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Gastrointestinal Dysmotility in Preterm Infants

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Abstract Gastrointestinal dysmotility is a common problem encountered in preterm infant due to immature control of the co-ordinated gastrointestinal movement. Various medications have been used to enhance the co-ordination and propulsive movement of gastrointestinal tract in preterm infants. However, evidence on the beneficial effects of these prokinetic agents is still conflicting and potential serious adverse effects had been reported. The usage of these prokinetic agents in preterm infant should therefore be cautious until further evidence on long term benefit and safety is available.

Key words Enteral feeding; Gastrointestinal dysmotility; Preterm; Very low birthweight infants

Introduction

Gastrointestinal dysmotility is commonly seen in preterm infants and it usually manifests as increase gastric residue before feed, abdominal distention or constipation.[1] Since feed intolerance is one of the presenting symptom of necrotizing enterocolitis, advancement of enteral feeding may be slowed down and hence the nutrition of the infant need to be supported parenterally. Prolonged use of parenteral nutrition predisposes infants to nosocomial infection, cholestasis, osteopenia, poor intestinal growth and prolong hospitalization.[2] In order to prevent these complications, various interventions have been used to modulate gastrointestinal motility in preterm infants. This article reviews the pathophysiology of gastrointestinal dysmotility and options for treatment in preterm infants.

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Pathophysiology

In the human gastrointestinal tract, smooth muscle extends from the mid-oesophagus to the anal canal. It is the co-ordinated contraction of these smooth muscle layers that propels nutrients forward through the intestinal tract. These muscle layers are regulated both by neural and hormonal control.[3]

In adults, there are two types of small intestinal motor patterns. Simultaneous contraction at multiple levels occurs when food is ingested. This results in mixing and churning of nutrients with gastric secretion and presentation of nutrients to the mucosal surface of the intestine. During fasting, the stomach and small intestine exhibit cyclic groups of caudally migrating contraction known as the migrating motor complex (MMC).[4] The MMC is thought to sweep residual products of digestion toward the colon, serving as a 'housekeeper'.[5] The control of MMC is primarily by local enteric nervous system[6] and modulated by hormones including motilin,[7] somatostatin[8] and pancreatic polypeptides.[9]

Motor patterns of the gastrointestinal tract differ in preterm infants as compared to adults.[10] During fasting, few infants display MMC but demonstrate episodes of motor quiescence that alternate with episodes of non-migrating

phasic activity. Characteristics of non-migrating activity change with gestational age, as episodes lengthen in duration and decrease in overall occurrence.[11] When preterm infants ingest milk, duodenal motor activity may increase as in adults (mature fed response), remains unchanged (intermediate fed response) or decrease (immature fed response).[12] The occurrence of these responses also changes with gestation age.[13] Among infants less than 36 weeks gestation, approximately two-thirds display an immature response. Whereas only 15% of term infants display this immature response.[14]

The presence of these differences in gastrointestinal motor function in preterm infants is reflected by less efficient gastric emptying and slower intestinal transit.

Gastric emptying depends upon intact motor function and coordinated contractions among the antrum, pylorus and duodenum.[15] Gastric emptying is delayed in preterm infants as compare to term infants[16] due to immaturity of duodenal motor function and absence of coordination between the antrum and duodenum.[17]

Intestinal transit is also slower in preterm infants than their term counterparts. Total gut transit time varies between 1 to 5 days in preterm infants as compare with 4 to 12 hours in adults.[18]

Interventions for Gastrointestinal Dysmotility

Various medications have been used to improve gastrointestinal dysmotility in preterm infants:

Metoclopramide

Metoclopramide's pharmacologic effects on gastro-intestinal tract work through dopamine receptor blockade and modulation of acetylcholine release.[19] In adult studies with gastro-oesophageal reflux, metoclopramide increases lower oesophageal pressure and enhances gastric emptying.[20]

Few controlled studies have evaluated the efficacy of metoclopramide in preterm infants. In an uncontrolled case series of 14 preterm infants (mean gestational age of 29 weeks), feed tolerance of enteral feed improved with decrease volume of gastric residuals after metoclopramide.[21] Sankaran, et al.[22] reported that metoclopamide shorten intestinal transit time and led to improve feed tolerance in 6 infants (gestational age range form 26 to 35 week). Blumenthal et al[23] reported a case series of 15 low birth weight infants treated with metoclopramide but did not show any beneficial effects on gastric emptying.

