Effects of Erythromycin on Gastric Emptying, Alcohol Absorption and Small Intestinal Transit in Normal Subjects

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The effects of erythromycin on gastric emptying and intragastric distribution of a mixed solid/liquid meal, alcohol absorption and small intestinal transit were examined in eight male volunteers. Each subject received, in double-blind randomized order, either erythromycin as the lactobionate (3 $mg \cdot kg^{-1}$ i.v. over 20 min) or saline immediately before the consumption of a radioisotopically labeled test meal, which consisted of 330 g minced beef and 400 ml of orange juice containing ethanol (0.5 $g \cdot kg^{-1}$ body weight) and 10 g lactulose. Erythromycin increased the rate of total stomach emptying and proximal stomach emptying of both the solid and liquid components of the meal ($p < 0.001$), but slowed small intestinal transit ($p < 0.01$). Peak blood alcohol concentrations ($p < 0.01$) were higher after erythromycin, with a mean increase of 40%. There was a significant inverse relationship between peak blood alcohol concentrations and the 50% emptying time for the liquid component of the meal after saline ($r = -0.70$, $p < 0.05$), but not after erythromycin ($r = -0.57$, $p < 0.1$). The total area under the venous blood alcohol concentration time curve (i.e., total absorption) was greater ($p < 0.01$) after erythromycin. These results suggest that: faster emptying from the proximal stomach contributes to more rapid gastric emptying induced by erythromycin, erythromycin retards small intestinal transit and that erythromycin increases the total amount of alcohol absorbed as well as the rate of alcohol absorption. These latter effects are likely to reflect more rapid delivery of alcohol to the small intestine and reduced metabolism of alcohol by the gastric mucosa.

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The widely used antibiotic erythromycin has recently been shown to have profound effects on gastrointestinal motor function in animals (*1,2*) and humans (*3–6*) which are believed to relate to its properties as an agonist of the gastrointestinal peptide motilin (*7*) and account for gastrointestinal side effects. Erythromycin increases the rate of gastric emptying in normal subjects and in various forms of gastroparesis (*3,8–11*), suggesting a potential role for this drug in the treatment of delayed gastric emptying. While the increase in gastric emptying caused by erythromycin may relate to the stimulation of high amplitude antral contractions (*6,11–13*), there is no information about the effects of erythromycin on proximal stomach motor function or the intragastric distribution of a meal. Erythromycin has been shown to modify small intestinal motility in animals (*1,2,14*). Information about the effect of erythromycin on small intestinal motor function in humans is limited and conflicting (*6,15*).

Alcohol, like many drugs, is absorbed more rapidly from the small intestine than the stomach, and its rate of absorption is therefore dependent on the rate of gastric emptying (*16–18*). Recent studies suggest that alcohol undergoes significant "first-pass" metabolism (*19–21*) by alcohol dehydrogenase present in the gastric mucosa (*22*). If this is correct, the rate of gastric emptying may theoretically also influence the total amount of alcohol absorbed, although this has not been evaluated to our knowledge. Small intestinal transit may also influence drug absorption (*23*).

The aim of this study was to evaluate the effect of erythromycin on gastric emptying and intragastric distribution of a mixed solid/liquid meal containing ethanol, alcohol absorption and small intestinal transit in normal volunteers. The basic hypothesis was that erythromycin, by accelerating gastric emptying, would increase the total amount of alcohol absorbed as well as the rate of alcohol absorption.

METHODS

Subjects

Paired studies were performed in eight normal male volunteers, mean age 23 yr (range 20–29) and mean body weight 70 kg (range 61–84), who were all nonsmokers, had no history of gastrointestinal disease or allergy to erythromycin and used no medication. All drank small quantities of alcohol on social occasions, but alcohol was not permitted for 24 hr before each

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gastric emptying measurement. Written informed consent was obtained in all cases and the study was approved by the Ethics Committee of the Royal Adelaide Hospital.

