Pharmacodynamics and Systemic Exposure of Esomeprazole in Preterm Infants and Term Neonates with Gastroesophageal Reflux Disease

Taher Omari, PhD, Per Lundborg, MD, Marie Sandström, PhD, Patrik Bondarov, MD, Mia Fjellman, MSc, Ross Haslam, MD, and Geoffrey Davidson, MD

Objective To characterize the pharmacodynamics and systemic exposure of esomeprazole in 26 preterm infants and term neonates with symptoms of gastroesophageal reflux and pathologic acid exposure.

Study design Enrolled patients received oral esomeprazole 0.5 mg/kg once daily for 7 days. Twenty-four–hour esophagogastric pH-impedance monitoring was performed at baseline and on day 7. Pharmacokinetic analysis was performed on day 7. Symptoms occurring during the baseline and day 7 studies were recorded on a symptom chart.

Results There were no significant differences from baseline to day 7 of therapy in the frequency of bolus reflux, consistency of bolus reflux (liquid, mixed, or gas), extent of bolus reflux, or bolus clearance time. Acid bolus reflux episodes were reduced on therapy (median 30 vs 8, $P < .001$), as was the reflux index (mean % time esophageal pH < 4, 15.7% vs 7.1%, $P < .001$). The estimated geometric mean of area under the plasma concentration time curve during the dosing interval and observed maximum plasma concentration was 2.5 μmol · h/L and 0.74 μmol/L, respectively. The number of gastroesophageal reflux symptoms recorded over 24 hours was lower on therapy (median 22 vs 12, $P < .05$).

Conclusions In preterm infants and term neonates esomeprazole produces no change in bolus reflux characteristics despite significant acid suppression. *(J Pediatr 2009;155:222-8)*.

Gastroesophageal reflux (GER) is a very common and usually benign physiological event in infants. A diagnosis of GER disease (GERD) is considered when GER is associated with presentations such as excessive irritability and crying, failure to thrive, feed refusal, apnea, and aspiration pneumonia. Many of these symptoms are not specific to GERD and can be due to other causes, such as feed intolerance, colic, constipation, or infection.[1-4] After excluding these possibilities a trial of conservative measures, such as parental reassurance, upright positioning, feed thickeners, antacids, and elemental formulas may improve symptoms and obviate the need for pharmacologic therapy. A recent study of the efficacy of such measures showed a significant improvement in parent-reported symptoms in more than 50% of infants and normalization of symptom scores in 24%.[5]

Therapeutic options for infants with symptoms of GERD who do not respond to conservative measures are currently limited to acid suppression therapy with H_2-receptor antagonists and proton pump inhibitors (PPIs). These options are effective for symptom relief and healing of esophagitis in older children and adolescents.[6-12] We have previously demonstrated that premature and term infants with symptoms of GERD exhibit increased triggering of acid reflux in association with transient lower esophageal sphincter relaxation.[13] These data suggest a role for acid suppression in infants with pathologic acid exposure. However, in a previous study of omeprazole in premature infants, we were unable to demonstrate symptomatic changes despite significant acid suppression.[14] This apparent lack of efficacy may have related to low statistical power, difficulties in diagnosis of GERD in the age group, difficulties in recording changes in symptomatic episodes, or the fact that symptoms may have been due to bolus reflux, which may not be adequately controlled by PPI therapy. Our previous investigation also did not characterize the effect of PPI therapy on bolus reflux as detected with intraluminal pH-impedance monitoring, which is now considered state-of-the-art and more accurately detects all forms of bolus GER

AUC_τ	Area under the plasma concentration time curve during the dosing interval
CI	Confidence interval
$C_{max,ss}$	Observed maximum plasma concentration at steady state
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
NS	Not significant
PPI	Proton pump inhibitor
t_{max}	Time to reach maximum plasma concentration

From the Gastroenterology Unit, Children, Youth and Women's Health Services, North Adelaide, and School of Paediatrics and Reproductive Health (T.O., G.D.), Department of Neonatal Medicine, Children, Youth and Women's Health Services, North Adelaide, and School of Paediatrics and Reproductive Health (R.H.), University of Adelaide, Adelaide, Australia, and AstraZeneca R&D, Mölndal, Sweden (P.L., M.S., P.B., M.F.)

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(acid, weakly acidic, weakly alkaline, liquid, gas, and mixed) than standard pH monitoring alone.

