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*REVIEW*

# Effect of erythromycin on gastric emptying

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## INTRODUCTION

Motility is a general term that embraces all movements of the gastrointestinal tract, such as smooth muscle contraction, intraluminal pressures, and transit time of chyme throughout the bowel. These movements are modified by the actions of specialized segments of the intestine and the sphincters, and the whole system is integrated by neural and humoral levels of control. Motility is best understood teleologically, *i.e.* as a process that facilitates other more fundamental functions of the gut.

The stomach has three major functions: accommodating meals of varying volumes; grinding solid food into small particles; and facilitating the process of gastric emptying.

The last function serves as an important control of the load of chyme presented to the small bowel for digestion and absorption. Thus, the gastric fundus exhibits "receptive relaxation, " which is a decrease in basal tone that is mediated by vagal reflexes and that reduces pressure in gastric body and fundus during the meal. Receptive relaxation provides accommodation for a meal, and food remains in the stomach for acid-peptic digestion to proceed. Later in the postcibal period, basal tone returns; this increase in intraluminal pressure facilitates emptying of the liquid phase of mixed meals[1-3].

Of all disorders of gastroduodenal motility, vomiting is the major manifestation and is the forceful expulsion from the upper gastrointestinal tract. When projectile, the symptom suggests mechanical obstruction, but less disturbed progression of chyme may produce effortless regurgitation. Vomiting can be either central or peripheral in origin, *e.g.*, intra-abdominal stimulation of the vomiting reflex (peritonitis) or mechanical obstruction of the upper gut (*e.g.*, pyloric stenosis).

Nausea and vomiting may be regarded as the body's defense against toxins. The vomiting reflex is initiated by the vomiting center in the medulla, which receives messages from various sources.

Vomiting caused by local irritation of chemoreceptors in the gut mucosa is mediated by afferent vagal and sympathetic pathways to the vomiting center. Toxins that reach the circulation after absorption (or intravenous injection) stimulate the chemoreceptor trigger zone (CTZ) in the area postrema, a circumventricular area which acts as a window in the blood-brain barrier, and neuronal afferents pass messages from here to the vomiting center. The area postrema receives input impulse from vagal afferents and also has neural links with the nucleus tractus solitarius, which is the main site for peripheral input from vagal and sympathetic afferents. Afferent neural impulses from the fauces also pass *via* the nucleus tractus solitarius to the vomiting center. The vomiting reflex is preceded by a prodromal vasovagal phase characterized by pallor, sweating and bradycardia, followed by elevation of the epiglottis and soft palate. Motor impulses activated by the vomiting center then result in relaxation of the stomach and the lower esophageal

sphincter and contraction of the pylorus, diaphragm and thoracic and abdominal muscles, resulting in expulsion of the stomach contents through the mouth.

Nausea is not necessarily a slow-level stimulation of the vomiting reflex. Vomiting may occur without nausea. Nausea is also more difficult to assess than vomiting, as will be discussed later.

Normally, progression of food through the small intestine is slow and steady, and an extensive spreading out of chyme allows its maximal contact with the digestive-absorptive surface. Although the "head" of a barium meal may reach the terminal ileum in 1 to 2 h, meal transit time (for 50% of a meal) is slower and the "tail" is even more delayed. This pattern of transit through the small bowel has led to the unsubstantiated proposal that "intestinal hurry" is a cause of malabsorption and diarrhea. Although appealing, the concept has received little experimental scrutiny. The only documented examples of intestinal hurry are those of "short bowel syndrome", seen after extensive resection of the small bowel, and in the malabsorption that accompanies jejunoileal bypass. In these conditions, the major defect is inadequate contact between chyme and the digestive-absorptive surface. Stanghellini *et al*[4] reported that patients with both ulcer and non-ulcer dyspepsia show interdigestive and postprandial antral hypomotility.

For disorders of gastroduodenal motility, the primary goals of therapy are[1] improving gastroduodenal emptying, intestinal decompression, restoration or maintenance of fluid and electrolyte balance, and treatment of the cause.

Most instances of adynamic ileus are transient, and a medical approach can achieve all three goals. However, when the obstruction is mechanical, initial decompression and removal of the cause of obstruction usually requires surgery.

