Randomised controlled study of oral erythromycin for treatment of gastrointestinal dysmotility in preterm infants

P C Ng, K W So, K S C Fung, C H Lee, T F Fok, E Wong, W Wong, K L Cheung, A F B Cheng

Abstract

***Aim*—To evaluate the effectiveness of oral erythromycin as a prokinetic agent for the treatment of moderately severe gastrointestinal dysmotility in preterm very low birthweight infants.**

***Methods*—A prospective, double blind, randomised, placebo controlled study in a tertiary referral centre of a university teaching hospital was conducted on 56 preterm infants (< 1500 g) consecutively admitted to the neonatal unit. The infants were randomly allocated by minimisation to receive oral erythromycin (12.5 mg/kg, every six hours for 14 days) or an equivalent volume of placebo solution (normal saline) if they received less than half the total daily fluid intake or less than 75 ml/kg/day of milk feeds by the enteral route on day 14 of life. The times taken to establish half, three quarters, and full enteral feeding after the drug treatment were compared between the two groups. Potential adverse effects of oral erythromycin and complications associated with parenteral nutrition were assessed as secondary outcomes.**

***Results*—Twenty seven and 29 infants received oral erythromycin and placebo solution respectively. The times taken to establish half, three quarters, and full enteral feeding after the drug treatment were significantly shorter in the group receiving oral erythromycin than in those receiving the placebo ($p < 0.05$, $p < 0.05$ and $p < 0.0001$ respectively). There was also a trend suggesting that more infants with prolonged feed intolerance developed cholestatic jaundice in the placebo than in the oral erythromycin group (10 *v* 5 infants). None of the infants receiving oral erythromycin developed cardiac dysrhythmia, pyloric stenosis, or septicaemia caused by multiresistant organisms.**

***Conclusions*—Oral erythromycin is effective in facilitating enteral feeding in preterm very low birthweight infants with moderately severe gastrointestinal dysmotility. Treated infants can achieve full enteral feeding 10 days earlier, and this may result in a substantial saving on hyperalimentation. However, until the safety of erythromycin has been confirmed in preterm infants, this treatment modality should remain experimental. Prophylactic or routine use of this medication for treatment of mild cases of gastrointestinal dysmotility is probably not warranted at this stage.**

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Keywords: erythromycin; gastrointestinal dysmotility; enteral feeding; preterm; very low birthweight infants; randomised controlled trial

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Erythromycin, a commonly used macrolide antibiotic, has been found to possess potent prokinetic properties and therefore enhances gastrointestinal motor activity.[1–3] Its motilin agonist action has been clinically exploited for the treatment of patients with chronic functional pseudo-obstruction,[4] gastro-oesophageal reflux,[5] postoperative intestinal dysmotility,[6] gastroparesis secondary to diabetes,[7] and scleroderma,[8] and after surgical vagotomy.[9] Erythromycin can also promote antroduodenal coordination and has been used in facilitating the transpyloric passage of endoscope,[10] Watson's capsule,[11] and nasoenteric feeding devices into the proximal small bowel.[12] Recently, its use as a prokinetic agent has further been extended to preterm very low birthweight (VLBW) infants for the management of non-anatomically obstructive gastrointestinal dysmotility. We and others have reported successful treatment of severe cases with intravenous and oral preparations of the drug.[13–16] A review of the statistics of our neonatal unit during the oral vancomycin trial indicated that infants under 1500 g often experienced protracted feed intolerance, and the median ages of achieving full enteral feeding were 27 and 28 days in the oral vancomycin and placebo group respectively.[17] As prolonged hyperalimentation has been associated with increased risks of serious and sometimes even life threatening complications, including cholestatic jaundice and liver impairment, nutritional deficiency, biochemical rickets, catheter related septicaemia, and pain, as well as anaesthetic risks from repeated intravenous and long line insertion,[13] prokinetic therapy can be considered for improving the gastrointestinal motility in selected preterm infants who have failed to establish full enteral feeding after an extended period and in whom an anatomically obstructive lesion of the gastrointestinal tract has been excluded. This prospective, randomised, placebo controlled study aims to evaluate the effectiveness of oral erythromycin as a prokinetic agent in promoting enteral feeding in preterm VLBW infants who have moderately severe gastrointestinal dysmotility.

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The potential adverse effects of erythromycin and complications from hyperalimentation are assessed as secondary outcomes.