Empiric use of PPIs in infants, without formal diagnostic testing, is also becoming more prevalent, and the prescription rate is increasing.[15] This practice is of potential concern, given that preterm infants and term neonates demonstrate immaturity of drug-metabolizing enzyme pathways, such as cytochrome P450 2C19 and 3A4.[16,17] Furthermore, recent evidence suggests that empiric use of PPIs in infants with crying symptoms unresponsive to conservative measures is both ineffective and potentially harmful.[18] The aim of this trial was to characterize bolus reflux and esophageal acid exposure and perform full pharmacokinetic analysis in preterm infants and term neonates receiving PPI therapy with esomeprazole for GERD.

Methods

Study Design

Subject to informed consent and eligibility, infants received 7 days' esomeprazole therapy in an open-label trial (AstraZeneca study code: SH-NEC-0002). The study was carried out at the Children, Youth and Women's Health Service, in accordance with the Declaration of Helsinki and codes of Good Clinical Practice. Ethical approval of the study protocol was obtained from the Human Research Ethics and Drug Therapeutics Committees of the Women's and Children's Hospital, North Adelaide (South Australia).

Patient Inclusion Criteria

We enrolled preterm infants and term neonates (aged <1 month term corrected age) with symptoms of GERD. Specialists responsible for the management of patients admitted to the neonatal and infant wards of the Children, Youth and Women's Health Service contacted the study team when they encountered patients in whom PPI therapy was indicated or had recently commenced. In practice, these patients had typical symptoms suggestive of GERD (vomiting, failure to thrive, feed refusal, irritability, crying, back arching, apnea, and coughing): all other causes (eg, infection, constipation) had been excluded, and a trial of feed thickeners and antacids had failed to produce any clinical improvement. Trials of elemental/semielemental formula were not attempted because most infants were breast-fed or receiving expressed breast milk that would have necessitated mothers going on exclusion diets, which was not considered practical. A minimum duration for conservative therapy to be allowed to take effect was not specified because, at the time, this judgment was considered best left to the specialists responsible for the management of patients. However, patients would only receive esomeprazole therapy subject to positive pH findings during a baseline pH-impedance monitoring study (see Study Procedures below).

Patient Exclusion Criteria

Patients were excluded if they had any current or previous clinically significant illness that might interfere with study procedures or metabolism of esomeprazole or that might have jeopardized their safety; receipt of any experimental drug or device in the 8-week period before screening; previous surgical resection; and congenital drug addiction. Concomitant therapy with anticholinergics, antineoplastic agents, H_2-receptor antagonists, sucralfate, bismuth-containing compounds, methylxanthines, promotility drugs, macrolide antibiotics, or barbiturates precluded enrollment.

Study Procedures

Patients were enrolled and underwent a baseline 24-hour pH-impedance monitoring study off-therapy (between study days −1 and 0). If PPI or other pharmacologic antireflux therapies had already commenced, these were withdrawn before baseline recordings (PPI, >72 hours; other medications, >24 hours).

The 24-hour intraesophageal pH recording was analyzed to assess the severity of esophageal acid exposure during the baseline period. Treatment with the study drug could only be ethically justified for patients with abnormal levels of esophageal acid exposure. Patients with a reflux index <5% were defined as having normal esophageal acid exposure, did not receive study drug, and were withdrawn from the study. All remaining patients with a reflux index >5% were defined as having *pathologic* acid exposure and therefore received esomeprazole therapy.

Treatment

Oral esomeprazole 0.5 mg per kilogram was administered for 7 days once daily in the morning, 30 minutes before feeding (study days 1 to 7). This dose was based on previous experience of omeprazole in this population[19] and consideration of the potential differences between esomeprazole and omeprazole. A funnel pan attached to a specially designed adapter was positioned in a teat and placed in the patient's mouth. The corresponding dose content of esomeprazole capsules was then emptied into the funnel pan and administered by flushing 1 mL of sterile water through the adaptor. Individual doses were based on infant weight at the prestudy assessment, and a table of doses was used to choose an appropriate capsule of study medication (1, 1.5, or 2.5 mg for infants weighing ≥1.8 to <2.5 kg, ≥2.5 to <4.0 kg, and ≥4.0 to ≤6.5 kg, respectively). For infants who were discharged during the treatment period, compliance with study medication was assessed by counting returned study medication to estimate the amount of drug administered to each infant.

Pharmacodynamic Assessments

The pharmacodynamic assessments performed at baseline (between study days −1 and 0) and on-treatment (between study days 7 and 8) consisted of either 24-hour pH monitoring with a dual-channel pH probe (Medtronic 24 ME multichannel pH probe, Digitrapper Mark III pH monitoring system; Medtronic, Salt Lake City, Utah) or pH-impedance monitoring with a dual-channel pH-impedance probe