Clinical Use of Erythromycin in Children with Gastrointestinal Dysmotility

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Abstract

Intolerant feeding is a common symptom in gastrointestinal disorders which is commonly found in systemic diseases. Prokinetic drugs play a role in management. A low dose of erythromycin has an effect on improvement of antroduodenal motility and gastric emptying in children and adults. The objective of this study was to evaluate the efficacy of intravenous erythromycin in the treatment of GI dysmotility in children.

Retrospective studies were performed in the Department of Pediatrics, Siriraj Hospital, Mahidol University between 1996 and 2000 in 22 patients with intolerance of feeding due to GI dysmotility. Their ages ranged from 11 days to 12 years (42.1 ± 48.1 months). The patients were divided into 2 groups : 12 critically ill and 10 non-critically ill patients. Dosages of intravenous erythromycin were 1-3 mg/kg/dose every 6 hours. The result of treatment was evaluated as : good (tolerant feeding), fair (tolerant feeding but needing erythromycin for longer than 1 month) and failed (intolerant feeding).

All non-critically ill patients had improved symptoms with 9 ± 4.3 days duration of treatment. In the other group, 8 patients had good results with 10.9 ± 6 days of treatment. Two patients needed the drug for longer than 1 month and the other 2 patients did not respond and died due to severe infection. Low dose intravenous erythromycin had good efficacy in the treatment of intolerant feeding related to GI dysmotility in children.

Key word : Erythromycin, GI Dysmotility, Gastroparesis, Paralytic Ileus, Critically Ill, Tube Feeding

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Gastrointestinal dysmotility can occur in many diseases in which chronic intestinal pseudo-obstruction is the most severe etiology. GI dysmotility results from disturbances of the control mechanism of gut motor activity, which may be produced by organic diseases involving enteric nerve, muscle and altered central nervous system input. Systemic diseases frequently have effects on the motility of the gastrointestinal tract such as systemic infection, drug, hypoxia, post-operative and metabolic causes (1). Recurrent vomiting, abdominal pain, abdominal distention and intolerance to feeding are the most common symptoms. Gastroparesis is the condition which has delayed gastric emptying in the absence of a demonstrable mechanical or mucosal lesion by radiologic or endoscopic studies(2). Intolerant enteral feeding due to gastroparesis and small bowel ileus will limit enteral feeding and predispose the patients to gastroesophageal reflux and aspiration. The treatment of gastrointestinal motility disorder is to use prokinetic drugs such as metoclopramide, domperidone, cisapride and erythromycin(3). Intravenous cisapride is not available, whereas erythromycin is administered orally, intravenously and intramuscularly(3).

Motilin is a 22 amino acid peptide, released from enterochromaffin cells of the proximal intestine, which appears to be involved in stimulating the gastric and small bowel contraction(4). Erythromycin, a commonly used antibiotic, has recently emerged as a potential gastrointestinal prokinetic agent. It acts as a motilin agonist by binding to the motilin receptors on smooth muscle in the stomach and intestine(4,5). Studies in adults and children have demonstrated improvement of antroduodenal motility and gastric emptying in healthy humans and those with diseases(6-10). There are a few reports in the clinical use of erythromycin in children with gastrointestinal dysmotility(11-14). The objective of this study was to evaluate the efficacy of intravenous erythromycin in the treatment of gastrointestinal dysmotility in children.

METHOD

The authors conducted a retrospective chart review of patients treated with intravenous erythromycin due to gastrointestinal dysmotility in the Department of Pediatrics, Siriraj Hospital. Mahidol University between 1996 and 2000. The inclusion criteria were patients having intolerant enteral feeding demonstrated by detecting the amount of gastric residue from nasogastric aspiration before feeding and having limited advance feeding. In addition, patients did not have any gastrointestinal obstruction diagnosed by symptoms, signs or X-ray studies.

Information about patients was collected including sex, age, underlying diseases, dosage of erythromycin, duration of treatment, results and side effects. Erythromycin lactobionate (Abbott laboratories, U.S.A.) was infused intravenously for 30 minutes every 6 hours. The results of treatment were evaluated as : good (tolerant feeding), fair (tolerant feeding but needing erythromycin for longer than 1 month) and failed (intolerant feeding).

