Efficacy and Safety of Once-Daily Esomeprazole for the Treatment of Gastroesophageal Reflux Disease in Neonatal Patients

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Objective To evaluate the efficacy and safety of proton pump inhibitors in infants aged <1 year with gastroesophageal reflux disease (GERD).

Study design In this randomized, double-blind, placebo-controlled multicenter study, neonates (premature to 1 month corrected age; n = 52) with signs and symptoms of GERD received esomeprazole 0.5 mg/kg or placebo once daily for up to 14 days. Change from baseline in the total number of GERD symptoms (from video monitoring) and GERD-related signs (from cardiorespiratory monitoring) was assessed with simultaneous esophageal pH, impedance, cardiorespiratory, and 8-hour video monitoring.

Results There were no significant differences between the esomeprazole and placebo groups in the percentage change from baseline in the total number of GERD-related signs and symptoms (−14.7% vs −14.1%, respectively). Mean change from baseline in total number of reflux episodes was not significantly different between esomeprazole and placebo (−7.43 vs −0.2, respectively); however, the percentage of time pH was <4.0 and the number of acidic reflux episodes >5 minutes in duration was significantly decreased with esomeprazole vs placebo (−10.7 vs 2.2 and −5.5 vs 1.0, respectively; $P \leq .0017$). The number of patients with adverse events was similar between treatment groups.

Conclusions Signs and symptoms of GERD traditionally attributed to acidic reflux in neonates were not significantly altered by esomeprazole treatment. Esomeprazole was well tolerated and reduced esophageal acid exposure and the number of acidic reflux events in neonates. *(J Pediatr 2013;163:692-8)*.

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Gastroesophageal reflux (GER) is common in preterm infants, healthy infants, and children.[1] Episodes of reflux can be asymptomatic or manifest as regurgitation or vomiting.[1,2] Uncomplicated GER in pediatric patients does not typically require medical therapy, but may be managed through dietary changes and other lifestyle modifications.[2] However, reflux may evolve into gastroesophageal reflux disease (GERD) and manifest as bothersome symptoms,[2,3] such as recurrent vomiting, regurgitation, back arching, crying, irritability, and food refusal.[1-3] More serious signs and symptoms can include failure to thrive, cardiorespiratory symptoms, esophagitis, apnea, and recurrent pneumonia.[1,2,4]

Oral proton pump inhibitors (PPIs), such as esomeprazole, are approved for the treatment of GERD in children aged 1-17 years.[1,5,6] Esomeprazole is a PPI approved for treatment of GERD with esophagitis due to acid reflux in infants from 1 month to 11 months of age. However, PPIs often are prescribed off-label to treat non-specific symptoms in infants.[7] A systematic review suggested that PPIs are not effective in reducing these symptoms[8]; this is either because the symptoms are not caused by GER or, if due to GER, because the symptoms are caused by volume reflux, rather than acidity. Results from available studies differ greatly in terms of study design, treatment regimens, and diagnostic criteria, and most outcomes are subjectively based on parental questionnaires.[9] Studies that measure both reflux episodes and symptoms using less subjective methods are limited.

In the present study, we used novel simultaneous and integrated pH/impedance, and cardiorespiratory and video monitoring to investigate the efficacy and safety of the PPI esomeprazole in preterm and full-term neonates. The use of combined pH/impedance monitoring allows evaluation of the effect of acid suppression therapy on all types of reflux (including acidic [pH < 4.0], weakly acidic [pH 4.0-6.9], and nonacidic [pH ≥ 7.0]), and

AE	Adverse event
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
LSM	Least square mean
ITT	Intent-to-treat
PPI	Proton pump inhibitor
SAE	Serious adverse event

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also allows signs and symptoms believed to be associated with GERD in this patient population to be evaluated more specifically. The primary objective of this study was to assess the difference between esomeprazole and placebo in the treatment of signs and symptoms of GERD as observed by 8-hour video and cardiorespiratory monitoring in neonatal patients.

