Azithromycin Induces Migrating Motor Complexes in Pediatric Patients Undergoing Antroduodenal Motility Studies

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OBJECTIVE Erythromycin (ERY) is used in the treatment of gastroparesis; however, this medication is associated with serious side effects, such as cardiac arrhythmias and consequent cardiorespiratory arrest. Azithromycin (AZM) has been suggested as an alternative to ERY as a result of its improved safety profile. Intravenous ERY (1 mg/kg) is administered during antroduodenal motility studies to induce migrating motor complexes (MMCs), the presence or absence of which helps diagnose motility disorders like gastroparesis and gastrointestinal dysmotility. However, there are no pediatric studies comparing the effects of AZM and ERY on antroduodenal pressure profiles. The goal of this study is to determine if AZM is comparable in inducing MMCs in pediatric patients undergoing antroduodenal motility studies.

METHODS We performed a retrospective chart analysis of gastric and small bowel manometric data in 2 adolescent patients, both age 15 years, who were given AZM (1 mg/kg) during antroduodenal motility studies. The pressure profiles obtained during motility studies were compared to those of patients of similar age and symptomology who were given the standard intravenous ERY dose during motility studies. We then compared the total duration of effect, mean amplitude of contractions, number of cycles per minute, and duration of highest antral and duodenal contractions.

RESULTS Intravenous AZM induces migrating motor contractions in the stomach followed by contractions in the small intestine. The mean amplitude of the stomach contractions was 259 mm Hg in patients who received AZM vs 241 mm Hg in patients who received ERY. The mean amplitude of small intestinal MMCs was 68 mm Hg in patients who received AZM and 72 mm Hg in patients who received ERY. Additionally, the frequency and duration of stomach and small intestinal contractions were also similar in the 2 groups.

CONCLUSIONS Intravenous AZM has similar prokinetic effects to intravenous ERY. Our study suggests that AZM is a suitable alternative to ERY in inducing MMCs without the concerning side effects related to ERY and may potentially be used in the management of gastroparesis and other small bowel motility disorders. However, larger prospective studies are required to better understand the long-term efficacy of AZM.

ABBREVIATIONS AZM, azithromycin; ERY, erythromycin; IV, intravenous; MMCs, migrating motor complexes

KEYWORDS antroduodenal motility; azithromycin; erythromycin; gastroparesis; pediatric

J Pediatr Pharmacol Ther 2018;23(5):390–394

DOI: 10.5863/1551-6776-23.5.390

Background

Gastroparesis is a chronic gastrointestinal motility disorder characterized by delayed gastric emptying in the absence of mechanical outlet obstruction. Patients with gastroparesis present with various symptoms, including early satiety, nausea, vomiting, epigastric abdominal pain, and bloating.¹ The true prevalence of gastroparesis is unknown. Gastroparesis can be due to several etiologies, including diabetes, postsurgical complications, medication-induced response, neurologic condition, or postinfectious process.¹ About one-third of adult patients with diabetes have abnormal gastric emptying studies; however, the etiology of gastroparesis in pediatric patients is often idiopathic.^{2,3}

In one study⁴ as many as 25% to 40% of adults and children initially diagnosed with dyspepsia were subsequently diagnosed with gastroparesis. Misdiagnosis of gastroparesis leads to delayed treatment, consequently increasing healthcare and workforce costs due to prolonged hospitalizations and missed work and school days.⁵

The diagnosis of gastroparesis is made with the demonstration of delayed gastric emptying on nuclear medicine gastric emptying scintigraphy after ruling out mechanical obstruction. Antroduodenal manometry, a less common and more invasive modality, is performed to show normal physiology in patients with symptoms of gastroparesis and intestinal failure (i.e., severe nausea and retching and the inability to tolerate enteral feeds).

