Oral Erythromycin for Treatment of Feeding Intolerance in Preterm Infants : A Preliminary Report

WIMOL SEKTEERA, M.D.*,
PRACHA NUNTNARUMIT, M.D.*,
SARAYUT SUPAPANNACHART, M.D.*

Abstract

Feeding intolerance is a common problem in preterm infants resulting in a prolonged hyperalimentation which is associated with an increased risk of serious and sometimes even life threatening complications, including cholestasis jaundice, liver impairment, nutritional deficiency, biochemical rickets and catheter-related septicaemia. Erythromycin, a commonly used macrolide antibiotic, has been reported as having potent prokinetic properties and enhancing gastrointestinal motor activity. The authors, therefore, conducted a preliminary study of oral erythromycin for the treatment of feeding intolerance in preterm infants to evaluate the safety and efficacy of this drug.

Aim : To evaluate the safety and efficacy of oral erythromycin as a prokinetic agent in promoting enteral feeding in preterm infants with feeding intolerance.

Method : Preterm infants, gestational age (GA) ≤ 36 wk, who met the feeding intolerance criteria, were enrolled in the study. Inclusion criteria included infants who received enteral feeding less than half of full feeding or less than 75 ml/kg/day by day 14 post-natal age or gastric residual ≥ 50 per cent of a given amount of feeding, more than 2 consecutive feeds by day 7 post-natal age. All patients received oral erythromycin ethylsuccinate 12 mg/kg every six hours for 2 days, then 3 mg/kg every six hours for 5 days. The times taken to establish full enteral feeding after the drug treatment and time to stop hyperalimentation were recorded. Potential adverse effects of erythromycin were assessed. Response to treatment was defined as decreased gastric residual < 30 per cent of a similar amount of the previous feed and was able to continue to full feeding.

Results : Ten preterm infants were enrolled in this study with a mean GA of 30.8 weeks (26-35), mean birth weight of 1,489 g (range 900-2,560 g) and mean age at entry of 9.2 days (range 7-12 days). Nine of 10 infants responded to treatment within 24 hours. The average time to establish full enteral feeding after the drug treatment was 6.6 days (range 4-10 days). None of the infants developed adverse effects such as vomiting, diarrhea, or pyloric stenosis.

Conclusion : The preliminary data indicates that oral erythromycin is effective and safe in facilitating enteral feeding in preterm infants with feeding intolerance. Infants can achieve full feeding within a week after treatment, and this may shorten the course of hyperalimentaiton. Further randomized controlled trials are warranted.

Key word : Erythromycin, Feeding Intolerance, Preterm Infants

SEKTEERA W, NUNTNARUMIT P, SUPAPANNACHART S
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* Department of Pediatrics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

The provision of adequate nutrition is a critical factor to an increased survival of preterm infants especially for very low birth weight infants. Aims of nutritional support are to provide nutrients and energy for metabolism and growth. However, preterm very low birth weight infants usually have some limitations both in digestion and absorption due to immaturity of digestive enzymes and gastrointestinal functions[1,2], making parenteral nutrition invariably employed during the first few weeks of life. Nevertheless, prolonged parenteral nutrition carries some potential risks such as catheter-related sepsis, metabolic disturbances and cholestasis jaundice[3]. Therefore, initiating enteral feeding in preterm infants as soon as possible is common practice as a trophic feeding or gut priming[2]. Several studies have shown the benefits of early enteral feeding including faster weight gain, shortening hospital stay, decreasing feeding intolerance and shortening duration of parenteral nutrition, thus, avoiding the chance of parenteral nutrition-related complications[2,4]. However, feeding intolerance frequently complicates the clinical course of preterm infants. Previous studies using a prokinetic drug such as cisapride reported contradictory results. In addition, recent studies reported fetal adverse effects such as long QT syndrome, causing sudden infant death[5,6]. Erythromycin, a macrolide antibiotic, has been found to have potent prokinetic properties by action on a motilin receptor[7-10]. Clinical trials have shown its efficacy in various gastrointestinal disorders e.g., chronic functional pseudo-obstruction, gastroesophageal reflux, post-operative intestinal dysmotility and gastroparesis secondary to diabetes or vagotomy[11-14]. It has also been reported to promote antroduodenal coordination[15]. In premature infants, studies of erythromycin for dysmotility or feeding intolerance are not conclusive due to lack of a standard regimen and wide heterogenicity of the studies[16-18]. A recent study using erythromycin orally 12.5 mg/kg/dose every 6 hours resulted in shortening parenteral nutrition and achieving full enteral feeding sooner without any side effects[16].

