

REVIEW ARTICLE

Erythromycin and the gut

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Abstract

The commonly reported gastrointestinal side effects that occur with erythromycin are related to its prokinetic action on the gut, mediated, at least in part, by its motilin receptor stimulating activity. This action may be of clinical use in conditions associated with gastrointestinal hypomotility such as diabetic gastroparesis and intestinal pseudo-obstruction, although further work needs to be done to establish the long term therapeutic uses of erythromycin in these disorders. Macrolide compounds with no antibacterial properties but which have a pronounced prokinetic action on the gut have already been synthesised and are currently being developed for future use in man. These 'motilides' should provide a useful addition to our rather limited armamentarium of effective gastrointestinal prokinetic agents.

Since the introduction of erythromycin into clinical practice, gastrointestinal side effects, commonly nausea and vomiting, cramping upper abdominal pain, and diarrhoea, have been consistently reported. Erythromycin, as far as we know, uniquely among antibiotics, is a motilin receptor agonist with a profound effect on gastroduodenal motor activity. It is this action which is accountable for many of its unwanted effects on the gut. More importantly, the prokinetic action of erythromycin and related molecules may be clinically useful in conditions associated with gastrointestinal hypomotility such as diabetic gastroparesis and idiopathic pseudo-obstruction. In this review the available evidence on the mode of action of erythromycin on the gastrointestinal tract will be outlined together with the results of studies supporting a potential clinical role in conditions associated with gastrointestinal hypomotility.

Gastrointestinal side effects associated with erythromycin

Erythromycin, originally isolated from an actinomycete in a soil sample from the Philippines¹ and purified and used clinically by McGuire *et al* in 1952,² has become established as a safe and useful antibiotic with a broad spectrum of action against many commonly acquired bacterial pathogens. Although remarkably free from serious adverse reactions, it has long been associated with gastrointestinal side effects such as nausea, vomiting, and diarrhoea. Although initial reports suggested that these side effects only occurred in 7 to 10% of subjects given oral

erythromycin,¹ recent studies suggest that this is an underestimate with up to 95% of subjects receiving intravenous erythromycin and 51% of subjects given oral erythromycin 1.5 g for dental prophylaxis experiencing gastrointestinal symptoms.³⁻⁵ In a study of 10 subjects given 800 mg erythromycin lactobionate intravenously, eight subjects experienced stomach discomfort, six were nauseated, and one vomited. There was a significant correlation between severity of symptoms, infusion rate, and plasma erythromycin concentration.⁶

Erythromycin and gastrointestinal motility

The propensity of erythromycin to produce gastrointestinal side effects is often rather vaguely ascribed to its antibiotic properties producing a change in intestinal flora. However, two studies reported in 1984 indicated that erythromycin has a direct effect on gastrointestinal motility and that this may be the mechanism whereby gastrointestinal side effects are induced. Pilot *et al* reported the effect of intravenous erythromycin on gastric antral, duodenal, and ileal motor activity in fasted conscious dogs.⁷ Intravenous infusion of a subtherapeutic bolus dose of erythromycin (1 mg/kg) stimulated a burst of contractions which originated in the proximal stomach and were propagated to the ileum. Propagation of the preceding migrating motor complex (MMC) was abolished and normal fasting activity altered, with continuous irregular activity recorded from stomach to ileum. The higher dose of 7 mg/kg caused an increase in electrical activity at all sites and all animals vomited. It was felt that the stimulation of small bowel motility by erythromycin might account for the gastrointestinal side effects experienced. These results were confirmed by another group of workers who were also investigating the gastrointestinal side effects of erythromycin.⁸ The erythromycin induced contractions in fasted dogs were similar to the naturally occurring MMC and identical to those induced by intravenous infusion of motilin. That is, they all originated in the stomach and were propagated caudally. There was a significant rise in plasma motilin during the erythromycin infusion. Pentagstrin and feeding inhibited the erythromycin induced contractions in a similar fashion to motilin suggesting that erythromycin exerted its effect on small bowel motility through release of endogenous motilin, although the mechanism for this release was obscure. The effect of erythromycin on gastrointestinal motor activity was found to be dose dependent: less than 50 µg/kg/hr

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failed to stimulate motor activity while doses of 200–400 µg/kg/hr induced strong contractions which failed to migrate to the upper jejunum.

Erythromycin has similar effects on antroduodenal motility in man, doses of 1–3 mg/kg/hr stimulating MMC-like motor activity.^{9–10} Plasma motilin, however, does not rise with erythromycin in man, suggesting that erythromycin may stimulate MMC activity in man in a different way to the dog.

