

## Gastric emptying in myotonic dystrophy

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### Abstract

**Background** Gastrointestinal symptoms are common and important for the quality of life in patients with myotonic dystrophy (MD). Gastric emptying was studied in patients with MD who suffered from symptoms suggesting slow gastric emptying and the effect of prokinetic treatment was evaluated.

**Methods** Gastric emptying was studied in 10 patients with MD who were suffering from nausea, early satiety, bloating, regurgitation, vomiting, or abdominal pain using a <sup>99</sup>Tc-labelled test meal, and was compared with gastric emptying in a group of healthy controls. The patients were subsequently treated with erythromycin and their gastrointestinal symptoms were recorded and the gastric emptying test was repeated.

**Results** Patients with MD had a significantly longer gastric lag phase ( $46.1 \pm 4.3$  vs.  $31.9 \pm 4.0$  min,  $P = 0.03$ ), a slower emptying phase ( $7.1 \pm 0.9$  vs.  $10.2 \pm 0.9$  kJ min<sup>-1</sup>,  $P = 0.02$ ) and a longer half-emptying time,  $T_{50}$  ( $141.7 \pm 10.5$  vs.  $98.6 \pm 8.7$  min,  $P = 0.01$ ) than a matched control group. Erythromycin did not stimulate the gastric emptying rate. The effect on gastrointestinal symptoms was modest, except for a reduction of diarrhoea.

**Conclusions** Patients with MD suffering from nausea, vomiting and early satiety, displayed a slow gastric emptying. Treatment with erythromycin had only moderate effect on gastric emptying or gastric symptoms, but reduced diarrhoea in a majority of the patients.

**Keywords** Erythromycin, gastric emptying, gastrointestinal, myotonic dystrophy.

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### Introduction

Myotonic dystrophy (MD) is a multiorgan disease affecting not only the striated and smooth muscles but also other tissues such as the hair (early baldness), the eyes (cataract) and various endocrine glands. The hallmark of the disease is myotonia in combination with progressive muscle wasting. The disease has an autosomal dominant mode of transmission and the genetic defect has been localized to chromosome 19 where a labile DNA sequence has been

detected [1]. This DNA sequence encodes a protein kinase, and the segment may expand between successive generations. The size of the fragment correlates broadly with the disease severity. The prevalence of the disease has been estimated to be at least 70 per 100 000 in Norrbotten, the most northern county of Sweden [2]. Gastrointestinal symptoms are common among affected individuals and they may be of considerable clinical relevance, e.g. abdominal pain, diarrhoea, or anal incontinence. In a recent study we have found that one-quarter of the patients considered their gastrointestinal symptoms to be the most troublesome consequence of the disease [3]. It has been reported that patients with MD have a delayed gastric emptying and that treatment with metoclopramide [4], as well as cisapride [5], may improve the gastric function.

The aim of this study was to investigate gastric emptying in a group of patients with MD and upper gastrointestinal symptoms. Since earlier studies have selected individuals without reference to their gastrointestinal symptoms, a careful description of the included patients' symptoms was performed. Among slightly more than 100 known individuals with MD in Norrbotten, 40 were interviewed regarding gastrointestinal symptoms [3]. Symptoms suggestive of slow gastric emptying (nausea, early satiety, epigastric pain, vomiting, or regurgitation) were reported to occur more

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**Table 1** Clinical data of patients with myotonic dystrophy

Patient no. and initials	Sex	Age (years)	Grading of disease severity*	Symptoms
1 UCB	F	45	II	Nausea, bloating, pain
2 UA	F	19	I	Nausea, early satiety, epigastric pain, vomiting
3 EB	F	41	III	Nausea, epigastric pain
4 BB	F	31	I	Nausea, epigastric pain
5 TN	M	47	I	Nausea, early satiety, vomiting, epigastric pain
6 EP	F	30	II	Nausea, vomiting, epigastric pain
7 YS	F	40	III	Nausea, vomiting
8 HS	F	35	II	Nausea, bloating, epigastric pain
9 NV	F	59	III	Dysphagia, regurgitation
10 BLL	F	53	I	Heartburn, early satiety, bloating, epigastric pain

\*I, mild muscular symptoms, no functional disturbances in activities of daily life; II, moderate symptoms, the patient can manage a light job; III, severe symptoms and major functional disturbances that prevent several normal activities.

than once a week in 19 of these patients. In an attempt to elucidate possible therapeutic effects of erythromycin, this drug was studied both with respect to the gastric emptying rate and to symptoms in 10 of these patients.

