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Erythromycin improves gastric emptying half-time in adult cystic fibrosis patients with gastroparesis ☆

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Abstract

Background: Gastrointestinal manifestations are frequently encountered in cystic fibrosis patients. Gastroparesis evidenced by a variety of diagnostic methods has been described in patients with cystic fibrosis, predominantly in children and in individuals with advanced lung disease. The presence of gastroparesis in adult patients with different degrees of lung involvement and its response to the acute and chronic administration of macrolides have not been reported.
Methods: Using the University of Florida Cystic Fibrosis database we identified symptomatic patients who had gastroparesis confirmed by a prolonged half-time during gastric emptying scintigraphy.
Results: Of 86 cystic fibrosis patients, periodically followed in our institution, we found five who had classical symptoms and prolonged gastric emptying half-time. Age 25.2±8 years, 80% females, BMI 22±9 kg/m^2, HbA1c 5.8±0.6 g/dl, FEV1 53.2±15% of predicted. Gastric emptying half-time was 191.4±91.4 min (range 100–300 min) and decreased to 12.2±6 min (range 5–20 min) after IV administration of erythromycin (p=0.043). Patients were followed up for 3±2.1 years. All patients but one, who was taking opiods, had good clinical response to PO macrolides.
Conclusions: Gastroparesis occurs in patients with cystic fibrosis, even in patients with relatively preserved lung function and in those without cystic-fibrosis related diabetes. Macrolides may be an effective therapy in cystic fibrosis patients with gastroparesis when administered acutely or chronically.

Keywords: Cystic fibrosis; Gastroparesis; Erythromycin; Gastric emptying scintigraphy

1. Background

Gastrointestinal complaints are commonly reported by cystic fibrosis patients and are generally related to exocrine pancreatic insufficiency, gastroesophageal reflux disease, distal intestinal obstruction syndrome, hepatobiliary tract involvement and complications related to previous abdominal surgeries.

Gastrointestinal dysmotility, and more specifically gastroparesis, have been described in association with cystic fibrosis predominantly in children and advanced lung disease. The published data is scant and confusing, as patients of different ages and degree of disease were included. In addition, diverse diagnostic methods were used to measure gastric emptying, including: 1) marker dilution technique, 2) electrogastrography, 3) epigastric impedance recording and 4) gastric emptying scintigraphy (using different meals and protocols). An appropriate correlation among these different modalities for assessing delayed gastric emptying is lacking [1], and of all the available tests, gastric emptying scintigraphy with ^{99m}Tc-sulfur colloid bound to solid food is the most accepted one for diagnosing gastroparesis.

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Little is known about the use of macrolides during gastric emptying scintigraphy, as well as for the chronic treatment of cystic fibrosis associated gastroparesis. We report the response to macrolide treatment in 5 patients with symptomatic gastroparesis confirmed by a prolonged gastric emptying half-time, who had different degrees of lung disease and body mass index.

2. Methods

We reviewed the charts of cystic fibrosis patients using the University of Florida Cystic Fibrosis database. We identified patients who had gastrointestinal symptoms and a nuclear gastric emptying scintigraphy reflecting gastroparesis.

The University of Florida gastric emptying study methodology is as follows: The patient was administered one whole scrambled egg meal with 2 pieces of white bread/one slab of butter and 50–100 cm^3 of water. This meal is labeled with 0.5–1.0 mCi of Tc-99m sulfur colloid. After administration of the meal, the patients were imaged continuously for 120 min at 1 min per frame using either a single-headed gamma camera, equipped with a low-energy, high resolution collimator, positioned in the left anterior oblique position to minimize the effects of varying gastric attenuation on quantitation of the gastric emptying rate or a dual-headed camera similarly positioned (the latter with calculation of geometric mean activity). A simple linear fit was applied to the rate of gastric emptying with calculation of the gastric emptying half-time (normal = 45–90 min). At 80 min into the examination, the patients were administered 250 mg of IV erythromycin, infused over 20 min, with calculation of the new post-erythromycin half-time. Before the study, patients had to stop for 48 h all medications known to affect gastric emptying. Serum glucose was measured before the test and was considered appropriate for the performance of the study if less than 140 mg/dl.

One patient underwent Antroduodenal Manometry, via a fluoroscopically placed catheter (with leads in the antrum and small intestine), that measures luminal pressure patterns (amplitude and frequency of antral pressure and characteristics of the activity front of the migrating motor complex). After a 7-hour baseline manometric recording and a 4-hour fed state a therapeutic portion was performed with erythromycin 250 mg IV, azithromycin 250 mg IV and octreotide 50 μg SQ. Gastroparesis is characterized by a decreased frequency of antral contractions and low or normal fasting migrating motor complexes. This test is predominantly used for excluding small intestinal dysmotilities [13].

