No Effect of Proton Pump Inhibitors on Crying and Irritability in Infants: Systematic Review of Randomized Controlled Trials

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Proton pump inhibitors are increasingly being used to treat infants with crying and/or irritability based on the assumption that these symptoms are attributable to gastroesophageal reflux. However, the data from a systematic review of randomized controlled trials do not support the use of proton pump inhibitors to decrease infant crying and irritability. *(J Pediatr 2015;166:767-70).*

Proton pump inhibitors (PPIs) are increasingly being used in the management of irritability and excessive crying in young infants,[1] despite evidence that their use increases the risk of gastrointestinal and respiratory tract infections.[2-4] This is mainly based on the assumption that these symptoms are attributable to gastroesophageal reflux (GER) or GER disease (GERD). We aimed to examine whether PPIs are effective in the management of excessive crying and irritability in infants.

Methods

In this systematic review, MEDLINE, EMBASE, and the Cochrane Central Register of Controlled trials (CENTRAL) databases, with no language restriction, as well as 2 registries for clinical trials (www.clinicaltrials.gov; www.clinicaltrialsregister.eu), were searched in July 2014 for randomized controlled trials (RCTs) that compared the effectiveness of PPIs with placebo or no intervention. Participants had to be infants with GER/GERD but otherwise healthy. The studies were recorded only if they reported outcomes related to crying/irritability such as the duration and/or number of episodes of crying and/or irritability, as assessed by the investigators. The secondary outcomes were adverse effects. For assessing risk of bias, the Cochrane Collaboration tool was used.[5] The data were analyzed using Review Manager (RevMan computer program v 5.2, 2012; The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). The dichotomous measure for individual studies is reported as the risk ratio (RR) between the experimental and control groups with 95% CIs. The mean difference between treatment and control groups was selected to represent the difference in continuous outcomes (with 95% CIs).

GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
PPI	Proton pump inhibitor
RCT	Randomized controlled trial
RR	Risk ratio

Results

Figure 1 (available at www.jpeds.com) is a flow diagram of the identification of eligible trials. Characteristics of included[6-10] and excluded trials[11-23] are summarized in **Tables I** and **II** (**Table II** available at www.jpeds.com). All 5 included RCTs (n = 430) were supported by the manufacturers of the PPIs, and some authors were either employees, or consultants, or own stock in these companies. **Table III** (available at www.jpeds.com) shows the results of the assessment of risk of bias of the trials included. Except for 1 RCT,[8] all trials had some methodologic limitations such as unclear sequence generation, unclear allocation concealment, or no true intention-to-treat analysis. All trials were reported to be double-blind. In 2 RCTs,[9,10] there was an initial open-label phase during which patients received standardized conservative treatment for GERD. There was variability in how crying/irritability outcomes were reported. In only 2 RCTs was 'crying/irritability' the primary outcome.[7,8] To assess crying/irritability, the investigators in trials used video monitoring,[6] a visual analog scale,[7] a validated cry diary by Barr et al,[7,24] a validated Infant Gastroesophageal Questionnaire,[8] or based the assessment on questionnaires.[9,10] Detailed description of individual RCTs is summarized in **Table IV** (available at www.jpeds.com).

Efficacy of PPIs in the Management of Crying/Irritability

Four RCTs[6-8,10] reported continuous data for the effect of use of PPIs on crying/irritability (**Figure 2**, A). None of them found a significant difference between the experimental and control study groups. One RCT[8] reported dichotomous

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Table I. Characteristics of the trials included

Study ID	Country and recruitment	Participants, diagnosis	Intervention (dose)	Control intervention	Crying/irritability as the primary outcome	Crying/irritability reporting	Sponsor	Reported adverse events
Davidson et al 2013[6]	RCT, DB (Australia, Germany, and the UK)	Infants (<1 y) with signs and symptoms of GERD.	Esomeprazole (0.5 mg/kg, for 14 d) (n = 26)	Placebo (n = 26)	No	Video monitoring	AstraZeneca LP (Wilmington, Delaware)	Similar between the treatment groups.
Moore et al 2003[7]	RCT, cross-over (Australia; GI clinics)	Irritable/crying/spilling infants (3-12 mo old) with a reflux index of >5% on pH monitoring and/or abnormal esophageal endoscopy/histology	Omeprazole (10 mg once or twice daily depending on weight, 2 wk) (n = 15)	Placebo (n = 15)	Yes	Validated Barr et al diary, and visual analogue score of parental impression of infant irritability.	JH & JD Gunn Medical Research Foundation and the Channel 7 Children's Research Foundation. The study products were supplied free of charge by Astra-Zeneca Pty Ltd.	No adverse effects reported.
Orenstein et al 2009[8]	Multicenter, general pediatric clinic (US, Poland)	Infants 1-11 months with symptomatic GERD (I-GERQ), crying during or within 1 h after >25% of feeds	Lansoprazole 0.2-0.3 mg/kg/d for infants age ≤10 wk and 1.0-1.5 mg/kg/d for infants age >10 wk, 4 wk (n = 81)	Placebo (n = 81)	Yes	Validated I-GERQ	Takeda Global Research and Development Center, Inc (Taked) sponsored the clinical trial and data analysis. Some authors have served as consultants to Takeda as well as to other companies making drugs in the same class. Some employed by Takeda.	Serious AEs occurred significantly more frequently in the lansoprazole group compared with the placebo group (<0.032)
Winter et al 2010[9]	RCT, DB, multicenter (US, South Africa, Poland)	Infants (1-11 mo) with a GSQ-I mean symptom frequency >16 at screening and baseline and a clinical diagnosis of suspected, symptomatic, or endoscopy proven GERD	Pantoprazole (weight-adjusted doses 5-10 mg/d, for 4 wk) (n = 52)	Placebo (n = 54)	No	An electronic diary; questions for the caregiver assessment of GERD symptoms in infants developed from the modified version of the GSQ-I.	Wyeth Pharmaceuticals, Collegeville, Pennsylvania (now Pfizer Inc). Some investigators and/or institutions received compensation. Some authors were employees of Wyeth Research.	No difference between the study groups. Serious adverse events occurred in 8 patients that were considered to be unrelated to the treatment.
Winter et al 2012[10]	RCT, DB, multicenter (US, France, Germany, and Poland)	Infants (1-11 mo) with a clinical diagnosis of suspected GERD based on symptoms or endoscopically proven GERD	Esomeprazole (weight-adjusted doses, 2.5-10 mg/d, for 4 wk) (n = 39)	Placebo (n = 41)	No	IVRS to capture patients' daily symptoms and use of rescue medications during the previous 24-hour period. Questions used in the IVRS assessment of GERD symptoms were based on the validated I-GERQ.	AstraZeneca LP. Some authors were consultants and/or and investigators and/or received grant/ research support and/or were employees and/or own stock of AstraZeneca (and/or one of the following companies: Centocor, Proctor and Gamble, Takeda Pharmaceuticals, UCB, Salix, and Wyeth, Johnson & Johnson, Centocor, and Proctor.	Similar between the 2 treatment groups.

AEs, adverse events; *DB*, double-blind; *GSQ-I*, GERD Symptom Questionnaire in Infants; *I-GERQ*, Infant GER Questionnaire; *GI*, gastrointestinal; *IVRS*, interactive voice response system.