## Methods

### Subjects

Ten patients with MD complaining of symptoms suggesting slow gastric emptying were studied (Table 1). Ten healthy individuals matched for age and sex served as controls.

### Gastric emptying

The method has been presented in detail elsewhere [6,7]. In brief, the investigation was performed after an overnight fast, the subjects then ingested a standardized radiolabelled test meal. An omelette was made using two eggs, 100 mL milk, 15 g wheat flour and 5 g margarine, with 10–15 MBq  $^{99}\text{Tc}$ -labelled macroaggregated albumin added (which binds to the protein), and cooked in a microwave oven. The omelette was composed of 18 g protein, 19 g fat and 17 g carbohydrate and was eaten together with a 150-mL soft drink containing 10% dextrose, making a total energy intake of 1593 kJ. The eating time was limited to 10 min.

The stability of the radioactive labelling was tested *in vitro* by adding 100 mL 0.1 M HCl to the chopped omelette. After incubation at 37 °C for 120 min the mixture was centrifuged and an average of 1.5% of the radioactivity was found in the supernatant.

Measurements were performed using a single-headed circular gamma camera (General Electric Maxicamera) with a diameter of 50 cm (energy level 140 keV, 20% window). The individuals were examined in a sitting position. Immediately after finishing the meal the gastric contents were considered as 100% at time-point 0 min. Anterior and posterior 1-min acquisitions were then performed every 5-min during the first 50 min and thereafter every 10-min during the remaining 70 min, after ingestion of the test meal.

### Evaluation

The radioactivity in the stomach was manually delineated as a Region-of-Interest (ROI) in each digitized image. The geometric mean of the anterior and posterior registration values of each image was calculated and data were fed into a computer program developed in Excel (Microsoft Corp., Redmond, WA, USA) for analysis based on the gastric handling of a solid meal. With automatic correction for physical decay of the isotope, the following parameters of the gastric emptying profile were calculated:

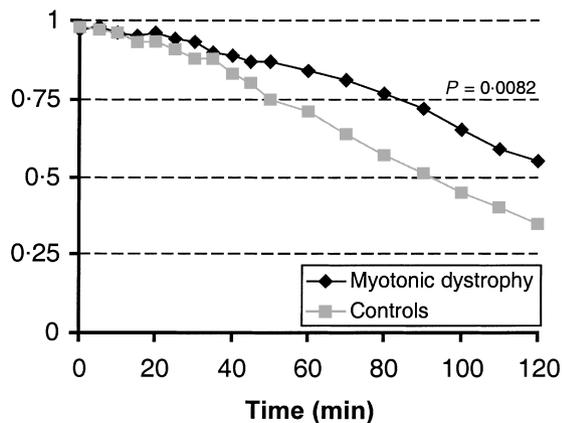
- (1) Gastric lag phase, defined as the time period expressed in minutes from termination of meal (100% gastric radioactivity) until 90% of radioactivity remained in the stomach.
- (2) Gastric emptying rate, defined as percentage decrease of gastric radioactivity per minute during the linear slope after termination of lag phase, also expressed as  $\text{kJ emptying min}^{-1}$ .
- (3) Gastric half-emptying time ( $T_{50}$ ), defined as the time-point for 50% emptying of the radioactivity expressed in minutes.

