Cyproheptadine: A Potentially Effective Treatment for Functional Gastrointestinal Disorders in Children

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ABSTRACT

Functional gastrointestinal disorders (FGIDs) negatively affect children’s quality of life and health care costs. It has been proposed that alteration of gut serotonin leads to gastrointestinal dysmotility, visceral hypersensitivity, altered gastrointestinal secretions, and brain-gut dysfunction. Cyproheptadine, a serotonin antagonist, has been shown to be a potentially effective and safe treatment option in children who meet the clinical criteria for FGIDs. Well-designed multicenter trials with long-term follow-up are needed to further investigate its efficacy. [Pediatr Ann. 2017;46(3):e120-e125.]

It is challenging to provide symptomatic relief for children suffering from functional gastrointestinal disorders (FGIDs). Understanding the pathophysiology of FGIDs will help the health care provider choose the appropriate treatment. FGIDs are clinical conditions that include functional abdominal pain (FAP), functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM), and cyclic vomiting syndrome (CVS), and they are diagnosed based on Rome III clinical criteria.1 FGIDs affect a large number of children (up to 19%) in the Western world,2 cause negative impact on children’s quality of life,3 and increase the risk of depression.4 It costs approximately $6,100 per patient for the initial gastroenterology consultation visit,5 and an average of $18,000 per hospital stay.6 Interactions of biological, psychological, and sociological factors contribute to its natural history.7 Proposed mechanisms for FGIDs include altered gut motility, visceral hypersensitivity, altered gastrointestinal secretion, and brain-gut dysfunction. Gut serotonin (5-HT) regulates gut motility, gastrointestinal secretion, and visceral sensitivity to normal sensations through specific gut receptors.

Cyproheptadine, a 5-HT receptor antagonist, is used off-label for several indications and is a potentially effective medication for FGIDs.8 Its efficacy in children with FAP has been reported in a double-blind, placebo-controlled trial,9 as well as in retrospective studies for treatment of FAP, FD, IBS, and AM.10-16 5-HT is a polyfunctional signaling molecule that serves as a paracrine factor, endocrine hormone, neurotransmitter, and growth factor.17 Various 5-HT receptor subtypes regulate gut motility, secretion, and visceral sensitivity.18-20 Intraluminal pressure changes, mechanical stimulation, vagal stimulation, ingestion of a meal, or the presence of acid, amino acids, or hypo- or hyperosmotic solutions in the duodenum cause release of 5-HT.21-25

PATHOPHYSIOLOGY AND TREATMENT OF FGIDS

Visceral hypersensitivity, gastrointestinal dysmotility, altered secretion, and brain-gut dysfunction are putative outcomes caused by alteration of gut 5-HT. Hypersensitivity is generalized in FAP,26 limited to the rectum in IBS,26 and limited to the stomach in FD.18 Decreased gastric accommodation results in early satiety and dyspeptic symptoms in FD.27,28 Dysmotility results in diarrhea, constipation, nausea, bloating, and abdominal distension in IBS.29-32 Altered selective serotonin transporter expression33-35 results in altered 5-HT levels in the intestinal mucosa, leading to IBS symptoms. The secretory effects of 5-HT are mediated through the 5-HT4 subtype in human ileal mucosa, but through the 5-HT2A subtype in the human sigmoid colon.19 The enteric nervous system and central nervous system...
are derived from the same embryologic tissues, have direct effects on each other, and are proposed to contribute to the gastrointestinal and neurologic symptoms of AM.36 In a person with chronically low levels of 5-HT, a sudden release of 5-HT might trigger a migraine.37 An autonomic neuropathy with impairment of the sympathetic nervous system but normal parasympathetic nerve function is a proposed cause of CVS.38 Excessive corticotropin-releasing factor due to stress reportedly decreases gastric vagal efferents, leading to gastroparesis and vomiting.39 Based on the available data, altered 5-HT appears to be involved in FGID symptoms; thus cyproheptadine, which is a 5-HT antagonist, is a potential treatment option for the symptomatic management of FGIDs.

**CYPROHEPTADINE FOR TREATMENT OF FGIDs**

Studies on use of cyproheptadine for treatment of FGIDs are summarized in Table 1. The following text provides a brief discussion of its role in each of the FGIDs.

