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Antroduodenal Motor Effects of Intravenous Erythromycin in Children with Abnormalities of Gastrointestinal Motility

Cucchiara, S.; Minella, R.; Scoppa, A.; Emiliano, M.; Calabrese, F.; Az- Zeqeh, N.; Rea, B.; Salvia, G.

Article Outline

Author Information

Department of Pediatrics, School of Medicine, University of Naples Federico II, Naples, Italy

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Address correspondence and reprint requests to Dr. S. Cucchiara; Department of Pediatrics, University of Naples Federico II, Via S. Pansini 5, 80131 Napoli, Italy.

Abstract

Background: The macrolide antibiotic erythromycin (EM) affects gastrointestinal motor activity by acting as agonist of motilin receptors located on the smooth muscle cells of the gastroduodenal tract. We studied the effect of intravenous EM on fasting antroduodenal motility in controls and children with gastrointestinal dysmotility.

Methods: EM lactobionate (rate, 3.0 mg/kg/h) was infused intravenously while antroduodenal manometry was recorded in 10 controls, in 7 patients with functional dyspepsia and in 6 patients with gut pseudo-obstruction. The mean (SD) age (years) was 5.7 (1.4), 6.5 (2.4), and 6.7 (3.2), respectively. Manometry was performed by means of a four- or six-lumen catheter introduced through the nose and perfused with a low compliance pneumohydraulic system. Five controls received EM and five received saline.

Results: EM, infused 5 minutes after passage of an activity front (AF), induced in controls a premature antroduodenal AF occurring 15.4 ± 3.2 minutes after starting infusion; no motor changes were seen after saline; duration and propagation velocity of EM-induced AFs did not differ from spontaneous AFs. In patients with functional dyspepsia EM induced various patterns such as premature antroduodenal AFs, antral phase III-like pattern with short duodenal bursts or prolonged phasic antral waves and no duodenal activity. In patients with neurogenic pseudo-obstruction rare or absent antral activity with incoordinated or absent duodenal activity was induced; no contractions were elicited in two patients with myogenic pseudo-obstruction.

Conclusions: It is confirmed that EM, given at subtherapeutic doses, is a powerful prokinetic agent that can have clinical applications in patients with gastrointestinal dysmotility; however, the effect of the drug seems to be influenced by the nature of the underlying disorder.

Recent studies have shown that the macrolide antibiotic erythromycin affects gastrointestinal motor activity [(1-3)]. The prokinetic effects of erythromycin seem to result from an interaction with specific motilin receptors located on the smooth muscle cells of the gastroduodenal tract [(4)]. Intravenous erythromycin has been shown to promote phase 3 of the migrating motor complex (MMC) both in dogs and in healthy humans [(3,5,6)]; furthermore, a recent study shows that the drug infused intravenously at high doses improved gastric emptying through stimulation of postprandial antroduodenal motor activity [(7)].

Despite several clinical applications of erythromycin in adults with upper gastrointestinal dysmotility, the drug has rarely been investigated in pediatric patients [8]. The prokinetic efficacy of erythromycin has been shown in children with chronic intestinal pseudo-obstruction of moderate degree [9]; the drug has also been effective in facilitating the transpyloric passage of a tube in children with a presumptive diagnosis of chronic intestinal pseudo-obstruction [10].

The present study was performed to investigate the acute effects of intravenous erythromycin on the fasting antroduodenal motor activity in control children and in children with disorders of intestinal motility. For this purpose, patients with functional dyspepsia and with chronic idiopatic intestinal pseudo-obstruction were enrolled.

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SUBJECTS AND METHODS

We studied 7 patients with functional dyspepsia, 6 patients with gut pseudo-obstruction, and 10 controls (C). The mean (SD) age (years) was 5.7 ± 1.4, 6.5 ± 2.4, and 6.7 ± 3.2, respectively. Patients with dyspepsia and those with pseudo-obstruction underwent upper gastrointestinal manometry during a diagnostic workup that also included radiologic study of the entire gastrointestinal tract, upper intestinal endoscopy, and exclusion of systemic, metabolic, and neurologic diseases. The controls subjects were affected by functional constipation (four cases), non-specific chronic diarrhea (two cases), recurrent functional abdominal pain (three cases), and ulcer peptic disease (one case) with abdominal pain located in the midabdomen and resistant to H2 receptor blockers: in all of them gastrointestinal manometry, performed to exclude gut dysmotility, showed a well-represented fasting gastrointestinal motor activity. The gastrointestinal manometry was performed after an overnight fast period by means of a four- or six-lumen catheter (outer diameter, 2.4 and 3.6 mm, respectively) positioned so that the two proximal recording sites (spaced 1 cm apart) were located in the distal antrum and the other side openings in the duodenum. The duodenal ports were 5 cm apart, the most proximal located 6 cm beyond the distal antral opening. The catheter was perfused continuously with an Andorfer low-compliance pneumohydraulic infusion system and connected to strain gauge transducers (Statham P23D), the output of which was recorded on an ink-writing poligraph (R611; Sensormedics, Milan, Italy). The rate of perfusion was 0.3 ml/min and the pressure rise at the sudden occlusion of the distal side openings of the catheter was >100 mm Hg/s. The probe was introduced through the nose along a guide wire and positioned under fluoroscopy.

