Effect of erythromycin on orocecal transit time in normal healthy male subjects: A double-blind, placebo controlled study

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ERYTHROMYCIN IS A MACROLIDE antibiotic whose specific actions on the motility of the human gastrointestinal tract have not been fully elucidated. Erythromycin produces a prokinetic effect on the stomach and duodenum (1) and mimics the action of exogenously administered motilin by initiating premature migrating motor complexes in the proximal gut of both dogs and humans (2-5). Erythromycin has been shown to displace iodinated motilin from its binding sites found in both canine and rabbit duodenal smooth muscle preparations (6). In contrast to its stimulatory effect on gastroduodenal motility, the effect of erythromycin on the distal small intestine may be inhibitory. Studies in animals and humans have demonstrated erythromycin to inhibit small bowel motor activity (7-9) and slow small intestinal transit (10). Others have suggested that erythromycin does not significantly alter small intestinal motility (11). If the actions of erythromycin on gastric emptying and small bowel transit in humans are indeed opposite, this will have important pharmacological and therapeutic implications. The treatment of gastroparesis with erythromycin may lead to intestinal pseudo-obstruction in susceptible individuals (eg, diabetes mellitus). Oroccecal transit time (OCTT) as assessed by


OBJECTIVE: To investigate the effect of erythromycin on orocecal transit time (OCTT) in 17 healthy male subjects in a double-blind, placebo controlled crossover trial.

SUBJECTS AND METHODS: After an overnight fast, each subject received 250 mg erythromycin base, 500 mg erythromycin base or placebo on three different days. A standardized breakfast meal plus 20 g lactulose was administered 30 mins after ingestion of the test dose. Exhaled breath was collected and hydrogen concentration was assessed over 4 h. Hydrogen concentrations over time for each session were analyzed by a generalized logistic function generating a sigmoidal curve. The 'front' transit time (T1) was taken as the time when a sustained rise in breath hydrogen concentration was first observed. The midpoint from baseline to peak hydrogen concentration was denoted T2 and represented the time when approximately half of the test meal had reached the cecum.

RESULTS: There was no effect of erythromycin on OCTT. The T1 (mean ± SEM) was 103.2±11.2, 103.3±15.3 and 70.9±15.9 mins for placebo, 250 mg erythromycin base and 500 mg erythromycin base, respectively (P>0.05). Similarly, the T2 was 113.3±11.3, 113.9±16.5 and 99.3±15.3 mins for the three regimes.

CONCLUSIONS: Oral administration of erythromycin does not alter OCTT in healthy male subjects.

Key Words: Erythromycin, Gastrointestinal motility, Orocecal transit

Effet de l’érythromycine sur le transit orocœcal chez des sujets sains de sexe masculin : étude à double insu contrôlée par placebo

OBJECTIF : Étudier l’effet de l’érythromycine (dont l’effet sur la motilité de l’intestin grêle est controversé) sur le temps de transit orocœcal chez 17 sujets en santé de sexe masculin dans le cadre d’un essai croisé, à double insu, contrôlé avec un placebo.

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S U J E T S E T M É T H O D E S : À jeun le matin, chaque sujet a reçu 250 mg d’érythromycine base, 500 mg d’érythromycine base ou du placebo, trois jours distincts. Un petit déjeuner standardisé, plus 20 g de lactulose ont été administrés 30 minutes après l’ingestion de la dose étudiée. L’haleine à l’expiration a été recueillie et la concentration d’hydrogène a été évaluée sur une période de 4 heures. Les concentrations d’hydrogène avec le temps pour chaque séance ont été analysées à l’aide d’une fonction logistique généralisée qui a produit une courbe sigmoïdale (le temps de transit du front (T1) a été pris comme temps correspondant à l’élévation initiale soutenue de la concentration d’hydrogène dans l’haleine. Le moment intermédiaire entre le départ et la concentration d’hydrogène de pointe a été nommé T2 et représentait le moment où environ la moitié du repas-test avait atteint le cæcum.

RÉSULTATS : L’érythromycine n’a produit aucun effet sur le temps de transit orocæcal. Le T1 (moyenne+écart type) a été de 103,2 ± 11,2, 103,3 ± 15,3 et 70,9 ± 15,9 minutes, pour le placebo, les 250 mg d’érythromycine base et les 500 mg d’érythromycine base respectivement (P>0,05). De même, le T2 a été de 113,3 ± 11,3, 113,9 ± 16,3 et 99,3 ± 15,3) minutes pour les trois schémas.

