Safety and Efficacy of Cyproheptadine for Treating Dyspeptic Symptoms in Children

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Objective To present our experience using cyproheptadine, a potent serotonin antagonist used to stimulate appetite, to treat dyspeptic symptoms in children.

Study design This was a retrospective open-label study conducted to evaluate the safety and efficacy of cyproheptadine in children with refractory upper gastrointestinal symptoms (eg, nausea, early satiety, vomiting, retching after fundoplication, abdominal pain). Response was graded as resolution if symptoms resolved and medication was discontinued, as significant improvement if symptoms resolved with no further interventions, and as failure with any other outcome.

Results A total of 80 children (65% females) aged <12 years (mean age, 10 years) were included. Response to therapy was reported in 55% of patients. Multivariate analysis revealed better response in children and females ($P = .04$ and .03, respectively). No associations were found between response to therapy response and gastric emptying, antroduodenal manometry, functional dyspepsia, vomiting, and use of cyproheptadine as first therapy. Early vomiting (occurring within 1 hour after starting a meal) responded better than late vomiting ($P = .03$), and patients with retching after undergoing Nissen fundoplication had an 86% response rate. Twenty-four patients (30%) complained of side effects, all mild, including somnolence (16%), irritability and behavioral changes (6%), increased appetite and weight gain (5%), and abdominal pain (2.5%), but only 2 of these patients discontinued therapy. Multivariate analysis demonstrated an association between side effects and lack of response to therapy ($P = .04$), but no associations with age and sex.

Conclusion Cyproheptadine is safe and effective for treating dyspeptic symptoms in children, particularly in young children and those with early vomiting and retching after fundoplication. *(J Pediatr 2013;163:261-7)*.

The main function of the gastric fundus is to accommodate ingested food without a significant increase in intragastric pressure. This is followed by trituration and further mixing with acid in the antrum, then emptying into the small bowel for further digestion and absorption. Some upper gastrointestinal symptoms, dyspepsia in particular, along with early satiety, postprandial fullness, nausea, and pain, have been associated with impaired gastric accommodation and/or increased gastric sensitivity to distention.[1-5] Most therapies evaluated to improve gastric accommodation and/or sensation to distention have either proven ineffective (eg, baclofen[6]) or have yielded contradictory results (eg, ondansetron[7-10]).

There is also evidence that fundic contraction is induced by stimulation of 5-hydroxytryptamine (5-HT; serotonin) 2A and 2B receptors located in the gastric fundus of rats,[11] guinea pigs,[12] and chickens,[13] as well as in the antrum in dogs,[14] and that fundic relaxation occurs when these receptors are blocked. Given that cyproheptadine, a medication initially developed as an antiallergic drug, is a well-known antagonist of serotonin, histamine H1, and muscarinic receptors, it is possible that its administration may improve gastric accommodation. Even though cyproheptadine is a safe drug that has been used to increase appetite,[15,16] there are no clinical reports of its use to improve gastric accomodation and/or gastric sensation to distention or to treat dyspeptic symptoms, although it is reportedly effective in managing functional abdominal pain in children.[17]

The aims of the present study were to evaluate the safety profile of and response to cyproheptadine in children with dyspeptic symptoms, and to identify factors associated with a positive response and the development of side effects.

Methods

This retrospective, open-label study evaluated the efficacy and safety profile of cyproheptadine for treating dyspeptic symptoms in children. The study design was approved by our center's Institutional Review Board.

5-HT	5-hydroxytryptamine
ADM	Antroduodenal manometry
FD	Functional dyspepsia
GES	Gastric emptying study

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Children referred to the Center for Gastrointestinal Functional and Motility Disorders between January 2008 and June 2011 for evaluation and management of upper gastrointestinal dyspeptic symptoms refractory to conventional therapy (ie, dietary changes and histamine H2 blockers and/or proton pump inhibitors) and who were given cyproheptadine to ameliorate those symptoms were identified. Patients who received cyproheptadine solely as an appetite stimulant were excluded from this analysis.

Two types of patients were included in the study, those with an underlying organic disease that could explain the dyspepsia and those in whom no organic cause explained their symptoms (idiopathic). In the latter group, functional dyspepsia (FD) was defined by the Rome III criteria,[18,19] requiring all of the following symptoms occurring at least once per week for at least 2 months before diagnosis: (1) persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus); (2) pain not relieved by defecation or associated with a change in stool frequency or stool form; and (3) no evidence of inflammatory, anatomic, metabolic, or neoplastic processes that could explain the symptoms.

