

# PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the  
University of Virginia Children's Hospital

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Volume 16 Number 4

April 2010

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## Erythromycin as a Gastrointestinal Prokinetic Agent in Infants

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Prokinetic agents have been used for several decades in infants with feeding intolerance and gastrointestinal dysmotility following gastrointestinal (GI) surgery. The ability to tolerate enteral feeding leads to a decreased reliance on parenteral nutrition and less risk for catheter-related infections or parenteral nutrition-associated cholestasis.<sup>1,2</sup> Erythromycin is increasingly being chosen for this use as the result of concerns over the toxicities associated with cisapride and metoclopramide. While the results of studies with erythromycin in infants have been mixed, there are a growing number which suggest it may be of benefit. This issue of *Pediatric Pharmacotherapy* will review the results of studies using erythromycin as a prokinetic agent in infants and assess the relative efficacy and safety of this therapy.

### Mechanism of Action

Erythromycin is a macrolide antibiotic known to produce abdominal cramping and diarrhea in some patients.<sup>3,4</sup> In 1984, Itoh and colleagues observed that an infusion of erythromycin lactobionate produced powerful contractions of the stomach and proximal small intestine in dogs.<sup>5</sup> The authors suggested that the prokinetic effects of erythromycin were similar to that of endogenous motilin, a 22-amino acid polypeptide produced in cells lining the duodenum and jejunum that binds to receptors in throughout the GI tract and stimulates contractions. Erythromycin was subsequently found to be a potent motilin receptor agonist. Further research in dogs, as well as in healthy adult volunteers, identified two distinct responses to erythromycin.<sup>6</sup> Low-dose treatment appears to act on neuronal motilin receptors, producing contractions that are propagated distally, known as phase III migrating motor complexes (MMC). Higher doses bind to muscle motilin receptors and produce strong non-propagated antral contractions. Erythromycin does not appear to stimulate colonic motor activity.<sup>1,7</sup>

The efficacy of erythromycin in preterm infants with feeding intolerance may be related to both dose and the functional development of motilin

receptors during gestation and early infancy. Tomomasa and colleagues found a four-fold increase in antral contractions in six infants (gestational age 23-31 weeks) given a 0.75 mg/kg IV dose of erythromycin, suggesting functional motilin receptors on the stomach surface.<sup>8</sup> Other investigators have replicated these findings, demonstrating an erythromycin-induced increase in antral contractility and gut transit time in patients  $\geq 26$  weeks gestation.<sup>9</sup>

In 2002, Jadcherla and Berseth studied motor activity in the GI tract of 25 premature and term infants given low-dose enteral erythromycin (0.75, 1.5, or 3 mg/kg).<sup>10</sup> A dose-dependent motilin-mediated increase in MMC was found only in infants 32 weeks gestational age and older. No change was observed in the infants younger than 31 weeks. Term infants also demonstrated a non-motilin mediated increase in contractions not observed in the preterm infants. These studies suggest that motilin receptors on gastric smooth muscle may become functional earlier in development than neuronal motor receptors in the intestine, explaining in part the feeding intolerance observed in preterm infants and the variation in response to erythromycin.<sup>11</sup>

### Pharmacokinetics

The oral bioavailability of erythromycin ranges from 18-45%, depending on the product administered. The ethylsuccinate salt is the best absorbed and can be taken with food. Erythromycin is widely distributed throughout the body, but does not readily cross the blood-brain barrier unless inflammation is present. It is extensively metabolized via cytochrome P450 3A4 and 2B6, with an elimination half-life in neonates of 2 hours. Less than 5% of an oral dose and 12-15% of an IV dose is excreted in the urine as unchanged drug.<sup>3,4</sup>

### Clinical Trials

#### *Feeding Intolerance in Premature Infants*

In 2001, Oei and Lui conducted a randomized, double-blind, placebo-controlled trial of low-dose erythromycin to improve feeding tolerance in preterm infants.<sup>12</sup> Forty-three infants  $\leq 32$

weeks gestational age were randomized to 2.5 mg/kg oral erythromycin every 6 hours or placebo for 10 days from the time of the first oral feeding. Treated infants had fewer large volume residual gastric aspirates ( $1.1 \pm 1.9$  episodes versus  $3.9 \pm 2.4$  episodes in the placebo group,  $p=0.0007$ ) and achieved full feeds significantly faster ( $6.0 \pm 2.3$  days versus  $7.9 \pm 3.5$  days,  $p=0.04$ ), suggesting a benefit from erythromycin. There was no difference in emesis, duration of parenteral nutrition, or adverse effects.