Protocol

Each volunteer received, in randomized order, an intravenous infusion of either erythromycin (3 $mg \cdot kg^{-1}$ body wt) as the lactobionate (Abbott Laboratories, Sydney, Australia) or normal saline over 20 min, immediately before eating a mixed solid/liquid meal. The volume of each infusion was 20 ml. The solid meal was 300 g of cooked minced beef containing 25–30 MBq of in-vivo labeled ^{99m}Tc-sulphur colloid chicken liver (30 g) and was eaten over 5 min. The caloric content of the solid meal (60 g protein, 21 g fat) was about 600 kcal. The liquid meal was 400 ml in volume and consisted of diluted orange juice (1:1), 0.5 $g \cdot kg^{-1}$ body wt ethanol, 10 g lactulose (Duphalac syrup) and 20–25 MBq ^{113m}In-diethylenetriaminepentaacetic acid (DTPA) and was consumed over 2 min immediately after the solid meal (*18*). The caloric content of the orange juice (total carbohydrate, 21.2 g; sugar, 16.4 g; protein, 1.6 g; fat, 0.2 g) was 96 kcal and for a 70-kg subject an additional 245 kcal were contained in the ethanol. The caloric density of the liquid meal for a 70-kg subject was therefore about 0.75 $kcal \cdot ml^{-1}$. The temperature of the liquid meal ranged from 20 to 21°C and its pH ranged from 3.9 to 4.1. Each test meal was ingested at 10:00 a.m. after the subject had eaten no solid food from 8.00 p.m. and drank no liquids from 10:00 p.m. the previous day and had avoided nonabsorbable carbohydrates for 24 hr. A bactericidal mouth wash (1% chlorhexidine) was given immediately before ingestion of the meals to prevent fermentation of carbohydrate by oropharyngeal bacteria (*18,24*). Blood samples to measure alcohol concentration were obtained via a cannula placed in a forearm vein. Gastric emptying was monitored for at least 180 min after ingestion of the test meal, and after completion of gastric emptying measurements, each subject sat in a chair while further blood samples were taken.

Measurement of Gastric Emptying

Details of this double-isotope test have been published (*25–27*). Technetium-99m-sulphur colloid-chicken liver and ^{113m}In-DTPA have been demonstrated to be precise markers of digestible solid and liquid phases, respectively (*18*). Each study was performed with the subject sitting with his back against the scintillation camera. Data were collected in 30-sec frames for the first 30 min, followed by 3-min frames for the subsequent 150 min. Data were corrected for subject movement, radionuclide decay, Compton scatter and gamma-ray attenuation using previously described methods (*18*). Time 0 was the time of liquid meal ingestion. The total stomach region of interest (ROI) was divided into proximal and distal regions using an automated computer program, with the proximal region corresponding to the fundus and the proximal corpus and the distal region representing the distal corpus and the antrum (*25,27*). From the curves of solid and liquid emptying, expressed as a percentage of the total meal remaining within total, proximal and distal stomach ROIs versus time, several parameters were derived for subsequent statistical analyses.

Solid Meal. For the total stomach, the parameters obtained for statistical analysis were the duration of the lag phase before any food entered the duodenum, the 50% emptying time (T50), T50-lag phase and the percentage remaining at 30, 60, 120 and 180 min after meal completion. The lag phase was determined visually by the frame preceding that in which activity appeared in the proximal small intestine (*25,26*). For the proximal stomach, the parameters were the 50% emptying time (prox T50) and the amount remaining at 30, 60, 120 and 180 min. For the distal stomach, the percentage remaining at 30, 60, 120 and 180 min and the maximum content was calculated (*25,27*).

Liquid Meal. For the total stomach, the parameters used were the duration of the lag phase, the 50% emptying time (T50), T50-lag and the percentage remaining at 10, 30, 60 and 120 min. For the proximal stomach, the 50% emptying time (prox T50) and the amount of isotope remaining at 10, 30, 60 and 120 min were derived. For the distal stomach, the percentage remaining at 10, 30, 60 and 120 min and the maximum content were calculated (*25,27*).