Otterson and Sarna have reported in more detail the effect of erythromycin on gastrointestinal motor activity in the dog, using different doses of oral and intravenous preparations.¹¹ Low doses (1 mg/kg) induced premature MMCs and also slowed the migration velocity of the MMC. At higher doses, erythromycin did not induce a premature MMC but altered the cycle length of the first MMC to occur after erythromycin administration. At all doses erythromycin disrupted the MMC in progress. Erythromycin also disrupted the normal electrical control activity (ECA) of the proximal small bowel and induced what Sarna has described as 'amyogenesis' – contractions which occur without the spatial and temporal control of the ECA and are usually disorganised.

Other sites of action of erythromycin on the gastrointestinal tract

Since the description of the effect of erythromycin on antroduodenal motor activity, other areas of the gastrointestinal tract have been studied. The ability of erythromycin to cause motor contraction varies from one region of the gut to another and in the rabbit, at least, this variability has been shown to correlate with motilin receptor concentration.^{12,13}

Erythromycin increases lower oesophageal sphincter pressure in man in the fasting and fed state, but has no effect on oesophageal body peristalsis.^{14,15} The effect of erythromycin on the lower oesophageal sphincter can be blocked by atropine, suggesting that it is vagally mediated.¹⁵

Colonic motor activity in the rabbit is stimulated *in vitro* by erythromycin.¹⁶ Erythromycin induced strong contractions in proximal colonic muscle strips which became less pronounced distally until strong contractions were again induced in the most distal part of the colon. Binding studies with homogenates of colonic smooth muscle incubated with radiolabelled motilin showed significantly more binding sites in the distal than in the proximal colon. As in other areas of the gut, erythromycin binds to motilin receptors in the rabbit colon.¹⁷ Using ingested radio-opaque markers these authors showed that oral erythromycin reduces transit time in the right colon in human volunteers. The subjects also noted an increase in stool frequency.

Interdigestive gall bladder motility in many species, including man, is related to antroduodenal motor activity, the gall bladder partially emptying in synchrony with phase II of the MMC. This evidence, together with studies showing that motilin given intravenously will provoke gall bladder contraction, allowed us to speculate that erythromycin may have an effect

on the gall bladder. We have reported the results of a preliminary study of the effect of erythromycin on gall bladder motor function in man, in normal and gall stone subjects.¹⁸ Oral erythromycin reduced both the fasting gall bladder volume and the residual volume after a liquid test meal without altering the rate of gall bladder emptying. Like others, we observed a subset of gall stone patients who had impaired gall bladder emptying, and interestingly this motility defect was completely reversed by erythromycin. The effect on gall bladder fasting and residual volumes was maintained after a month of intermittent administration of oral erythromycin (500 mg three times a week), at least in the normal subjects.¹⁹

In vitro studies in the opossum have shown that erythromycin has a similar effect to motilin on sphincter of Oddi muscle strips, increasing tone and peak tension. These contractions are dependent on extracellular calcium.²⁰

Mechanisms of action of erythromycin on gastrointestinal motility: evidence that erythromycin is a motilin receptor agonist

The characteristics of the motor stimulating action of erythromycin on the gastrointestinal tract are similar to those of motilin; however, although plasma motilin values are increased in dogs by erythromycin this does not seem to be so in man.^{9,10} Erythromycin may, however, act as a motilin receptor agonist and indeed there is good evidence that this is so. Erythromycin causes a dose dependent contraction of isolated rabbit duodenal muscle strips, and (to a lesser extent) of stomach, proximal, and distal ileal and colonic muscle strips.¹² This effect is species specific; in contrast to the rabbit, rat and guinea pig smooth muscle strips do not contract in the presence of erythromycin. Motilin shows a similar species specificity and activity profile. The smooth muscle contractions in the rabbit were not inhibited by atropine, hexamethonium, naloxone, diphenhydramine, methysergide, procaine, trypsin, indomethacin, or sodium nitroprusside but were blocked by nifedipine, indicating that the action of erythromycin is calcium dependent.²¹

Erythromycin therefore seems to act directly on the smooth muscle cell, possibly via the motilin receptor, and work by Depoortere *et al* in Belgium²² and Kondo *et al* in Japan supports this hypothesis.²³ Rabbit duodenal smooth muscle showed a similar contractile dose response curve to erythromycin and motilin and erythromycin displaced iodinated motilin from the preparation. Furthermore, the ability of structural analogues of erythromycin to cause smooth muscle contraction is perfectly correlated with their ability to displace motilin. Kondo *et al* have shown that erythromycin and related compounds inhibit the binding of radiolabelled motilin to smooth muscle in a dose dependent fashion and that the inhibitory activity is not related to antibacterial activity. One derivative of erythromycin, EM-536, with no antibacterial activity, has motilin-like activity 2890 times as high as that of erythromycin and of a similar order of magnitude to motilin itself. The actions

of motilin and erythromycin on rabbit duodenal muscle contraction are additive and the contractions induced by erythromycin are insensitive to pretreatment with tetrodotoxin or atropine.¹² Erythromycin and its analogues therefore seem to stimulate gastrointestinal contraction *in vitro* by acting directly on the motilin receptor on smooth muscle via a calcium dependent system. Neural mechanisms do not appear to be involved.