That same year, Ng and colleagues found similar benefit from erythromycin (12.5 mg/kg every 6 hours) in preterm infants with severe GI dysmotility.<sup>13</sup> Fifty-six infants were enrolled in this two-week randomized, double-blind, placebo-controlled trial. Mean time to full feeds was significantly shorter in the treatment group (13.5 days versus 25 days in the controls,  $p<0.005$ ). Although not statistically significant, more patients in the placebo group developed cholestasis (10 versus 5 treated infants). There were no adverse effects related to erythromycin and no difference in the incidence of sepsis. In contrast, ElHennawy and colleagues found no benefit from erythromycin.<sup>14</sup> They studied 27 preterm infants who had failed to achieve full feeds within 8 days of initiation of enteral feeding. The patients were randomized to receive either erythromycin 1.5 mg/kg enterally every 6 hours 30 minutes before a feeding or placebo for 8 days. Antroduodenal motor activity, gastric emptying times, and time to reach full enteral feeds ( $31 \pm 15$  days in the erythromycin group and  $36 \pm 16$  days in the controls) were no different between the groups.

In 2005, Nuntnarumit and coworkers conducted another randomized, double-blind, placebo-controlled study of erythromycin in preterm infants.<sup>15</sup> They randomized 46 infants < 32 weeks gestational age to enteral erythromycin (10 mg/kg every 6 hours for 2 days, followed by 4 mg/kg every 6 hours for 5 days) or placebo. Time to full feeds was significantly shorter in the treatment group (median 7 days versus 13 days in the controls,  $p<0.001$ ). There were also significantly fewer held feeds or large gastric residuals in the treatment group. The duration of parenteral nutrition was significantly shorter (13 days versus 17 days in the controls,  $p=0.03$ ). There were no differences in rates of sepsis, necrotizing enterocolitis, or cholestasis.

In 2007, Aly and colleagues enrolled 60 preterm infants in a randomized, double-blind, placebo-controlled trial of erythromycin for feeding intolerance.<sup>16</sup> Patients received low-dose erythromycin (1 mg/kg given enterally every 8 hours) or a saline placebo. There was no significant benefit in infants  $\leq 32$  weeks

gestational age, but infants > 32 weeks who received erythromycin had a shorter time to full enteral feeds compared to the placebo group ( $10.5 \pm 4.1$  days versus  $16.3 \pm 5.7$  days,  $p=0.01$ ). Ng and colleagues also published a second erythromycin study that year.<sup>17</sup> Infants were enrolled only after failing to tolerate half their goal feeds by 2 weeks. At that time, the patients were randomized to receive either erythromycin (12.5 mg/kg every 6 hours) or placebo. The treated infants achieved full feeds significantly earlier than the controls (26 versus 38 days,  $p<0.001$ ), had a shorter duration of parenteral nutrition (23 versus 33 days,  $p<0.001$ ), and a lower incidence of parenteral nutrition-associated cholestasis (18% versus 37%,  $p=0.003$ ).

The mixed conclusions from these six trials are representative of the numerous papers published on erythromycin use in preterm infants. The differences are likely the result of variations in patient selection, sample size, erythromycin dosing strategies, and assessment of outcome measures.<sup>2,18</sup> A meta-analysis published by the Cochrane Collaboration in 2008 concluded that there was insufficient evidence to recommend routine use of erythromycin for the prevention or treatment of feeding intolerance in preterm infants.<sup>18</sup> Evaluation of individual study results, however, suggests that benefit is most likely to occur with the administration of intermediate to high-dose erythromycin (12 mg/kg/day or more) to infants  $\geq 32$  weeks gestational age.