## PATHOPHYSIOLOGY ON GASTROINTESTINAL EMPTYING

Up to now, although gastric emptying disorders are relatively uncommon, they are potentially devastating conditions resulting from pathophysiologic motor disturbances. Rapid gastric emptying of liquids is the hallmark of dumping syndrome and occurs after operations, including vagotomy. Vagal denervation abolishes receptive relaxation and accommodation in the proximal stomach (the storage site for ingested liquids) resulting in increased intragastric pressure that forces liquids through an ablated or bypassed pylorus. Dumping symptoms may occur in up to 50% of postgastrectomy patients, but most patients are treated satisfactorily by dietary manipulation or, in the rare incapacitated patient, by the long-acting somatostatin analogue octreotide. Reconstructive gastric surgery may rarely be indicated to slow gastric emptying and alleviate dumping syndrome. Re-operative procedures include pyloric reconstruction after pyloroplasty, generation of small intestinal pouches, interposing of isoperistaltic and antiperistaltic jejunal segments, and the Roux-en-Y gastrojejunostomy. Interposed jejunal loops and the Roux-en-Y gastrojejunostomy provide the most satisfactory results.

Delayed gastric emptying may occur in the acute postoperative period or be a late complication of gastric surgery. Loss of vagal input to the gastricantrum and resection of the antrum with vagotomy may produce an atonic stomach or atonic gastric remnant, respectively, which fails to grind and propel solids into the small intestine. Scintigraphic imaging of both the liquid and solid components of a meal is a valuable diagnostic adjunct. Gastric ileus occurring in the early postoperative period generally resolves within 6 wk after operation, and the temptation to re-operate on a non-obstructed stomach should be avoided.

Pharmacologic therapy of chronic gastric stasis with the benzamide prokinetic agents (metoclopramide, cisapride, renzapride), domperidone, or the motilin agonist erythromycin may be effective initially but long-term results are still undefined, and post-vagotomy and post-gastrectomy patients have not been studied adequately[5]. The effects of erythromycin on different parts of the rabbit intestine have been reported[6]; in particular, the effect of erythromycin on the rabbit intestinal smooth muscle was investigated and was compared to that of motilin. Whole isolated segments from the duodenum, jejunum, ileum and ascending colon, as well as strips from the circular and longitudinal smooth muscle of the ascending colon, were used. Erythromycin was found to possess a concentration-dependent contractile effect on the above intestinal parts but to different degrees of intensity. The order of the sensitivity of the intestinal parts to erythromycin was reported as duodenum = jejunum > ascending colon > ileum. The circular smooth muscle of the ascending colon was found to be more sensitive than the longitudinal smooth muscle; moreover, a similar contractile effect, but at lower concentrations, and the same regional specificity were observed with motilin.

During phases Ⅱ and Ⅲ of the migrating motor complex, there is an increase in plasma motilin level that is synchronous with phasic and tonic contractile activity of the lower esophageal sphincter and of the stomach. The action of motilin on human lower esophageal sphincter is proposed to be mediated by cholinergic mechanisms. Recently, it has been shown that erythromycin was a motilin agonist. That study evaluated the pharmacological effects and the mechanisms of action of intravenous erythromycin on esophageal motility in humans. Healthy volunteers were studied three times at 7-d intervals in a randomized, double-blind fashion. Subjects were first studied for 10 min before drug administration. Afterwards, they received an intravenous injection of placebo or atropine (12 mg/kg), in a blind and random manner, followed by a 20 min continuous intravenous infusion of placebo or erythromycin (150 mg). The difference (delta) between lower esophageal sphincter pressure and the duration, amplitude and velocity of peristaltic contractions during the control period and after administration of drugs was compared. Erythromycin significantly increased ($P < 0.05$) the lower esophageal sphincter pressure to 2234.4 ± 625.1 Pa (16.8 ± 4.7 mmHg) compared to placebo -3.9 ± 186.2 Pa (-0.029 ± 1.4 mmHg). Erythromycin significantly decreased peristaltic contraction velocity compared to placebo ($P < 0.05$). The effects of erythromycin on lower esophageal sphincter pressure were completely blocked by previous administration of intravenous atropine. Erythromycin increased the number of fundic contractions compared to the placebo, but this effect was not blocked by prior atropine administration[7,8].

## USEFULNESS OF ERYTHROMYCIN FOR GASTROINTESTINAL EMPTYING DISORDERS

### *Postoperative gastroparesis*

Erythromycin has recently been shown to exert a great effect on gastroduodenal motor activity. This prokinetic action may be clinically useful to patients with gastrointestinal hypomotility, such as diabetic or postoperative gastroparesis. A diabetic patient who underwent antrectomy Billroth Ⅱ for gastric cancer was presented; severe gastroparesis appeared after surgery and nasogastric aspiration could not be removed, although the patient was treated with metoclopramide and glucose, the water and electrolyte imbalance and nutritional status were corrected. Forty-one days after the first operation, a second gastrectomy with Billroth Ⅱ reconstruction was performed because of suspicion of anastomotic narrowing, which was not confirmed at surgery. Fourteen days later, *i.v.* erythromycin (200 mg/4 h) was started owing to persistent gastroparesis. Six days after treatment, the patient tolerated oral ingestion. Prokinetic drugs constitute the specific therapy for gastroparesis. Metoclopramide is the most commonly used, although its efficacy is limited. In the last few years, erythromycin has been proven to have a powerful effect on gastroduodenal motility. This effect is mediated, at least in part, by its motilin-stimulating activity that accelerates gastric emptying; our patient completely recovered with it. Recent results of erythromycin therapy in patients have been promising, despte the difficult management involved[9].