Table 1. Patient Characteristics

	ERY 1	ERY 2	AZM 1	AZM 2
Age (yr)	14	16	15	15
Sex	Female	Female	Female	Female
Presenting symptoms	GERD; abdominal pain; bloating; nausea; vomiting	Abdominal pain; nausea; vomiting	Abdominal pain; vomiting; weight loss	Abdominal pain; nausea; vomiting
Prior gastric emptying scan	Abnormal	Abnormal	Normal	Abnormal
Antroduodenal motility study	Normal	Normal	Normal	Normal

AZM, azithromycin; ERY, erythromycin; GERD, gastroesophageal reflux disease

Antroduodenal manometry is a sensitive indicator of postprandial antral hypomotility and a useful tool in studying the initiation and propagation of migration motor complexes (MMCs). There are 2 distinct phases in normal antroduodenal manometry: 1) a fasting or interdigestive phase and 2) a postprandial phase. Migrating motor complex is a cyclic pattern that occurs in the gastrointestinal tract during the fasting stage. Migrating motor complexes have been divided into 3 phases: phase I, or the quiescent phase, has no contractions; phase II is characterized by random contractions of variable amplitude and frequency; and phase III is characterized by the highest amplitude contractions. Phase III contractions occur in the antrum at a rate of 2 to 3 per minute for at least 2 minutes, and they occur in the small intestine at a rate of 11 to 12 per minute for at least 3 minutes. These phase III contractions are organized and migrate distally with variable velocity. The velocity of the propagation of the phase III contraction progressively decreases from proximal to distal small intestine and is accompanied by a progressive increase in the duration of phase III. The presence of phase III activity marks neuromuscular integrity, while the absence and abnormalities in phase III activities diagnose pseudobstruction.^{6,7}

Currently, erythromycin (ERY) is the most potent prokinetic agent used in the treatment of gastroparesis in children.⁸ Previously used medications like domperidone and metoclopramide have fallen out of favor in the pediatric population as a result of the unsafe side effect profile of these medications.⁹ Erythromycin is a macrolide antibiotic that is a motilin receptor agonist in gastrointestinal smooth muscle. Motilin induces the interdigestive phase III of the MMCs in the stomach

that are then propagated to the small intestine. Caution must be used with ERY, as it has several drug-related interactions because it interacts with the cytochrome P450 pathway of hepatic metabolism. Erythromycin has been associated with increased incidence of pyloric stenosis in infants, sudden cardiac death due to prolongation of QTc intervals, and initiation of torsade de pointes.^{10–14} Azithromycin (AZM) is a semisynthetic macrolide similar to ERY, but since it does not interact with the cytochrome P450 pathway, it has fewer drug-related interactions and cardiac side effects. Few prospective and retrospective adult studies have found AZM to be comparable to ERY in inducing MMCs not only in the stomach but also in the small intestine.^{5,8} To date, there are no reported cases in the literature of the use of AZM in inducing antroduodenal MMCs in pediatric patients.

Methods

We performed a retrospective chart review of the electronic medical record for patients who had antroduodenal motility studies done at our tertiary care center from 2010 through 2012. Per protocol, all medications that alter gastrointestinal motility are discontinued at least 72 hours prior to procedure. We used a 10Fr solid-state Unisensor high-resolution motility catheter and analyzed with motility software from MMS (Medical Measurements System, Amsterdam, The Netherlands). All patients underwent anesthesia without sedatives, narcotics, and muscle relaxants. The motility catheter was placed endoscopically with the help of fluoroscopy. All patients were given about 1 to 2 hours of recovery time until they were fully awake before we initiated the

Table 2. Antroduodenal Manometry Values by Patient

	Normal	ERY 1	ERY 2	AZM 1	AZM 2
Mean amplitude of small intestinal MMCs (mm Hg)	>20	66 ± 8	78 ± 10	62 ± 15	74 ± 12
Frequency of contractions in stomach (contractions/min)	2–3	3.5	3.5	3.5	3.5
Frequency of contractions in intestine (contractions/min)	10–12	12	12	12	12
Duration of stomach contractions (min)	>2	10	20	10	16

AZM, azithromycin; ERY, erythromycin; MMCs, migrating motor complexes

Table 3. Mean Antroduodenal Manometry Values by Drug

	Normal Values	Erythromycin (n = 2)	Azithromycin (n = 2)
Mean amplitude of stomach contractions (mm Hg)	>40	241	259
Mean amplitude of small intestine MMCs (mm Hg)	>20	72	68
Mean frequency of contractions in stomach (contractions/min)	2–3	3–4	3–4
Mean frequency of contractions in small intestine (contractions/min)	11–12	11–13	11–13
Mean duration of contractions in stomach(min)	>2	14	12

MMC, migrating motor complexes

motility study. The motility study protocol consisted of at least 2 hours of fasting, followed by the administration of intravenous (IV) ERY or AZM given over 30 minutes, followed by another hour of monitoring, and then the patient was given a high-fat meal over the course of 30 minutes and was monitored for another hour.