Demographic characteristics, genetic mutation, body mass index, spirometric values and HbA1c were recorded. All of these patients were followed by a gastroenterologist at our institution. All of them received treatment with macrolides in an elixir form. The medications were modified according to response. Initial symptoms and response to treatment were recorded. Patients were followed for different intervals of time.

We used Wilcoxon Signed Rank test to compare the gastric emptying half time before and after the IV administration of erythromycin. When appropriate we provide numeric values as mean ± standard deviation.

3. Results

Of the total of 86 active patients in our clinic (those who were regularly followed-up at our institution), five individuals with the classic symptoms of gastroparesis confirmed by gastric emptying scintigraphy were included. Mean age was 25.2 ± 7.7 years, four patients were females, four patients had typical cystic fibrosis associated mutations and the remaining patient had a positive sweat chloride test. Mean body mass index was 21.98 ± 9.1 kg/m^2. Nearly all patients complained of nausea, vomiting, bloating, early satiety and abdominal pain. Two of five patients had cystic fibrosis-related diabetes and were receiving insulin. Mean HbA1c was 5.8 ± 0.55 g/dl and FEV1 was 53.18 ± 15% of predicted. Three patients were receiving azithromycin 500 mg/day 3 times a week that they stopped 48 h before the test. Before the gastric emptying half time the serum glucose was 105.8 ± 17 mg/dl. Mean gastric emptying half-time was 191.4 ± 91.4 min (range 100–300 min) and decreased to 12.2 ± 5.8 min (range 5–20 min) after IV erythromycin ($p = 0.043$) (Table 1 and Fig. 1).

One patient (patient #1) also underwent Gastroduodenal Manometry that showed decreased antral contractions and normal small bowel activity. Both erythromycin and azithromycin induced adequate antral contractions.

Patients were followed for 3 ± 2.1 years (range 1–6 years). All patients were treated with erythromycin elixir (200 mg three times a day with meals) or azithromycin elixir (400 mg once a day) as part of a protocol used at our institution. To assess the clinical effect to macrolide therapy we define four possible types of clinical response: 1) excellent, 2) very good, 3) good and 4) no response. Four of five patients noted a significant

Table 1
Baseline characteristics of cystic fibrosis patients included in the study.

Pt	Age	Sex	Genetic mutation	BMI (kg/m^2)	HbA1c DM Tx	FEV1 (% of pred)	GE 1/2 time (min)	GE 1/2 time after erythromycin (min)
1	38	F	ΔF508/ΔF508	37.4	5.2%	73	300	5
2	19	F	Sweat Cl^- 110 mEq/l	20.5	5.8%	44.8	270	16
3	21	F	ΔF508/E60X	19.6	6% on insulin gargline 5 Units/day	44.1	179	10
4	21	F	ΔF508/ΔF508	13.2	6.6% on insulin gargline 18 Unit/day	65.3	100	20
5	27	M	ΔF508/2184 insA	19.2	5.4%	38.7	108	10

F: female, M: male, BMI: body mass index, DM Tx: treatment for diabetes mellitus, FEV1: forced expiratory volume in 1 s, % of pred: percentage of predicted, GE 1/2: gastric emptying half-time.