The usage of metoclopramide is further limited by its adverse effects include extrapyramidal symptoms like dystonia.[24] Routine use of metoclopramide for gastrointestinal dysmotility in premature infants is therefore cannot be recommended.

Cisapride

Cisapride, a benzamide compound, enhances acetylcholine release from postganglionic nerve endings of the myenteric plexus, thereby increases antral motility and duodenal contractility; increases co-ordination of antroduodenal function; and accelerates gastric emptying.[25] Because cisapride does not affect the dopamine receptor, it lacks the extrapyramidal effects associated with metoclopramide.

Early uncontrolled studies showed cisapride decreases gastric residue and increases feeding volume in premature infants with feeding intolerance.[26] However, more recent randomised controlled studies fail to show these beneficial effects of cisapride[27-29] and may even associated with delay gastric emptying, prolong whole gut transit time[30] and increase thickness and length of pyloric muscle.[31]

Cisapride has been associated with deleterious cardiac side effects, such as QT interval prolongation and life threatening ventricular arrhythmia.[32] Risk factors for cardiac adverse effects of cisapride include conditions leading to elevated serum concentration, such as excessive dosing; concurrent treatment with drugs known to inhibit CYP3A4 isoform of hepatic cytochrome P450 (e.g. erythromycin, clarithromycin, ketoconazole, itraconazole, fluconazole, indinavir, ritonavir, sequinavir and troleandimycin)[33] and underlying cardiac diseases with prolonged QT intervals e.g. Romano-Ward syndrome and Jervell-Lange-Nielsen syndrome. Premature infants are also prone to cisparide toxicity because of the developmental immaturity of the hepatic cytochrome system.[34] A prospective evaluation of electrocardiogram in 25 preterm infants before and after cisapride administration showed that 32% of the infants had QT_c prolongation (≥0.45 second). Infants less than 32 weeks significantly prolonged their QT_c interval from 0.41±0.02 to 0.44±0.02 second.[35]

Because of its potentially life-threatening side effect, cisapride has been withdrawal from the United State market since year 2000.

Erythromycin

Erythromycin is a macrolide antibiotic used since 1950's. Unwanted side effects as an antibiotic include diarrhoea, abdominal colic, dyspepsia, nausea and vomiting were frequently described in early reports of clinical experience

with erythromycin.[36] These effects were subsequently found to related in part to stimulation of gastric and small intestinal motility.

Because of this prokinetic property, erythromycin has been used in patients with chronic functional pseudo-obstruction,[37] gastro-oesophageal reflux,[38] post-operative intestinal dysmotility,[39] gastroparesis secondary to diabetes,[40] scleroma[41] and after surgical vagotomy.[42] Its use as a prokinetic agent has also been extended to preterm infants with gastrointestinal dysmotility.

The prokinetic property of erythromycin was first discovered in the 1980's. Itoh et al demonstrated intravenous erythromycin induced powerful contractions in the stomach and duodenum in dogs which were propagated distally along the small intestine.[43] The authors suggested the prokinetic activity of erythromycin resembled that of motilin. In human and dogs, increased plasma concentration of motilin are associated with migrating motor complex (MMC) and gastrointestinal contraction.[44] Erythromycin has a high affinity for motilin receptors[45] which has been recently identified in human gastrointestinal tract[46] and its prokinetic activity is thought to be act through these receptors.

Premature infants do not demonstrate cyclical fluctuations in plasma motilin levels, which may explain why they have absent or sparse MMC. Stimulation of motilin receptors results in increase antral contraction[47] and reduce pyloric outlet resistance.[48] Human data suggest that erythromycin enhance MMC at the antral level and antroduodenal co-ordination[49] which are responsible for the propulsive force to move gastric contents distally towards the intestine and hence improve gastrointestinal motility.