RESULT

Twenty two patients met our criteria. There were 14 girls and 8 boys with ages ranging from 11 days to 12 years (42.1 ± 48.1 months). The patients were divided into 2 groups, critically ill and non-critically ill.

In the critically ill group, there were 9 girls and 3 boys, their ages ranging from 1 month to 11 years (35.9 ± 48.8 month). Their diagnoses are shown in Table 1. The patients had organ failure and some also needed a ventilator. Five patients had symptoms that had started in the newborn period. One patient received erythromycin 1 mg/kg/dose. The other 5 and 6 patients received 2 mg/kg/dose and 3 mg/kg/dose respectively. Eight patients (66.6%) had good results. Two patients still needed erythromycin for longer than 1 month. The other two patients did not respond to erythromycin (dosage, 3 mg/kg/dose) and died due to severe infection. The duration of treatment in patients with a good result was 10.9 ± 6 days.

In the non- critically ill group, there were 5 girls and 5 boys with ages ranging from 11 days to 12 years (49.6 ± 48.7 months). The diagnoses are shown in Table 2. Two patients were treated with 1 mg/kg/dose of erythromycin. Five and 3 patients received 2 mg/kg/dose and 3 mg/kg/dose respectively. All patients had good results in which the duration of treatment was 9 ± 4.4 days. There were no side effects from erythromycin observed in either group during this study.

DISCUSSION

In adults, erythromycin has been shown to improve gastric emptying in patients with gastroparesis in association with numerous disorders such as DM with delayed gastric emptying(9,15), patients

Table 1. Description of critically ill patients.

Case	Sex	Age	Diagnosis	Dose (mg/kg)	Duration (day)	Result
1	girl	7 yr	Encephalitis, convulsion	1	6	Good
2	girl	1 m	Nesidioblastosis, pancreatectomy	2	14	Good
3	girl	4 m	Prematurity, birth asphyxia, BPD	2	7	Good
4	girl	4 m	ALL, intussusception, post laparotomy	2	7	Good
5	girl	6 m	Prematurity, BPD, Pneumonia	2	7	Good
6	boy	1.5 yr	CP, BPD, pylorospasm	3	24	Good
7	girl	4 yr	Status epilepticus	3	11	Good
8	boy	11 yr	Chronic renal failure, sepsis	3	11	Good
9	girl	3 m	Prematurity, BPD, NEC	3	> 30	Fair
10	girl	8 m	BPD	3	> 30	Fair
11	girl	2.5 m	Prematurity, BPD, NEC	3	14	Failed, death
12	boy	10 yr	Status epilepticus, septicemia	2	7	Failed, death

Table 2. Description of non-critically ill patients.

Case	Sex	Age	Diagnosis	Dose (mg/kg)	Duration (day)	Result
1	girl	6 yr	Appendectomy	1	7	Good
2	girl	7 yr	Hypothyroidism	1	6	Good
3	boy	13 d	Midgut volvulus, lysis Ladd band	2	8	Good
4	boy	1 m	Prematurity, sepsis	2	19	Good
5	girl	2.5 m	CP, intestinal pseudo-obstruction	2	7	Good
6	boy	4 yr	AML, bowel ileus post chemotherapy	2	7	Good
7	girl	5 yr	CP, malnutrition	2	7	Good
8	boy	11 d	Birth asphyxia, BPD, pylorospasm	3	8	Good
9	boy	7 yr	CP, GER, status post fundoplication	3	6	Good
10	girl	12 yr	SLE, bowel ileus	3	15	Good

after vagotomy[16], patients with chronic intestinal pseudo-obstruction[17,18], systemic sclerosis[19] and anorexia nervosa[20].

