Pediatrics and Neonatology (2012) 53, 34—40

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.pediatr-neonatol.com

ORIGINAL ARTICLE

Efficacy of Intermediate-Dose Oral Erythromycin on Very Low Birth Weight Infants With Feeding Intolerance

Yan-Yan Ng [a], Pen-Hua Su [a,b], Jia-Yuh Chen [a,b,*], Yeak-Wun Quek [a], Jui-Ming Hu [a,c], Inn-Chi Lee [a], Hong-Shen Lee [b,d], Hua-Pin Chang [c,e]

[a] Department of Pediatrics, Chung Shan Medical University Hospital, Taichung, Taiwan
[b] School of Medicine, Chung Shan Medical University, Taichung, Taiwan
[c] Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan
[d] Department of Public Health, Chung-Shan Medical University, Taichung, Taiwan
[e] Department of Nursing, Chung Shan Medical University Hospital, Taichung, Taiwan

Received Apr 13, 2010; received in revised form Jan 10, 2011; accepted Feb 22, 2011

Key Words
feeding intolerance;
oral erythromycin;
very low birth weight infants

Background: Erythromycin is generally used as a prokinetic agent for the treatment of feeding intolerance in preterm infants; however, results from previous studies significantly vary due to different medication dosages, routes of administration, and therapy durations. The effectiveness and safety of intermediate-dose oral erythromycin in very low birth weight (VLBW) infants with feeding intolerance was examined in this study.
Methods: Between November 2007 and August 2009, 45 VLBW infants with feeding intolerance, who were all at least 14 days old, were randomly allocated to a treatment group and administered 5 mg/kg oral erythromycin every 6 hours for 14 days ($n = 19$). Another set of randomly selected infants was allocated to the control group, which was not administered erythromycin ($n = 26$).
Results: The number of days required to achieve full enteral feeding (36.5 ± 7.4 vs. 54.7 ± 23.3 days, respectively; $p = 0.01$), the duration of parenteral nutrition ($p < 0.05$), and the time required to achieve a body weight $\geq$2500 g ($p < 0.05$) were significantly shorter in the erythromycin group compared with the control group. The incidence of parenteral nutrition-associated cholestasis (PNAC) and necrotizing enterocolitis (NEC) $\geq$ stage II after 14 days of treatment were significantly lower ($p < 0.05$) in the erythromycin group. No significant differences were observed in terms of the incidences of sepsis, bronchopulmonary dysplasia, or retinopathy of prematurity. No adverse effects were associated with erythromycin treatment.

* Corresponding author. Department of Pediatrics, Chung Shan Medical University Hospital, No. 110, Chien-Kuo N. Road, Section 1, Taichung 402, Taiwan.
E-mail address: jen@csh.org.tw (J.-Y. Chen).

doi:10.1016/j.pedneo.2011.11.007

Conclusions: Intermediate-dose oral erythromycin is effective and safe for the treatment of feeding intolerance in VLBW infants. The incidences of PNAC and $\geq$ stage II NEC were significant lower in the erythromycin group.

1. Introduction

Premature, very low birth weight (VLBW) infants frequently develop feeding intolerance. Neonatologists often choose to withhold feeding or hesitate to advance daily feeding volumes in these neonates. Full enteral feeding, with the aim of delivering a total daily fluid intake of 150 mL/kg/day, is difficult to achieve. Inadequate caloric intake can result in postnatal growth restriction and hasten the complications of parenteral nutrition.[1]

Although the exact mechanisms remain unclear, macrolide antibiotic erythromycin has been used for decades as a prokinetic agent to facilitate the advancement of enteral feeding in preterm infants. Data from previous clinical trials are inconsistent, possibly due to variations in times and routes of erythromycin administration, as well as varying durations of erythromycin therapy.[2,3]

In the past, metoclopramide or domperidone have been prescribed to treat feeding intolerance in premature infants. However, we were unable to treat refractory gastrointestinal motility in a VLBW infant until intermediate-dose oral erythromycin was administered on postnatal day 78. The time required to reach full enteral feeding after beginning erythromycin therapy was 15 days. No adverse effects were noted. Consequently, this prospective study was conducted to determine the effectiveness and safety of intermediate-dose oral erythromycin in VLBW infants with feeding intolerance.

2. Patients and Methods

2.1. Patients

This study was approved by the institutional review board of Chung Shan Medical University Hospital. Informed consent was obtained from all parents before the study was initiated. The trial was conducted at the neonatal intensive care unit (NICU) of Chung Shan University Hospital. Infants were eligible for this study if they met the following criteria: (I) gestational age $<$32 weeks, (II) birth body weight $<$1500 g, (III) had been receiving $<$50% of the total daily fluid intake or $<$75 mL/kg/day of milk via oral feedings after 14 days of life (DOL). Infants were excluded from this study if they had major congenital malformations, such as congenital heart disease (except persistent patent ductus arteriosus or patent foramen ovale), gastrointestinal anomalies, hypoxic injury, current or previous history of necrotizing enterocolitis (NEC) within 7 days of the onset of feeding intolerance, or suspected or confirmed sepsis. The administration of other prokinetic agents or probiotics was not allowed in the erythromycin group during the study period.

2.2. Sample size

The sample size was calculated based on the primary outcome, i.e., the time required for the infant to tolerate a full feeding. Our unit statistics revealed a consistently high prevalence of milk intolerance in preterm VLBW infants during the 2 consecutive years before this study was initiated. The mean total time required to tolerate a full enteral feedings in our unit was 50 days. Assuming that the median time to full feeding was 33 days in the erythromycin group, with an α-error of 0.05 (two-tailed) and a power of detection of 0.9, a sample size of 30 subjects (15 in each group) was required.

2.3. Medication

In the erythromycin group, the infants were given 5 mg/kg of erythromycin estolate (Ulosina in an oral suspension diluted to 20 mg/mL with sterile water; U-Liang Pharmaceutical Co., Ltd., Taiwan) every 6 hours for 14 days. Erythromycin was administered 30 minutes before feeding. Infants in the control group received 2 cc/kg of 5% dextrose water when three feedings were attempted every 3 hours, and then oral milk feedings were initiated. The medications and dextrose water were suspended if oral feedings were discontinued and then resumed afterward.

2.4. Enteral and parenteral nutrition

According to the NICU feeding protocol, parenteral fluids with glucose are required to meet the immediate fluid and energy requirements of all VLBW infants. Parenteral nutrition solutions (e.g., glucose, amino acids, calcium, vitamins, etc.) were started on DOL 2, and a 20% intralipid solution with trace elements of various supplements was supplied on DOL 3. Oral milk feedings were usually started at a volume of 10—20 mL/kg/day as soon as possible and increased to 10—35 mL/kg/day unless feeding intolerance was encountered.

The presence of any one of the following signs indicated feeding intolerance: (I) emesis, (II) increased residual on nasogastric (NG) aspiration ($>$50% of the previous feeding or $>$30% of multiple previous feedings), (III) findings of abdominal distention and tenderness on physical examination, or (IV) the presence of bloody stools.

Milk feedings were administered as a continuous infusion under gravity through an orogastric tube or nasogastric tube every 3 hours. The attending nurse aspirated the stomach once every 3 hours to measure gastric residuals, and the attending clinician would either withhold enteral feeding altogether or discontinue the advancement of feeding if intolerance was noted.