Under fasting conditions the antrum and the small intestine exhibit a distinct cyclical motor pattern that essentially consists of three consecutive phases: phase I, characterized by almost-complete motor quiescence; phase II, consisting of spontaneous irregular activity; and phase III [or activity front (AF)], which is an uninterrupted and propagated short burst of phasic contractions, during which the antrum and the duodenum contract at their maximal frequency, 3 and 11-12 cycles/min, respectively (Fig. 1). Fasting baseline antroduodenal motility was recorded until two interdigestive AFs were identified at the level of the duodenal ports. Five minutes after passage at the duodenal level of an AF, erythromycin lactobionate was infused intravenously at a rate of 3.0 mg/kg/h, as a continuous drip, and recording of motor activity carried out for at least 120 min after starting infusion. Five controls received erythromycin and five had saline; the choice of erythromycin or saline was done randomly. Patients with functional dyspepsia and pseudo-obstruction received only erythromycin. Tracings were coded and analyzed visually in a blind manner by one of the authors (R.M.), who was unaware of the clinical history and diagnosis of the patients. Antroduodenal motor activity was analyzed for the presence of antral component of the AFs. The parameters measured were duration of the AFs; calculated at the duodenal level; duration of the interdigestive cycle, that is, the time interval between the end of one duodenal AF and the end of the next one; and velocity of propagation of AFs from the antrum to the proximal duodenum, calculated by dividing the distance traversed by the time taken to pass from the distal antral side opening to the proximal duodenal port. Phase III-like activity was defined as phasic and rhythmic motor waves occurring at the maximal frequency lasting for at least 2 min and without a subsequent phase 1. Data are given as mean ± SD. Statistical analysis was performed using Student's t test and p values <0.05 were considered significant. The study was approved by the Pediatric Department's Ethical Committee. Parents gave informed written consent.

Fig. 1
Image Tools

Patients with chronic pseudo-obstruction included in this study were part of a larger population reported previously [11].

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RESULTS

All control subjects showed, at baseline manometry, regularly occurring interdigestive motor activity, with AFs starting at the level of the antrum and propagating distally. In all five controls who had received erythromycin, a premature antroduodenal phase III occurred 15.4 ± 3.2 min after starting infusion (Fig. 2): this phase III always showed an antral component and was followed by a phase of motor quiescence. No significant changes of the interdigestive activity occurred in the five controls following infusion of saline; the length of the cycle (min) was 72 ± 26 at baseline and 78 ± 37 after saline (NS). In the five controls receiving erythromycin the velocity of propagation (cm/s) of antroduodenal phase III was 0.32 ± 0.17 in spontaneous AFs and 0.22 ± 0.06 in erythromycin-induced AFs (NS); the durations of spontaneous AFs (5.24 ± 0.9 min) and erythromycin-induced AFs (4.79 ± 0.7 min) were not statistically different. In the five controls receiving saline, no significant changes occurred in the velocity of propagation and duration of AFs either at baseline or following infusion of saline (velocity of propagation, 0.25 ± 0.14 and 0.26 ± 0.66, respectively; duration, 4.99 ± 0.64 and 4.9 ± 0.47, respectively).

Fig. 2
Image Tools

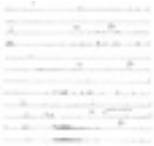

Fig. 2
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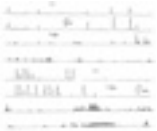

Fig. 2
Image Tools

In the seven patients with functional dyspepsia, intravenous erythromycin induced the following patterns: (a) in two patients, a premature coordinated AF, propagating from the antrum to the duodenum, occurring 9 and 13 min after infusion, respectively; (b) in two cases, an antral phase III-like activity followed by a short phasic burst at the proximal duodenal port (Fig. 3); and (c) a prolonged period of phasic antral contractions without significant motor activity at the level of the small intestine (three cases) (Fig. 4). The first two dyspeptic patients had regular AFs (with an antral component) at the baseline recordings. In the remaining five dyspeptic patients baseline tracings were characterized by irregularities consisting of short-lasting AFs (four cases), bursts of sustained phasic duodenal activity uncoordinated with the adjacent gut segments (three cases), abnormal propagation of AFs (three cases), and intermittent clustered phasic contractions (three cases); a typical antral phase 3 activity propagating to the duodenum was never detected in the baseline tracings of the latter five dyspeptic patients.

Fig. 3
Image Tools

Fig. 4
Image Tools

In four patients with a previously established neurogenic CIIP, intravenous erythromycin induced rare phasic antral activity and absent (one case) or uncoordinated (three cases) duodenal activity (Figs. 5 and 6, respectively); baseline tracings of these patients were characterized by the absence of well-differentiated phases of MMC, extremely disordered motor activity consisting of retrograde duodenojejunal clusters, and/or incoordinated groups of phasic activity in adjacent gut segments. In two patients with myogenic CIIP and marked fasting and fed antroduodenal hypomotility at baseline, no significant motor activity was induced by erythromicin.