Measurement of Blood Alcohol Concentrations

In each study, venous blood samples for ethanol determination were taken at −5, 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 210, 240, 270, 300 and 330 min after drinking the liquid meal. Samples of whole blood were stored at 4°C and assayed within 48 hr for alcohol using gas-liquid chromatography. The peak blood alcohol concentration and the areas under the venous blood alcohol concentration-time curve between 0 and 15 min, 0 and 30 min, 0 and 60 min, 0 and 330 min and 90 and 330 min were determined. The blood alcohol concentration in the venous blood sample obtained 5 min before the subject drank the liquid meal was considered to be blood ethanol at time 0.

Measurement of Small Intestinal Transit

Orocecal and small intestinal transit were determined by measurement of breath hydrogen concentrations after ingestion of the liquid meal, which contained the nonabsorbable carbohydrate lactulose (*28*). End expiratory breath samples were obtained immediately before ingestion of the meal and subsequently at least at 15-min intervals for up to 240 min. Hydrogen concentration was determined by a gas chromatographic method (*28*). The time period between ingestion of the liquid meal and the first sustained rise in breath hydrogen (an increase of at least 5 ppm over baseline that was maintained for at least 30 min) was defined as the orocecal transit time. The difference between orocecal transit and the lag phase for the liquid meal was defined as the small intestinal transit time (*18*).

Statistical Analysis

Data were analyzed using Student's t-test (paired data) and linear regression analysis since the data conformed to a normal distribution. The level of significance, $p < 0.05$, was adjusted according to the number of variables tested (Bonferroni correction). Mean values ± s.e.m. are reported in the text.

RESULTS

All subjects tolerated the study well. During the infusion of erythromycin, two subjects reported mild nausea and three subjects experienced muscle cramps in the upper arm above the site of administration. These effects were minor and transient. No untoward effects were reported during the infusion of saline.

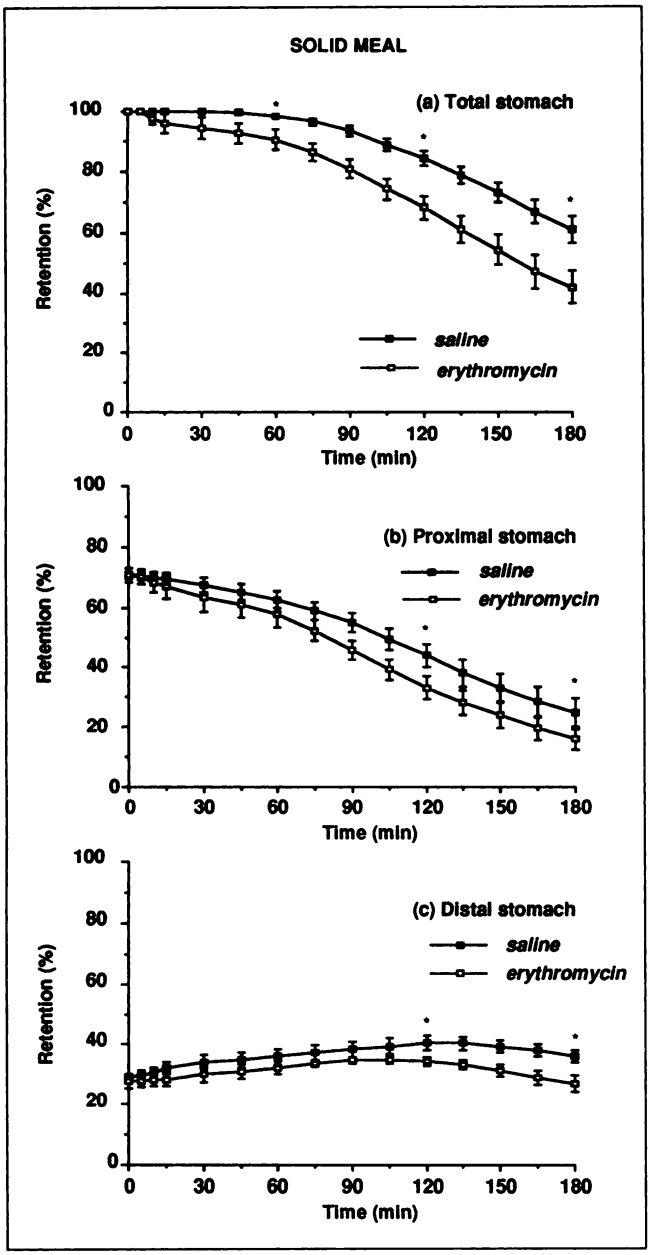

FIGURE 1. Gastric emptying and intragastric distribution of the solid meal after saline and erythromycin. (*p < 0.05 adjusted for the number of variables tested.) Data are mean values ± s.e.m.

