

Erythromycin

Dr Fahad Wali Ahmed

MBBS, MRCP(UK), Clinical Research Associate,
Newcastle University, UK

Dr Devesh Sennik

MBBS, MRCP(UK), Speciality Registrar (ST5), Diabetes
& Endocrinology, Royal Surrey County Hospital, UK

Correspondence to: Dr Fahad Ahmed, Institute of Cellular Medicine, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK; email: fahadwali@yahoo.com

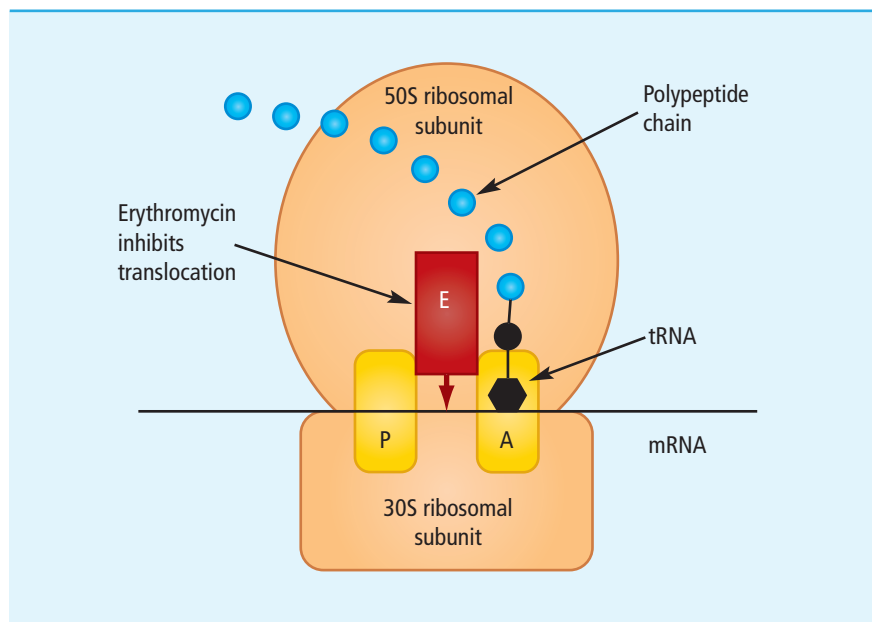


Figure 1. Erythromycin inhibits the translocation of the polypeptide chain from A site to P site

Introduction

Erythromycin remains one of the safest and most important broad spectrum antibiotics available, even though it was discovered nearly 60 years ago. It was the first macrolide antibiotic to become available for clinical use and has served as the prototype for newer macrolides. Erythromycin was discovered by McGuire and coworkers in 1952. It was initially isolated in a metabolic product of a strain of *Streptomyces erythreus* which was originally found in the soil sample from a small island in the Philippines. Its popularity increased in 1976 when it was extensively used to treat outbreaks of pneumonia caused by *Legionella pneumophila*. In addition to its antibacterial activity, erythromycin has immunomodulatory, anti-inflammatory and prokinetic activity.

Pharmacology

Erythromycin is a bacteriostatic agent and in high concentration may have bactericidal activity. Its main action is to inhibit protein synthesis. In bacterial protein synthesis, the peptide chain residing at the A site of the transferase reaction moves to the P side. It binds reversibly to the 50S ribosomal subunit and inhibits the translocation step. (Figure 1.)

Erythromycin is known to exert anti-inflammatory and immunomodulatory effects; the exact underlying mechanism is not known. Erythromycin is known to decrease the oxidative production of cytokines by neutrophils (IL-1, IL-6, IL-8 and TNF). In addition, production of IL-10 and platelet count are increased.

Erythromycin rarely causes serious side effects. The most common side effects include nausea, vomiting, abdominal cramps and diarrhoea. The severity of gastrointestinal (GI) side effects is dose related. Some studies have suggested that up to 95% and 51% of patients experience GI side effects with IV and oral erythromycin, respectively. GI side effects are directly related to erythromycin's prokinetic action. Erythromycin acts as a motilin receptor agonist. This results in increased GI motility by inducing phase III migratory motor complex contraction. This starts in the stomach and migrates through the small intestine. *In vitro* studies on rabbit duodenal muscle showed dose dependent contraction with erythromycin. There was some indication that this is a calcium dependent mechanism as this action is inhibited by nifedipine.

Fever, eosinophilia and skin eruptions can occur as a part of allergic

reaction. Other striking side effects include cholestatic hepatitis; this may be due to a hypersensitivity reaction. IV infusion of erythromycin can result in thrombophlebitis. Transient auditory impairment is noted in some cases after large oral or IV administration.

