

## What is the optimal prokinetic dose of erythromycin in adults?

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### Background

Gastrointestinal (GI) smooth muscle has intrinsic activity which can be modified by nerves, local reflexes, and gastrointestinal hormones. This activity produces waves of contraction, which move the gut contents from the stomach to the anus encouraging digestion. (1) Impaired GI motility arising from functional disorders such as constipation dependent irritable bowel syndrome and functional dyspepsia, as well as chronic constipation and gastro-oesophageal reflux disease may be improved by the use of prokinetic drugs. (2) In addition, post-operative ileus, diabetic gastroparesis and delayed gastric emptying in critically ill patients have also been treated with prokinetic agents. (1, 2)

Prokinetic drugs either stimulate the motility of the GI tract or promote the electrolyte/water secretion across the GI tract lumen (1, 2) A number of drugs with prokinetic properties have been considered for clinical use, including metoclopramide, domperidone, tegaserod, cisapride and erythromycin. (1) None have a UK license for use as a prokinetic and tegaserod and cisapride are not licensed in the UK. (2, 3)

### Why erythromycin?

Erythromycin is a macrolide antibiotic. The usual antibiotic dose in adults is 1-2g daily in two or four divided doses. (3) It was first established as a potential gastrokinetic agent in the early 1990's (4) and has been used in a variety of patient populations. (2) Erythromycin acts as a motilin agonist through its interaction with motilin receptors found in the stomach and upper GI tract. Erythromycin accelerates gastric emptying by increasing the frequency and amplitude of stomach and duodenal contractions. (5)

### Answer

Both the oral and intravenous (IV) route of erythromycin as a prokinetic agent have been studied, however, there is a lack of evidence from large randomised controlled trials in this area, and studies have tended to include small patient numbers and only consider short term use. (4, 6-11) Long term oral use is limited by poor tolerance, modest efficacy and the development of tachyphylaxis (rapidly diminishing response to drug therapy). (12, 13)

The BNF provides an oral dose for gastrointestinal stasis of 250 to 500mg three times a day for up to 4 weeks, with doses to be taken before meals. It also provides an IV dose of 3mg/Kg three times a day. (3)

A NICE evidence summary for unlicensed and off label uses of medicines reviewed the evidence for oral erythromycin treating gastroparesis in adults in June 2013. Oral erythromycin has been administered at doses ranging from 125mg three times daily to 500mg four times daily for 2-4 weeks. The summary concluded that only 1 small single-blind, crossover study (n=13) identified in a systematic review (5 studies, varying designs, n = 60) found a statistically significant benefit for erythromycin (250mg three times daily) in the short term for improving symptoms of gastroparesis compared with metoclopramide (10mg three times daily). The other studies identified in the systematic review did not provide reliable evidence of the effectiveness, safety and tolerability of erythromycin for gastroparesis in either the short or longer term. (14)

The NICE Clinical Knowledge Summary for constipation in palliative care suggests that erythromycin 250-500mg four times a day can be used for gastric emptying in palliative patients with chronic constipation unresponsive to laxatives. (15) Erythromycin is also used in palliative care for other

indications including gastroparesis. The Palliative Care Formulary suggests a starting dose of erythromycin suspension of 50–100mg four times a day. This can be increased every few days by 25–50mg to a maximum dose of 250mg four times a day. (16)

A clinical guideline for management of gastroparesis recommends that erythromycin improves gastric emptying and symptoms from delayed gastric emptying. Administration of IV erythromycin should be considered when IV prokinetic therapy is needed in hospitalised patients. 3mg/kg every 8 hours by IV infusion over 45 minutes to avoid sclerosing veins is effective. (17) A small randomised controlled trial (n = 132) has investigated the use of IV erythromycin 3mg/Kg for gastric emptying in patients undergoing general anaesthesia for emergency surgery. Empty stomach was defined as a gastric volume of 40ml or less and erythromycin was administered 15 minutes prior to tracheal intubation. The trial found that erythromycin cleared the stomach in 80% of patients compared to 64% who received placebo (risk ratio 1.26; 95% CI 1.01 – 1.57). (18)