**Functional Dyspepsia**

The symptoms of FD have been explained by gastric hypersensitivity to distension and decreased gastric accommodation in response to a meal.40,41 Animal studies have shown that fundic contraction and relaxation of the stomach are regulated by 5-HT via 5-HT2A and 5-HT2B receptors as reported in rats,42 guinea pigs,43 and chickens,44 as well as in the antrum in dogs.11,45 Stimulation of the 5-HT2 receptor in dogs induced lower esophageal sphincter contractions, which were later inhibited by cyproheptadine.46

A 5-HT3 receptor antagonist (ondansetron) is known to be effective in treatment of postinfectious dyspeptic symptoms.47 Cyproheptadine, a nonselective antagonist of 5-HT2A and 5-HT2B, has not been formally studied in FD in humans.18 To date, there are only two published retrospective studies (Madani et al.10 and Rodriguez et al.11) that showed efficacy of cyproheptadine in a majority of children diagnosed with Rome III-defined FD (77% and 55% resolution of symptoms, respectively).

**Functional Abdominal Pain**

Studies in mice showed that 5-HT receptors, including 5-HT1, 5-HT2, 5-HT6, and especially 5-HT1B and 5-HT2A, are all involved in peripheral nociceptive response induced by 5-HT.48 Cyproheptadine showed marked inhibition of 5-HT nociceptive response, possibly due to its nonselective binding properties, allowing it to target more than one receptor and leading to a wide-ranging effect. Cyproheptadine is also known to inhibit calcium channel in the intestinal muscle, providing relief of pain.49-53

To date, there have been two studies attesting to its efficacy in FAP. A prospective double-blind study by Sadeghian et al.9 in 2008 among 29 children with FAP demonstrated statistically significant improvement of pain frequency, intensity, and overall improvement in the cyproheptadine group. Efficacy of cyproheptadine was also demonstrated in a retrospective study in 2016 among 55 patients who met Rome III criteria for FAP, with 66% experiencing complete resolution of abdominal pain.10

**Abdominal Migraine**

Although cyproheptadine has been shown to be effective in prevention of migraine headache in children,54 there are data suggesting its beneficial effects in AM10,12,13 (Table 1). Pfau et al.13 reported complete abatement of symptoms in 3 of 4 patients with AM treated with cyproheptadine. Worawattanakul et al.12 studied the role of cyproheptadine in abdominal migraine prophylaxis in 12 patients, and 10 of these patients had fair to excellent response. Madani et al.10 demonstrated complete resolution of symptoms in 13 of 18 patients with AM treated with cyproheptadine (72% response rate). Lewis55 noted that cyproheptadine is a simple, effective, and safe treatment option for AM in children younger than age 10 years who are not overweight.

**Irritable Bowel Syndrome**

Similar to FD, patients with IBS have alterations in rectal sensitivity with lowered thresholds for pain and motility disturbances, as well as altered intestinal secretion.30 Diarrhea-predominant IBS is associated with elevated 5-HT, whereas constipation-predominant IBS is associated with decreased levels of 5-HT in the colon mucosa.33 The etiology of IBS is unclear, but likely due to alterations in 5-HT metabolism resulting in impaired gastrointestinal motility and IBS.56,57 Multiple medications have been reported to improve IBS symptoms including alosetron, tegaserod, cilostamide, amitriptyline, dicyclomine, and hyoscycamine via effects on serotonin, on the cholinergic pathway, and as antidepressants. Cyproheptadine, a nonselective serotonin antagonist with mild anticholinergic effect, might also be beneficial in the treatment of IBS. Cyproheptadine was found to block the 5-HT2 receptor, resulting in decreasing contraction of longitudinal smooth muscles of small intestine in mice.58 Another animal study in rats demonstrated that cyproheptadine also has a direct effect on the inhibition of electrogenic ionic secretion in intestinal epithelium.59 There have been no studies demonstrating a direct effect of cyproheptadine use in the treatment of IBS in humans; however, a recent study by Madani et al.10 reported, for the first time, a complete resolution of symptoms.
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<tr>
<td>Sadeghian et al.</td>
<td>Children age</td>
<td>FAP (Rome III)</td>
<td>Dose 0.25-0.5 mg/kg/day (maximum 12 mg/day children 2-6 y, maximum 16 mg/day children 7-14 y)</td>
<td>Self-reported scales: Frequency and intensity of abdominal pain</td>
<td>Improved/resolved pain frequency ($P = .002$) with RR 2.43 (95% CI, 1.17-5.04), Decreased pain intensity ($P = .001$) with RR 3.03 (95% CI, 1.29-7.11)</td>
<td>Increased appetite 3%</td>
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<td>Madani et al.</td>
<td>Children age</td>
<td>Rome III-defined FGIDs</td>
<td>Mean initial dose 0.14 mg/kg/day</td>
<td>Graded responses</td>
<td>Complete improvement in FD 77% (26 of 34) in FAP 66% (36 of 55) in AM 72% (13 of 18) in IBS 100% (10 of 10) in CVS 75% (6 of 8)</td>
<td>Somnolence 12%</td>
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<tr>
<td>Rodriguez et al.</td>
<td>Children age</td>
<td>Dyspepsia organic cause or FD (ROME III) refractory to conventional treatment, given Cyp</td>
<td>Median dose 0.19 mg/kg/day (range 0.04-0.62 mg/kg/day)</td>
<td>Graded responses</td>
<td>Significant response 41%, resolved 14%, failed 45%</td>
<td>Side effects 30%</td>
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<tr>
<td>Worawattanakul et al.</td>
<td>Children age</td>
<td>AM treated with medication</td>
<td>Dose 0.25-0.5 mg/kg/day</td>
<td>Graded responses: excellent, fair, poor</td>
<td>12 patients treated with Cyp: Excellent 33% Fair 50%, Poor 17%</td>
<td>Drowsiness 8%</td>
</tr>
<tr>
<td>Pfau et al.</td>
<td>Children age</td>
<td>Undiagnosed recurrent vomiting</td>
<td>4 of 19 patients with AM received Cyp</td>
<td>Graded responses: complete resolution, some response, or no response</td>
<td>Complete resolution 75% (3 of 4 patients)</td>
<td>No report</td>
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Efficacy of Cyproheptadine in Children with Functional Gastrointestinal Disorders