Erythromycin has some action on cellular electrical activity and can affect cardiac action potential. Erythromycin causes prolongation of the QT interval resulting in torsades de pointes; this is common in patients with cardiac disease. Erythromycin can cause worsening of symptoms of myasthenia. In some cases, it can produce myasthenic-like symptoms in a normal individual.

Erythromycin is well known for its drug interaction profile. It inhibits cytochrome P450 enzymes; this results in an increase in the serum concentration of drugs such as carbamazepine, theophylline, cyclosporine, digoxin, sodium valproate and warfarin.

Use of erythromycin

Erythromycin is commonly used to treat community acquired pneumonia, especially that caused by *Mycoplasma pneumoniae* and *Legionella pneumophila* for which it is the drug of choice. It is also used as a first-line treatment against *Corynebacterium diphtheria* and *Bordetella pertussis*. In addition, it has been used to effectively treat respiratory, neonatal, ocular or genital infection caused by Chlamydia.

Erythromycin is an alternative in penicillin allergic patients with streptococcal or mild staphylococcal infection. Unfortunately, both strains have developed erythromycin resistance. This has resulted in erythromycin being a less attractive choice against these organisms. It can be used as a prophylaxis against recurrence of rheumatic fever in penicillin allergic individuals. Similarly, it has been used to prevent bacterial endocarditis after dental procedures. However, this has been largely replaced by clindamycin as a better alternative in penicillin allergic patients.

The potential use of erythromycin as an anti-inflammatory and immunomodulating agent is still in development. It has been used successfully to treat idiopathic thrombocytopenic purpura, and has been shown to have a steroid sparing effect in asthma.

Furthermore, long-term use of erythromycin has been shown to reduce airway hyper-responsiveness to bronchospasm and effectively treat diffuse pan-bronchiolitis, a chronic inflammatory condition.

Specific evidence for use in diabetes

Erythromycin has shown efficacy in improving gastric emptying in a number of studies and has therefore been used in patients with diabetic gastroparesis. A single administration of IV erythromycin improves gastric emptying significantly when compared with placebo. Similar results have been noted with oral administration.¹

Limited head-to-head data are available about erythromycin versus other prokinetic agents. Oral erythromycin is non-inferior to oral metoclopramide² but superior to oral cisapride.³ However, both studies were unblinded with a small group size. Furthermore, evidence to assess if improved gastric emptying is translated into symptomatic improvement is limited. It has mainly shown to improve bloating rather than nausea or satiety.⁴ One of the reviews found improvement in 48% of diabetic and non-diabetic patients;⁵ however, this review consisted of small, unblinded studies which did not use symptoms as a primary endpoint. Methodological problems are present with most trials on gastroparesis. One study did show improvement in dyspeptic symptoms after short-term low dose erythromycin administration; this improvement continued during long-term follow up. However, the long-term treatment effect was not as statistically significant as the short-term one. This is probably due to tachyphylaxis because of down regulation of motilin receptors.⁶

Because of its prokinetic effect, erythromycin has been used post-operatively to improve gastric emptying and in facilitating transpyloric placement of nasogastric tube. However, the evidence so far has revealed contradictory results without showing tangible clinical efficacy.

Discussion

There is evidence to show that erythromycin has efficacy in gastric emptying in patients with diabetic gastroparesis. However, is it going to improve symptoms or not? This is not very clear.

Key points

- Erythromycin is one of the safest and commonly used antibiotics. It has strong prokinetic properties and is used in patients with diabetic gastroparesis
- Evidence to support symptomatic benefit in patients with diabetic gastroparesis is limited. Long-term oral treatment is complicated by tachyphylaxis
- Erythromycin can be used in patients who have not shown any benefit with other prokinetic agents, or in combination with other prokinetic agents. Treatment decision should be based on individual patient symptom benefit

Erythromycin is a powerful prokinetic agent when used intravenously and may have a role in the hospitalised patient with severe gastroparesis. Nevertheless, its side effect profile and drug interactions need to be considered. Low dose oral erythromycin may be used. However, long-term treatment may result in tachyphylaxis.

Several synthetic erythromycin analogues (ABT229, KC11458 etc) have been developed. These are devoid of a side effect profile and antibacterial effect. However, they retain their motilin receptor agonist properties. It has been disappointing that no study to date has demonstrated any significant benefit.

The use of erythromycin in diabetic gastroparesis is limited. It is worth trying erythromycin in patients who have not shown benefit with commonly used prokinetic agents such as metoclopramide or domperidone. As long-term use of metoclopramide or domperidone can also result in tachyphylaxis, erythromycin can be used during drug holidays. Treating diabetic gastroparesis is difficult. No one treatment has proven to be 100% efficacious. Thus, erythromycin may have a role in the treatment of difficult diabetic gastroparesis. The development of a better synthetic erythromycin analogue may be the way forward.

Declaration of interests

There are no conflicts of interest declared.

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References are available online at www.practicaldiabetes.com.

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