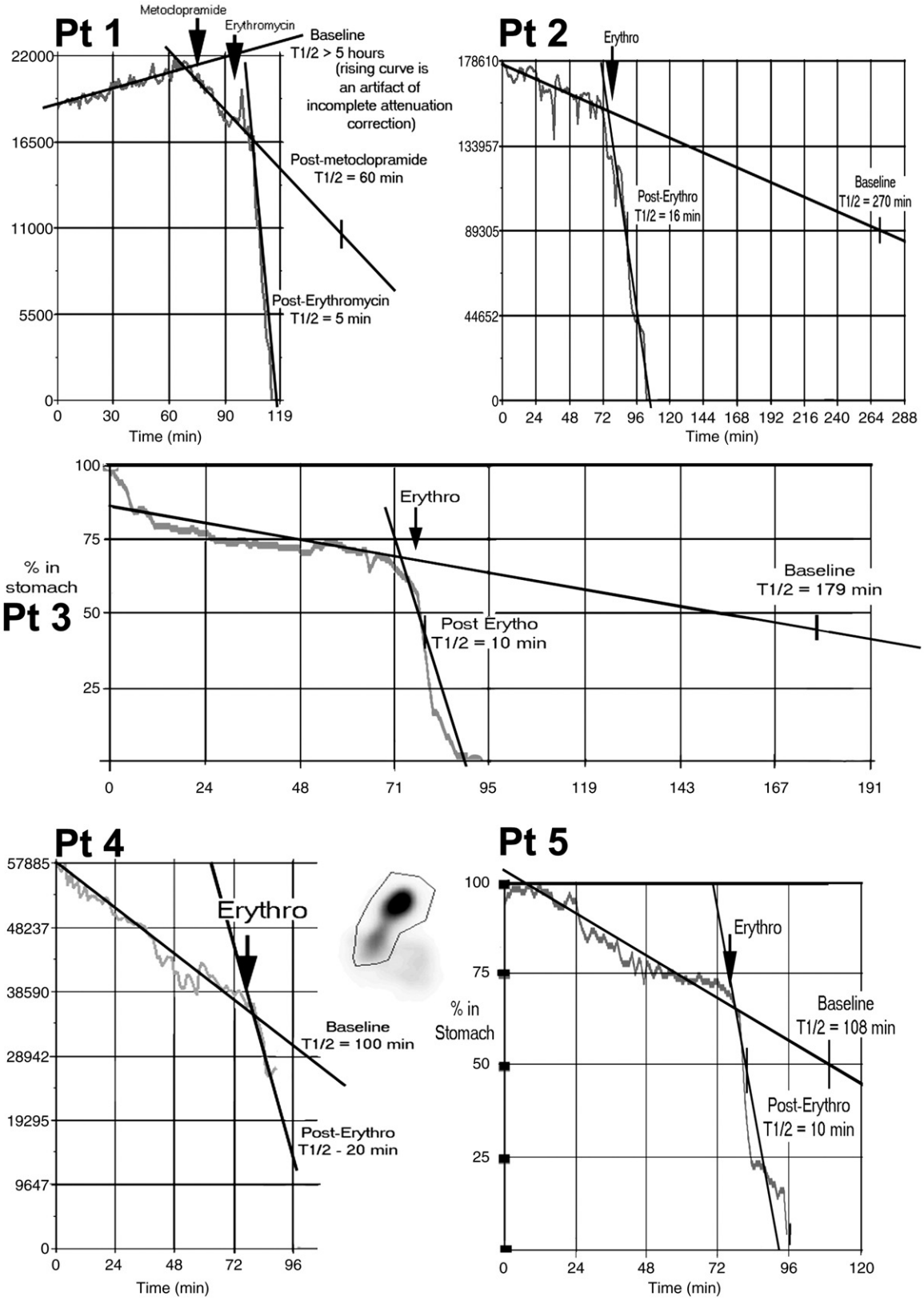

Fig. 1. Gastric emptying scintigraphy with decay correction. In patient 1 the gastric emptying half-time was more than 300 min. IV metoclopramide (Reglan®) was given at 75 min and IV erythromycin administered at 95 min, decreasing the half-time to 60 and 5 min respectively. In patient 2 gastric emptying half-time was 270 min that decreased to 16 min after the administration of IV erythromycin at 82 min of the test. In patient 3 the half-time decreased from 179 min to 10 min after administration of IV erythromycin at 76 min of the test. In patient 4 the half-time decreased from 100 min to 20 min after administration of IV erythromycin at 76 min of the test. In patient 5 the half-time decreased from 108 min to 10 min after the administration of IV erythromycin at 75 min of the study. T1/2: gastric emptying half-time, Erythro: erythromycin.

clinical response to treatment (good or above) during the first clinical visit to the gastroenterologist after macrolide therapy was instituted. One patient did not experience any relief of symptoms either initially or during the follow up, but was receiving high doses of narcotics for epigastric pain attributed to chronic pancreatitis. At the end of the follow-up, one patient scored the effectiveness of therapy as excellent (while receiving azithromycin), one patient as very good (while on azithromycin), two patients as good (one treated with azithromycin and the other with erythromycin, the patient receiving azithromycin required the addition of bethanecol after several months of treatment, as she had return of symptoms) and the last of the patients had no response (while receiving erythromycin). Of interest is that all five patients with gastroparesis had associated gastrointestinal conditions such as gastroesophageal reflux disease (3 of 5 patients) or pancreatic insufficiency (5 of 5 patients).

4. Discussion

In this study we described the presence of gastroparesis in 5 out of 86 adult patients with cystic fibrosis who are periodically followed at our Cystic Fibrosis Care Center. Gastroparesis was identified in patients with a wide variety of BMI, HbA1c and degree of respiratory involvement (measured by FEV1). All five patients with gastroparesis had pancreatic insufficiency and three had gastroesophageal reflux disease.

It is relevant that all patients had dramatic improvements on the gastric emptying half-time with IV administration of erythromycin and all the patients except one experienced different degrees of symptomatic relief during the follow-up. The patient that did not notice any benefit was concomitantly receiving large doses of opioids for severe epigastric pain attributed to chronic pancreatitis. Four patients are currently treated with azithromycin and one of them required the addition of bethanechol as she noticed return of some gastrointestinal symptoms after several months of receiving treatment with erythromycin. None of the patients with gastroparesis received metoclopramide as maintenance therapy, because of concerns regarding extrapyramidal side effects and risk of tardive dyskinesia.

