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A prospective randomized controlled study of erythromycin on gastric and small intestinal distention: Implications for MR enterography☆

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ABSTRACT

Objectives: To assess if erythromycin increases gastric emptying and hence improves small intestinal distention during MR enterography.
Methods: Gastric, small intestinal, and large intestinal volumes were assessed with MR after neutral oral contrast (1350 ml in 45 min) and balanced randomization to erythromycin (200 mg i.v., age 31 ± 3y, 13 females), or placebo (37 ± 3y, 13 females) in 40 healthy asymptomatic volunteers. Fat-suppressed T2-weighted MR images of the abdomen were acquired on a 1.5 T magnet at standard delay times for enterography. Gastric, small, and large intestinal volumes were measured by specialized software. In addition, two radiologists manually measured diameters and percentage distention of jejunal and ileal loops. Treatment effects were evaluated by an ITT analysis based on ANCOVA models.
Results: All subjects tolerated erythromycin. MRI scans of the stomach and intestine were obtained at 62 ± 2 (mean ± SEM) and 74 ± 2 min respectively after starting oral contrast. Gastric volumes were lower ($P < 0.0001$) after erythromycin (260 ± 49 ml) than placebo (688 ± 63 ml) but jejunal, ileal, and colonic volumes were not significantly different. However, maximum (76–100%) jejunal distention was more frequently observed ($P = 0.03$) after erythromycin (8/20 subjects [40%]) than placebo (2/20 subjects [10%]). The diameter of a representative ileal loop was greater ($P = 0.001$) after erythromycin (18.8 ± 4.3 mm) than placebo (17.3 ± 2.8 mm) infusion.
Conclusions: After ingestion of oral contrast, erythromycin accelerated gastric emptying but effects on small intestinal dimensions were variable. In balance, erythromycin did not substantially enhance small intestinal distention during enterography using current standard delay times.

1. Introduction

MR and CT enterography are very useful cross-sectional imaging techniques for assessing the bowel wall and perienteric fat in patients with suspected small bowel disease [1,2]. MRI provides excellent soft-tissue contrast and avoids ionizing radiation. In addition, recent advances in MR imaging techniques have improved spatial and temporal resolution and reduced motion artifacts. Nonetheless, small bowel distension is a prerequisite for an adequate enterography exam [1,2]. Collapsed intestinal segments may conceal pathological findings, and conversely, may falsely mimic inflammation or a tumor [1,2].

The bowel can be distended by enteroclysis or enterography. Enteroclysis provides excellent distension but requires placement

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of a nasoenteric tube, which is not as well tolerated as enterography, which requires ingestion of large volumes of oral contrast. Intravenously administered spasmolytic agents (e.g., glucagon or buscopan) can reduce bowel motion artifacts but may not optimize distention [1]. Two primary approaches (i.e. increasing the volume and osmolality of the oral solution) are used to facilitate bowel distention during MR enterography. A comparison of 4 volumes (450, 900, 1350, and 1800 ml) of each of four contrast compounds (0.2% locust bean gum plus 2.5% mannitol, VoLumen containing 2.0% sorbitol, VoLumen containing 1.4% sorbitol, and tap water) observed that distention was better with solutions containing a sugar alcohol than water but was not significantly different among various agents containing osmotic additives [3]. A volume of 900 ml achieved sufficient duodenal distention whereas 1350 ml was preferable for visualizing the jejunum and ileum. While adequate distention can be accomplished with a smaller volume of highly concentrated sorbitol solutions (e.g., 450 ml), these solutions are more likely to cause diarrhea [4]. Despite development of these dedicated enteric-distending contrast agents, the small bowel, especially the jejunum, is often poorly distended during routine computed enterography [1]. Adequate jejunal distension and visualization are important in the evaluation of celiac disease, for detecting small bowel masses, and also for Crohn's disease. While Crohn's disease has a predilection for the distal ileum, it can skip the terminal ileum [5]. In our experience, Crohn's disease involving the jejunal loops can be more subtle and overlooked.

Drugs which accelerate gastric motility such as metoclopramide are also used to increase gastric emptying and facilitate intestinal distention in clinical practice [6]. Metoclopramide (10 mg oral) facilitated ileal but not jejunal distention evaluated by computed tomography compared to patients in whom it was not used; however, this was not a randomized study [7]. By stimulating motilin receptors, erythromycin can increase antral motility and accelerate gastric emptying [8,9]. One study evaluated the effects of administering erythromycin before oral contrast during MRI [3]. For a 70 kg person, the dose used in that study i.e., 100 mg i.v. was approximately 50% of the dose (3 mg/kg i.v.) required to increase gastric motility [9]. Because the effects of erythromycin were not compared to placebo, it is not known to our knowledge if erythromycin increased small intestinal distention. Hence, the effects of prokinetic agents on small intestinal distention during MR enterography are unknown.