In children, Di Lorenzo C, et al[8] reported the effect of erythromycin on antroduodenal motility in children with chronic functional gastrointestinal symptoms. Erythromycin induced phase 3 of the migrating motor complex (MMC) originating in the antrum in children with spontaneous phase 3 during fasting, but not in children without MMC. The duodenal motility did not change. A dose of 3 mg/kg/dose produced a higher antral contraction than a dose of 1mg/kg/dose. Cucchiara S, et al[7] studied antroduodenal motor effects of intravenous erythromycin in children with abnormal gastrointestinal motility. The study showed a low dose of erythromycin improved antral contraction without coordinated antroduodenal motor pattern. The efficacy of the drug was influenced by the nature of the underlying diseases.

Both studies suggested the role of intravenous erythromycin in the treatment of gastroparesis in children ; however, not much data are available about the clinical use of erythromycin in children. Erythromycin has been effective in facilitating the transpyloric passage of a tube in children with a presumptive diagnosis of chronic intestinal pseudo-obstruction[11]. Others studies have reported the improvement of symptoms in patients with post-viral gastroparesis[14] and intolerant feeding in the newborn[12,13]. Our study demonstrated good efficacy of low dose intravenous erythromycin in the treatment of gastrointestinal dysmotility in children. Eighteen patients had good results and only 2 patients failed. Fifty five per cent of patients were critically ill and were in the ICU or NICU, and 66.6 per cent of these had good results. Early enteral feeding improved the outcome in critically ill patients [21]. Impaired tolerance to gastric feeding is common in critically ill patients as a result of slow

gastric emptying[22] which increased the risk of regurgitation and pulmonary aspiration. In mechanically ventilated adult patients, intravenous erythromycin increased antral motility and accelerated gastric emptying[23]. Erythromycin has been shown to facilitate passing of a feeding tube[24,25]. Chapman MJ, et al[24] studied the effect of erythromycin on gastric emptying during feeding in 20 mechanically ventilated patients. Erythromycin improved gastric emptying and enteral feeding was subsequently successful. Our study confirmed the suggestion that intravenous erythromycin may be used clinically to improve the success of enteral feeding in critically ill patients.

Newborn patients who have perinatal asphyxia, respiratory distress and necrotizing enterocolitis always have intolerant feedings. The etiologies may be due to the delayed start of feeding, enteral and parenteral infection, hypoxia, metabolic disturbance and prematurity. In this study, there were 9 patients with symptoms which started in the newborn period, but only two patients were treated with erythromycin at 11 and 13 days of age due to pylorospasm and status post lysis Ladd band respectively. The other 7 patients had chronic gastrointestinal dysmotility; however, the majority of cases had improved symptoms after treatment. In previous studies, Ng PC, et al[12] reported good efficacy of oral erythromycin for the treatment of severe intestinal dysmotility in 7 preterm infants. Simkiss DE, et al[13] showed successful treatment in neonatal post-operative intestinal dysmotility.

The effect of erythromycin on gastric motor activity is dose dependent[10]. Small doses stimulate antral activity which migrates into the duodenum[27]. Higher doses induce strong contractions of antrum which do not propagate and small transit time may be slower[28]. A dose lower than 2 mg/kg/dose is to induce phase 3 of MMC which may be preferable for small bowel dysmotility. The dose of 3 mg/kg/dose is preferable for clearance of gastric residue[29]. The doses of erythromycin used in children are 1-3 mg/kg/dose[7,8]. Because our study is a retrospective study, the criteria for using different doses were not set, so the doses varied from 1 to 3 mg/kg/dose every 6 hours. Because of the limited number of patients, we could not compare the result between different doses in this study.

The authors reported good efficacy of intravenous erythromycin in children with intolerance to feeding due to gastrointestinal dysmotility without any side effects. Eythromycin has proved to be a good prokinetic agent.