Gastroparesis should be suspected in cystic fibrosis patients that experience symptoms associated with gastric retention (nausea, vomiting, bloating, early satiety, abdominal pain and heartburn). The abnormality should be confirmed by objective evidence of delayed gastric emptying in the absence of mechanical obstruction, since there is a poor correlation between clinical manifestations and gastric emptying abnormalities [2,3].

Multiple diagnostic modalities using a variety of protocols have provided conflicting results regarding the presence of gastric dysmotility in patients with cystic fibrosis. Studies have described normal [4–6], delayed [2,7–10] or accelerated [11,12] gastric emptying rates. Gastroparesis has been described in cystic fibrosis predominantly in children and patients with advanced lung disease.

Liquid–solid gastric emptying scintigraphy in cystic fibrosis patients before lung transplant (mean 1.6 years before) revealed that 67% and 13% of the patients had delayed gastric emptying for solids (half-time 160.86±59.21 min) and liquids, respectively; showing a high prevalence of solid gastroparesis in end-stage cystic fibrosis patients. In addition, gastric emptying times for solids and liquids were significantly prolonged after lung transplantation [2]. In contrast, in relatively healthy cystic fibrosis patients the solid phase gastric emptying half-time was significantly faster when compared with matched controls, probably due to relatively higher energy intake in patients with cystic fibrosis [11].

The diverse results found in these studies may be explained by different ages, disease severity (respiratory and pancreatic), diagnostic methodologies used (solid gastric emptying studies are more sensible and this is the current state of care), and the multi-factorial origin of gastroparesis [2,9,18–26].

The identification of gastroparesis in patients with cystic fibrosis is relevant as it 1) generates significant discomfort, 2) may affect the absorption and/or effect of medications such as pancreatic enzyme replacement since patients with slow gastric emptying have lower activity of pancreatic replacement therapy [4], 3) may affect timing of medications, as pancreatic enzyme microspheres may empty earlier than food, following the liquid phase of gastric emptying [13], and 4) may cause unpredictable gastric emptying and therefore affect glycemic control in cystic fibrosis-related diabetes [3].

There are no data regarding management of cystic fibrosis related gastroparesis. Treatment for gastroparesis in general includes 1) dietary modifications (frequent small and low fat meals, maintain normal glucemia and avoid medications that further delay gastrointestinal motility), 2) gastric emptying stimulants (metroclopramide, domperidone, macrolides and bethanechol), 3) invasive approaches (botulinum injection in the pylorus to reduce tone, venting gastrostomies, and enteral and parenteral nutrition), 4) psychological interventions, and 5) alternative devices (gastric electrical stimulation and TENS: transcutaneous electrical nerve stimulation) [14].

Of the gastric emptying stimulants, erythromycin is the current first line therapy for gastroparesis. It is a powerful stimulator of antral contractions through activation of motilin receptors. It better accelerates gastric emptying and controls symptoms when compared with other available alternatives [15]. It has been shown to improve solid gastric emptying in patients with gastroparesis (diabetic or idiopathic) acutely (IV administration) and after 4 weeks of therapy (oral administration) [16].

A relevant problem with erythromycin is that it may increase the risk of sudden death particularly in patients receiving CYP3A inhibitors by prolonging cardiac repolarization and predisposing patients to torsades de pointes [17]. Another macrolide, azithromycin, has minimal effect on the cardiac repolarization and only minimally interacts with CYP3A inhibitors [3].

In summary, we observed symptomatic gastroparesis in a wide variety of patients with cystic fibrosis. No association was found between gastric emptying half-time and BMI, presence of diabetes and severity of respiratory disease. All our patients had pancreatic insufficiency and were receiving pancreatic replacement therapy. The exact mechanism involved in the development

of gastroparesis in our patients is unclear. We noticed a good initial symptomatic response with erythromycin, but over the course of months some symptoms returned and the medication was switched to azithromycin with good response.

Our current report is limited by the retrospective nature of the examination, and by the small sample size ($n = 5$). A prospective study comparing CF patients of different ages and degrees of respiratory disease, including individuals with cystic fibrosis related diabetes mellitus, using the state of the art diagnostic modalities for gastroparesis is necessary but unlikely to occur as patients would have to be exposed to radiation or relatively invasive procedures. In addition, as the great majority of cystic fibrosis patients receive treatment with azithromycin thrice a week, it would be interesting to prospectively compare this intervention with the daily use of 400 mg of azithromycin elixir on the control of symptoms of gastroparesis and occurrence of adverse effects.

5. Conclusions

Gastroparesis occurs in patients with cystic fibrosis, even in patients with relatively preserved lung function and in those without cystic fibrosis-related diabetes. Intravenous erythromycin significantly reduced the gastric emptying half time. Chronic macrolide antibiotics may be an effective treatment in cystic fibrosis patients with gastroparesis.

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