The objectives of our study were to assess if erythromycin increases gastric emptying, hence improves small intestinal distention during MR enterography in healthy subjects.

2. Material and methods

2.1. Subjects

Forty three healthy asymptomatic volunteers were recruited from the local community by public advertisement and consented to participate in this study, which was approved by the Institutional Review Board. A gastroenterologist interviewed and examined all subjects to ensure they were healthy and did not have any of the following: symptoms of a functional gastroduodenal or bowel disorders by questionnaire [10], prior gastrointestinal surgery other than appendectomy, cholecystectomy, hysterectomy, tubal ligation, or inguinal hernia repair, medication use (except for stable doses of birth control pill, L-thyroxine, or estrogen replacement therapy), claustrophobia or metal objects in the body. An EKG was obtained to ensure the corrected Q–T interval was $\leq$460 ms because erythromycin can prolong the Q–T interval and rarely induce torsades de pointes [11].

2.2. MR enterography

MR images of the abdomen were acquired with a torso phased-array coil and a 1.5 T magnet MRI (GE Healthcare, Waukesha, WI). First, gastric volumes were assessed by an axial 2D half-Fourier acquisition single-shot turbo spin echo (HASTE) sequence (i.e., TR 900 ms, TE 90 ms, 5 mm slices with 0 mm gap, matrix size 256 $\times$ 256, 1 NEX), which imaged the entire stomach in 28 s, during two breath-holds. Thereafter, small bowel and colonic volumes were evaluated with 5 mm thick coronal slices using a fat-suppressed TrueFISP (Fast Imaging Employing Steady State Acquisition, FIESTA) sequence (TE 1.8 ms, TR 3.8 ms, a fractional field of view of 40 $\times$ 32 cm, and an acquisition matrix of 256 $\times$ 192), also during breath-holding. The TrueFISP sequence was not used to evaluate gastric volumes because black band artifacts in the left upper quadrant projected over the stomach and hindered segmentation.

2.3. Medication and oral contrast

Subjects were instructed to fast for 4 h prior to the study. Upon arrival, they were randomized to receive either erythromycin lactobionate (Hospira, Lake Forest, Il) at a dose of 3 mg/kg intravenously or matched placebo (sodium chloride [0.9%]). To minimize venous irritation, erythromycin was given as a bolus of 0.5 mg/kg over 10 min followed by an infusion of 2.5 mg/kg in 5% dextrose solution over the next 50 min.

Oral contrast (1350 ml) was ingested over 45 min beginning 25 min after erythromycin was started. Since erythromycin was given over 60 min, the oral contrast was completely ingested 10 min after the erythromycin infusion was completed. A low concentration barium solution (VoLumen (1350 ml), Bracco Diagnostics, Monroe Township, NJ), which contains 0.1% weight/volume barium and 2% sorbitol, was used to provide oral contrast. This agent is FDA-approved for use in CT and is widely used for CT and MR enterography in the United States. Its use in MR is considered an off-labeled use. This agent has been shown to provide better small bowel distention than water in the upper and lower abdomen [12]. Sorbitol, available commercially as a sweetening agent, is a sugar alcohol that promotes peristalsis and is a mild osmotic laxative [13].

2.4. Data analysis by software

Gastric volumes were evaluated using the ANALYZE software system (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN) [14]. Where feasible, a validated semi-automated algorithm was used with manual tracing in the remaining subjects. For the manual analysis, the results of which were detailed previously [15], a region of interest (ROI) was manually drawn around gastric contents on each slice. The count of all pixels within each appropriate ROI for all slices was multiplied by voxel size to obtain the volume of gastric contents excluding air. Small intestinal loops were characterized as jejunum or ileum based on their location in the upper and lower abdomen (i.e., above and below the pelvic brim) respectively. Trained technicians segmented images and a radiologist (JF or JH) verified the same. Thereafter, small intestinal and colonic fluid volumes were calculated as described for the stomach. One technician segmented all small intestinal and colonic images and another segmented all gastric images. This analysis was blinded to drug assignment.

2.5. Data analysis by radiologists

Two radiologists (JF, JEH), who were blinded to drug assignment, simultaneously reviewed and measured the representative and maximum short axis diameter of jejunal and ileal loops on coronal images on a computer workstation (GE Advantage Windows