### *Diabetic gastroparesis*

To compare the effects of erythromycin and metoclopramide on gastric emptying and improving symptoms of gastroparesis in diabetic patients with delayed gastric emptying, Erbas *et al*[10] used a study group consisting of 13 patients with symptoms of severe gastroparesis and delayed gastric emptying. Gastric emptying was evaluated using a radionuclide method, and gastrointestinal symptoms were scored. The patients were given either erythromycin (250 mg 3 times/d) or metoclopramide (10 mg 3 times/d) in random order for 3 wk, and after a washout period of 3 wk they were crossed-over to the other medication for another 3 wk. Parameters of gastric emptying were assessed before treatment and after both erythromycin and metoclopramide. The half-time of gastric emptying in diabetic subjects was 110 (77-120) min before treatment. At 60 and 90 min, the median value of residual isotope activity was 66.5% (55%-83.5%) and 55% (43%-74.3%) respectively. The half-time decreased to 55 min (28.6-115) after 3 wk of treatment with erythromycin and percentages of meal retention in the stomach at 60 and 90 min were 49.9% (38.4%-70%) and 40.5% (29.7%-60%) respectively. After taking metoclopramide, the median value of half-time was 67 (15-115) min and percentages of meal retention at 60 and 90 min were 51% (34.5%-93.9%) and 42% (24%-71.2%) respectively. When compared with baseline values, a significant difference in gastric emptying parameters was found after both erythromycin and metoclopramide treatment. A significant improvement of the total score for gastrointestinal symptoms was observed with both drugs, but this improvement was more pronounced with erythromycin. The data suggest that erythromycin, a motilin receptor agonist appears to stimulate intestinal motility and seems to be an alternative agent for the treatment of gastroparesis caused by diabetic autonomic neuropathy[10].

Gallbladder motor function is impaired in some patients with diabetes. It has been suggested that the abnormalities of gallbladder motility are confined to those patients with autonomic neuropathy. Erythromycin, a motilin receptor agonist causes gallbladder contraction in both normal subjects and patients with gallstones and impaired gallbladder emptying. The effect of erythromycin on gallbladder motility in 7 diabetic patients with autonomic neuropathy, 6 diabetic patients without autonomic neuropathy, and 17 normal subjects was studied using ultrasound. There was no significant difference in the gallbladder fasting volume between the three groups, but the diabetic patients with autonomic neuropathy had impaired postprandial gallbladder emptying compared with normal subjects (percentage emptied $\bar{x} \pm s$, 40% ± 10.3% *vs* 64% ± 2.8%, $P < 0.01$) and the patients with autonomic neuropathy (48% ± 7.7%) (NS). Erythromycin produced a dramatic reduction in gallbladder fasting volume in diabetic patients with autonomic neuropathy, compared with either normal subjects or diabetic patients without autonomic neuropathy (percentage reduction of 62% ± 4.6% in patients with autonomic neuropathy *vs* 37% ± 17.6% in those without autonomic neuropathy, and 26% ± 7.3% in the normal subjects; $P < 0.02$), and returned gallbladder emptying to normal in all patients with impaired emptying. The pronounced effect of erythromycin in diabetic autonomic neuropathy suggests denervation supersensitivity and that the action of erythromycin on the gallbladder is neurally modulated[11].

### *Gastroesophageal reflux disease*

Erythromycin and some of its analogues stimulate gastrointestinal smooth muscle contractions. Because gastroesophageal reflux disease (GERD) in humans is in part caused by a reduction in lower esophageal sphincter (LES) pressure, one study aimed to investigate the effect of LY267108 (an erythromycin-A analogue with no significant antimicrobial activity) on LES function. In ketamine-anesthetized cats, LES pressure was recorded using a Dent sleeve. In cats, LY267108 increased LES pressure, as did motilin and erythromycin-A. Neither LY267108, erythromycin-A, nor motilin altered LES relaxation in response to a swallow. LY267108 increased LES pressure in cats in which the basal LES pressure was lowered experimentally by perfusing the distal esophagus with HCl (0.1 N for 3 d) or following isoproterenol (3.0 mg/kg *i.v.*). In summary, LY267108 increases LES pressure not only in normal cats, but also in animals with an experimentally-induced decrease in LES pressure, but it does not affect the relaxation of LES in response to a swallow. The results suggest that LY267108 may be useful in treating GERD because of its ability to increase LES pressure and thus present a barrier for gastroesophageal reflux[12].

