). There was no improvement in gastric emptying following treatment with erythromycin in patients with a pre-treatment GEC greater than 3.2 (normal emptying; Fig. 2). In patients with delayed emptying, $t_{1/2}$ was reduced after treatment with erythromycin than before treatment: 70 mg, 99±15 vs. 250±78 min; 200 mg, 98±31 vs. 226±82 min (p<0.05). The three groups receiving saline or 70 or 200 mg erythromycin did not differ significantly in gastric aspirate volumes either before (38±19, 110±31, 128±38 ml, respectively) or after treatment (32±12, 59±19, 13±3 ml, respectively).

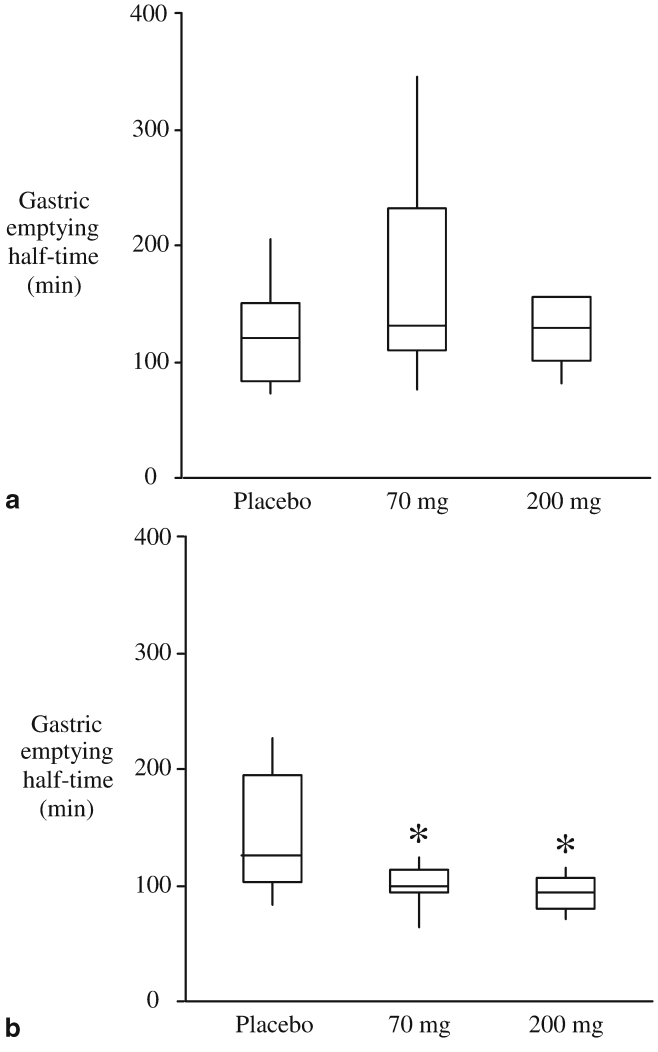

Fig. 1 Comparisons of gastric half-emptying time ($t_{1/2}$) before (**a**) and after (**b**) treatment between placebo and erythromycin-treated groups. There was no difference in gastric half-emptying times between the groups before treatment. The gastric half-emptying time was reduced after treatment with both doses of erythromycin compared to placebo (*p<0.05). Data are median and interquartile range