Dyspeptic symptoms were defined as nausea, early satiety, abdominal pain, retching after fundoplication, and vomiting. In all patients, upper gastrointestinal endoscopy with biopsy analysis and/or imaging studies were obtained to rule out anatomic or mucosal diseases as causes of symptoms. All patients were followed by the same physicians at the center.

The following information was obtained for each patient: age (as both a continuous variable and a categorical variable, classified as children aged <12 years and adolescents aged >12 years), duration of symptoms, cyproheptadine dose, duration of therapy, gastric emptying study (GES) by scintigraphy as percentage of emptying at 60 minutes (defined as abnormal when <40% of the standard at our center), primary diagnosis classified as idiopathic or nonidiopathic, presence of vomiting, antroduodenal manometry (ADM; with an abnormal antrum identified by evidence of antral hypomotility, defined as no increase in motility index after a meal and erythromycin challenge), presence of side effects, and use of other medications. Symptoms studied included nausea; early satiety; vomiting, classified as early (within the first hour after starting a meal) or late (more than 1 hour from starting a meal) according to patient report; retching after fundoplication; and abdominal pain.

Response was assessed at the clinical visits after the initiation of cyproheptadine therapy and was graded as follows: (1) failure, no improvement in symptoms with therapy, including those who improved but in whom the medication was stopped owing to side effects and those exhibiting some improvement but still requiring further therapy; (2) significant, symptoms improved and no other therapy was required; and (3) resolution, symptoms resolved and no other therapy was required. Side effects were classified as mild when self-limited (ie, responded to dosage reduction or subsided with continuing use of cyproheptadine) and refractory when cyproheptadine had to be stopped.

For the statistical analyses, continuous variables were expressed as mean ± SD or median (range). Proportions were compared using the χ^2 or Fisher exact test. Comparisons of continuous variables were done using either a parametric test (*t* test) or a nonparametric test (Wilcoxon signed-rank test). Correlations were calculated using Pearson or Spearman correlation functions. Multivariate logistic regression models were used to establish the factors associated with response and the presence of side effects; the enter variable method was used, with a probability for stepwise entry of 0.05, removal of 0.10, classification cutoff of 0.5, and a maximum of 20 iterations.

Results

The study group comprised 80 patients, including 52 females (65%), with a median age of 9.8 years (range, 0.75-20 years). There were 48 children (60%) aged <12 years (62%) and 32 adolescents (40%). The patients' demographic and clinical characteristics are summarized in Table I. The median patient weight at the start of cyproheptadine therapy was 30.9 kg (range, 7-145 kg). The median follow up was 24 months (range, 4-80 months).

The frequency of presenting symptoms was as follows: nausea in 24 patients (30%), early satiety in 7 (9%), vomiting in 27 (34%) (early in 9 [11%] and late in 18 [23%]), retching in 14 (17%), and abdominal pain in 8 (10%). Forty-four patients met the criteria for FD; the diagnosis was gastroesophageal reflux in 14, retching after fundoplication in 14, associated with mitochondrial dysfunction in 4, associated with diabetes mellitus in 2, and associated with surgical correction for malrotation in 2.

GES was performed in 52 patients. Median emptying of solids at 60 minutes was 43% (range, 0-99%). Gastric emptying was normal in 29 of the 52 patients (56%). ADM was performed in 23 patients. Results were normal in 8 patients (35%), but showed evidence of antral hypomotility in 15 (65%).

Table I. Demographic and clinical characteristics

Characteristic	All patients (n = 80)	Responders (n = 44)	Nonresponders (n = 36)	*P* value
Age, years, median (range)	9.8 (0.75-20)	8.1 (0.75-20)	12.8 (1.6-20)	.01
Sex, n (%)	52 (65%) F	32 (73%) F	20 (56%) F	.11
Weight, kg, median (range)	30.9 (7-145)	25.1 (7-106)	38.8 (9.6-145)	.01
GES, median (range)	43 (0-99)	51 (0-89)	34 (8-99)	.42
Dose, mg/kg, median (range)	0.19 (0.04-0.6)	0.22 (0.04-0.6)	0.17 (0.04-0.6)	.17
Duration of treatment, weeks, median (range)	20 (2-222)	23.5 (4-222)	12 (2-86)	<.01