Patients and methods

PATIENTS

Preterm infants consecutively admitted to the neonatal unit at Prince of Wales Hospital, Hong Kong between November, 1998 and May 2000 were eligible for inclusion in the study if they satisfied the following criteria: birth weight less than 1500 g; received less than half the total daily fluid intake or less than 75 ml/kg/day of milk feeds by the enteral route on day 14 of postnatal age; parental consent to be entered into the study. The following infants were excluded: those with lethal congenital anomalies; those with anatomical gastrointestinal abnormalities, such as oesophageal atresia, intestinal stenosis or atresia, Hirschsprung's disease or necrotising enterocolitis; those with congenital cyanotic heart diseases; and those who had received major gastrointestinal surgery within the first two weeks of life.

SAMPLE SIZE

Our unit statistics revealed a consistently high prevalence of milk intolerance during the three consecutive years before the study. Over 75% of VLBW infants did not receive full enteral milk feeding by day 14 of life. The mean (SD) age at which full enteral feeding was achieved in the latter group of patients was 35 (18.4) days. In addition, our previous experience in using oral erythromycin suggested that most infants with uncomplicated gastrointestinal dysmotility could achieve full enteral feeding by between 5 and 10 days after initiation of the drug treatment. It was determined that 28 infants would be required in each arm of a randomised controlled study to detect a significant difference at the 5% level with a power of 80%, if the mean age of achieving full enteral feeding was to decrease from 35 days to 21 days. As about 65–70 VLBW infants were admitted to the neonatal unit each year and the predicted rate of consent from the parents approached 80%, we expected to complete the study within 18 months.

RANDOMISATION

Eligible infants were randomly assigned by computer on day 14 to receive either oral erythromycin or normal saline. A designated member of staff not involved in the clinical care of the newborns performed the randomisation by minimising three important variables: gestational age; birth weight; age of introduction of milk feeds. The attending neonatal team caring for the infants was unaware of the randomisation assignments.

DRUG

The oral route of drug administration was preferred to the intravenous route because all life threatening and fatal cardiac complications related to erythromycin had been associated with the parenteral route of drug delivery.[18 19] Typically, the peak serum drug concentration achieved after an intravenous infusion of erythromycin is 4–10 times higher than when the drug is administered by the oral route.[20–22] As the safety dose limit of intravenous erythromycin in preterm infants has not yet been determined,[23] administration by this route is best avoided. With regard to the dose of oral erythromycin, we opted to use a slightly higher dose (12.5 mg/kg/dose) than the lower dose regimen (3–5 mg/kg/dose)[14 15] commonly used for the management of gastrointestinal dysmotility because: (*a*) our previous success in treatment of severe gastrointestinal dysmotility in preterm infants indicated that the higher dosage was effective[13]; (*b*) former studies using a lower dose regimen often required large intravenous loading doses of erythromycin (15–30 mg/kg/day) for the initial few days of treatment[14 15]; (*c*) the serum drug concentration achieved by oral medication is likely to be lower than that achieved by the intravenous route[20–22]; (*d*) larger doses of erythromycin have also been shown to facilitate gastric emptying by stimulating postprandial antroduodenal motor activity.[24] Infants allocated to receive active drug were given oral erythromycin (Ery-Ped; erythromycin ethyl succinate diluted to 12.5 mg/ml with sterile water; Abbott Laboratories, Abbott Park, Illinois, USA) 12.5 mg/kg, every six hours. Those allocated to receive placebo solution were given an equivalent volume of normal saline. As the oral erythromycin preparation is a white liquid suspension, both active drug and normal saline were mixed thoroughly into the milk feeds to mask their appearance from the attending clinical team. This procedure was performed by two designated staff not involved in the clinical management of these infants at that time. In addition, the oral drug was identified only by a code number to ensure effective blinding. The drug treatment was started on day 15 of postnatal age immediately after randomisation, and all patients received a 14 day course of treatment. When oral feeding had to be discontinued after the start of the study, all oral mediations including erythromycin and placebo solution were also suspended. Administration of the study solutions was resumed after the infant was restarted on enteral nutrition. During the study period, the use of other prokinetic agents such as cisapride, levosulpiride, and metoclopramide was strictly prohibited. Electrocardiography was performed immediately before and on the second week of drug treatment for the measurement of QT intervals.