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<tr>
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<tr>
<td>Li et al. 14</td>
<td>Children younger than age 18 y (N = 214) Chart review and structured interviews</td>
<td>CVS by Consensus Diagnostic Criteria 61 At least three discrete episodes of vomiting Diagnosed with other diseases</td>
<td>Unknown dose and duration of treatment</td>
<td>Percent reduction in numbers of emesis or episodes</td>
<td>&gt;50% reduction in vomiting in 46% in migraine-associated CVS (N = 32), 0% in nonmigraine-associated CVS (N = 5)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Boles et al. 15</td>
<td>Patients (N = 62 total, 58 children) Clinical interview using questionnaire</td>
<td>CVS by Fleisher 62 and LF 61 Met 2 or more of the 9 criteria: global cognitive delay, seizure disorder, myopathy, growth retardation, family history suspicious for maternal inheritance Malrotation, intracerebral tumor, fetal alcohol syndrome, abnormal karyotype, metabolic disorder</td>
<td>Unknown dose and duration of treatment</td>
<td>Report per parent</td>
<td>Beneficial in 8 of 14 patients (57%)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Andersen et al. 16</td>
<td>Children age 2-16 y (N = 27) Retrospective review</td>
<td>CVS by Fleisher 62 and LF 61 Organic causes</td>
<td>Dose 0.1-0.3 mg/kg/day</td>
<td>Graded response</td>
<td>66% (4 of 6) complete response 17% (1 of 6) partial response</td>
<td>Sedative effects and weight gain in some patients; no other significant side effects</td>
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Abbreviations: AM, abdominal migraine; CI, confidence interval; CIG, complete-improvement group; Cyp, cyproheptadine; CVS, cyclic vomiting syndrome; ECG, electrocardiogram; FAP, functional abdominal pain; FD, functional dyspepsia; FGID, functional gastrointestinal disorders; IRB, irritable bowel syndrome; mo, month; NIG, no-improvement group; PIG, partial-improvement group; RLQ, right lower quadrant; RR, relative risk; RUQ, right upper quadrant; wk, week; y, year.

ADVERSE EFFECTS OF CYPROHEPTADINE

The antihistaminergic properties of cyproheptadine may cause drowsiness and disturbance of coordination, its antiserotonergic effect may explain increased appetite and weight gain, and its anticholinergic properties may result in constipation.

Table 1 (continued)

Dosage of Cyproheptadine

The recommended dose for children depends on the age of the patient. The recommended dosages are 2 mg to 3 mg twice daily in children age 2 to 6 years, 4 mg to 3 times daily in children age 7 to 14 years, and 4 mg to 3 times daily in patients age 15 years and older.

DOSAGE OF CYPROHEPTADINE

The recommended dose for children younger than age 5 years. However, there is no role of cyproheptadine in acute attack of CVS.
cause anticholinergic syndrome with either central or peripheral nervous system symptoms. Symptoms of peripheral anticholinergic syndrome include tachycardia, mydriasis, facial flushing, hyperpyrexia, urinary retention, dry mucous membranes, depressed or absent bowel sounds, and decreased sweating. Central nervous system manifestations in children include agitation, hallucination, ataxia, atethosis, and seizures. Details of all potential adverse effects are beyond the scope of this article.

CONCLUSION
Cyproheptadine has been shown to be a potentially effective and safe treatment option in children with FGIDs. It can be prescribed in primary care and gastroenterology practices before resorting to expensive and invasive investigations in children if they meet the clinical criteria for FGIDs. Well-designed multicenter trials with long-term follow-up are needed to further investigate its efficacy in these children.

REFERENCES