#### *Administration after Bowel Surgery*

Results of trials using erythromycin as a prokinetic after bowel surgery in neonates have also been mixed. In 2004, Curry and colleagues published the results of a multicenter, randomized, double-blind, placebo-controlled trial of erythromycin in 62 term infants with gastroschisis.<sup>19</sup> Patients received erythromycin, 3 mg/kg given enterally four times daily, or placebo. There was no significant difference between the groups in time to full enteral feeds ( $27.2 \pm 7.4$  days in the controls and  $28.7 \pm 11.6$  days in the treatment group,  $p=0.75$ ) or duration of parenteral nutrition ( $24.9 \pm 13.2$  days versus  $25.6 \pm 16.4$  days,  $p=0.065$ ). There were also no differences in time to first feeding, length of stay, or catheter-related sepsis. No adverse effects were reported. The authors theorized that the lack of response to erythromycin might be related to damage to tissue from the defect or the repair, a suboptimal dose, or poor absorption of the drug after bowel surgery.

Conversely, Razzaq and colleagues found a beneficial effect of erythromycin given after surgery for intestinal atresia.<sup>20</sup> The authors enrolled 30 infants in this randomized controlled study. The erythromycin dose was the same as in

the Curry study. Fifteen infants were randomized to receive erythromycin starting on the second postoperative day; the rest served as controls. Infants given erythromycin had a shorter time to first feeding (6.42 days versus 8.53 days in the controls,  $p=0.022$ ), a shorter time to full feeds (13.1 days versus 16.1 days,  $p=0.009$ ), and duration of parenteral nutrition (10.5 days versus 13.7 days,  $p=0.004$ ). There was a trend towards a shorter length of stay. There were no adverse effects and no difference in rates of sepsis.

#### Precautions

Erythromycin administration during the first months of life has been associated with the development of infantile hypertrophic pyloric stenosis (IHPS).<sup>21</sup> It has been postulated that erythromycin-induced contractions may produce muscle hypertrophy. Studies have suggested potential relationships between risk and onset or length of therapy.<sup>22,23</sup> In a review of infants born in Tennessee from 1985 to 1997, 814 cases of IHPS were identified.<sup>23</sup> Nine infants had received erythromycin within the first 3 months of life. Exposure to erythromycin was associated with an adjusted incidence rate ratio of 2.05 (95% CI 1.06-3.97). When only infants given erythromycin between 3 and 13 days of life were evaluated, the rate ratio increased to 7.88 (95% CI 1.97-31.57), suggesting a greater risk with early exposure. Although there have not been any reports of IHPS in preterm infants enrolled in trials of erythromycin as a prokinetic agent, this adverse effect must be considered as a potential risk of therapy.<sup>2</sup>

Administration of erythromycin, has been associated with the development of *Clostridium difficile* associated diarrhea (CDAD). Once CDAD has been diagnosed, the potential causative antibiotic should be discontinued and the patient treated with an antibiotic known to be effective against this organism.<sup>3,4</sup>

Intravenous erythromycin lactobionate contains benzyl alcohol, which has been associated with gasping syndrome in infants. This syndrome, consisting of metabolic acidosis, respiratory depression, central nervous system toxicity, and cardiovascular collapse, has been reported in infants receiving a cumulative benzyl alcohol exposure of  $\geq 99$  mg/kg/day. In addition, a metabolite of benzyl alcohol, benzoate, may displace bilirubin from its protein binding sites.<sup>3,4</sup>

#### Other Adverse Effects

The most frequently reported adverse effects associated with erythromycin are nausea, vomiting, abdominal pain, and diarrhea. Rare, but serious, adverse effects associated with erythromycin include hypersensitivity reactions (ranging from hives to anaphylaxis), erythema

multiforme or Stevens Johnson syndrome, seizures, and hepatic dysfunction. Erythromycin administration, particularly IV administration, may produce QT interval prolongation, resulting in ventricular arrhythmias (including torsades de pointes). Patients with underlying cardiac disease, hepatic dysfunction, or electrolyte imbalance may be at greater risk for these effects. Reversible hearing loss has been reported in elderly patients with renal dysfunction receiving high-dose therapy.<sup>3,4</sup>