Structure-activity relations of the action of macrolides on gastrointestinal motor activity

Erythromycin is a 'macrolide' compound, so called because of the giant lactone nucleus consisting of 14 carbon atoms joined in a ring. Macrolides fall into two categories depending upon the number of carbon atoms in the lactone ring; either 14 or 16. Sugar molecules – either a dimethylaminosugar or neutral sugar – are bound to the lactone ring in glycosidic linkage. 14-membered macrolides usually have a dimethylaminosugar (desosamine) and neutral sugar linked to the lactone ring in parallel at C-5 and C-3. In 16-membered compounds, the dimethylaminosugar (mycaminose) is bound to the lactone ring at C-5 and a neutral sugar (mycarose) is bound at C-4 prime (see figure). Compounds within these two groups may have variations on this basic structure. Acetylspiramycin, for example, has an additional neutral sugar, forosamine, bound at C-9 of the lactone ring, while tylosin has mycinose, also a neutral sugar, bound at C-14.

Macrolides other than erythromycin have been investigated for their ability to produce gastrointestinal side effects and to stimulate antroduodenal contraction. The 16-membered macrolides josamycin,²⁴ spiramycin,²⁵ leucomycin, acetylspiramycin, and tylosin²⁶ have no effect on gastrointestinal contractile activity. Furthermore, these compounds are not associated with side effects in clinical use. Oleandomycin, however, which has a 14-membered lactone ring, was found to stimulate antral motor activity in the dog in a similar fashion to erythromycin, although the minimum

dose required to do this was 20 times greater than for erythromycin.²⁶

These studies suggest that the molecular structure of the macrolide is critical in determining its ability to stimulate gastrointestinal motor activity and that a 14-membered lactone ring and a dimethylaminosugar at C-5 and neutral sugar at C-3, in glycosidic linkage are vital in conferring MMC stimulating activity. Although the difference in structure between erythromycin and oleandomycin is small, with variation only in the radicals bound at C-8, this seems to be important in determining the ability to cause gastrointestinal contraction. Intravenous infusion of oleandomycin, like erythromycin (but not the 16-membered macrolides) significantly raised plasma motilin concentrations in the dog²⁶ suggesting that the 14-membered but not the 16-membered macrolides were able to stimulate gastrointestinal motor activity by inducing the release of endogenous motilin.

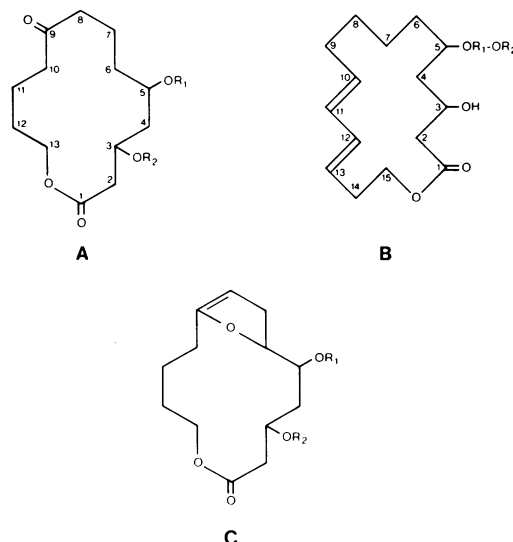
The motilin receptor has not yet been isolated and nothing is known about its structure. Motilin, a 22 amino acid peptide, has been sequenced and although the amino acids involved in binding to the receptor have not been identified, studies of the contractile effects of motilin fragments suggest that both the NH₂- and COOH-terminals are necessary to activate the receptor.²⁷ The molecular structure of erythromycin is very different to that of motilin yet their spatial configuration and charge distribution must be similar in order to activate the same receptor.

In vivo studies in dogs showing that erythromycin releases endogenous motilin do not contradict the evidence that erythromycin is a motilin receptor agonist; it is known that motilin can induce its own release and presumably binding of erythromycin to the receptor can have the same effect.