Methods

This was a randomized, double-blind, placebo-controlled phase III study conducted at 3 centers (1 each in Australia, Germany, and the United Kingdom). The study protocol was approved by an Institutional Review Board at each study center. Written informed consent was obtained from each neonate's parent or guardian before any study procedure was performed. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki consistent with International Conference of Harmonization/Good Clinical Practice. Infants who were full-term or had a gestational or post-conception age of 28 to 44 weeks and were inpatients in a Neonatal Intensive Care Unit special care nursery or equivalent hospital ward at study entry, and were expected to remain inpatients for the duration of the treatment period, were eligible to participate. Patients aged <28 weeks gestation were considered if they met inclusion criteria and could undergo all study-related procedures as judged by the investigator. Patients must have been suspected of having any 2 of the following clinical findings, either individually or in combination: apnea with or without bradycardia and with or without oxygen desaturations, vomiting or gagging, and irritability or pain at least every second feed or at least twice every 8 hours. At least two of these occurrences had to be reproducible during an 8-hour video monitoring period. Patients were excluded if they had a history or current need for resectional or reconstructive surgery of the gastrointestinal tract or could require surgery during the study, if they had a disease or condition (active gastrointestinal bleed, allergic gastroenteropathies, eosinophilic gastroenteritis, bleeding disorders, active seizure disorder, ongoing treatment for seizure disorder, acute pancreatitis, meningitis, or acute respiratory distress) or needed concomitant medications (eg, antiemetics, H_2-receptor antagonists, narcotics, warfarin, bismuth-containing products, barbiturates, anticonvulsants, antineoplastic agents, sucralfate, or promotility drugs) that could interfere with the conduct of the study. Eligible patients were sequentially randomized to receive esomeprazole 0.5 mg/kg or placebo once daily for up to 14 days. A block randomization scheme was used, stratified by center. Study drug or placebo concentrate were thawed at room temperature and diluted with a thawed sodium bicarbonate solution prior to use. Each dose (0.5 mg/kg/d) was administered in a volume of 2 mL/kg of liquid (0.5 mmol sodium bicarbonate and 0.5 mg esomeprazole/placebo of diluted solution per kg). The dose was administered via oral gavage or nippling 30 minutes before morning feeding and followed by administration of 5-10 mL of sterile water or formula. Simultaneous esophageal pH, impedance monitoring, cardiorespiratory monitoring, and 8-hour video monitoring were performed at baseline and on final study day (end of 14-day treatment or early discontinuation). A nasal thermistor or capnograph, oxygen saturation and cardiorespiratory skin probes, actimeter, and thoracic belts were connected to the neonate,[10] and a combined pH/impedance probe was placed in the patient's esophagus before feeding. Esophageal pH/intraluminal impedance was measured for 18-24 hours using the Sandhill Scientific Insight Esophageal Function Testing System (Sandhill Scientific, Highlands Ranch, Colorado).[10] Cardiorespiratory data including respiration rate, heart rate, electrocardiogram, and oxygen levels were recorded for 8 hours during the pH/impedance monitoring period with the Respironics Alice 5 Diagnostic Sleep System (Respironics, Murrysville, Pennsylvania). A video camera recorded 8 hours of sound and movement during the pH/impedance monitoring period and ideally included at least two feedings and included dosing on the final study day (2 hours before and 6 hours after dosing). The video camera was focused on the abdomen, upper body, and face of the neonate and captured respiration and reflux-related behavioral events (eg, arching, facial expressions, spitting, coughing, fussiness, and eructation).[10] Cardiorespiratory, pH/impedance, and video data were synchronized by a Synchronization Box (Sandhill Scientific).[10]

During pH/impedance monitoring, reflux-related behavioral events were recorded by qualified staff and integrated with the system data. Two blinded central readers independently (to avoid potential bias) reviewed 8 hours of integrated data to identify the start and stop times of predefined signs and symptoms of GERD and types of reflux events. Temporal correlation of signs and symptoms of GERD with reflux events was performed programmatically. The timing and duration of gagging, back arching, irritability/crying/fussing, vomiting, oxygen desaturation (defined by a decrease in oxygen saturation to <85%), bradycardia (defined by a decrease in heart rate <100 beats per minute for ≥5 seconds), and apnea (defined by a pause in respiratory effort for ≥20 seconds) were recorded. Recordings were considered evaluable if ≥6 hours of unambiguous video of the upper body and face of the neonate were captured. Patients with <6 hours of evaluable video at baseline were to be discontinued.

The primary efficacy outcome was change from baseline to end of treatment in the total number of GERD symptoms (video recording) and GERD-related signs (cardiorespiratory monitoring). Secondary efficacy outcomes included mean change from baseline in the number of signs and symptoms of GERD by type and individual symptom: gastrointestinal (vomiting), cardiorespiratory (apnea, bradycardia, and oxygen desaturation), and neurobehavioral (gagging, back arching, and irritability/crying/fussing). Pharmacodynamic efficacy assessments included assessments of GER episodes (the number of acidic [pH < 4.0], weakly acidic [pH 4.0-6.9], and nonacidic reflux [pH ≥ 7.0] episodes, the number of liquid reflux, number of mixed gas/liquid reflux, and the