In a retrospective chart analysis, 25 patients with dyspepsia symptoms with gastroparesis were treated with low dose oral erythromycin suspension 50 – 100mg three times a day and at bedtime and a low-bulk diet. Of the 25 patients, 18 had short-term follow-up, 18 had long-term follow-up, and 14 had both. On short-term follow-up, 15 patients experienced some or dramatic improvement, while 3 experienced worsening or no change in symptoms ( $p=0.005$ ). Mean duration of long-term use was  $11\pm 7$  months. On long-term follow-up, 12 patients noticed some or dramatic improvement, while 6 experienced worsening or no change in symptoms ( $p=0.16$ ), which was not a significant difference. Correlation between short and long-term response was significant ( $p<0.005$ ). Of the 3 patients with poor short-term response, none did well long-term. Of the 11 patients with some or dramatic response in the short-term, 7 continued to have some response long-term. The authors conclude that the treatment of gastroparesis with low dose erythromycin and low-bulk diet results in a dramatic short-term improvement in the majority of patients. Short-term response predicts long-term response although this response may not be as great, possibly due to tachyphylaxis. (6) One review recommends that because of the risk of tachyphylaxis, treatment should not exceed 4 weeks. (19)

DiBaise et al also conducted a retrospective chart review of 11 outpatients with gastroparesis who were treated with intravenous erythromycin administered via a peripherally inserted central venous catheter for at least one month. (7) The 11 patients received a total of 14 courses of intravenous erythromycin for a median of 6.5 months (range 1 to 19 months) at a median dosage of 300mg/day (range, 150–1000mg/day). One patient received no benefit, two had complete responses, and all the others reported some benefit. Two had dramatic relapse on cessation of therapy and subsequently improved on its resumption. Parenteral nutrition was discontinued in one of four patients. There were four episodes of line sepsis and two required catheter removal. A non-occlusive thrombus developed at the site of a central line in one patient. Secondary infections or antibiotic resistance were not encountered. The study authors concluded that the small, uncontrolled retrospective study of administration of intravenous erythromycin for prolonged periods in an outpatient setting is feasible, well tolerated and effective in patients with severe gastroparesis. (7)

Enteral nutrition is part of standard care for critically ill patients and is most commonly delivered via the gastric route. Prokinetic drugs are commonly administered to increase the amount of nutrient delivered to the small intestine during intragastric feeding. (20) In a prospective randomised controlled study, Reignier et al examined the effects of erythromycin on early enteral nutrition in mechanically ventilated critically ill patients. 40 patients were randomly assigned to receive either intravenous erythromycin 250mg four times a day or placebo for 5 days. The treated group experienced a significant decrease in residual gastric volume for the first 3 days of feeding and a significant decrease in the number of patients unable to tolerate enteral nutrition (35% vs. 70%). (8)

In a study involving 35 randomly selected, mechanically ventilated, enterally fed, critically ill patients, 2 doses of intravenous erythromycin were compared for their effect on gastric emptying. Treatment with 70mg and 200mg intravenous erythromycin given over 20 minutes were shown to be equally effective in accelerating gastric emptying in these patients. (9)

A prospective, randomized, controlled trial studied 68 critically ill trauma patients who had failed to tolerate gastric feeding at any time during the first 48 hours since admission. Patients were randomized to placebo or intravenous erythromycin 250mg four times daily and treatment continued in patients who tolerated gastric feeds until the feeds were no longer required. There was significant difference between the groups for the amount of feedings tolerated at 48 hours after randomization ( $p=0.001$ ). However, there was no difference in the amount of feeding tolerated during the entire study period ( $p=0.061$ ). The authors concluded that erythromycin was useful in the short term for delayed gastric emptying. (10)

In an observational comparative study, 29 medical, feed intolerant, mechanically ventilated critically ill patients, were treated with intravenous erythromycin 200mg twice daily to improve feed tolerance. Plasma erythromycin levels were measured 1 hour and 7 hours after drug administration for 7 days. The success of enteral feeding was defined as 6 hourly gastric residual volume  $\leq 250$ ml with a feeding rate  $\geq 40$ ml/hour. At day 7, 38% (11 of 29) of patients were feed tolerant. Feed-intolerant patients who had lower plasma erythromycin concentrations had a longer response to therapy. The authors suggest the use of low doses of erythromycin not exceeding 200mg twice daily. Tailoring the dose of erythromycin to plasma concentrations may also be useful in reducing erythromycin tachyphylaxis. (11)

In a 2015 review of the current advances in the treatment of gastroparesis, oral erythromycin at a dose of 100 – 125mg two to three times a day was sufficient to improve gastric emptying and controlling gastrointestinal symptoms. For IV administration, a dose of 1.5 – 3mg/Kg every 6 to 8 hours can facilitate the placement of enteral feeding tubes, decrease tube feeding residuals and to manage gastroparesis flares in palliative patients. (19)

