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Edited by WFB Safety and efficacy of cyproheptadine for treating dyspeptic symptoms in children

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Abstract

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

Study design—Retrospective open label study evaluating the safety and efficacy of cyproheptadine in children with refractory upper gastrointestinal symptoms (nausea, early satiety, vomiting, retching post-fundoplication and abdominal pain). Response was graded as resolution if symptoms resolved and medication was discontinued, significant improvement if symptoms resolved with no further interventions, and anything else as failure.

Results—A total of 80 children were included (mean age 10 years and 65% were female). Response to therapy was reported in 55% of patients. Multivariate analysis showed children and female sex respond better ($p=0.04$ and 0.03 , respectively). We found no association of therapy response and gastric emptying, antroduodenal manometry, functional dyspepsia, vomiting and use of cyproheptadine as first therapy. Vomiting within an hour after starting meals responded better than late vomiting ($p=0.03$) and patients with retching after a Nissen fundoplication had an 86% response rate. A total of 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 discontinued therapy. Multivariate analysis demonstrated an association between presence of side effects and lack of response to therapy ($p=0.04$) and no association with age and sex.

Conclusions—Cyproheptadine is safe and effective in the treatment of dyspeptic symptoms in children, particularly in young children and those with early vomiting and retching post-fundoplication.

The main function of the gastric fundus is to accommodate the ingested food without a significant increase in intra-gastric pressure. This is followed by trituration and further mixing with acid in the antrum to then emptying into the small bowel for further digestion

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and absorption. Some upper gastrointestinal symptoms, dyspepsia in particular, along with early satiety, postprandial fullness, nausea and pain have all 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 are either ineffective (baclofen(6)) or have shown contradictory results (ondansetron (7-10)).

There is also evidence that fundic contraction is induced by stimulation of 5-HT_{2A} and 5-HT_{2B} receptors located on the gastric fundus of rats(11), guinea pigs(12), and chickens(13) as well as in the antrum in dogs(14); fundic relaxation occurs when these are blocked. Given that cyproheptadine, a medication initially developed as an antiallergic drug, is a well-known antagonist of serotonin (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}), histamine (H-1) and muscarinic receptors, it is possible that its administration may improve gastric accommodation. Even though it is a safe drug that has been used to increase appetite (15, 16), there are no clinical reports of its use to improve gastric accommodation and/or gastric sensation to distention and to treat dyspeptic symptoms, although it has been reported to be effective in the management of functional abdominal pain in children(17).

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

METHODS

This is a retrospective, open label study to evaluate the efficacy and safety profile of cyproheptadine for the treatment of dyspeptic symptoms in children. IRB approval was obtained to conduct this review.

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

Two types of patients are included. Those with an underlying organic disease that could explain the dyspepsia, and those patients in whom no organic cause was found to explain their symptoms (idiopathic). In the latter group functional dyspepsia was defined by the Rome III criteria(18, 19): must include all of the following 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) not relieved by defecation or associated with the onset of a change in stool frequency or stool form; and (3) no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms.

Dyspeptic symptoms were defined as nausea, early satiety, abdominal pain, retching post-fundoplication and vomiting. Upper gastrointestinal endoscopy with biopsies and/or imaging studies were obtained to rule out anatomical and mucosal disease as causes of their symptoms in all patients. All patients were followed by the same physicians at the Center.

The following information was obtained: age (both as continuous variable as well as categorical variable classified as children <12 years old and adolescents when >12 years old), symptom duration in months, dose of cyproheptadine in mg/kg, duration of therapy in weeks, gastric emptying study (GES) by scintigraphy as percentage of emptying at 60 minutes (defined as abnormal when <40% by standards at our Institution), primary diagnosis classified as idiopathic or non-idiopathic, presence of vomiting, antroduodenal manometry

(ADM) (considered to have an abnormal antrum when there was evidence of antral hypomotility defined as lack of increase in motility index after meal and challenge with erythromycin), presence of side effects, and other medications.

Symptoms were divided in the following categories: nausea, early satiety, vomiting classified as early (within first hour of starting a meal) or late vomiting (>1h from starting meal) according to patient description to when most of the vomiting occurs, retching post-fundoplication, and abdominal pain.