Early case series suggested erythromycin could improve gastrointestinal motility in feed intolerant preterm infants.[2,50,51] A randomised controlled study reported by Stenson et al did not shown any beneficial effect of intravenous erythromycin in improving feed intolerance in preterm infants.[52] However, this study was primarily designed to investigate the relationship between chronic lung disease and erythromycin treatment for presumed Ureaplasma urealyticum infection. So infants enrolled in this study are not infants with severe feed intolerance who may benefit from prokinetic treatment. In fact, both the treatment and the placebo group achieved full enteral feeding within a short period after birth (median of 8 and 9 days respectively). A more recent randomised controlled trial reported by Costalos et al showed that erythromycin (10 mg/kg/dose, 8 hourly) enhances both antral contractility and reduces whole gut transit time in a group of preterm infants with median gestational age of 32 week.[53]

A randomised controlled study had been performed in the neonatal unit of Prince of Wales Hospital, HKSAR.[54] Feed intolerant preterm infants who received less than 75 ml/kg/day of milk feeds by enteral route on day 14 of life were enrolled. They were randomised into treatment group who received oral erythromycin (12.5 mg/kg/dose every 6 hourly for 14 days) or placebo group (received equal volume of normal saline). For the treatment group, the time taken to establish half (median: 3.5 days Vs 6 days), three quarter (median: 8.5 days Vs 13 days), and full enteral feeding (median: 13.5 days Vs 25 days) after drug treatment were significantly shorter than the placebo group. There was also a trend suggesting that more infants in the placebo group developed cholestatic jaundice (control group: 10/29 Vs treatment group: 5/27).

There are some recent randomised controlled studies looking at the effects of low dose erythromycin (1-3 mg/kg/dose, 3 to 4 times/day) on gastrointestinal dysmotility in preterm infants. It is suggested that low dose erythromycin can reduce gastric residue volume,[55,56] achieve full enteral feeding earlier[56,57] and shorten whole gut transit time[58] in preterm infants.

Besides the known gastrointestinal adverse effects, erythromycin is also associated with other non-gastrointestinal adverse effects. QT prolongation has been reported following intravenous administration of erythromycin.[59] Ferrar et al described two premature infants who developed bradycardia and hypotension requiring cardiopulmonary resuscitation in association with intravenous infusion of erythromycin.[60] In randomised controlled studies that cardiac side effects were reported, there was no identified adverse cardiac events[57] or significant change in QT interval before and after treatment of oral erythromycin.[54]

Other adverse effects associated with erythromycin include the potential for drug interaction caused by its inhibitory effect on hepatic cytochrome CYP3A4. Drug commonly used in newborns which may interacts with erythromycin include theothylline, cisapride, carbamazepine and midazolam.

Erythromycin may alter gut flora and encourage emergence of resistant organisms. Although data from randomised controlled trial demonstrated no significant different stool cultural pattern between erythromycin treated and control group,[54] injudicious and prolonged use of erythromycin is still not recommended.

Recently, the use of erythromycin in newborns has been questioned because of the association with the development

of hypertrophic pyloric stenosis. Heinien et al compared a cohort of 200 infants who received erythromycin as post-exposure prophylaxis for pertussis. An almost seven-fold increase in the incidence of pyloric stenosis was found as compare to control. Risk for the development of hypertrophic pyloric stenosis did not vary by erythromycin preparation. Affected infants received erythromycin at a younger age as compare to control (median age at starting treatment is 5 days vs 13 days in the unaffected group) and were more likely to have received erythromycin for more than 10 days.[61]

Subsequent retrospective cohorts support that erythromycin treatment within 2 weeks after birth[62,63] and treatment duration more than 14 days[63] increase the risk in development of hypertrophic pyloric stenosis.

Other Treatments

New motilin receptor agonists, such as ABT-229 and GM-611, that are devoid of antibiotic activity but possess potent prokinetic properties are currently under investigations.[64] Although initial adult data on ABT-229 has not been encouraging,[65,66] further investigations on these agents as a prokinetic in preterm infants are still warranted.

A pilot study in using enteral administration of insulin showed that it may enhance feed tolerance in preterm infants with 30% shorter time to full enteral feed and fewer gastric residue.[67] But this is a pilot trial using historical control and hence a proper randomised controlled study may need to assess the beneficial effects of enteral insulin.

Summary

Management of enteral feeding in premature infants is still a great challenge to neonatologists. Many aspects of the forward propulsion of enteral nutrients are not fully mature in preterm infants. Various medications have been tried to enhance the gastrointestinal motility in preterm infants. However, the beneficial effects of these agents are still not certain and may associate with serious adverse effects. Before further evidence to confirm beneficial effects and safety is available, the use of these prokinetic agents in preterm infants should be limited to those with protracted feed intolerance and under cautious monitoring. Further investigations on prokinetic agents should not just focus on short term outcomes like gastric residue as these may not be extrapolated to long term benefits such as shorten hospitalization and cholestatic jaundice. And these need to be answered by larger scale randomised controlled trials.

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