Pharmacologic Therapy for Gastroesophageal Reflux Disease in Children

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Clinical Question
Are medications for gastroesophageal reflux disease (GERD) safe and effective in children?

Evidence-Based Answer
Among infants younger than 12 months diagnosed with GERD, weak evidence supports the use of proton pump inhibitors (PPIs) and histamine H\(_2\) antagonists. Among children 12 months and older, studies have shown moderate benefit from PPIs and weak benefit from H\(_2\) antagonists for providing symptomatic relief and/or improving histologic or pH indices of disease. No serious adverse effects were noted in the studies reviewed for any of the treatments. (Strength of Recommendation: B, based on inconsistent randomized controlled trials [RCTs].)

Practice Pointers
Gastroesophageal reflux is a benign, self-limited process caused by transient, intermittent relaxations of the lower esophageal sphincter. Gastroesophageal reflux often occurs postprandially and lasts less than three minutes with minimal symptoms. Most children with gastroesophageal reflux have normal weight gain, minimal irritability, and no respiratory symptoms.\(^1\) GERD occurs when reflux symptoms are more severe or when complications arise.\(^2\) The classic picture of infantile GERD is an irritable baby with poor weight gain and arching of the back during feeding, but symptoms may also include wheezing or coughing.\(^{1,2}\)

The authors of this Cochrane review evaluated 24 RCTs examining pharmacologic management of GERD in children younger than 16 years. A subgroup analysis focused on infants younger than 12 months. Studies were small, often industry sponsored, varied in outcomes measured (symptom scores, pH levels, endoscopic appearance), and lacked head-to-head comparisons. Infants born prematurely, with neurologic impairments, or with anatomic malformations were not addressed in this review.

The PPIs reviewed included omeprazole (Prilosec), lansoprazole (Prevacid), pantoprazole (Protonix), and esomeprazole (Nexium). The H\(_2\) antagonists reviewed included ranitidine (Zantac), cimetidine (Tagamet), and nizatidine (Axid). Other agents in this review included the prokinetic agent domperidone (not available in the United States), the compound alginate agent Gaviscon Infant, and baclofen (Lioresal), an antispasmodic agent. Currently, ranitidine is the only antacid approved by the U.S. Food and Drug Administration for infants younger than 12 months.\(^1\)

The authors concluded that there is weak evidence to support the use of PPIs and H\(_2\) antagonists in infants younger than 12 months. Several studies demonstrated that infants given PPIs had improvement in symptom scores, but these improvements were not significantly different than in infants given placebo. Weaknesses of the evidence included the small size of the trials, and the fact that trials in infants are based on parent or physician interpretation of cry/fuss time, and that many of these patients did not have GERD but merely functional reflux. The only agent that showed consistent benefit in two RCTs was domperidone. However, domperidone could not be evaluated for effectiveness by meta-analysis given differences in study design and outcomes.

Gaviscon Infant is a preparation of sodium and magnesium alginate that reportedly acts as a thickener to mitigate gastric acid. Because of toxicity concerns, it was reformulated in 1999 as an aluminum-free compound. Although individual trials were somewhat positive, showing improvement in vomiting as well as parent perceptions of symptoms, Gaviscon Infant was most effective when prescribed in combination...
with a PPI, and meta-analysis could not be performed. It is not widely available in the United States.

Among children 12 months and older, there was moderate-quality evidence that PPIs can improve reflux symptoms in those with erosive esophagitis. Analysis could not demonstrate the superiority of one PPI over another. Of the three H\textsubscript{2} antagonists studied, only nizatidine showed improvement in objective indices in a single study of 26 patients. Ranitidine and cimetidine were each studied in an individual trial; neither revealed superiority to placebo or control. There was also inconclusive evidence to support the use of baclofen. In the single RCT that involved baclofen, the drug was compared with placebo in 30 children with a mean age of 10 years. The study demonstrated improvement in reflux symptoms and manometry but took place over only two hours.