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

Statistical analyses

Continuous variables are expressed as mean $\pm$ SD or medians (range) as indicated. Proportions were compared using χ^2 or Fischer exact tests. Comparisons of continuous variables were done either with parametric tests (t-test) or non-parametric tests (Wilcoxon signed ranks test) as indicated. Correlations were performed using Pearson or Spearman correlations as indicated. Multivariate logistic regression models were used to establish the factors associated with response and presence of side effects; enter variable method was used with a probability for stepwise entry of 0.05 and removal of 0.10 and classification cutoff of 0.5 and a maximum of 20 iterations.

RESULTS

A total of 80 patients were included, and their clinical characteristics are shown in Table I. The median follow up was 24 (range 4-80 months), 52 (65%) were female and the median age was 9.8 (range 0.75-20 years) with 48 (60%) children (<12 years of age) and 32 (40%) adolescents. Median weight at the start of the cyproheptadine was 30.9 (range 7-145 kg).

Frequency of presenting symptom was as follows: nausea in 24 (30%) patients, early satiety in 7 (9%), vomiting in 27 (34%) (early in 9 or 11%, and late in 18 or 23%), retching in 14 (17%) and abdominal pain in 8 (10%). A total of 44 subjects met criteria for functional dyspepsia. The diagnosis was gastroesophageal reflux in 14, retching after fundoplication in 14, associated to mitochondrial dysfunction in 4, to diabetes mellitus in 2, and after surgical correction for malrotation in 2.

GES was performed in 52 subjects, with a median emptying at 60 minutes of 43% for solids with a range of 0-99. Gastric emptying was reported as normal in 29 (56%) of the studied patients. ADM was performed in 23 patients; it was interpreted as normal in 8 (35%) and showed evidence of antral hypomotility in 15 (65%).

Response to cyproheptadine

Median dose of cyproheptadine was 6mg per day, equivalent to 0.19mg/kg/day with a range of 0.04-0.62 mg/kg/d. Median duration of therapy was 20 weeks with a range of 2-222 weeks. Only 1 patient was treated for 2 weeks (stopped due to side effects) and the rest for > 4 weeks. For those patients who failed to respond at initial dose and have minimal or no side effects we increased the dose before considering it a failure.

A significant response was reported in 33 (41%) patients, and resolution of symptoms in 11 patients (14%). A total of 36 patients (45%) failed therapy. This demonstrates an overall improvement in 44 (55%) patients. The response according to presenting symptom is shown in the Figure. Early vomiting responded better to treatment with cyproheptadine than late vomiting ($p=0.03$), and we noticed a high frequency of responders (12/14 or 86%) among those complaining of retching after a Nissen fundoplication.

Cyproheptadine was used before prokinetic agents in 54 (67%) patients and after failed therapy with prokinetics in 26 (33%). The prokinetics used included erythromycin in 20 patients, domperidone in 4, metoclopramide in 1 and cisapride in 1. Other medications used before cyproheptadine included: asthma medications in 3 patients, antiepileptic drugs in 5, growth hormone in 1 and methotrexate in 1.

From those 36 patients who failed cyproheptadine, further therapies were recommended and subsequently provided to 11 patients with delayed gastric emptying by scintigraphy as follows: gastrojejunostomy tube placement in 5, endoscopic intrapyloric botulinum toxin injection in 3, jejunostomy tube placement in 2 and gastrostomy tube in 1, all resulting in significant improvement and/or resolution of symptoms.

Factors associated to response—Univariate analysis of categorical factors associated to overall response is shown in Table II. Children < 12 years responded better than adolescents ($p=0.03$). We found a difference on the median weight between responders and non-responders with a lower weight in those that responded ($p=0.01$). We found no association of response to cyproheptadine and GES results, ADM results, presence of vomiting, and using cyproheptadine as first therapy or after failed prokinetic therapy, and we observed a tendency towards an association between lack of response to therapy and functional dyspepsia ($p=0.06$). More females responded to therapy (62% females vs. 43% males), although this was not statistically significant by Univariate analysis. However, once controlling for other variables in the multivariate analysis, females responded better than males (see below). Also there was no difference in the median cyproheptadine dose among responders and non-responders ($p=0.16$). We found a difference on the median duration of therapy between responders and non-responders ($p<0.01$), probably explained because those responding were more likely to continue on the medication as those failing to respond.