Gastric Emptying

Solid Meal

Total Stomach. In all subjects, solid emptying was slower than liquid emptying after both saline and erythromycin and was characterized by an initial lag phase followed by an emptying phase that approximated a linear pattern (Fig. 1a). Erythromycin resulted in more rapid emptying, with reductions in the lag phase (35 ± 7 min versus 63 ± 8 min, p = 0.002), the T50 (166 ± 13 min versus 220 ± 15 min, p = 0.001) and the T50-lag (131 ± 10 min versus 157 ± 13 min, p < 0.05).

Proximal Stomach. The prox T50 (77 ± 11 min versus 109 ± 12 min, p < 0.05) and the amount remaining at 120 and 180 min were less (p < 0.03) after erythromycin when compared to the placebo (Fig. 1b).

Distal Stomach. The amount of the meal in the distal stomach at 120 and 180 min was less after erythromycin (p < 0.03) (Fig. 1c). During the 3-hr period, there was no difference in the maximum content of the distal stomach (38% ± 1% versus 42% ± 2%, ns) or the time of maximum content (94 ± 17 min versus 103 ± 15 min, ns).

Liquid Meal

Total Stomach. In all subjects, the emptying curve for the liquid meal was nonlinear and usually approximated a mono-exponential pattern after a short lag phase (Fig. 2a). Total gastric emptying was faster after erythromycin when compared to saline, with a decrease in the lag phase (2 ± 0.3 min versus 5 ± 0.6 min, p = 0.001), the T50 (34 ± 4 min versus 76 ± 9 min, p < 0.001) and the T50-lag (32 ± 4 min versus 71 ± 8 min, p < 0.001).

Proximal Stomach. The prox T50 (6 ± 2 min versus 20 ± 3 min, p < 0.001) and the amount remaining at 10, 30, 60 and 120 min were less (p < 0.05) after erythromycin when compared to the placebo (Fig. 2b).

Distal Stomach. The amount of liquid meal in the distal stomach at 30, 60 and 120 min was less (p < 0.02) after erythromycin (Fig. 2c). There was no significant difference in the maximum content of the distal stomach between the two tests (41% ± 2% versus 39% ± 2%, ns).

Rate of Caloric Gastric Emptying

The rate at which calories entered the duodenum was faster after erythromycin than saline in the postprandial period between 0 and 60 min (4.1 ± 0.3 kcal·min^{-1} versus 2.7 ± 0.2 kcal·min^{-1}, p = 0.001) and 60 and 120 min (3.0 ± 0.3 kcal·min^{-1} versus 2.4 ± 0.3 kcal·min^{-1}, p = 0.029), but not between 120 and 180 min (3.1 ± 0.3 kcal·min^{-1} versus 3.0 ± 0.3 kcal·min^{-1}, ns).

Blood Alcohol Concentrations

The blood alcohol concentration was zero in all subjects at 330 min. The areas under the venous blood alcohol concentration-time curves between 0 and 15 min, 0 and 30 min, 0 and 60 min, 0 and 330 min and the peak blood alcohol concentration were all higher (p < 0.01) after erythromycin compared to saline (Table 1, Fig. 3). The mean peak blood alcohol concentration was about 40% higher after erythromycin and total alcohol absorption (area under curve between 0 and 330 min) was about 14% higher after erythromycin when compared to saline. There was no significant difference between the two tests in the area under the blood alcohol concentration-time curve between 90 and 330 min (Table 1).

