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 Philippines and purified and used clinically by McGuire et al in 1952, 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, 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. 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.

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. 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. 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. Pentagastrin 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...
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. However, 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. 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 ‘amyogenesia’ – 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. Erythromycin increases lower oesophageal sphincter pressure in man in the fasting and fed state, but has no effect on oesophageal body peristalsis. The effect of erythromycin on the lower oesophageal sphincter can be blocked by atropine, suggesting that it is vagally mediated. Colonic motor activity in the rabbit is stimulated in vitro by erythromycin.
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 dimethyl-
aminosugar (desosamine) and neutral sugar
linked to the lactone ring in parallel at C-5 and
C-3. In 16-membered compounds, the dimethyl-
aminosugar (mymycosine) 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. Acetylsyrapimycin, 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
antrudodenal contraction. The 16-membered
macrolides josamycin,22 spiramycin,23 leu-
comycin, acetylsyrapimycin, and tylosin24 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.25

These studies suggest that the molecular
structure of the macrolide is critical in deter-
mining 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 erythro-
ymycin 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
intestinal 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
erthyromycin 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 presum-
ably 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 erythro-
ymycin on small bowel motor activity is not com-
pletely analogous to that of motilin.11 Unlike
erthyromycin, 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 animal28 29 but no effect on canine
muscle strips.30 31 The contractions produced by
erthyromycin on muscle strips cannot be blocked
by tetrodotoxin or atropine,32 33 in contrast to the
in vivo situation where both the actions of
erthyromycin 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 the macrolide antibiotics. (A) 14-membered lactone ring with sugar moieties bound in glycosidic linkage at C5 and C3 (R1 and R2). (B) 16-membered lactone ring with a sugar moiety bound at C5(R1) with a neutral sugar bound at C4-prime (R2). (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. 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. 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 ileal 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 fibres 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. 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 may develop with long term administration. 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 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. Two patients with Ogilvie’s syndrome (reflex ileus) were treated successfully with oral erythromycin.

The effect of intravenous erythromycin on gastrointestinal motility in eight patients with chronic idiopathic intestinal pseudo-obstruction has also been studied. Erythromycin induced phase III motor contractions in all the patients. The usefulness of long term erythromycin in these subjects, and more importantly the effect of 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 sitting of naso- or oro-duodenal tubes as erythromycin enhances the transit of the tube through the pylorus.

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