Multivariate analysis showed that children <12 years old and females responded better to cyproheptadine ($p=0.04$ and 0.03 , respectively). We found no effect of dose (mg/kg), duration of therapy in weeks, presence of vomiting and result of gastric emptying study on the overall response (Table III).

Side effects of cyproheptadine

A total of 24 (30%) patients complained of side effects while taking cyproheptadine. Side effects were mild in majority of patients and reported in decreasing frequency as follows: somnolence in 13/80 (16%), irritability and behavioral changes in 5/80 (6%), increased appetite and weight gain in 4 (5%) and abdominal pain in 2 (2.5%). First strategy to manage side effects was to wait for 2 weeks in those who can tolerate the symptoms and if not improved or not tolerated then to proceed with 50% dose reduction. A total of 4 patients (3 with somnolence and 1 with increased appetite) responded to dose reduction and they continued to respond favorably, 18 continued the medication at same dose and reported eventual resolution of the side effects and only 2 patients (1 with abdominal pain and other with somnolence) stopped the medication due to side effects (refractory and included in analysis as non-responders).

Factors associated with side effects—Univariate analysis of factors potentially associated to side effects is shown in Table IV. We found no association between presence of side effects and age, sex, GES results, ADM results and diagnosis of functional dyspepsia. We did observe a significantly higher weight on those reporting no side effects compared with those with side effects (25 vs. 41kg for $p=0.03$). We found a tendency towards a significant difference in the median dose (mg/kg) of cyproheptadine between those with side effects and those with no side effects (0.16 range 0.04-0.38 mg/kg vs. 0.21 range 0.04-0.62 mg/kg, respectively, $p=0.06$) and no correlation between the dose (in mg/kg) and duration of therapy in weeks (Pearson correlation 0.162, $p=0.151$). We found a difference on the median duration of therapy between those reporting side effects and those with no side effects (10 range 4-83 weeks vs. 24 range 2-222 weeks, respectively, $p=0.01$). Furthermore, we found an association between response to cyproheptadine and absence of side effects, with responders reporting less side effects than non-responders (18 vs. 42%, $p=0.02$).

Multivariate analysis demonstrated an association of side effects with lack of response to therapy and only a tendency towards an association with shorter duration of therapy ($p=0.04$ and 0.08 , respectively) and no effect of cyproheptadine dose used. We found no effect of age and sex on side effects, as it was seen in response to cyproheptadine (Table V).

DISCUSSION

We report of the safety and efficacy of cyproheptadine in treating children with functional dyspepsia and other upper gastrointestinal symptoms other than abdominal pain(17). We have shown that cyproheptadine was effective in the treatment of children and adolescents with dyspeptic symptoms. These patients are refractory to conventional therapy, and cyproheptadine, a safe and widely used drug to increase appetite, can be considered as a therapy before more invasive testing or other higher risk therapies.

The mechanism by which cyproheptadine improves upper gastrointestinal symptoms is unknown. Given that the anti-serotonergic effects of cyproheptadine, including its well-known and widely reported effectiveness for treating serotonin syndrome(20-22), we believe the effect on dyspeptic symptoms may be resulting mostly from increasing gastric accommodation. Our hypothesis is that such effect may be related to its high affinity to block the 5-HT_{2A} and/or 5-HT_{2B} receptors. There is evidence that the stimulation of 5-HT_{2A} and 5-HT_{2B} receptors located on gastric fundus on rats(11), guinea pigs(12) and chicken(13) induces fundic contractions, and fundic relaxation is observed when such receptors are blocked. Also, 5HT₂ stimulation in dogs induces LES contraction that is inhibited by cyproheptadine(23). This is also supported by the knowledge of other 5HT inhibitors currently used to treat dyspeptic symptoms, like the 5HT₃ antagonists (with no 5HT₄ agonist effect) ondansetron in treating emesis in acute gastroenteritis(24) and post-infectious dyspeptic symptoms(25) and granisetron in postoperative(26) and chemotherapy-induced nausea and vomiting(27).

The other possibility is that the improvement on dyspeptic symptoms in our study after using cyproheptadine is associated to an improvement on the gastric hypersensitivity to distention that has been reported in patients with such symptoms, including functional abdominal pain in children(17). This effect may also be mediated by anti-serotonergic effect in the central nervous system. It has been hypothesized that the appetite stimulation effect of the drug is mediated by blocking 5HT₂ receptors in the brain, and recently it has been reported to increase leptin levels(28, 29).