CONCLUSION : L’administration orale d’érythromycine ne modifie pas le temps de transit orocæcal chez des sujets en santé de sexe masculin.

Hydrogen breath test is not affected by gastric emptying and provides a good assessment of small intestinal motility in healthy subjects. To our knowledge, only one other study has investigated the effect of erythromycin on OCTT in humans (12). In that study, OCTT was measured following ingestion of a lactulose only, and this has poor reproducibility. In addition, no definite conclusions of erythromycin’s effect on intestinal transit of a physiological meal can be drawn. Our prospective, double-blind, placebo controlled study was specifically designed to determine the effects of two standard doses of orally administered erythromycin on OCTT of a breakfast meal with lactulose in healthy male subjects.

S U B J E C T S A N D M E T H O D S

Healthy males between the ages of 18 and 60 were offered participation in the study. Patients with a history of gastrointestinal dysmotility, three or more stools per day, previous gastrointestinal surgery, endocrinological disease or disease of the gastrointestinal tract were excluded. Subjects who had taken laxatives, antacids, or prescription or over-the-counter drugs on a regular basis in the two weeks before entry, or antibiotics in the preceding month, as well as those who were hypersensitive to erythromycin, were also excluded. Females were not considered for the study due to the variable effects of the different phases of the menstrual cycle on gastrointestinal motility. The study protocol was approved by the Institutional Review Board at the University of Louisville Hospital, Louisville, Kentucky. Written informed consent was obtained from all subjects.

Study design: The study was conducted in a double-blind, placebo controlled crossover fashion. After an overnight fast, subjects were randomized to receive 500 mg erythromycin base, 250 mg erythromycin base or an equivalent amount of placebo in a single morning dose. A standardized test meal, consisting of two slices of white toast (57 g), one slice processed American cheese (28 g), 14 g margarine, 240 mL orange juice and 20 g lactulose, was administered 30 mins after the medication. The complete meal contained 390 kCal; 48% of the calories were derived from carbohydrates, 14% from protein and 38% from fat. During the test period, subjects were allowed to stand, walk or proceed with routine activity. They were not allowed to exercise, eat, drink, chew gum or smoke until the end of the study period. Following the initial session, each subject served as his own control and was randomly crossed over to the next test dose at least three days later.

Measurement of OCTT: After an overnight fast, the subject ingested 20 g lactulose with the test meal 30 mins after administration of erythromycin (Abbott Laboratories, Illinois) or placebo. To minimize the effect of exponential gastric elimination of lactulose, it was administered halfway through the test meal. Breath hydrogen concentration was determined 30 mins before testing, at baseline (0 mins) and at 10 min intervals for the first 2 h, then at 15 min intervals for the next 2 h for a total of 4 h. Expired breath air samples were collected in polyethylene bags and transferred to 20 mL glass syringes. Hydrogen concentration was measured by a research chromatograph (Quintron Microlizer 12, Wisconsin). Hydrogen concentrations for each session were analyzed over time by a generalized logistic function generating a sigmoidal curve.

The time point when a sustained or persistent rise in breath hydrogen concentration was first observed was taken as ‘front’ transit time (T1). Front transit time presumably represents the forward portion of the bulk meal as it reaches the cecum (12). The midpoint from the baseline to peak breath hydrogen concentration (the midpoint of the middle limb of the sigmoid curve) was denoted T2, and represents the time when approximately 50% of the test meal had reached the cecum. The time points T1 and T2 were generated by the computer based on the sigmoid shape of the curve.

Statistical analysis: Statistical analysis was done using Statview program (BrainPower Inc, California). Mean transit times and SEM were calculated for each dose. Analysis of variance was used to test for statistical significance between dosages. Significance was taken a priori at the 95% confidence limit.

R E S U L T S

Seventeen male subjects were enrolled into the study. The subjects ranged from 25 to 38 years (mean 30.9). All were of a normal body weight and on regular diet. One of the subjects was a nonhydrogen producer and was excluded. No significant gastrointestinal side effects were reported during the study. The OCTT (T1 and T2) of the
solid meal following the various doses is shown in Table 1. There was a trend towards a shorter OCTT with administration of 500 mg erythromycin but analysis of variance did not show this difference to be significant (P>0.05).