Relationship Between Gastric Emptying and Alcohol Absorption

There was an inverse relationship between peak blood alcohol concentration and the total stomach T50 for the

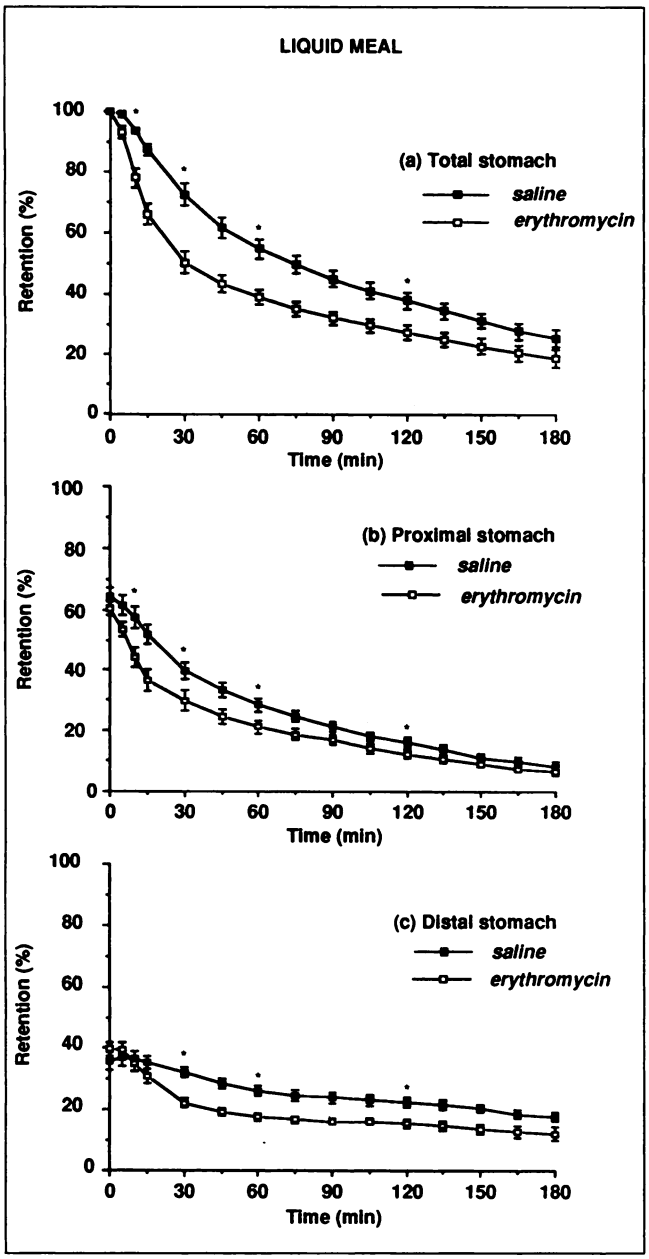

FIGURE 2. Gastric emptying and intragastric distribution of the liquid meal after saline and erythromycin. (*$p < 0.05$ adjusted for the number of variables tested.) Data are mean values ± s.e.m.

liquid meal after saline ($r = 0.70$, $p < 0.05$), but not after erythromycin ($r = -0.57$, $0.05 < p < 0.1$, ns) (Fig. 4). The areas under the venous blood alcohol concentration-time curve between 0 and 30 min and 0 and 60 min correlated with the amount of liquid emptied from the total stomach at 30 min and 60 min after saline ($r = 0.69$, $p < 0.05$ and $r = 0.68$, $p < 0.05$, respectively) but not after erythromycin ($r = 0.05$, ns and $r = 0.11$, ns, respectively).

TABLE 1
Blood Alcohol Concentrations*

Parameter	Saline	Erythromycin	p
Peak alcohol (mg/100 ml)	55 ± 4	77 ± 4	0.002
Area under curve 0–15 min (mg/100 ml/min)	338 ± 45	585 ± 56	0.002
Area under curve 0–30 min (mg/100 ml/min)	1057 ± 80	1610 ± 72	0.001
Area under curve 0–60 min (mg/100 ml/min)	2528 ± 123	3369 ± 91	0.001
Area under curve 0–330 min (mg/100 ml/min)	6658 ± 269	7614 ± 346	0.008
Area under curve 90–330 min (mg/100 ml/min)	2908 ± 243	3033 ± 312	ns

*Data are mean values ± s.e.m.