ENTERAL AND PARENTERAL NUTRITION

All VLBW infants were started on parenteral nutrition (6% TrophAmine (McGaw Inc, Irvine, California, USA) and 20% Intralipid (Kabi Pharmacia AB, Stockholm, Sweden)) on day 3 of life. Oral milk feeds were usually started in the first 5 days of life at the discretion of the attending neonatologist and were given as intermittent boluses through an orogastric tube starting at 1 ml/hour. Oral intake was increased cautiously at a rate of 0.5–1 ml/hour/day according to tolerance. Infants were fed mother's milk whenever possible, but preterm

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Table 1 Comparison of the clinical characteristics of the infants receiving oral erythromycin and those receiving placebo

Clinical features	*Oral erythromycin group (n=27)*	*Placebo group (n=29)*
Gestational age (weeks)	29.6 (28.6–30.7)	29.3 (27.5–31.0)
Birth weight (g)	1180 (985–1395)	1160 (1004–1389)
Sex (female : male)	12 (44%) : 15 (56%)	15 (52%) : 14 (48%)
Inborn : Outborn	26 (96%) : 1 (4%)	28 (97%) : 1 (3%)
Mode of delivery*		
Vaginal	6 (22%)	15 (52%)
Caesarean section	20 (74%)	14 (48%)
Forceps	1 (4%)	0 (0%)
Apgar scores		
1 min	7 (5–8)	6 (5–7)
5 min	9 (8–9)	9 (8–9)
Umbilical arterial blood gas variables		
pH	7.29 (7.23–7.32)	7.29 (7.19–7.32)
Base excess	−4.1 (−5.6–−2.3)	−6.1 (−9.0–−0.8)
First venous haematocrit after delivery	0.52 (0.44–0.54)	0.50 (0.42–0.54)
Temperature on admission (°C)	36.2 (36.0–36.6)	36.3 (36.0–36.8)
Umbilical arterial catheter:		
Infants with UAC (n)	14 (52%)	18 (62%)
Duration (days)	8 (7–14)	6.5 (5–13)
Umbilical venous catheter:		
Infants with UVC (n)	20 (74%)	23 (79%)
Duration (days)	14 (8–17)	13.5 (6–17)
Respiratory distress syndrome		
Grade 0–2	14 (52%)	14 (48%)
Grade 3–4	13 (48%)	15 (52%)
Drugs		
Antenatal dexamethasone		
Number of mothers	24 (89%)	25 (86%)
Doses (n)	2 (1–4)	2 (1–4)
Indomethacin		
Number of infants	10 (37%)	12 (41%)
Fentanyl		
Number of infants	22 (82%)	25 (86%)
Duration (days)	5 (1–7)	3 (1–11)
Vecuronium		
Number of infants	8 (30%)	12 (41%)
Duration (days)	0 (0–2)	0 (0–2)

Continuous variables are expressed in median (interquartile ranges) and proportions in number of patients (%); *p<0.05.
UAC, Umblical arterial catheter; UVC, umbilical venous catheter.

commercial milk formulas were also used if parents preferred. All infants were examined at least twice a day and closely monitored for the occurrence of emesis, diarrhoea, abdominal distension, and volume of gastric residuals. Strict guidelines were provided on stopping and restarting of enteral feeding. The attending neonatologist considered discontinuing enteral feeding when: vomiting occurred more than twice in 24 hours; the volume of gastric residuals exceeded half of the oral intake in the previous four hours on two occasions within the same day; the clinical signs and symptoms were suggestive of necrotising enterocolitis or other ominous intra-abdominal pathologies; or repeated regurgitation and aspiration pneumonia were suspected. Oral feeding together with the study drug was resumed as soon as the above signs and symptoms subsided.

Table 2 Outcomes of enteral feeding and other clinical features of the two groups

