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Review Article

Erythromycin and gastrointestinal dysmotility in preterm infants

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Abstract. Gastrointestinal dysmotility is a common condition in preterm infants due to immature development of gastrointestinal peristalsis. Erythromycin, with its motilinomimetric effect, has been used to facilitate enteral feeding in preterm infants. Various regimens, including prophylaxis *versus* rescue treatment and low dose *versus* high dose therapy have been investigated. The results suggest that intermediate or high doses oral erythromycin used as rescue treatment is associated with a shorter time to attain full enteral feeding, a decrease in the duration of parenteral nutrition requirement, a reduction of parenteral nutrition-associated cholestasis and a decrease in catheter-associated recurrent septicemia. Although none of the studies reported any sinister adverse effects, neonatologists should use this class of drug cautiously and selectively in preterm infants with refractory functional gastrointestinal dysmotility.

Key words: Gastrointestinal dysmotility, enteral feeding, preterm, very low birthweight infants

1. Introduction

Functional gastrointestinal (GI) dysmotility is a common condition in preterm infants and may manifest as an increase in gastric residue after feeding, marked abdominal distension or constipation (1). As feeding intolerance is also one of the early presenting symptoms of necrotising enterocolitis (NEC), advancement of enteral feeding may need to be stopped and nutrition of the infant requires to be supported parenterally. However, prolonged use of parenteral nutrition can predispose to catheter-related nosocomial infection, cholestasis, osteopaenia, poor intestinal growth and prolonged hospitalization (2). In an attempt to minimise these devastating complications, various medications, including metoclopramide and cisapride have been tried to improve the GI motility in these infants. However, none of these treatments has been proven to be useful and many are associated with serious adverse effects. After several case series studies have shown that erythromycin could facilitate enteral feeding in preterm infants (2-4), 10 randomised controlled trials (RCTs) have so far been conducted in the last decade (5-14). This article examines the results of these studies, and assesses the efficacy and safety of erythromycin as a prokinetic agent in preterm infants.

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2. Pathophysiology

Co-ordinated contraction of smooth muscle that propels food forward through the intestinal tract is regulated both by neural and hormonal control (15). There are two types of small intestinal motor patterns in adults. The first type is the simultaneous contraction at different levels of the GI tract when food is ingested. This results in mixing and churning of ingested food with gastric secretion, and thus, facilitates the presentation of nutrients to the mucosal surface of the intestine. The second type occurs during fasting. The stomach and small intestine exhibit cyclic groups of caudally migrating contractions known as the migrating motor complex (MMC) (16). This phenomenon is thought to sweep residual products of digestion towards the colon and serves as a 'housekeeper' (17). The MMC is primarily controlled by the local enteric nervous system (18) and modulated by hormones, including motilin (19), somatostatin (20) and pancreatic polypeptides (21).

Motor patterns of the GI tract in preterm infants are different to adults (22). Very few infants

display MMC during fasting but instead demonstrate episodes of motor quiescence that alternate with episodes of non-migrating phasic activity. The characteristics of non-migrating activity change with maturity, as episodes will lengthen in duration and decrease in overall occurrence with increasing gestational age (23). When preterm infants ingest milk, duodenal motor activity may either increase (mature fed response) simulating an adult response, remain unchanged (intermediate fed response) or decrease (immature fed response) (24). The type of response depends on gestational age (25). Among infants less than 36 weeks gestation, approximately two-thirds display an immature response, whereas only 15% of term infants display this type of activity (26). Gastric emptying depends on intact motor function and coordinated contractions in the antrum, pylorus and duodenum (27). Gastric emptying is delayed in preterm infants, compared to term infants (28), due to immaturity of duodenal motor function and absence of coordination between the antrum and duodenum (29). In addition, the total gut transit time varies between 1 and 5 days in preterm infants, whereas those in adults are between 4 and 12 hours (30). The presence of immature GI motor activity results in less efficient gastric emptying and slower intestinal transit in preterm infants.

3. Erythromycin

Erythromycin is a macrolide antibiotic discovered in the 1950s. Untoward effects include diarrhoea, abdominal colic, dyspepsia, nausea and vomiting (31). The prokinetic property of erythromycin was first discovered in the 1980s. Itoh *et al* demonstrated that intravenous erythromycin could induce powerful smooth muscle contractions in the stomach and duodenum of dogs (32). The activity of erythromycin resembles that of motilin-induced intestinal contraction. In both human and dog, increased plasma concentration of motilin are associated with increase in magnitude and frequency of MMC and GI contraction (33). Stimulation of motilin receptors results in increased antral contraction (34) and reduced pyloric outlet resistance (35). Erythromycin has a high affinity for 2 main types of motilin receptors (36). The neural motilin receptor on cholinergic neurons is principally stimulated by low dose (1–3 mg/kg) erythromycin and can augment phase III MMCs, whilst the smooth muscle motilin receptor responds to higher doses and produces sustained antral contractions which facilitates antroduodenal coordination (37-40). In view of its prokinetic property, erythromycin has been used in patients with chronic functional pseudo-obstruction (41), gastro-oesophageal reflux (42), post-operative intestinal dysmotility (43), gastroparesis secondary to diabetes (44), scleroma (45) and after surgical vagotomy (46). Recently, its use has been extended to preterm infants with GI dysmotility (47). Early case series studies suggested that erythromycin could improve GI motility in preterm infants (2-4), and thus far, 10 RCTs have been performed.

