Erythromycin for the Treatment of Feeding Intolerance in Preterm Infants

Feeding intolerance is a frequent problem among preterm infants in intensive care. The condition usually manifests as a large residue of food in the stomach at the next feed, and may be associated with abdominal distension, intermittent regurgitation or vomiting. Earlier feeding can assist normal development of the gastrointestinal tract, and also avoid health problems related to feeding by intravenous lines. Slow progression to enteral feeding often predisposes preterm infants to prolonged use of parenteral nutrition, nosocomial infections, hepatic dysfunction, and prolonged hospitalization.1

In this issue of Pediatrics and Neonatology, Ng et al2 report their finding that intermediate-dose erythromycin (20 mg/kg/day) used as rescue treatment is associated with quicker attainment of full enteral feeding and a body weight ≥2500 g, shorter duration of the need for parenteral nutrition, and less parenteral nutrition-associated cholestasis. Feeding intolerance is a result of ineffective, infrequent, uncoordinated bowel activity secondary to immaturity of the gastrointestinal tract.3 Term infants exhibit multiphasic cycles of intestinal motor activity, termed migratory motor complex, during the interdigestive period. Preterm infants of less than 32 weeks’ gestational age lack the propagative phase III of the migrating motor complex in the upper gastrointestinal tract.4 Their interdigestive activity consists of random periods of quiescence and nonpropagated contractions. This functional immaturity predisposes them to feeding intolerance.

The peptide motilin may initiate phase III activity of the interdigestive migratory motor complex in the upper gastrointestinal tract, regulate gastrointestinal motility, and stimulate postprandial gastric muscle contractions and gastric emptying.4,5 In-vitro studies have shown that erythromycin is a motilin agonist.6 Erythromycin, a commonly used macrolide antibiotic, acts as a nonpeptide motilin agonist by binding to the motilin receptor and has been used to facilitate enteral feeding in preterm infants. Various treatment regimens, including prophylaxis versus rescue treatment and low dose (3–15 mg/kg/day) versus high dose (50 mg/day), have been investigated. The gastrointestinal motor effects of erythromycin are well documented in clinical studies and the use of erythromycin as a prokinetic agent became fairly common in neonatal units.7 The mechanism by which erythromycin enhances enteral feeding in preterm infants is not completely known. Current evidence suggests that its prokinetic action is mediated via the motilin pathway.4 Erythromycin enhances the release of endogenous motilin and stimulates cholinergic nerves of the gastrointestinal tract at the pre- and post-ganglionic levels, resulting in the release of calcium and contraction of muscles of the gut.

There is one major concern with the study by Ng et al.2 The intervention was not blinded from the clinical team, raising the possibility that the choice of treatments (including parenteral nutrition regimen and feeding schedule) after randomization was biased by knowledge of the allocation group. Although the role of erythromycin as a prokinetic agent in preterm infants has been recently investigated in a number of randomized control trials, there remains much controversy concerning its efficacy in promoting enteral feeding and possible adverse effect. The Cochrane Collaboration concluded that there is insufficient evidence to show benefit from erythromycin used in large or small doses for the prevention or treatment of feeding problems in premature infants.7 This is possibly because of the varying dosages, times, routes, and duration of erythromycin administration used in different studies.

Further studies are needed to investigate the pathophysiologic mechanisms of functional gastrointestinal dysmotility in preterm infants and only large-scale randomized controlled trials will determine the efficacy and safety of using macrolides for treating gastrointestinal dysmotility in very preterm infants. Although no study has reported any ominous adverse effects, neonatologists should be cautious in their use of this class of drug in preterm infants with functional gastrointestinal dysmotility.
References