Despite case reports and theoretic concerns of PPIs contributing to pneumonia and gastroenteritis, adverse effects reported in these trials were relatively benign, but included headache and diarrhea. Although 2009 specialty guidelines allow for a two-week trial of antisecretory therapy if conservative measures have failed, a 2013 Centers for Medicare and Medicaid Services publication stated that PPIs were not indicated for use in infants because of the possibility of \textit{Clostridium difficile}–associated diarrhea.\textsuperscript{2,3} Guidelines in the United Kingdom support a four-week trial of H\textsubscript{2} antagonists or PPIs for infants with feeding difficulties and poor growth.\textsuperscript{4}

**REFERENCES**


**Tricyclic Antidepressants for the Treatment of ADHD in Children and Adolescents**

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**Clinical Question**

Do tricyclic antidepressants (TCAs) effectively treat attention-deficit/hyperactivity disorder (ADHD) in children and adolescents?

**Evidence-Based Answer**

TCAs, specifically desipramine and nortriptyline (Pamelor), are superior to placebo at reducing ADHD symptoms in the short term (two to six weeks); however, the quality of evidence is low. Increased heart rate and diastolic blood pressure may be noted with treatment. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

**Practice Pointers**

ADHD is defined as a pattern of behavior with onset before 12 years of age with components of inattention, hyperactivity, and impulsivity that are present in multiple settings and cause impairment.\textsuperscript{1} Stimulants are first-line treatment for patients with ADHD, but they are associated with decreased appetite, decreased height, and development or worsening of tic disorder.\textsuperscript{2,3}

This review included six double-blind, randomized controlled trials (RCTs) with a total of 216 patients treated for ADHD with desipramine, clomipramine (Anafraniil), and nortriptyline. Two of the trials had coexisting tic disorder or Tourette syndrome as inclusion criteria, and in one of these, clonidine was compared with desipramine. Of the 216 participants, 90% were males from urban areas, with a mean age...
of 9.9 years (range = six to 17 years). More than 50% of participants had been treated with stimulants in the past. Symptoms were assessed during a two- to six-week treatment period. Only studies with low risk of selection, performance, or attrition bias were used in the review.

Primary outcome measures were an improvement in core ADHD symptoms, the proportion of patients achieving a set improvement in those core symptoms (as measured by parents, teachers, or clinicians), and adverse effects of treatment. The scales used included the Conners’ Rating Scale,4 which is rated by parents or teachers, the Child Behaviour Checklist,5 which is rated by parents or teachers, and the Clinical Global Impression (CGI),6 a clinician-rated scale.

Because of the range of outcomes and the variety of instruments used to rate those outcomes, making comparisons was challenging. However, three trials compared TCAs with placebo using the same rating scale, the CGI. These three trials included 125 participants and found that desipramine and nortriptyline were more effective than placebo in improving core ADHD symptoms (odds ratio = 18.50; 95% confidence interval [CI], 6.29 to 54.39). The number needed to treat to benefit one additional person was two.

Two additional trials compared desipramine with placebo using teacher rating scales; core ADHD symptoms improved more in patients taking desipramine than in those given placebo (standardized mean difference [SMD] = –0.97; 95% CI, –1.66 to –0.28). Two trials using different parent rating scales also found that desipramine improved ADHD symptoms more than placebo (SMD = –1.42; 95% CI, –1.99 to –0.85).

Although no serious adverse effects were noted, desipramine was associated with mild increases in diastolic blood pressure and heart rate, as well as higher rates of appetite suppression compared with placebo. Other adverse effects included dry mouth, abdominal discomfort, diaphoresis, sedation, fatigue, headache, confusion, blurred vision, constipation, and urinary retention. None of the studies looked at long-term adverse effects of chronic use. Treatment discontinuation was similar for desipramine and placebo.

Current guidelines recommend the use of medications approved by the U.S. Food and Drug Administration (FDA) for patients diagnosed with ADHD.7 TCAs are not FDA-approved for children, and further study is warranted to determine if they are an appropriate treatment for patients with ADHD.


The practice recommendations in this activity are available at [http://summaries.cochrane.org/CD006997](http://summaries.cochrane.org/CD006997).

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**REFERENCES**