Orocecal and Small Intestinal Transit

Erythromycin prolonged both orocecal (101 ± 13 min versus 73 ± 9 min, $p < 0.01$) and small intestinal (99 ± 13 min versus 68 ± 9 min, $p < 0.01$) transit (Fig. 5).

DISCUSSION

Effect of Erythromycin on Gastric Emptying, Intragastric Distribution and Small Intestinal Transit

Our results show that erythromycin in an intravenous dose of 3 $mg \cdot kg^{-1}$ increases the rate of gastric emptying of solid and caloric liquid meal components in normal subjects and that this is associated with changes in the lag phase, the emptying phase and proximal stomach emptying of a meal. This latter observation suggests that erythromycin influences proximal stomach motor function and is consistent with a recent report of patients with progressive systemic sclerosis in which an increase in the number of fundic contractions was observed after erythromycin (*29*). Similar doses of erythromycin have been reported to increase the number and amplitude of antral contractions in both fasting and postprandial states (*6,12,13*) and to decrease the number of pressure waves isolated to the pylorus (*12*) in normal subjects. The increase in antral contractions caused by erythromycin in dogs is associated with impaired trituration of a solid meal, so that a greater proportion of larger particles (>0.5 mm) enter the small intestine (*30*). While our results indicate that faster emptying from the proximal stomach contributes to more rapid gastric emptying induced by erythromycin, effects on distal stomach motility are also likely to be important (*2,12,13*). Distal stomach emptying is difficult to evaluate with scintigraphic methods because of the variable input from the proximal stomach.

Urbain et al. (*3*) and Janssens et al. (*8*) reported that erythromycin abolished the characteristic difference in gastric emptying of solids and liquids in normal subjects and patients with diabetic gastroparesis. We found that gastric emptying of the solid meal was still substantially

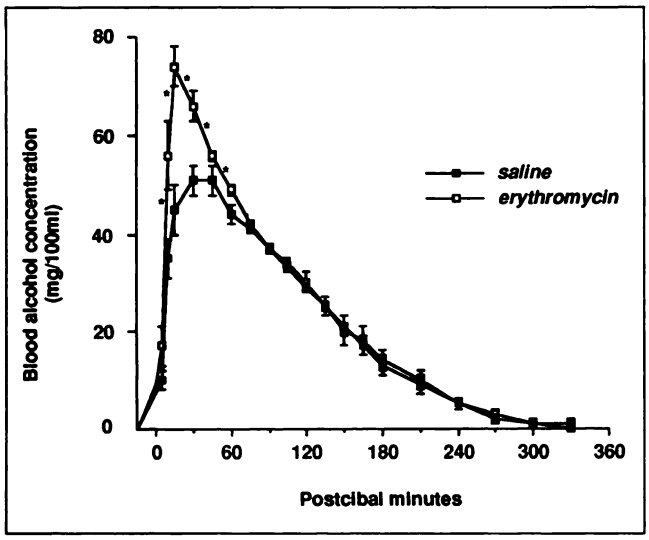

FIGURE 3. Blood alcohol concentrations after saline and erythromycin. (*p < 0.05 adjusted for the number of variables tested.) Data are mean values ± s.e.m.