We found cyproheptadine is particularly useful in two situations: early vomiting and retching after a Nissen fundoplication. In both cases, the positive effect may be the result of the potential effect of cyproheptadine in improving gastric accommodation and/or gastric hypersensitivity to distention that may be affected in these situations. There is evidence of decreased gastric accommodation after fundoplication(30-32) and in patients with functional dyspepsia presenting with early satiety(33). Others have also reported a significant correlation between increased gastric sensitivity to distention and upper gastrointestinal symptoms in patients with functional dyspepsia(34). In the only report of adolescent females with dyspeptic symptoms, it was shown using a barostat there was evidence of a lower threshold for discomfort with gastric distention and also lower accommodation(35).

We found that female sex and younger age were associated to a response to cyproheptadine. The positive response noticed on younger patients may be the result of a higher weight on the non-responders; however we found no significant difference in dose per weight given between responders and non-responders. We found no published information in regards to response to cyproheptadine and sex, We observed that 34/44 patients with FD were female in our study, The higher response observed in females in our study may be confounded by the fact that most studies report a higher incidence of FD in females compared to males(36, 37) and the overlap with other conditions like idiopathic gastroparesis(38) that was not evaluated in all patients. Although FD seems to differ between male and female in regards to pattern of symptoms, pain perception or modulation, and anti-nociceptive mechanisms(39), response to therapy has not been systematically evaluated. Furthermore, the placebo response in FD seems to be the same between males and females(40, 41).

The safety profile of the drug was acceptable. Despite our finding of 30% reporting side effects, all were mild and self-limited when used in therapeutic doses. Only 2 patients discontinued the drug because of side effects. This is consistent with previous publications. After long term use (9 months) to stimulate appetite, the side effects reported were mild and the effects were reported as sustained in patient with cystic fibrosis(42).

As we have noticed in our study, cyproheptadine has also been associated to self-limited behavioral changes, including irritability and aggressive behavior(43). A rare side effect reported is ACTH suppression with subsequent adrenal insufficiency(44). Although the exact dose to stimulate appetite is not known, dose recommended for appetite stimulation with cyproheptadine ranges from 0.25-0.4mg/kg/d(45). In our study, the highest dose was 0.62mg/kg/d, which is very low compared with the doses mentioned above associated with significant side effects. We found an association between presence of side effects and lack of response to therapy and a tendency towards an association with shorter duration of therapy, likely due to the fact that those with side effects would stop the medication and those improving would be more likely to stop the medication earlier than those not experiencing side effects, although only 2 patients stopped the medication due to side effects, 4 other responded to dose reduction and the rest were able to tolerate those until they eventually disappeared. Most of the severe acute side effects reported in the literature occur after acute overdose and are anticholinergic symptoms, including psychosis, agitation and hallucinations(46-48). In a large study in Hong Kong, 83% of patients with intentional cyproheptadine overdose reported mild to no sedative effects, 17% reported symptoms of delirium at very high doses of 188mg compared with 49mg on those asymptomatic, with most of those presenting symptoms in the first 6 hours after ingestion(49). Another study evaluating accidental overdose reported no life threatening events with doses ranging from 0.3-6.16mg/kg, but they reported a large frequency of side effects, mostly 6-12h after the ingestion and recommended caution and careful monitoring when prescribed(50).

This study has important limitations, with its retrospective and open label nature being the most significant, so placebo responses cannot be excluded. However the fact that all patients had failed multiple initial therapies, including acid blockade and in many cases prokinetics, makes a placebo effect less likely. The fact that serotonin inhibitors have been shown to be effective in other studies makes the effect of cyproheptadine more plausible. The availability and good safety profile of the drug make it an attractive therapeutic option, so larger and prospective studies are needed to evaluate the specific role of cyproheptadine in upper gastrointestinal symptoms, functional dyspepsia and on gastric accommodation and gastric sensation to distention.

In conclusion, we have shown that cyproheptadine is useful in the treatment of children with functional dyspepsia and other upper gastrointestinal symptoms, including retching after fundoplication.