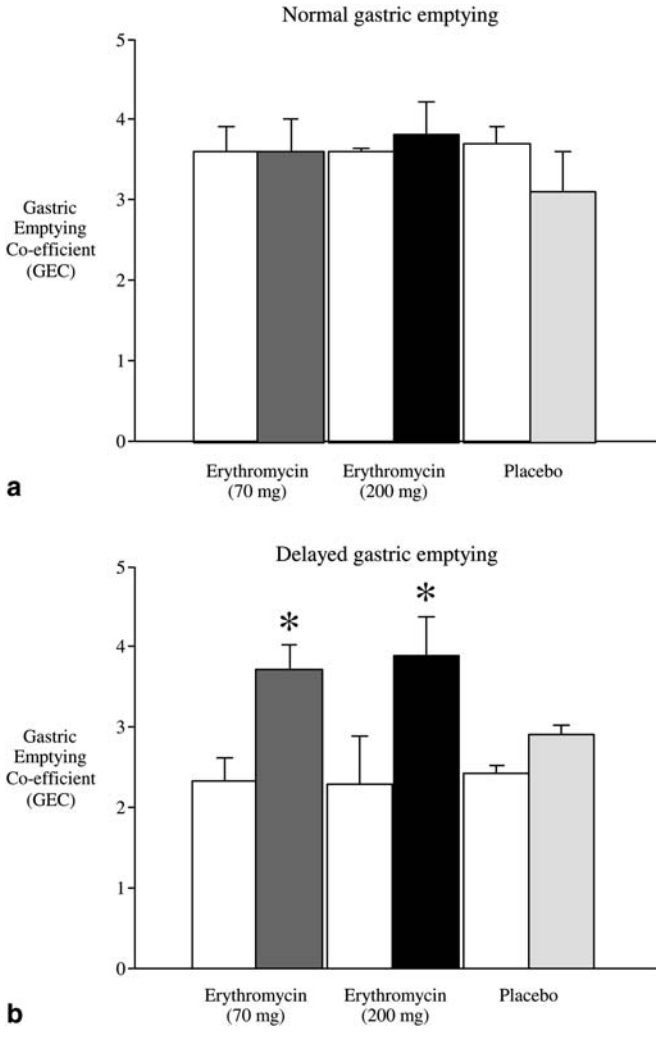

Fig. 2 Comparisons of gastric emptying coefficient (*GEC*) before (day 1; *white columns*) and after (day 2) treatment in patients with (**a**) normal and (**b**) delayed gastric emptying at baseline [1]. Erythromycin is only effective in stimulating gastric emptying when pre-treatment gastric emptying is delayed; *$p<0.05$ pre- vs. post-treatment). The two doses of erythromycin were equally effective in accelerating gastric emptying in patients with delayed gastric emptying. Data are mean ±SEM

Discussion

Previous studies have shown that intravenous erythromycin markedly accelerates gastric emptying in diabetic patients with gastroparesis [8] and other patient groups with gastroparesis, such as after surgery [20, 21, 22], radiotherapy [23], anorexia nervosa [24], scleroderma [25] and the critically ill [9]. The optimal dose of erythromycin remains unclear. For acute treatment most studies use 200 mg erythromycin delivered intravenously over 20–30 min [8, 9, 10]. However, reports in healthy volunteers [11] suggest that a dose of 50 mg is as effective as one of 200 mg at accelerating gastric emptying, and a reduction in side effects has been noted [11]. Another potential benefit of using a lower dose of erythromycin is a reduced risk of tachyphylaxis. For the purpose of this study we compared 70 mg erythromycin (approx. 1 mg/kg) to the standard dose of 200 mg (approx. 3 mg/kg) delivered intravenously over 20 min. The major finding in this study is that an intravenous dose of 70 mg is as effective as one of 200 mg in accelerating gastric emptying in critically ill patients.

Very low doses of erythromycin (40 mg) have different effects on motility than low doses (200 or 350 mg) of the drug. In healthy volunteers and diabetic patients with gastroparesis an intravenous dose of 40 mg induces premature antral phase III activity which migrates down to the small intestine, whereas a dose of 200–350 mg leads to prolonged periods of strong antral contractions that do not migrate and are not followed by motor quiescence [12, 26]. The motor patterns that are reported after very low doses of erythromycin are likely to accelerate gastric emptying in a very efficient way. A reduction in side effects has also been reported with the lower dose [11]; however this was not formally assessed in the current study.

The current study showed that with both doses of erythromycin the prokinetic effect is confined to patients with delayed gastric emptying. These results contradict those of previous studies in which erythromycin accelerated gastric emptying in healthy subjects [12]. This almost certainly reflects methodological differences, such as the volume of nutrient delivered and the rate of administration of erythromycin. The results of the current study suggest that erythromycin should be used therapeutically when gastroparesis is evident and not for the prevention of feed intolerance.

In critically ill patients, intravenous erythromycin accelerates gastric emptying [9] and improves the success of enteral feeding [10, 27]. This is supported by the current study, which showed the acceleration of gastric emptying and a reduction in gastric residuals after treatment with both doses of erythromycin. However, there are no data on the effectiveness of erythromycin in the management of feed intolerance over longer-term usage (more than 7 days) in the critically ill. In the treatment of diabetic gastroparesis there is evidence that tachyphylaxis develops with chronic use of erythromycin (50–500 mg three to four times daily for $\geq$ 4 weeks) [28, 29]. Erythromycin may therefore have a therapeutic role in overcoming feed intolerance and initiating early feeding in the critically ill.

A potential limitation of the present study is the age difference between the placebo and erythromycin-treated groups. Although age may have an effect on gastric emptying, our results showed no difference in pre-treatment emptying between the three groups. Increased age may also prolong the effect of opioids, thus having an indirect influence on gastric emptying and response to prokinetics. However, this effect would be expected to be relevant only in extreme older age. Furthermore, the in-

fluence of opioids on gastric emptying in the critically ill is debated [30, 31].

In conclusion, low doses of the macrolide antibiotic erythromycin are effective as a prokinetic in the short term. Doses as low as 70 mg (approx. 1 mg/kg) accelerate gastric emptying in the critically ill, improving the success of enteral feeding. This effect is seen only in patients with delayed gastric emptying. Further studies are required to determine the role of the drug in long-term administration and the most appropriate dosing schedule.

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