Motilin induces phase Ⅲ activity of the gastrointestinal tract. Erythromycin has a motilin-like effect on the stomach and significantly increases the LES pressure in normal volunteers. This investigation was performed to evaluate the effects of erythromycin on esophageal function in patients with GERD. Esophageal manometry was performed

in 10 GERD patients before and after intravenous infusion of 500 mg of erythromycin; values were expressed as x- ± s. LES pressure increased from 1848.7 ± 385.7 Pa (13.9 ± 2.9 mmHg) at baseline to 3843.7 ± 478.8 Pa (28.9 ± 3.6 mmHg) after infusion of erythromycin ($P < 0.01$). The duration of contractions in the proximal, middle, and distal esophagus was significantly prolonged from 3.5 ± 0.4 s, 3.8 ± 0.4 s and 4.1 ± 0.5 s to 4.2 ± 0.2 s, 4.6 ± 0.5 s and 5.6 ± 0.6 s respectively after infusion of erythromycin ($P < 0.05$ for each comparison). Erythromycin did not affect esophageal body contraction amplitude or velocity, or the upper esophageal sphincter. Serum motilin decreased slightly after the administration of erythromycin.

The authors concluded the following[11]. Erythromycin profoundly stimulates the defective LES in patients with GERD; this appears to be a direct motilin agonist-like effect rather than being mediated by release of endogenous motilin. Erythromycin has less effect on the esophageal body, although it does prolong the duration of esophageal contractions.

## ADVERSE EFFECTS OF ERYTHROMYCIN

It is long known that erythromycin may cause unpleasant gastro-intestinal side-effects, such as nausea and vomiting. Recent studies, however, show that at low dosage erythromycin may have a beneficial effect. Erythromycin induces the migrating motor complex in the fasted state and after a meal it accelerates gastric emptying. Although largely preliminary, studies in pathological conditions are being conducted on its effects on esophageal, small intestinal, colonic and biliary tract motility.

Erythromycin is certainly a powerful gastrokinetic agent. Its antibiotic properties are a disadvantage, but more powerful derivatives devoid of antibacterial properties may soon become available, and they form a new family of prokinetics[8].

Erythromycin is generally well tolerated at the recommended dose of 400-600 mg daily. The renewed interest in macrolide antibacterials with expanded indications for clinical use, as well as their markedly increased usage, justifies the continuous search for new compounds designed to offer the patient not only enhanced bioavailability but also a reduced incidence of adverse effects. Macrolides are an old and well-established class of antimicrobial agents that account for 10% to 15% of the worldwide oral antibiotic market. Macrolides are considered to be one of the safest anti-infective groups in clinical use, severe adverse reactions being rare. Newer products with improved features have recently been discovered and developed, maintaining or significantly expanding the role of macrolides in the management of infection. This review deals with the tolerability of the clinically available macrolide antibacterials. With the exception of drug interactions, adverse effects have been analyzed during the last 40 years in many thousands of adult and pediatric patients. Recently developed derivatives have been compared with the older compounds, and the expected and well-assessed adverse effects have been set apart from those which are unusual, very rare or questionable.

Gastrointestinal reactions represent the most frequent disturbance, occurring in 15% to 20% of patients on erythromycins and in 5% or fewer patients treated with some recently developed macrolide derivatives that seldom or never induce endogenous release of motilin, such as roxithromycin, clarithromycin, dirithromycin, azithromycin and rikamycin (rokitamycin). Except for trioleandomycin and some erythromycins administered at large dosage and for long periods of time, the hepatotoxic potential of macrolides, which rarely or never form nitrosoalkanes, is low for josamycin, medecamycin, miocamycin, flurithromycin, clarithromycin and roxithromycin; it is negligible or absent for spiramycin, rikamycin, dirithromycin and azithromycin. Transient deafness and allergic reactions to macrolide antibacterials are extremely unusual effects and have definitely been shown to be more common following treatment with the erythromycins than with the recently developed 14-, 15- and 16-membered macrolides.

There have been case reports in the literature of 51 patients during the last 30 years who experienced uncommon or dubious adverse effects after treatment with older compounds and in whom there appeared to be strong evidence of a causal relationship with the drug. Only 3 cases had an unfavorable outcome, and these were patients administered erythromycin lactobionate intravenously at either too rapid a rate or at too large a dose. Targets of these occasional reactions are generally the heart, liver and central nervous system. Other unusual organ pathologies are related more to immunomediated disorders than to primary parenchymal toxicity, or to the rarely serious consequences of macrolide-induced alterations in intestinal microflora[13].

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