### Gastrointestinal symptoms

Each patient received a diary for recording symptoms during the two 4-week periods, first during a run-in period, then during treatment with erythromycin. The first period was followed by a 2-week wash-out period. The diary outlined 'gastric' symptoms (regurgitation, early satiety, nausea, vomiting, bloating, pain) for each day during treatment.

### Treatment

The study was performed as an open study. During the first period no prokinetic treatment was given. After the wash-out, erythromycin (Ery-Max<sup>®</sup>, AstraZeneca, Södertälje, Sweden; powder 200 mg dissolved in water) was administered. The patients were instructed to start with 100 mg erythromycin 15–30 min before each main meal, with dose adjustments up to a maximally effective dose according to subjective feelings, or in case of side-effects, a dose reduction. This maximally effective dose was regularly reached at 50–200 mg before food intake.



**Figure 1** Gastric emptying profile in patients with myotonic dystrophy vs. controls. The difference in gastric retention at 120 min,  $P = 0.0082$ .

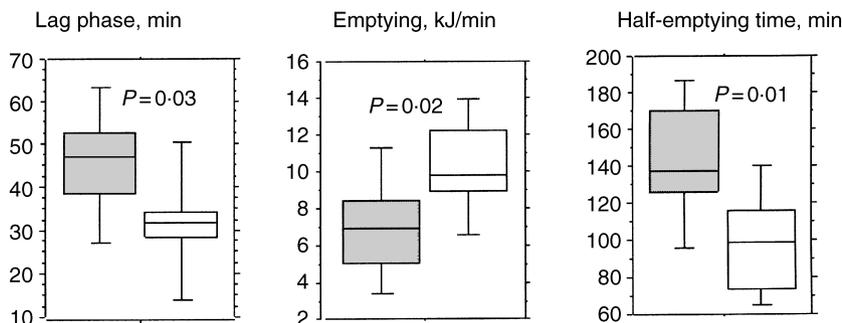
### Ethics and statistics

The study was approved by the local ethics committee of Umeå University. Values are given as mean  $\pm$  SEM. For comparisons between patients and controls, the Mann-Whitney  $U$ -test was used. A  $P$ -value  $< 0.05$  was considered significant.

## Results

### Gastric emptying in myotonic dystrophy

Seven of the 10 patients and all the control subjects completed their test meal. The remaining three were unable to complete the meal because of early satiety. The gastric emptying profiles are illustrated as graphs of radioactive gastric content against time in patients with MD and in healthy volunteers (Fig. 1). The patients with MD had a prolonged lag phase compared to the controls, a slower gastric emptying rate, and a prolonged  $T_{50}$  (Fig. 2). The patients' symptoms were not confined to any specific part of the gastric emptying process.



**Figure 2** Gastric emptying characteristics in patients with myotonic dystrophy (shaded bars) vs. controls (white bars). Values are mean with SEM and 25–75 percentiles. Mann-Whitney  $U$ -test (two-sided).

**Table 2** Gastric emptying in patients with myotonic dystrophy before and during treatment with erythromycin

Gastric emptying characteristic	No treatment ( $n = 10$ )	Erythromycin ( $n = 10$ )	$P$ -value*
Lag phase (min)	46.1 $\pm$ 4.3	37.7 $\pm$ 5.1	0.28
Emptying rate (% min <sup>-1</sup> )	0.47 $\pm$ 0.05	0.44 $\pm$ 0.05	0.80
Emptying rate (kJ min <sup>-1</sup> )	7.1 $\pm$ 0.9	6.5 $\pm$ 0.7	0.65
$T_{50}$ (min)	141.7 $\pm$ 10.5	144 $\pm$ 18.2	0.88

Mean  $\pm$  SEM; \*Wilcoxon signed rank test (two-sided).

**Table 3** Symptomatic improvement of treatment in patients with myotonic dystrophy

Erythromycin ( $n = 10$ )	$n$
Less nausea	1
Ability to eat more	1
Less pain	2
Less diarrhoea	5

### Effect of erythromycin on gastric emptying and symptoms

Treatment with erythromycin had no effect on gastric emptying (Table 2). No immediate improvements were found in the patients' gastrointestinal symptoms. However, after the 4-week treatment period careful examination of the patients' diaries indicated less nausea, greater ability to eat and reduced diarrhoea during treatment (Table 3).