Outcomes	*Oral erythromycin group (n=27)*	*Placebo group (n=29)*
Age started on enteral feeding (days)	6 (4–11)	8 (5–11)
Volume of enteral feeding on enrollment (ml/kg/day)	43 (17–58)	51 (39–68)
Time after enrollment achieved half enteral feeding (days)	3.5 (2–7)	6 (4–11.5)*
Time after enrollment achieved three quarters enteral feeding (days)	8.5 (6–19)	13 (9–22)*
Time after enrollment achieved full enteral feeding (days)	13.5 (8–22)	25 (16–33)**
Type of milk feeds		
Breast	5 (19%)	3 (10%)
Formula	8 (30%)	8 (28%)
Mixed	14 (51%)	18 (62%)
Exchange tranfusion (n)	2 (7%)	2 (7%)
Patent ductus arteriosus (n)	9 (33%)	13 (45%)
Necrotising enterocolitis (n)	0 (0%)	0 (0%)
Duration of IPPV (days)	5 (3–11)	5 (2–15)
Duration of mechanical ventilation (days)	16 (8–30)	16 (8–36)
Duration of O_2 dependence (days)	18 (8–34)	16 (8–36)
Periventricular haemorrhage		
Grade 0–2	25 (93%)	26 (90%)
Grade 3–4	2 (7%)	3 (10%)

Continuous variables are expressed in median (interquartile ranges) and proportions in number of patients (%); *p<0.05, **p<0.005.
IPPV, Intermittent positive pressure ventilation.

MICROBIOLOGICAL STUDIES

Stool samples for microbiological culture were collected from all infants studied immediately before treatment and immediately after and four weeks after the treatment had been stopped. All specimens were cultured on a wide range of selective media as previously described.[17] Stool pathogens, including *Salmonella* spp, *Shigella* spp, thermophilic *Campylobacter* spp, and *Vibrio* spp, were identified using standard biochemical tests, the API systems (bioMérieux, Marcy-I' Etoile, France), and serological tests where appropriate. Heavy predominant growth and pure growth of aerobes, anaerobes, and fungi were recorded. The microbiologists who performed the stool culture were unaware of the randomisation assignments.

STATISTICAL ANALYSIS

Fisher's exact test, the Mann-Whitney U test, and the Wilcoxon rank sum test were used to compare proportions and continuous variables where appropriate. Spearman's correlation was also used to assess the relation between different variables that may affect enteral nutrition (table 1) and the time to achieve half, three quarters, and full enteral feeding after the drug treatment. All tests were performed by SPSS for Windows (Release 9.0; SPSS Inc, Chicago, Illinois, USA), and the level of significance was set at 5% for all comparisons. The results were analysed on an intention to treat basis.

ETHICS

The study was approved by the clinical research ethics committee of the Chinese University of Hong Kong, and informed parental consent was obtained before randomisation and enrolment.

Results

Ninety five VLBW infants were admitted to the neonatal intensive care unit during the 19 month period. Eight infants died from extreme prematurity and respiratory disease before 14 days of age, 21 infants received more than half of the total daily fluid volume by enteral feeding at 14 days of age and did not satisfy the entry criteria, and 10 parents did not give consent. Fifty six infants were enrolled in the study.

Twenty seven infants received oral erythromycin and 29 received the placebo solution. Tables 1 and 2 summarise the clinical characteristics and the time taken to reach different stages of enteral feeding after treatment respectively. The age at which enteral feeding was started and the milk intake (ml/kg/day) on the day of randomisation did not differ significantly between the two groups ($p = 0.81$ and $p = 0.11$ respectively). Infants in the oral erythromycin group achieved half, three quarters, and full enteral feeding significantly earlier

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Table 3 Comparison of the potential complications of prolonged total parenteral nutrition and erythromycin treatment between the oral erythromycin and the placebo group

Clinical features or complication	*Oral erythromycin group (n=27)*	*Placebo group (n=29)*
QT interval before drug treatment (ms)	0.37 (0.34–0.38)	0.37 (0.34–0.40)
QT interval during drug treatment (ms)	0.36 (0.35–0.40)	0.38 (0.35–0.38)
Pyloric stenosis (n)	0 (0%)	0 (0%)
Septicaemia (no of episodes)		
Gram positive bacteria	7	4
Gram negative bacteria	3	3
Fungi	1	2
Stool culture (Gram positive : Gram negative : fungi)		
Immediately before drug treatment	10 : 6 : 2	12 : 9 : 1
During drug treatment	13 : 6 : 3	11 : 14 : 1
4 weeks after drug treatment was stopped	5 : 7 : 0	6 : 11 : 2
Cholestatic jaundice (n)	5 (19%)	10 (35%)
Maximum serum conjugated bilirubin concentration (mmol/l)	18 (8–34)	18 (8–50)
Duration of hospital stay (days)	73 (64–97)	86 (64–109)
Number who died	0 (0%)	3 (10%)

Continuous variables are expressed in median (interquartile ranges) and proportions in numbers of patients (%).

than those in the placebo group ($p < 0.05$, $p < 0.05$ and $p < 0.0001$ respectively). By chance, more infants were born by caesarean section in the oral erythromycin group than in the placebo group ($p < 0.05$). All other parameters did not differ significantly between the two groups (tables 1 and 2).