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Figure 1.
Response to cyproheptadine according to presenting symptom.

Table 1

Demographics and clinical characteristics

	All patients (n=80)	Responders (n=44)	Non-responders (n=36)	P value
Age (y)	9.8 (0.75-20)	8.1 (0.75-20)	12.8 (1.6-20)	0.01
Sex	52 (65%) F	12 (27%) M	16 (44%) M	0.11
Weight (kg)	30.9 (7-145)	25.1 (7-106)	38.8 (9.6-145)	0.01
GES	43 (0-99)	51 (0-89)	34 (8-99)	0.42
Dose (mg/kg)	0.19 (0.04-0.6)	0.22 (0.04-0.6)	0.17 (0.04-0.6)	0.17
Treatment duration	20 (2-222)	23.5 (4-222)	12 (2-86)	<0.01

Values expressed as median (range). SE: side effects, Y: years, GES: percentage of gastric emptying at 1 hour, Treatment duration in weeks

Table 2

Univariate analysis for factors associated to response to cyproheptadine.

Variable	Responders	Non-responders	P value
Age			0.03
Children	31/48 (65%)	17/48 (35%)	
Adolescents	13/32 (41%)	19/32 (59%)	
Sex			0.11
Male	12/28 (43%)	16/28 (57%)	
Female	32/52 (62%)	20/52 (38%)	
Gastric emptying study			0.22
Normal	20/29 (69%)	9/29 (31%)	
Abnormal	12/23 (52%)	11/23 (48%)	
Antroduodenal manometry			0.31
Normal	6/8 (75%)	2/8 (25%)	
Abnormal	8/15 (53%)	7/15 (47%)	
Functional dyspepsia			0.06
Yes	20/44 (45%)	24/44 (55%)	
No	24/36 (67%)	12/36 (33%)	
Vomiting			0.18
Yes	12/27 (44%)	15/27 (56%)	
No	32/53 (60%)	21/53 (40%)	
Cyproheptadine			0.11
First therapy	33/54 (61%)	21/54 (39%)	
After failed prokinetic therapy	11/26 (42%)	15/26 (58%)	

Table 3

Multivariate analysis for factors associated to response to cyproheptadine.

		95% C.I. for OR		
	P value	OR	Lower	Upper
Children <12 years old	0.04	5.17	1.01	26.27
Female	0.03	4.71	1.08	20.60
Dose (mg/kg)	0.70	0.30	0.00	127.41
Duration of therapy (weeks)	0.72	1.00	0.98	1.02
Absence of vomiting	0.45	1.72	0.41	7.22
GES (% emptying at 1 hour)	0.87	1.00	0.97	1.02

All variables included in the model are shown.

Table 4

Univariate analysis of factors associated with side effects.

Variable	Side effects	No side effects	P value
Age			0.36
Children	13/48 (27%)	35/48 (73%)	
Adolescents	11/32 (34%)	21/32 (66%)	
Sex			0.98
Male	8/28 (29%)	20/28 (71%)	
Female	16/52 (30%)	36/52 (70%)	
Gastric emptying study			0.25
Normal	6/29 (21%)	23/29 (79%)	
Abnormal	9/23 (39%)	14/23 (61%)	
Antroduodenal manometry			0.65
Normal	1/8 (13%)	7/8 (87%)	
Abnormal	3/15 (20%)	12/15 (80%)	
Functional Dyspepsia			0.06
Yes	17/44 (39%)	27/44 (61%)	
No	7/36 (26%)	29/36 (74%)	
Vomiting			0.36
Yes	7/27 (26%)	20/27 (74%)	
No	36/53 (68%)	17/53 (32%)	
Cyproheptadine			0.80
First therapy	16/54 (30%)	38/54 (70%)	
After failed prokinetic therapy	8/26 (31%)	18/26 (69%)	

Table 5

Multivariate analysis for factors associated with side effects.

		95% C.I. for OR		
	P value	OR	Lower	Upper
Children <12 years old	0.32	1.86	0.54	6.42
Female	0.71	1.25	0.38	4.09
Duration of therapy in weeks	0.08	0.98	0.96	1.03
Dose in mg/kg	0.10	0.07	0.00	2.75
Lack of response to therapy	0.04	3.20	1.02	10.03

All variables included in the model are shown.