Two textbooks on drug dosing in critical care patients (20, 21) give dosing suggestions for erythromycin when used as a prokinetic agent. Paw and Shulman advise a dose of 125mg four times a day orally or via a nasogastric tube or 125mg- 250mg intravenously every 6-12 hours. They also suggest that the use of erythromycin as a prokinetic may increase patient colonization with resistant bacterial species including methicillin resistant staphylococcus aureus (MRSA). (20) The Oxford Handbook of Critical Care gives a dose of 250mg four times a day orally or intravenously when erythromycin is used as a gut motility agent. (21)

Two antimicrobial resources provide erythromycin dosing for gastroparesis. The Sanford guide provides an oral dose of 250mg twice a day and an IV dose of 1.5-3mg/Kg four times a day given over 45 minutes. It states that it improves gastric emptying for around 2 weeks but not thereafter due to down regulation of motilin receptors. (22) The John Hopkins Antibiotics guide provides an oral dose of 150 to 250mg three to four times a day given 30 minutes before meals. (23)

There have been concerns that the use of low dose erythromycin may lead to the development of macrolide resistance and increase the risk of Clostridium difficile (CD) diarrhoea and nosocomial infections. (24, 25) Hawkyard and colleagues suggested further work is needed to fully assess the potential epidemiological impact of the increased use of macrolides on the spread of resistance given the lack of convincing evidence that erythromycin is a superior prokinetic agent compared with alternatives in the critical care setting. (24) However, one study in 2008 looked at 183 intensive care patients who had received low dose erythromycin prokinetic therapy and found that diarrhoea was not found to have been caused by CD or bacterial infections but may have been due to the pro-motility effects of erythromycin. (25) The use of erythromycin in trauma patients also did not increase the risk of nosocomial infections. (10)

Cardiovascular complications such as QTc prolongation and an association with torsades de pointes, should be considered before prescribing erythromycin as a prokinetic agent. One prospective study reviewed the effect that IV erythromycin 200mg twice a day as a prokinetic had on the QTc in intensive care patients (n = 51). In these patients, the QTc increased significantly from 430 ms at baseline to 439 ms (p=0.03) after 15 min and 444 ms (p=0.01) after 24 hours. Although no QTc-related arrhythmias were seen, precautions should be taken when used in patients at risk of QT prolongation. (26) Other safety considerations such as the numerous drug interactions with erythromycin due to the inhibition of the cytochrome P450 pathway need to be considered. (12, 27).

## Summary

- The ideal prokinetic dose of erythromycin is yet to be established but is less than the maximal antibacterial dose of erythromycin.
- There is not a standard regimen for erythromycin when used as a prokinetic agent and it is unlicensed for this indication.
- With intravenous erythromycin, the BNF provides a dose of 3mg/Kg three times a day. Satisfactory outcomes have also been achieved with doses of 300 to 400mg daily in divided doses, with 250mg four times a day, and with single doses of 70mg and 200mg.
- Oral erythromycin has been used effectively as a prokinetic at doses from 50mg three times daily up to 500mg four times daily. The BNF provides a dose of 250 to 500mg three times a day.
- Short-term use (up to 4 weeks) is recommended. Prolonged therapy can result in down-regulation of motilin receptors resulting in tachyphylaxis.
- When prescribing erythromycin as a prokinetic, consideration should be given to its potential to interact with other drugs, and the possibility of cardiovascular complications. It has been suggested that the use of lower doses may be as effective as higher doses and reduce the risk of tachyphylaxis, although these concepts require further study.

## Limitations

This Q&A has not evaluated the use of erythromycin as a prokinetic in children or the use of any other prokinetic agents. It has also not considered whether erythromycin is the most suitable prokinetic agent to use.

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## Quality Assurance

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### Search strategy

- BNF, NICE, NICE Evidence, Cochrane library, Clinical Knowledge Summaries, UpToDate, Sanford guide, John Hopkins ABX guide; search terms = erythromycin AND prokinetic.
- Micromedex via [www.micromedexsolutions.com](http://www.micromedexsolutions.com), search terms = erythromycin AND prokinetic
- Medicines Complete (Martindale, AHFS), search terms = erythromycin AND prokinetic.
- Palliative Care Formulary, Handbook of drugs in intensive care, Oxford handbook of critical care.
- Medline:  
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