Table 3 summarises the potential adverse effects of erythromycin treatment and the potential complications of parenteral nutrition. The QT interval was not prolonged and did not differ significantly between the oral erythromycin and the placebo group before and during treatment. Although 10 of 29 infants in the placebo group and five of 27 infants in the oral erythromycin group developed cholestatic jaundice (serum conjugated bilirubin concentration > 34 mmol/l) as the result of prolonged hyperalimentation, this trend did not reach significance ($\chi^2 = 1.82$, $p = 0.18$). None of the infants developed pyloric stenosis. All infants in the oral erythromycin group survived, but three infants in the placebo group died.

Eleven and nine episodes of septicaemia were documented in the oral erythromycin and the placebo group respectively. Coagulase negative staphylococcus (five cases), *Staphylococcus aureus* (one case), *Enterococcus* (one case), *Klebsiella* spp (one case), *Escherichia coli* (one case), *Serratia* spp (one case), and *Candida parasilosis* (one case) were isolated in the oral erythromycin group. Coagulase negative staphylococcus (four cases), *Serratia* spp (two cases), *E coli* (one case), and *C albicans* (two cases) were isolated in the placebo group. In addition, there was no significant difference in the stool culture pattern between the two groups of infants (table 3).

In the oral erythromycin group, there was significant association between the number of septicaemic episodes and the age at which half enteral feeding was established ($r = 0.41$, $p < 0.05$). There was also a significant association between the number of septicaemic episodes and the age at which three quarters enteral feeding was achieved ($r = 0.48$, $p < 0.05$) in the placebo group. There were, however, no significant correlations between the age at which half, three quarters, and full enteral feeding were reached and gestational age, birth weight, perinatal asphyxia indices, duration of umbilical arterial and venous catheterisation, patent ductus arteriosus, different drug treatment including antenatal corticosteroids, indomethacin, fentanyl, and paralysing agents, severity of respiratory distress syndrome, and periventricular haemorrhage.

Discussion

Our results indicate that VLBW infants with feed intolerance due to non-anatomically obstructive gastrointestinal dysmotility achieved full enteral feeding significantly earlier after treatment with oral erythromycin. The median times taken to establish half, three quarters, and full enteral nutrition were 3.5, 8.5, and 13.5 days after the start of oral erythromycin. The median times taken to achieve half and full oral feeding in the placebo group were almost twice as long (table 2). These findings agree with those of previous case series in preterm infants.[13–15] Although a recent randomised controlled study did not show any benefit of intravenous erythromycin in improving the tolerance of enteral feeding in preterm infants,[25] these findings were not entirely unexpected because the study was not primarily designed to investigate the effectiveness of erythromycin on enteral feeding, but rather focused on the relation between chronic lung disease and intravenous erythromycin treatment for presumed *Ureaplasma urealyticum* infection.[26] Even more important, the study did not specifically select infants with protracted feed intolerance who were in most need of prokinetic treatment. Therefore most of the patients did not have appreciable gastrointestinal dysmotility. In addition, an antimicrobial dose of intravenous erythromycin may not be ideal for producing its prokinetic effect and could even be dangerous as it may induce severe arrhythmia in preterm infants.[18 19]

Gestational age, birth weight, perinatal asphyxia indices, severity of the initial pulmonary disease, duration of umbilical arterial and venous catheterisation, and commonly used drugs such as antenatal corticosteroids, fentanyl, and paralysing agents were expected to influence tolerance to oral feeding; however, none were found to significantly affect the age at which full enteral nutrition was established. Septicaemia, however, did significantly delay enteral feeding as it was often associated with paralytic ileus and feed intolerance. Severely ill and septic infants may also inadvertently be kept nil by mouth for a prolonged period for fear of necrotising enterocolitis.