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REFERENCES

1. Di Lorenzo C, Hyman PE. Gastrointestinal motility in neonatal and pediatric practice. Gastroenterol Clin North Am 1996; 25: 203-24.
2. Di Lorenzo C, Hyman PE. Gastric motility disorder. In : Wyllie R, Hyams JS, eds. Pediatric gastrointestinal diseases. Philadelphia: Saunders, 1999: 251-64.
3. Grill BB, Flores AF. Pharmacotherapy. In : Hyman PE, Di Lorenzo C, eds. Pediatric gastrointestinal motility disorders. New York : Acadamy Professional Information Services Inc, 1994: 377-86.
4. Weber FH Jr, Richard RD, Mc Callum RW. Erythromycin : a motilin agonist and gastrointestinal prokinetic agent. Am J Gastroenterol 1993; 88: 485-90.
5. Peeters T, Matthijs G, Depoortere I, Cachet T, Hoogmartens J, Vantrappen G. Erythromycin is a motilin agonist. Am J Physiol 1989; 257: G 470-4.
6. Annese V, Janssens J, Vantrappen G, et al. Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. Gastroenterology 1992; 102: 823-8.
7. Cucchiara S, Minella R, Scoppa A, et al. Antroduodenal motor effect of intravenous erythromycin in children with abnormalities of gastrointestinal motility. J Pediatr Gastroenterol Nutr 1997; 24: 411-8.
8. Di Lorenzo C, Flores AF, Tomomasa T, Hyman PE. Effect of erythromycin on antroduodenal motility in children with chronic functional gastrointestinal symptoms. Dig Dis Sci 1994; 39: 1399-404.
9. Janssens J, Peeters TL, Vantrappen G, et al.

Erythromycin improved delayed gastric emptying in diabetic gastroparesis. N Engl J Med 1990; 322: 1028-31.

10. Tomomasa T, Karouma T, Arai H, Wakabayashi K, Itoh Z. Erythromycin induces migrating motor complex in human gastrointestinal tract. Dig Dis Sci 1986; 31: 157-61.
11. Di Lorenzo C, Lachman R, Hyman PE. Intravenous erythromycin for postpyloric intubation. J Pediatr Gastroenterol Nutr 1990; 11: 45-7.
12. Ng PC, Fok TF, Lee CH, Wong W, Cheung KL. Erythromycin treatment for gastrointestinal dysmotility in preterm infants. J Paediatr Child Health 1997; 32: 148-50.
13. Simkiss DE, Adams IP, Myrdal U, Booth TW. Erythromycin in neonatal post-operative intestinal dysmotility. Arch Dis Child 1994; 71: F 128-9.
14. Sigurdsson L, Flores A, Putnam PE Hyman PE, Di Lorenzo C. Postviral gastroparesis: Presentation, treatment and outcome. J Pediatr 1997; 130: 751-4.
15. Annese V, Lombardi G, Frusciante V, Germani U, Andriulli A, Bossotti G. Cisapride and erythromycin prokinetic effects in gastroparesis due to type 1 diabetes mellitus. Aliment Pharmacol Ther 1997; 11: 599-603.
16. Mozwecz H, Pavel D, Pitrak D, Orellana P, Schlesinger PK, Layden TJ. Erythromycin stearate as prokinetic agents in postvagotomy gastroparesis. Dig Dis Sci 1990; 35: 902-5.
17. Chami TN, Schuster MM, Crowell MD. Effect of low dose erythromycin on gastrointestinal motility and symptoms in chronic intestinal pseudo-obstruction. Gastroenterology 1991; 100: A 41.
18. Miller SM, O Dorisio TM, Thomas FB, Mekhjian HS. Erythromycin exerts a prokinetic effect in patients with chronic intestinal pseudo-obstruction Gastroenterology 1990; 98: A375.
19. Dull JS, Raufman JP, Zakai MD, Strashun A, Straus EW. Successful treatment of gastroparesis with erythromycin in a patient with systemic sclerosis. Am J Med 1990; 89: 528-30.
20. Stacher G, Peeters TL, Bergmann H, et al. Erythromycin effects on gastric emptying, antral motility and plasma motilin and pancreatic polypeptide concentration in anorexia nervosa. Gut 1993; 34: 166-72.
21. Zaloga GP. Early enteral nutritional support improves outcome. Hypothesis or fact ? Crit Care Med 1999; 27: 259-61.
22. Dive A, Moulart M, Jonard PH, Jamart J, Mahieu P. Gastroduodenal motility in mechanically ventilated critically ill patients: A manometric study. Crit Care Med 1994; 22: 441-7.
23. Dive A, Miesse C, Galanti L, et al. Effect of erythromycin on gastric motility in mechanically ventilated critically ill patients: A double-bind, randomized, placebo-controlled study. Crit Care Med 1995; 23: 1356-62.
24. Griffith DP, McNally AT, Battey CH. Efficacy of erythromycin for small intestinal feeding tube placement in ICU patients : A double-blind, randomized, placebo-controlled study. J Parenter Enteral Nutr 1997; 21: S3.
25. Kalliafas S, Choban PS, Ziegler D, Drago S, Flancbaum L. Erythromycin facilitates postpyloric placement of nasoduodenal tubes in intensive care unit patients: Randomized, double-blinded, placebo-controlled trial. J Parenter Enteral Nutr 1996; 20: 385-8.
26. Chapman MJ, Fraser RJ, Kluger MT, Buist MD, De Nichilo DJ. Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. Crit Care Med 2000; 28: 2334-7.
27. Otterson MF, Sarna SK. Gastrointestinal motor effects of erythromycin. Am J Physiol 1990; 259: G 355-63.
28. Coulie B, Tack J, Peeters T, Jassens J. Involvement of two different pathways in the motor effects of erythromycin on the gastric antrum in humans. Gut 1998; 43: 243-5.
29. Farrugia G, Camilleri M, Whitehead WE. Therapeutic strategies for motility disorder: medication, nutrition, biofeedback and hypnotherapy. Gastroenterol Clin North Am 1996; 25: 225-46.