The aim of the present pilot study was to evaluate the safety and efficacy of oral erythromycin for feeding intolerance in preterm infants using low dose oral erythromycin. The authors hypothesized that the initial loading dose followed by low dose erythromycin would reduce feeding intolerance without significant side effects.

METHOD

The study was conducted at the newborn intensive care nursery and special nursery, Ramathibodi Hospital. Informed consent was obtained from the parents. Preterm infants, gestational age less than 37 weeks and having feeding intolerance, were enrolled. Feeding intolerance was defined as having enteral feeding less than 50 per cent of full feeding or less than 75 ml/kg/day by day 14 post-natal age or having gastric residual of more than 50 per cent of the given amount of enteral feed more than 2 consecutive feeds by day 7 post-natal age. Infants with severe congenital anomalies, intestinal stenosis or atresia, necrotizing enterocolitis, previous gastrointes-

Table 1. Outcome of all enrolled infants.

Case	Gastational age (week)	Sex	Birth weight (g)	Age at enrollment (day)	Primary disease	Time to full feeding after receiving treatment (day)	Clinical outcome
1	34	F	1,460	7	Normal preterm	7	NEC
2	35	F	1,720	8	RDS	8	BPD, sepsis
3	29	M	1,340	12	RDS, PDA	Fail	BPD
4	35	F	2,220	8	RDS	4	Normal
5	31	F	1,540	7	RDS, PDA	8	Normal
6	30	M	1,150	12	RDS	4	Normal
7	26	F	900	9	RDS	6	BPD
8	34	M	2,560	8	Bilateral hydronephrosis, pulmonary hypoplasia	7	Normal
9	26	M	975	9	TTNB	10	BPD
10	28	F	900	11	RDS	6	NEC, sepsis, dead

RDS = respiratory distress syndrome, PDA = patent ductus arteriosus, TTNB = transient tachypnea of the newborn, BPD = bronchopulmonary dysplasia, NEC = necrotizing enterocolitis

tinal surgery, congenital cyanotic heart diseases or having clinical sepsis were excluded. All infants were fed by bolus feeding of either breast milk or infant formula through a nasogastric tube within 10-15 minutes. The enrolled infants received erythromycin (ethyl succinate) orally with an initial loading dose of 12 mg/kg/dose every 6 hours for 2 days followed by a dose of 3 mg/kg/dose every 6 hours for 5 days. Stool cultures before and 24-hours after discontinuation of erythromycin were obtained.