Antroduodenal motility study is considered normal if there is normal phase III MMC (defined by 2–3 antral contractions/min and 10–12 small bowel contractions/min, lasting at least 2 minutes with anterograde propagation) and normal antral and small bowel response after a meal.¹⁵

Patient names were deidentified. We identified 2 patients who had received IV AZM (1 mg/kg) and 2 patients with similar age and symptomology who received IV ERY (1 mg/kg) for comparison around the same time period. The 2 patients received AZM because ERY was not available as a result of a national shortage from the manufacturer at the time of the antroduodenal motility study. We determined the age of the patients and results of the gastric emptying studies, and presenting symptoms were obtained from ICD-9 codes entered by the provider. We evaluated the pressure profiles of each of the 4 patients and obtained data on induction of MMC, amplitude of MMC, frequency of contractions, and length of MMC propagation. This study was approved by our institutional review board.

Results

The most common presenting symptoms were vomiting and abdominal pain. Three of the 4 patients had abnormal gastric emptying studies; however, all had normal antroduodenal motility studies (Table 1). The antroduodenal manometry tracings after administration of IV AZM (1 mg/kg) were similar to those after administration of IV ERY (1 mg/kg). Most importantly, AZM induced MMCs that were similar in amplitude, frequency, and duration to MMCs induced by ERY (Table 2). The mean amplitude, mean frequency, and duration of contractions were similar in antroduodenal manometry tracings after administration of IV AZM (1 mg/kg) and IV ERY (1 mg/kg) (Table 3).

Antroduodenal manometry tracing after administra-

tion of IV ERY (1 mg/kg) shows phase III contraction starting in the antrum (top 4 channels) and propagating to the duodenum (bottom 5 channels). The y-axis represents pressure (0–150 mm Hg) for each sensor and the x-axis represents time (minutes) (Figure 1). Antroduodenal manometry tracing after administration of IV AZM (1 mg/kg) shows phase III contraction starting in the antrum (top 4 channels) and propagating to the duodenum (bottom 5 channels). The y-axis represents pressure (0–150 mm Hg) for each sensor and the x-axis represents time (minutes) (Figure 2).

Discussion

Our findings suggest that AZM is a promising prokinetic agent in pediatric patients with gastroparesis and may be used as an alternative to ERY. Our study reflects similar findings in adults—that AZM induces MMCs in both the stomach and small intestine. While ERY is efficacious in the management of gastroparesis, caution must be given to cardiac side effects and drug-related interactions, especially in children, as a result of its inhibition of the cytochrome P450 pathway.¹⁴ Azithromycin is advantageous over ERY because it has the highest intracellular concentrations among the macrolides, which provides prolonged tissue concentration and lends itself to once-a-day dosing.¹⁶

Interestingly, in our very small cohort of patients, 3 out of 4 (75%) patients had abnormal gastric emptying studies; however, with normal antroduodenal motility studies another etiology for delayed gastric emptying must be worked up. The patient who had a normal gastric emptying study was eventually diagnosed with an eating disorder and is receiving cognitive behavioral therapy. These observations can lead to potential future areas of research to better understand the utility and relationship of performing gastric emptying studies and antroduodenal manometry in patients with symptoms of gastroparesis.

Our study was limited by its small number of patients who received AZM (n = 2), its retrospective nature, and its lack of randomization. Larger, randomized, prospective, long-term studies need to be performed in children to study symptom management, side effect profile, and safety.

Figure 1. Antroduodenal manometry tracings with administration of erythromycin (ERY).

Conclusions

Azithromycin may be a safer prokinetic alternative to ERY in the management of gastroparesis in pediatric patients. However, large-scale prospective studies are required to further study AZM's long-term efficacy and safety profile.

ARTICLE INFORMATION

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data and take responsibility for the integrity and accuracy of the data analysis.

Accepted March 7, 2018

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Figure 2. Antroduodenal manometry tracings with administration of azithromycin (AZM).

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