**DISCUSSION**

Erythromycin has been used with some preliminary success to treat gastroparesis (13-15). There have been conflicting reports regarding its effect on small bowel motility. In animal and human studies, erythromycin has been shown to have an inhibitory effect in the small bowel (8,10,16,17), while others (18) have demonstrated an excitatory effect. The present study attempted to resolve this important issue in humans by studying the effect of erythromycin on small bowel transit of a physiological breakfast meal plus lactulose.

We used the lactulose hydrogen breath test to assess intestinal transit from mouth to cecum in normal male subjects. Although this test does not separate the effects of gastric emptying from small intestinal motility, it has been shown to correlate closely with small intestinal transit time as measured by scintigraphy (19). While this test may not theoretically separate the effects of gastric emptying from small intestinal motility, Read et al (20) have shown that OCTT is not influenced by the rate of gastric emptying. As such, OCTT is a valid measure of small intestinal motility. Ladas and colleagues (21) reported similar results.

While the results of Read et al and Ladas et al may not be applicable to subjects with profound gastroparesis, they certainly are applicable to healthy subjects used in our study. Females were excluded from our study because gastrointestinal motility varies with the hormonal fluctuations observed during the menstrual cycle (22). The results of our placebo controlled study suggest that erythromycin in a single dose of 250 or 500 mg does not significantly alter the OCTT in healthy subjects. The doses used in our study have been used to treat gastroparesis effectively (13,14). Twelve subjects are needed to show a 30% difference in OCTT at alpha level of 5% for power of 80% (23). While it is possible that we missed a very small difference on account of type II error, it is unlikely that such a difference would be clinically significant.

Only one other study has evaluated erythromycin’s effect on small intestinal transit in humans. Lehtola et al (12) investigated the effect of 800 mg erythromycin acistrate and 1000 mg erythromycin stearate on OCTT in normal subjects; they showed that erythromycin significantly shortens the OCTT. Significant adverse gastrointestinal side effects were also noted presumably because of the high doses. There may be several reasons for the different results seen in their versus our study. Lehtola and co-workers assessed OCTT for lactulose because no meal was given with the lactulose. Ingestion of lactulose alone induces an abnormally rapid OCTT. The results of our study reflect the OCTT of a physiological breakfast meal with lactulose, which correlates much better with small intestinal transit and which is much more reproducible (21). Other factors that may contribute to the discordant results between the two studies include the different drug doses (250 and 500 mg versus 800 and 1000 mg) and agents (base versus salt) used. Error could also be introduced in their study because of the fewer number of subjects enrolled (n=11), especially since they used lactulose alone (23). In addition, females have variable gastrointestinal motility during different phases of the menstrual cycle; this factor was not controlled in their study (22).

The prokinetic effect of erythromycin is related to its agonistic action on motilin receptors. Studies suggest that porcine and canine motilin do not stimulate contractions of guinea-pig

**TABLE 1**

Orocecal transit times in normal males after placebo and after 250 mg and 500 mg of erythromycin base

<table>
<thead>
<tr>
<th>Erythromycin dose (mg)</th>
<th>Orocecal transit time mean ± SEM (mins)</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>103.2±11.2 113.3±11.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>103.3±15.3 113.9±16.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>70.9±15.9 99.3±15.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T1: Time point when a sustained or persistent rise in breath hydrogen concentration is first observed, i.e., ‘front’ transit time; T2: Time point representing the midpoint from the baseline to peak breath hydrogen concentration (the midpoint of the middle limb of the sigmoid curve), i.e., the time when approximately 50% of the test meal has reached the cecum.
in intestine (24,25). In humans, motilin receptors predominate in the gastrointestinal region and are scarce in the more distal small bowel. Erythromycin does not affect the frequency and the duration of small intestine contractions in the fasting state in humans (9). Intravenous erythromycin does not relieve postoperative ileus (26).

REFERENCES


CONCLUSIONS

The specific actions of erythromycin on human gastrointestinal motility have not been clearly established. Based on our study, we conclude that erythromycin does not affect orocecal transit in healthy male subjects.
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