การใช้ยาอีรีย์โธรมัยซินในการรักษาผู้ป่วยเด็กที่มีการเคลื่อนไหวกระเพาะลำไส้ผิดปกติ

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การศึกษาทำย้อนหลังในผู้ป่วยเด็กที่มีปัญหาท้องอืด มี gastric content เหลือและไม่สามารถให้อาหารทางสายยางได้เนื่องจากมี GI dysmotility ในช่วงปี พ.ศ. 2539 ถึง 2543 ที่ภาควิชากุมารเวชศาสตร์ โรงพยาบาลศิริราช มีจำนวนผู้ป่วย 22 รายได้รับยา erythromycin ฉีดเข้าเส้นขนาด 1-3 มิลลิกรัม/กิโลกรัม/ครั้ง ทุก 6 ชั่วโมง ผู้ป่วยแบ่งออกเป็น 2 กลุ่ม โดยมีผู้ป่วย 10 รายในกลุ่มที่อาการไม่หนักและมีผู้ป่วย 12 รายในกลุ่มผู้ป่วยที่มีอาการหนัก ผู้ป่วยทุกรายในกลุ่มแรกจะตอบสนองต่อยาดีและสามารถหยุดยาโดยมีระยะเวลาในการรักษา 9 $\pm$ 4.3 วัน ส่วนในผู้ป่วยที่มีอาการหนักมีจำนวน 8 ราย ที่ตอบสนองต่อยาดีและมีระยะเวลาในการรักษา 10.9 $\pm$ 6 วัน ผู้ป่วยอีก 2 รายตอบสนองต่อยาดีแต่ยังต้องได้รับยานานมากกว่า 1 เดือน ส่วนผู้ป่วยอีก 2 รายไม่ตอบสนองต่อการรักษาและเสียชีวิตเนื่องจากการติดเชื้อที่รุนแรง ผู้ป่วยทุกรายไม่มีผลข้างเคียงจากการใช้ยา ยา erythromycin แบบฉีดเข้าเส้นสามารถรักษาผู้ป่วยเด็กที่มีปัญหาไม่สามารถรับอาหารเนื่องจากมี GI dysmotility ได้อย่างมีประสิทธิภาพ

คำสำคัญ : อีรีย์โธรมัยซิน, การเคลื่อนไหวผิดปกติของกระเพาะอาหารและลำไส้, กระเพาะอาหาร, เคลื่อนไหวช้า, ลำไส้ไม่เคลื่อนไหว, ผู้ป่วยหนัก, ให้อาหารทางสายยาง

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