RESULTS

There were 10 infants enrolled into the study. The mean gestational age was 30.8 weeks (range 26-35 weeks) with a mean birth weight of 1,489 g (range 900-2,560 g). Mean post-natal age at enrollment was 9.2 days (range 7-12 days) with an average enteral intake of only 23.5 ml/kg/day (range 0-76.5 ml/kg/day). Two infants were formula-fed, one infant was only breast-fed, and 7 were combined. Nine out of the 10 infants responded to the treatment within 24 hours after starting the initial loading dose of erythromycin with the mean gastric residual of only 6.5 per cent of the amount given and were able to advance feeding with an increment of 15-25 ml/kg each day to full feeding without any problem. Only one infant had partial response, whereas, minimal gastric residual was observed initially, but by day 5 it bounced back to more than 50 per cent. In responders, the average day of full feeding after receiving erythromycin was 6.6 (range 4-10) days and the average day on parenteral nutrition was 7 (range 4-12) days. No side effects related to erythromycin were observed during therapy such as diarrhea, vomiting, or hypertrophic pyloric stenosis. Bacterial colonization pattern from stool cultures showed no significant change. The details of all the enrolled infants are shown in Table 1. One infant, case 10, died on day 32 due to severe sepsis and necrotizing enterocolitis (NEC) stage II. This infant did not show any side effects related to erythromycin during therapy; an ischemic bowel predisposed to NEC believed to be associated with coarctation of the aorta which was diagnosed by echocardiogram later in life during critical illness. One infant, case 1, developed suspected NEC clinically with abdominal distension, bloody stool and generalized bowel ileus (no pneumatosis intestinalis) 7 days after starting erythromycin. This infant had been doing well during the erythromycin trial, but at the end of the trial, feeding was deviated from the protocol with a rapid increased feed (an increment of 75 ml/kg/day) a day before. The gastrointestinal symptom in this case might be a feeding intolerance secondary to a rapid increased feed. However, the infant was treated as NEC and did well afterward. One infant, case 2, developed clinical sepsis 5 days after stopping erythromicin, and blood culture was positive for Staphylococcus coagulase negative.

DISCUSSION

This preliminary report indicates the clinical efficacy and safety of oral erythromycin in pre-

term infants with feeding intolerance. Nine of 10 enrolled infants showed dramatic response within 24 hours after starting the treatment and all responders were able to advance to full feeding without any problems or side effects related to erythromycin. It was noted that the mean age at enrollment was 9 days by which time full enteral feeding was expected. However, the infants could tolerate only 23.5 ml/kg/day. A full enteral feeding (150 ml/kg/day) could be achieved in 6 days after starting the treatment.

The authors decided to use low dose erythromycin instead of high dose and to use a short course with a total of 7-days since there was evidence that low dose erythromicin could stimulate antrum contraction and also improve antroduodenal contraction[19,20]. The mechanisms by which erythromycin improves gastrointestinal motility are reducing pyloric outlet resistance by suppression of pyloric pressure wave[15] and increasing duodenal contraction frequency[21], thus, resulting in improved antroduodenal co-ordination and contraction. Previous human studies[22,23] indicated that erythromicin acts as a potent prokinetic by activating motilin receptors and cholinergic neurons on the proximal small bowel, resulting in increased amplitude and frequency of antral contraction and increased gastric tone[22-24]. Motilin receptor can be found in a fetus beginning at approximately 20 weeks of gestation and able to form a completed gastrointestinal neuroendocrine network at approximately 25 weeks of gestation[25].

There were no significant side effects related to erytromycin observed in the present study and death and NEC did not seem to be related to the treatment with this drug. The stool culture showed no significant change of bacterial pattern. All of these might due to the short course and low dose protocol that was used in order to avoid any possible side effects and also make this drug as an alternative therapy for feeding intolerance. Hence, this pilot study demonstrated the possibility of further studies in a larger scale randomized clinical trial.

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ผลของยาอีรีโธรมัยซิน ในการรักษา Feeding Intolerance ในทารกเกิดก่อนกำหนด

วิมล เสกธีระ, พ.บ.,*
ประชา นันท์นฤมิต, พ.บ., สรายุทธ สุภาพรรณชาติ, พ.บ.**

การดูแลด้านโภชนาการแก่ทารกแรกเกิดก่อนกำหนด มีส่วนสำคัญอย่างยิ่งต่อการรอดชีวิตของทารก และลดภาวะแทรกซ้อนลง ข้อมูลปัจจุบันพบว่าการให้อาหารทางระบบทางเดินอาหารมีประโยชน์มากกว่า ผลแทรกซ้อนน้อยกว่าการให้ทางหลอดเลือด ผู้วิจัยสนใจศึกษาการใช้ยา erythromycin ในแง่การกระตุ้นให้การทำงานของลำไส้ดีขึ้น และทำให้สามารถรับสารอาหารทางระบบทางเดินอาหารได้ดีขึ้น เพื่อได้รับนมเต็มที่ (full enteral feeding) และให้เกิดการเจริญเติบโตอย่างสมบูรณ์ และลดภาวะแทรกซ้อนจากการให้สารอาหารทางระบบหลอดเลือดดำ