## Discussion

The study demonstrates that patients with MD showing symptoms of early satiety, nausea, vomiting and abdominal pain, have a delayed emptying of the stomach, as reflected by a prolonged lag phase of gastric emptying, a slower emptying rate, and prolonged  $T_{50}$ .

Since MD is a systemic disease, not only a disorder affecting skeletal muscles, there could be multiple reasons for the slow gastric emptying. An early report [8] found that the morphology of the gastric smooth muscle was only rarely affected in MD, however, gastric myocyte function has never been studied. It has been proposed that abnormal electrical control of duodenal activity could contribute to the chronic intestinal pseudo-obstruction occasionally seen in MD [9], and likewise a malfunctioning electrical control of gastric activity may be the cause of slow gastric emptying. In addition, the neuroendocrine cell content in the duodenal mucosa in MD patients with diarrhoea is increased [10] and an abnormal hormonal control of gastrointestinal motility may also influence gastric function. This is verified by our finding that the postprandial increase in plasma motilin is significantly less pronounced in patients with MD compared with controls. In addition, this study also showed the most blunted hormone response to take place in those patients with the most prominent slowing of gastric emptying [11].

The relationship between gastric function and symptoms is unclear and has been extensively studied in diabetics [12]. It was demonstrated that many diabetics even have an accelerated emptying of gastric contents. However, the diabetic subjects with upper gastrointestinal symptoms did not differ significantly from controls regarding the half-time of gastric emptying.

Gastric emptying has previously been studied in a group of patients with MD [4]. However, in the cited study the patient group was investigated without respect to symptoms, but the majority of them were found to have retarded gastric emptying. No correlation between symptoms and gastric emptying rate was found. In their study, Horowitz *et al.* [4] treated the MD patients with metoclopramide 10 mg three times a day, which was demonstrated to improve gastric emptying of both solid and liquid food. Later, a study with cisapride was performed in MD [5] and a dose of 10 mg four times a day was found to improve both gastric emptying and a 'gastric symptoms score' consisting of symptoms of anorexia, nausea, early satiety, distension, vomiting and abdominal pain. Erythromycin has previously been shown to improve gastric emptying in patients with diabetic gastroparesis [12]. To our knowledge this therapeutic step has not been tried in patients with MD. Furthermore, the effect of erythromycin seems to be mediated via motilin receptors [13] and patients with MD may suffer from neuroendocrine disturbances [10,14], which may limit its therapeutic applicability.

In spite of prokinetic treatment, the patients did not improve as regards their gastric symptoms, and no general positive effect could be attributed to changes in the gastric emptying parameters. Nevertheless, in general the patients considered the treatment effective. This could be explained by possible effects of the drugs on parts of the gastrointestinal tract other than the stomach [15,16] due to the widespread involvement of the gastrointestinal tract in MD [9,17]. This assumption gains support in our study from the fact that six out of 10 patients experienced reduced symptoms of diarrhoea. Five of these patients had previ-

ously been found to have a reduced or borderline retention in the <sup>75</sup>Se-homocholic acid taurine (SeHCAT test), suggesting a bile acid malabsorption, possibly due to bacterial overgrowth in the ileum, as the main reason for diarrhoea [18]. The impaired ileal function may be explained by disturbed intestinal motility giving rise to defective mixing of the intestinal contents in the terminal ileum [19]. Alternatively, erythromycin may have reduced a bacterial overgrowth causing the diarrhoea.

In conclusion, we have found that patients with MD presenting symptoms traditionally attributed to slow gastric emptying do have retarded gastric emptying. However, these symptoms could not be treated with erythromycin as a prokinetic on a short-term basis, whereas patients suffering from concomitant diarrhoea experienced reduced symptoms.

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