#### Drug Interactions

The potential of erythromycin to prolong the QT interval may be heightened when administered with other drugs posing the same risk or drugs which might inhibit the clearance of erythromycin by inhibiting CYP3A. It should be avoided in patients receiving amiodarone, bretylium, disopyramide, dofetilide, procainamide, quinidine, sotalol, fluoroquinolones, artemether, chlorpromazine, cisapride, dolasetron, droperidol, mefloquine, pentamidine, pimozide, probucol, tacrolimus, thioridazine, or ziprasidone.<sup>1-4</sup> These agents are capable of producing an additive effect on the QT interval, increasing the risk for torsades de pointes. For a complete list of drugs, see the Arizona Center for Education and Research in Therapeutics website at <http://www.azcert.org/index.cfm> (accessed 2/27/10).

Co-administration of theophylline and erythromycin may decrease erythromycin serum levels and increase levels of theophylline, leading to an increased risk for toxicity. Patients requiring this combination may need a lowering of their theophylline dose. Although the interaction has not been well characterized, erythromycin could potentially produce a similar increase in caffeine levels. Erythromycin may increase the effects of alfentanil, bromocriptine, buspirone, cabergoline, carbamazepine, cilostazol, clozapine, colchicine, cyclosporine, digoxin, eletriptan, felodipine, methylprednisolone, quetiapine, rifabutin, rifampin, sildenafil, verapamil, vinblastine, and HMG-CoA reductase inhibitors (such as atorvastatin, lovastatin, and simvastatin). It increases the risk for ergotism when given with dihydroergotamine or ergotamine. Erythromycin may decrease the antiplatelet effect of clopidogrel. It may increase the anticoagulant effects of warfarin, necessitating dosage adjustment. Diltiazem and verapamil increase erythromycin levels.<sup>3,4</sup>

#### Dosing Recommendations

Erythromycin may be administered to infants as an enteral product (erythromycin ethylsuccinate suspension) or an IV product (erythromycin lactobionate injection). Oral therapy is

recommended to avoid the adverse effects associated with IV administration. Based on the studies published to date, a dose of 4 to 12.5 mg/kg every 6 hours appears adequate to produce clinical benefit in most patients.<sup>2,12-20</sup> If IV erythromycin lactobionate is needed, it should be given over 60 minutes to minimize the risk for arrhythmias and reduce vein irritation. The IV product must be diluted with dextrose or saline solutions to a final concentration no more than 5 mg/mL prior to administration however, a concentration of 1 mg/mL or less is recommended to avoid irritation to the vein.<sup>3,4</sup>

#### Availability

Erythromycin ethylsuccinate is available as 400 mg tablets and as an oral suspension, with concentrations of 100 mg/5 mL, 200 mg/5 mL, or 400 mg/mL. Erythromycin lactobionate injection is available in vials containing 500 mg and 1 gram lyophilized erythromycin powder to be reconstituted with sterile water.<sup>3,4</sup>

#### Summary

Erythromycin appears to be a useful prokinetic agent in infants. Although study results have been mixed, erythromycin has the potential to reduce length of time to full enteral feeds and minimize the need for parenteral nutrition. Although it is generally well tolerated, all infants receiving erythromycin should be monitored for drug interactions, CDAD, and IPHS. Additional large-scale studies are needed to determine the optimal dose and duration of therapy.

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#### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 3/26/10:

1. Pneumococcal 13-valent conjugate vaccine (Prevnar 13<sup>™</sup>) was added to the Formulary.
2. Dexrazoxane (generic) was added for the prevention or reduction of doxorubicin-associated cardiomyopathy.
3. Epirubicin (generic) was added.
4. Ofatumumab (Arzerra<sup>™</sup>) was added with restriction to relapsed or refractory CLL.

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