วัตถุประสงค์ : เพื่อศึกษาประสิทธิภาพและผลข้างเคียงของยา erythromycin ในการรักษาภาวะการรับสารอาหารทางระบบทางเดินอาหารล่าช้า (feeding intolerance) ในทารกเกิดก่อนกำหนด

วิธีการศึกษา : ศึกษาทารกเกิดก่อนกำหนดอายุครรภ์น้อยกว่าหรือเท่ากับ 36 สัปดาห์ ที่มีปัญหาการรับสารอาหารทางระบบทางเดินอาหารล่าช้า โดยนิยามคือรับสารอาหารทางปากน้อยกว่าร้อยละ 50 ของสารอาหารทั้งวันที่ควรจะได้รับ หรือน้อยกว่า 75 มล/กก/วัน ขณะอายุหลังเกิด 14 วัน หรือเหลืออาหารค้างอยู่ในกระเพาะอาหารมากกว่าร้อยละ 50 ของที่ได้รับมื้อนั้นมากกว่า 2 ครั้งติดต่อกัน ขณะอายุหลังเกิด 7 วัน ผู้ป่วยทุกรายได้รับยา erythromycin ethylsuccinate ในขนาด 12 มก/กก/ครั้ง ทางปากทุก 6 ชั่วโมงนาน 2 วัน จากนั้นลดขนาดยาเป็น 3 มก/กก/ครั้ง ทางปากทุก 6 ชั่วโมงนาน 5 วัน ส่งเพาะเชื้ออุจจาระก่อนและหลังการศึกษา

ผลการศึกษา : ผู้เข้าเกณฑ์การศึกษา 10 ราย เพศชาย 4 ราย หญิง 6 ราย อายุครรภ์เฉลี่ย 30.8 สัปดาห์ (26–35 สัปดาห์) น้ำหนักแรกเกิดเฉลี่ย 1,489 กรัม (900–2,560 กรัม) อายุเฉลี่ย 9.2 วัน (7–12 วัน) พบว่าทารก 9 ใน 10 รายมีปริมาณนมที่ค้างในกระเพาะอาหารลดลงชัดเจนเหลือเพียงร้อยละ 6.5 ของนมที่ได้รับ ภายใน 1 วันหลังได้รับยาและรับนมได้เต็มที่ (150 มล/กก/วัน) เฉลี่ยหลังให้ยา 6.7 วัน (พิสัย 4–10 วัน) และหยุดการให้สารอาหารทางหลอดเลือดดำเฉลี่ยหลังให้ยา 7.2 วัน (พิสัย 4–12 วัน) ไม่พบผลข้างเคียงจากยา เช่น hypertrophic pyloric stenosis

สรุป : Erythromycin น่าจะมีฤทธิ์กระตุ้นการทำงานของลำไส้ ทำให้ทารกสามารถรับสารอาหารทางระบบทางเดินอาหารได้ดีขึ้นภายในเวลา 1 วันหลังได้ยา และเพิ่มความสามารถมากขึ้นจนสามารถรับสารอาหารได้เต็มที่ หลังเริ่มให้ยาเฉลี่ย 6.7 วัน และหยุดการให้สารอาหารทางหลอดเลือดดำหรือน้ำเกลือเฉลี่ย 7.2 วันหลังให้ยา โดยไม่พบผลข้างเคียงของยา

คำสำคัญ : อีรีโธรมัยซิน, ภาวะได้รับสารอาหารทางระบบทางเดินอาหารล่าช้า, ทารกเกิดก่อนกำหนด

วิมล เสกธีระ, ประชา นันท์นฤมิต, สรายุทธ สุภาพรรณชาติ
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* ภาควิชากุมารเวชศาสตร์, คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400