The potent prokinetic action of erythromycin has been shown to act principally at the level of the stomach and the proximal small bowel in both human and animal studies.[3 27 28] There is substantial evidence to support the suggestion that erythromycin exerts its gastrointestinal motor effects through activation of the neural motilin receptors on cholinergic neurones and the smooth muscle motilin receptors of the upper gastrointestinal tract.[29] Stimulation of the motilin pathway results in greater amplitude and more frequent antral contractions,[7 30–32] an increase in proximal gastric tone,[33] suppression of pyloric pressure

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waves, which is associated with reduced pyloric outlet resistance,[27] and an increase in duodenal contraction frequency.[34] Human studies further suggest that low dose (1–3 mg/kg) erythromycin predominantly enhances the phase III migrating motor complex at the antral level, whereas high doses of the drug are mainly responsible for the production of sustained antral contractile activity and improved antroduodenal coordination.[24 28 32] In addition, a phase III-like motor pattern was observed with the higher dose of the drug.[24] Combination of the aforementioned mechanisms is thus likely to produce powerful propulsive forces, which effectively propel the gastric luminal contents distally towards the small and large bowels and improve gastrointestinal motility. Despite some reports suggesting immaturity and a paucity of migrating contractile activity in infants below 32 weeks gestation,[3 35 36] our findings and the results of other studies indicate a dramatic improvement in milk tolerance and an increase in gastric emptying after introduction of oral or intravenous erythromycin in extremely premature and VLBW infants.[13–16] In fact, the pattern of distribution of motilin in the gastrointestinal tract at 20 weeks gestation closely resembles adult patterns, and the development of the gastrointestinal neuroendocrine network is almost complete by 25 weeks gestation.[35–37] It has also been shown that infusion of exogenous motilin may promote an earlier appearance of the migrating motor complex,[38 39] and the introduction of enteral feeding to the neonatal gut has resulted in premature detection of phase III motor activity than would normally be expected for the gestational age.[40] These studies illustrate the important concept that preterm infants are already equipped with the necessary anatomical and physiological apparatus at a very early gestation, and it is possible that erythromycin, a competitive analogue of motilin, can act on such motilin receptors and enhance upper gastrointestinal motility.

We admit that the design of the study is not perfect, as we were unable to find a good placebo substitute for erythromycin, which is a white liquid suspension with a distinct odour. However, we sought to overcome some of the difficulties of the blinding procedure by designating staff not involved in the daily care of the newborns to perform the randomisation procedure and to prepare the drugs and mix them into the milk feeds to mask their appearance. Therefore, the attending neonatologists, intensive care team, and microbiologists were completely unaware of the randomisation assignments and were truly blinded to the treatment given to these infants.

Our findings did not show a significant reduction in the incidence of cholestatic jaundice and systemic infection, despite the favourable outcome of achieving enteral feeding earlier in the oral erythromycin group. However, there was a trend suggesting that more infants with protracted feed intolerance developed cholestatic jaundice in the placebo group (table 3). As this study was principally designed to investigate the effectiveness of oral erythromycin in the promotion of enteral feeding, it may not have sufficient statistical power to detect small changes in associated benefits or complications. It is, however, reassuring that none of the infants in the oral erythromycin group developed cardiac dysrhythmia, pyloric stenosis, or septicaemia from multiresistant organisms. In addition, the patterns of the stool culture before, during, and after the treatment were very similar in the two groups. There were no deaths in the oral erythromycin group, but three infants died in the placebo group. One had severe chronic lung disease and died from respiratory failure. The other two had Gram negative septicaemia and died from multiorgan failure. Two of these infants never received more than three quarters of the total volume of enteral feed and none achieved full enteral feeding during the course of their illness.

In summary, this study shows that oral erythromycin is effective in facilitating enteral feeding in VLBW infants with moderately severe gastrointestinal dysmotility. Oral erythromycin can therefore be considered for use in preterm infants who fail to establish enteral feeding after an extended period and in whom an anatomically obstructive pathology of the gastrointestinal tract has been excluded. Although our results indicate that oral erythromycin at the dose used here is safe and does not appear to promote the emergence of resistant organisms, we caution against prophylactic or routine use of this treatment in preterm infants. Until the safety of erythromycin has been confirmed, this treatment should remain experimental, and liberal use of erythromycin as a prokinetic agent for mild cases of gastrointestinal dysmotility should be advised against. New macrolide analogues, such as ABT229, that are devoid of antibiotic activity but possess potent motilinomimetic properties are currently under intense investigation.[41 42] These new classes of drug may prove to be powerful prokinetics which are free from major adverse cardiac effects and will not promote the emergence of multiresistant organisms.

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