Fig. 5
Image Tools

Fig. 6
Image Tools

No untoward side effects such as abdominal pain, vomiting, nausea, or change in biochemical variables were observed; furthermore, no changes of blood pressure or pulse rate were seen during or after erythromycin infusion.

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DISCUSSION

Our study shows that intravenous low doses of erythromycin are able to elicit in normal subjects a premature MMC phase III, starting in the antrum and propagating to the upper small intestine. These findings have been reported previously in humans as well as in dogs [3,5,6] and are commonly believed to result from an interaction between erythromycin and receptors of motilin that are mainly located on smooth muscle cells of the gastroduodenal tract [8]. Motilin is a 22-amino acid peptide cyclically released into the blood during the fasting period: its plasma peaks usually occur during the passage of MMC phase III at the antroduodenal level [12]. It has been shown that plasma motilin peaks characteristically occur only in the presence of MMC AFs having a clear antral component [13].

The fact that premature MMC phase III induced by erythromycin in the control subjects had the same characteristics (velocity of propagation and duration) as those occurring spontaneously and had a well-defined antral component strongly supports the view that erythromycin acts mainly as a motilin receptor agonist; furthermore, it is worth mentioning that previous reports have shown that antroduodenal motor changes in humans following intravenous infusion of erythromycin are not associated with an increase in plasma motilin levels [3,14,15].

In our patient population, represented by functional dyspeptic children and subjects with chronic idiopathic pseudo-obstruction, erythromycin produced coordinated antroduodenal fronts only in two dyspeptic patients who had a regularly occurring antroduodenal phase III of MMC at baseline recording, whereas various motor patterns were elicited in the other dyspeptic subjects, whose baseline tracings were characterized by markedly disordered motility with an absence of regular antroduodenal phase III of MMC. Changes following intravenous erythromycin consisted mainly of prolonged phasic antral activity, and no coordinated antroduodenal motor pattern was elicited.

In patients with neurogenic pseudo-obstruction and severely deranged gastrointestinal motility, the effect of erythromycin was trivial, consisting of rare antral contractions and uncoordinated bursts of phasic duodenal contractions. The fact that no contractions were elicited in patients with pseudo-obstruction whose manometric features suggested a myogenic disorder comes as no surprise since the inconsistency of other available prokinetic agents in myogenic gut motor disorders has already been proved [16].

Erythromycin has previously been given to adults and children with disorders of gastrointestinal motility. In adults with gut pseudo-obstruction the drug has induced either rhythmic bursts of antral contractions that migrate to the duodenal tract [17] or antral phase III-like patterns migrating into the proximal small bowel [18]. Intravenous erythromycin, given to dyspeptic children at a dose of 3 mg/kg over 1 h, was more effective in those patients with less deranged gastrointestinal motility at baseline recording; interestingly, the drug elicited AFs in children who had them at preinfusion manometry [9]. Our data suggest that the prokinetic effects of erythromycin depends strongly on the nature of the underlying gut motor disorder. Despite erythromycin's being primarily a motilin receptor agonist, our results indicate that its effects are modulated through the intrinsic neuronal circuitry. The latter is believed to be the main factor implicated in the regulation of intestinal motility [19]. Whereas in vitro effects of erythromycin appear to be a consequence of a direct action on smooth muscle cell, in vivo effects seem to indicate an activity at the level of the presynaptic neurons, since they can be reduced by hexamethonium and/or atropine [20,21]. There is also recent evidence that both motilin and erythromycin can act on the same population of myenteric neurons in the antrum of the guinea pig [22].

Whether doses of erythromycin higher than those used in the present study might have been effective in improving and coordinating motility in our patient population is not settled. Indeed, high doses of intravenous erythromycin given in the fed state to normal subjects have been shown to induce powerful prolonged antral contractions and to improve antroduodenal coordination; interestingly, a phase III-like motor patten superimposed on fed motility was also elicited [7]. In adult patients with diabetic gastroparesis 40 mg of erythromycin given intravenously promoted different patterns, ranging from a premature antroduodenal phase III to nonmigrating bursts of powerful rhythmic antral contractions, nonpropagated and not followed by a quiescence phase. However, this antral pattern might have a prokinetic effect and explain previous views that erythromycin improves gastric emptying in diabetic gastroparesis [23]. We conclude that the effects of low doses of intravenous erythromycin in children with gastrointestinal dysmotility seem to be influenced by the underlying motor disorder, whereas a coordinated antroduodenal motility is always elicited in normal children. Future work should be focused on testing different doses of erythromycin in patients with intestinal dysmotility, during both fasting and fed conditions; furthermore, assessment of gut motor effects of erythromycin as well as of other prokinetic drugs should be done in patients whose pathophysiologic aspects are clearly defined to relate the effects of the drugs to the nature of the underlying disorder.

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