Evidence that erythromycin is not solely a motilin receptor agonist

Despite good evidence that erythromycin acts as a motilin receptor agonist, the effect of erythromycin on small bowel motor activity is not completely analogous to that of motilin.¹¹ Unlike erythromycin, exogenously administered motilin, even in high doses, has been reported to initiate only a premature MMC. It does not affect cycle length or inhibit the MMC in progress. Erythromycin also causes other motor effects, retrograde giant contractions and clustered duodenal contractions, which have not been described with motilin. Furthermore, there are significant species differences between the *in vitro* and *in vivo* data. Erythromycin has a pronounced effect on canine duodenal muscle in the intact animal^{28,29} but no effect on canine muscle strips.^{12,23} The contractions produced by erythromycin on muscle strips cannot be blocked by tetrodotoxin or atropine,^{12,21} in contrast to the *in vivo* situation where both the actions of erythromycin and motilin are inhibited by atropine.³⁰⁻³³

There is some evidence that erythromycin has actions on neuromuscular transmission and cellular electrical activity; erythromycin given to



Schematic representation of the chemical structures of macrolide antibiotics. (A) 14-membered lactone ring with sugar moieties bound in glycosidic linkage at C5 and C3 (R_1 and R_2). (B) 16-membered lactone ring with a sugar moiety bound at C5 (R_1) with a neutral sugar bound at C4-prime (R_2). (C) Basic structure of erythromycin derivatives EM201 and EM536, with alteration in the arrangements of C6, 8, and 9 of the lactone ring, conferring pronounced motilin receptor binding activity.

normal subjects produces myasthenic like changes in neuromuscular transmission on electromyography but without clinical weakness.³⁴ These changes could be reversed by edrophonium suggesting that erythromycin has a presynaptic action at the neuromuscular junction. Recently, a patient has been described with myasthenia gravis whose symptoms were worsened by erythromycin.³⁵ The effect of erythromycin on the ECA of the small bowel with consequent disruption of motor activity might be related to an effect on the cholinergic intrinsic neurones which are thought to be important in the control of the ECA. Erythromycin also has an effect on the cardiac action potential; intravenous infusions of erythromycin lactobionate have been reported in several instances to provoke polymorphic ventricular tachycardia – ‘torsades de pointes’ – associated with a prolonged Q-T interval on the electrocardiogram. Nattel *et al* examined the effect of erythromycin on canine isolated Purkinje fibres³⁶ and found that erythromycin caused dose related reversible prolongation of the Purkinje fibre action potential and reduction of the maximum rate of voltage rise during phase 0. The mechanisms are unknown but one could speculate that erythromycin has an action on the sodium channel of the cell.

Potential therapeutic uses of erythromycin as a promotility agent

The prokinetic effect of erythromycin may be of use in certain clinical situations where gastrointestinal smooth muscle function is impaired. Janssens *et al* examined the effect of erythromycin on impaired gastric emptying in patients with severe diabetic gastroparesis.³⁷ Intravenous erythromycin (200 mg) shortened prolonged gastric emptying times for both liquids and solids to normal. Four weeks' treatment with oral erythromycin (250 mg three times a day) also improved gastric emptying, but to a lesser degree, suggesting tachyphylaxis. Three of the four patients who had reported symptoms related to gastroparesis were improved with erythromycin. Similar findings were reported with a single intravenous dose of erythromycin having a pronounced effect on gastric emptying in patients with diabetic gastroparesis. Again chronic oral administration (500 mg three times a day) had a reduced effect and the authors concluded that these findings indicated that tolerance to erythromycin developed with long term administration.³⁸ However, it may not be valid to compare directly the effect of an intravenous and an oral dose of erythromycin; blood erythromycin concentrations were not measured and an intravenous bolus of erythromycin may be a more potent stimulus than the oral preparation and could possibly act by a different mechanism.

The effect of erythromycin in other situations where gastrointestinal motility is impaired has since been examined and although thus far the studies reported are small or only anecdotal, there is an accumulation of evidence that the promotility actions of erythromycin will be useful in a variety of clinical situations. A dose of 250 mg oral erythromycin before each meal

returned gastric emptying to normal in a patient with postvagotomy gastroparesis and this improvement was maintained over eight months' therapy.³⁹ Two patients with Ogilvie's syndrome (reflex ileus) were treated successfully with oral erythromycin.⁴⁰

The effect of intravenous erythromycin on gastrointestinal motility in eight patients with chronic idiopathic intestinal pseudo-obstruction has also been studied.⁴¹ Erythromycin induced phase III motor contractions in all the patients. The usefulness of long term erythromycin in these subjects, and more importantly the effect on symptoms, has not been established. Erythromycin has not so far been reported as a potential prokinetic agent in visceral aganglionosis but it might be anticipated that it is more likely to be helpful in situations where the neural circuitry is preserved, such as intestinal myopathies. Whether current tests of motility are of help in predicting clinical response to erythromycin (or other prokinetic agents) is as yet unclear.

The prokinetic actions of erythromycin have also been put to good use in the siting of naso- or oroduodenal tubes as erythromycin enhances the transit of the tube through the pylorus.⁴²⁻⁴³

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