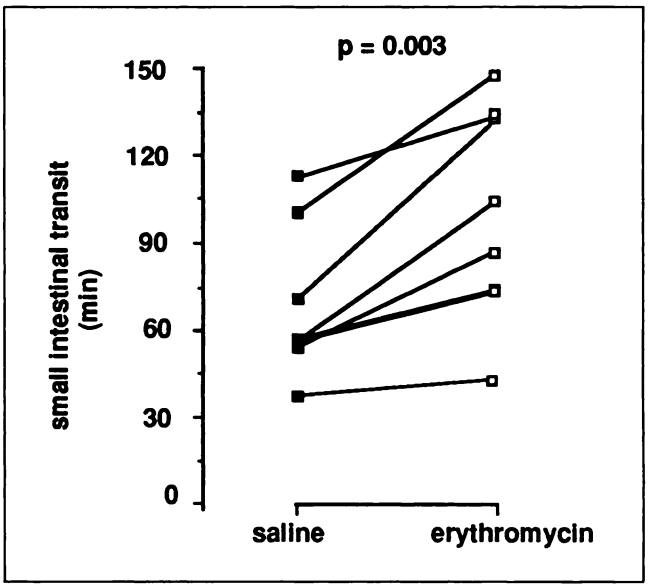

FIGURE 5. Small intestinal transit after saline and erythromycin. Small intestinal transit was determined by subtracting the lag phase of the liquid component of the meal from the orocecal transit time measured by breath hydrogen analysis.

slower than that of the liquid meal after erythromycin injection. The explanation for this apparent discrepancy may relate to technical factors or the composition of the test meal. The frequent data acquisition used in our study enabled accurate quantification of patterns of gastric emptying. A short lag phase, or the early phase of liquid gastric emptying, may not be able to be evaluated accurately by acquisition rates of 10–15 min (*3,8*). The test meal used by Urbain et al. (*3,8*) was smaller in volume, incorporated a noncaloric (water) rather than a caloric liquid component and solid components (eggs, bread) which may have been easier to triturate than the minced beef used in our study. It is nevertheless clear that erythromycin in low dosages (~3 $mg \cdot kg^{-1}$ i.v.), unlike other gastrokinetic drugs (*31*), significantly increases the rate of gastric emptying in normal subjects to above "physiological" levels (*18,32,33*), which is consistent with the observation that erythromycin is able to override the small intestinal feedback signals that regulate gastric emptying (*12,31,32*). Our observation that the rate of caloric delivery to the small intestine was not enhanced by erythromycin between 120–180 min likely reflects the lower plasma concentrations of erythromycin at this time and is consistent with Sarna et al. (*6*) who reported that the increase in antral contractions after erythromycin (500 mg i.v.) is most marked in the first 30 min after drug administration and is related to plasma concentrations of erythromycin.

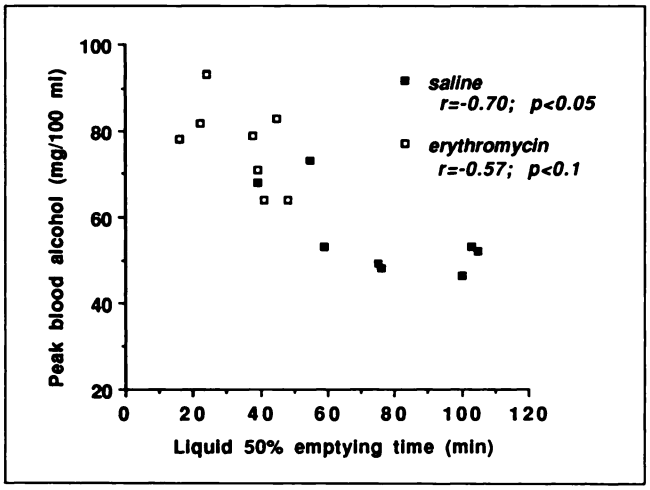

FIGURE 4. Relationship between peak blood alcohol levels and the 50% emptying time of the liquid test meal after saline and erythromycin.

Intravenous administration of erythromycin has been shown to improve delayed gastric emptying in patients with gastroparesis secondary to diabetes mellitus (*3,8*), vagotomy (*34*), progressive systemic sclerosis (*10*) and primary anorexia nervosa (*11*) and its action appears to be more potent when compared to other gastrokinetic drugs, such as metoclopramide and cisapride. Erythromycin has also been used to facilitate the transpyloric passage of enteric feeding tubes (*35*) and manometric catheters (*36*). Enthusiasm for the potential role of erythromycin in the treatment of gastroparesis should, however, be tempered with the realizations that: oral administration may be less effective [although it has been shown to increase gastric emptying substantially (*3,8*)], the effects of erythromycin on gastrointestinal symptoms associated with gastroparesis have not been evaluated and that the long-term efficacy of erythromycin in improving gastric emptying has not been clearly established (*9*). In particular, it has been suggested that its gastrokinetic action will diminish with

time due to down-regulation of motilin receptors (*37*). There is considerable interest in derivatives of erythromycin that are motilin agonists devoid of antibiotic activity (*38*).