4. Review of randomized control trials

The RCTs can be categorised into 2 groups, universal prophylaxis for all preterm infants and rescue treatment for those having feeding intolerance. Two out of 3 prophylactic RCTs (5-7) did not demonstrate any benefit of erythromycin as an effective prokinetic agent (5,6). However, the objective of the study by Stenson *et al* (5) primarily concerned the use of intravenous erythromycin for eradication of *Ureaplasma urealyticum* and prevention of chronic lung disease. Their investigation on the effect of erythromycin on enteral feeding was a secondary data analysis. Thus, the study was not originally designed nor intended to answer the question on feeding intolerance. In this category, only the study by Oei *et al* (7) suggested that oral erythromycin was associated with significantly fewer episodes of significant residual gastric aspirates and treated infants were able to attain full enteral feeding more rapidly. On the whole, prophylactic studies (5-7) suffer the prejudice of indiscriminately treating all infants and do not specifically target those who are most in need of prokinetic treatment. Prophylactic RCTs may not necessarily reveal the full potential of erythromycin in facilitating enteral feeding. Further, as this agent has bacteriostatic properties, neonatologists would be most reluctant to prescribe the medication routinely due to worries of promoting the emergence of multidrug-resistant organisms and alteration of microbiological flora in the GI tract at such an early stage in life.

There are seven RCTs which used erythromycin as a rescue treatment for preterm infants with feeding intolerance. Four clinical trials used low doses (3-15mg/kg/day) administering the medication either orally or intravenously (8-11), whereas the other 3 trials used either an intermediate/high dose tapering regimen (40 mg/kg for 2 days followed by 16 mg/kg for 5 days) (12) or high doses (50 mg/day) (13,14). Three of the 4 RCTs using a low-dose regimen did not show any beneficial effect of

erythromycin as a prokinetic agent (8-10). Only one study demonstrated that low-dose oral erythromycin was effective in facilitating enteral feeding, decreasing the number of episodes of gastric residuals and shortening the duration of parenteral nutrition, in preterm infants more than 32 weeks' gestation (11). Nonetheless, no improvement was observed in infants with lower gestational ages in this study. In contrast, all studies utilising an intermediate or a high dose of oral erythromycin showed beneficial effects in promoting milk feedings and shortening the duration of parenteral nutrition requirements (12-14). Additionally, the study which concentrated on long term outcome (14). had sufficient statistical power to demonstrate that the use of erythromycin could reduce the incidence of parenteral nutrition associated cholestasis by 49% and significantly fewer treated patients had abnormally raised serum alanine aminotransferase concentration (14) This study also revealed a significant reduction in recurrent septicemia, and that the use of high (antimicrobial) dose oral erythromycin did not promote the emergence of multidrug-resistant organisms during the prolonged investigation period (69 months) (14). Further, none of the RCTs reported a mean/median duration for achieving full enteral feeding that was longer in the erythromycin group than in the placebo group (5-14). The overall findings suggested that the discrepancy of results between studies could have been related to the small sample size in some clinical trials (8,9), as well as the different dosages used. It appears that in rescue treatment, the intermediate and high doses are probably more effective in stimulating the human GI tract and promoting milk feeding in preterm infants (12-14).

5. Adverse effects of erythromycin

Despite the effectiveness of facilitating enteral feeding in preterm infants, neonatologists are still concerned with the potential adverse effects of macrolides. None of the RCTs reported any major adverse effects associated with use of erythromycin (5-14). In particular, pyloric stenosis was not reported in any of the clinical trials (5-14). The incidence of this complication is estimated to be 1–3 cases per 1,000 live births in the Western population and administration of erythromycin will substantially increase the risk by 8-fold to 1 case per 41-125 treated infants (48). With this prevalence, definitive cases should have been identified by the outcome study (14) or the combination of RCTs (5-14). The fact that no cases have been identified suggests that the relationship between erythromycin and development of pyloric stenosis is likely to be a weak association. Thus, the benefits of erythromycin for treatment of GI dysmotility in preterm infants probably outweigh the risk. Prolongation of QT interval in electrocardiogram has also been reported following intravenous administration of erythromycin (49). Severe bradycardia and hypotension requiring cardiopulmonary resuscitation were reported in 2 preterm infants after receiving intravenous infusion of the drug (50). These adverse cardiac effects have never been reported in oral treatment (13,51). However, we must be cautious in patients taking drugs which inhibit the hepatic cytochrome CYP3A4 system, including theophylline, cisapride, carbamazepine and midazolam, as these medications may potentially interact with erythromycin and increase the risk of adverse effects. Erythromycin can potentially alter gut flora and encourage emergence of resistant organisms. Although preliminary evidence from the outcome study demonstrated no significant difference of bacterial pattern in stool culture between treated and non-treated infants (13), injudicious and prolonged use of macrolide antibiotic is not recommended.

6. Summary

The management of enteral feeding in premature infants remains a major challenge to neonatologists, but the current evidence of erythromycin as a prokinetic agent is encouraging. RCTs in the past decade have shown that the use of oral erythromycin was associated with shorter time to attain full enteral feeding and could also decrease the duration of parenteral nutrition requirement (7,12-14). The use of high-dose oral erythromycin could reduce the incidence of parenteral nutrition-associated cholestasis and catheter-associated recurrent septicemic episodes (14). It was reassuring that none of the studies reported any life-threatening side effects or complications that required surgical intervention (5-14). The available information probably favours the use of rescue rather than prophylactic treatment, intermediate to high doses rather than low-dose erythromycin and administering the medication intragastrically rather than intravenously, for the management of moderately severe functional GI dysmotility in preterm infants. However, the long-term effects on bowel microflora and the emergence of multidrug-resistant organisms in neonatal intensive care units require further evaluation. A

large multicentre RCT should be performed to delineate the long-term benefits and adverse effects of erythromycin as a prokinetic agent for treatment of GI dysmotility in preterm infants.

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