It is clear that the effects of erythromycin on human gastric and intestinal motility are dose-dependent (*6*). For example, in the small intestine, low doses (1–3 $mg \cdot kg^{-1}$) of erythromycin induce phase-3 activity in normal subjects (*5*) and in patients with intestinal pseudo-obstruction (*39*), while higher doses (7 $mg \cdot kg^{-1}$) prolong the cycle length of the interdigestive migratory motor complex and induce giant retrograde contractions (*5*). Our observation that erythromycin retards small intestinal transit is consistent with the findings of Sarna et al. (*6*) who reported that erythromycin in an intravenous dose of 500 mg reduced the frequency and duration of small intestinal contractions in the fed state. This is in contrast with Lehtola et al. (*15*) who reported that single oral doses of erythromycin stearate (1000 mg) or erythromycin acistrate (800 mg) shortened orocecal transit in healthy subjects. The lactulose load in their study was greater (26 g) and was consumed without a meal. Because gastric emptying was not quantified, it is possible that the observed decrease in orocecal transit simply reflected enhanced gastric emptying of lactulose rather than more rapid small intestinal transit. It is also possible that the accelerated rate of gastric emptying may have contributed to slower small intestinal transit. For example, the presence of nutrients in the ileum delays small intestinal transit (*40*). However, the most likely explanation for this discrepancy relates to a difference in dosage of erythromycin in our study (*2,6*). In particular, Lehtola et al. (*15*) used an oral dose of erythromycin. An indirect effect of erythromycin on small intestinal transit related to alterations in colonic bacterial flora can be excluded in both studies on the basis that only a single dose of erythromycin was used at submaximal antimicrobial dosages (*41*). The measurement of small intestinal transit by hydrogen breath analysis does not allow us to speculate whether the delay in small intestinal transit induced by erythromycin reflects slowing of transit in the jejunum or ileum (or both).

Effect of Erythromycin on Alcohol Absorption

Our study demonstrates that erythromycin in an intravenous dose of 3 $mg \cdot kg^{-1}$ increases the total amount of alcohol absorbed and the rate of alcohol absorption. The close relationship between peak alcohol levels and the rate of liquid emptying after intravenous saline is consistent with previous observations, indicating that the major factor influencing the rate of alcohol absorption is the rate of delivery to the small intestine from which it is rapidly absorbed (*16–18*). For example, peak blood alcohol concentrations are increased by metoclopramide (*42*) and after a gastric drainage procedure (*16,43*). Factors which slow gastric emptying, such as ingestion of a solid meal (*18*), anticholinergic drugs (*42*), cigarette smoking (*44*) and infusion of fat into the small intestine (*45*), decrease peak blood alcohol levels. Recent studies indicate that alcohol, when administered in low doses (0.15 $mg \cdot kg^{-1}$), is subjected to significant first-pass metabolism (*19–21*), probably by alcohol dehydrogenase present in the gastric mucosa (*22*). The results of our study support the hypothesis that first-pass metabolism of alcohol by the gastric mucosa is clinically important. Erythromycin is not known to affect alcohol metabolism directly and the increased total alcohol absorption of about 14% is likely to be related to more rapid gastric emptying and hence reduced exposure of alcohol to the gastric mucosa. Slower small intestinal transit may also favor increased drug absorption (*23*), but since there was no difference in alcohol absorption after the first 90 min, this is unlikely to be a major factor.

Our observations potentially have both social and medicolegal implications for patients who are prescribed erythromycin. It is the task of the treating physician to point out the possible effects of erythromycin (and other drugs that influence gastric emptying) on alcohol absorption, although it is possible that oral erythromycin will have less effect (*8,9*). Our results suggest that the effects of erythromycin on blood alcohol concentrations are likely to be greater in those patients who have reduced levels of gastric alcohol dehydrogenase, including women (*21*), patients after gastrectomy (*20*) and patients taking cimetidine (*46*).

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