

Empiric treatment of children with gastroesophageal reflux-like symptoms: Effect of proton pump inhibitors

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Gastroesophageal reflux disease is an important cause of morbidity in childhood. Although various diagnostic methods are available, short course of empiric treatment with a proton pump inhibitor is widely used in adults as a diagnostic test. Data about empiric treatment is scarce in children. The aim of this study is to evaluate the effectiveness of empiric treatment of reflux-like symptoms in children.

Pediatric gastroenterology outpatient files were searched and patients with a diagnosis of gastroesophageal reflux were found. Patient complaints, history and the treatments provided were recorded. Treatment naive patients older than 2 years of age with symptoms suggestive of gastroesophageal reflux were selected and included if they were given empiric treatment with a proton pump inhibitor.

Empiric treatment was found to be effective in 78% of patients. Treatment response tended to be better in children older than 5 years of age. Of the 22 non-responders 9 underwent endoscopy and pathological findings were discovered in 7 of them.

Treatment of children with gastroesophageal reflux symptoms with a proton pump inhibitor might significantly decrease the need for extensive evaluations. However it is important to investigate non-responders to empiric therapy, as it seems there might be high probability of pathological findings.

Key words: children, empiric treatment, gastroesophageal reflux, proton pump inhibitor.

Gastroesophageal reflux (GER) is very common in infancy and is usually self-limited and not associated with significant symptoms or disease conditions. Prevalence of gastroesophageal reflux disease (GERD) differs between 5-9% in infants with gastroesophageal reflux¹. However the prevalence of symptoms that can be attributed to gastroesophageal reflux is low after infancy². Parental reported heartburn frequency is 1.8% in children 3-9 years of age and 3.5% in adolescents between 10-17 years of age. Frequency and complications of GER increase in adulthood. Although the prevalence of adult GER symptoms is 10% for heartburn and 15.6% for regurgitation, the prevalence of erosive esophagitis in patients with GERD symptoms was 17%³. In children with epigastric

pain, prevalence of erosive esophagitis was found to be 19.9%⁴.

In adults, short term omeprazole, so-called one-week "omeprazole test" was shown to be useful and cost-effective method in diagnosing adult patients with GERD like symptoms⁵. Moreover in adults with erosive esophagitis, omeprazole test was demonstrated to be as sensitive as 24-hour pH monitorization⁶. Other studies have also shown that adult patients with non-erosive reflux disease might respond to 4 weeks of therapy with proton pump inhibitors (PPI)⁷. Empiric therapy of classical symptoms such as heartburn or regurgitation suggestive of GER without alarm symptoms for 2-4 weeks with a proton pump inhibitor might be a conservative method⁸.

In the international consensus of European and North American Societies of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN and NASPGHAN), expert opinion suggested that empiric proton pump inhibitor treatment is justified in older children and adolescents for up to 4 weeks as a diagnostic method⁹. Empiric treatment of reflux symptoms in children and adolescents have shown that it might be helpful to reduce symptoms in a considerable percentage of children^{10,11}. However there are few studies on this subject. The aim of this study is to evaluate the effectiveness of empiric treatment of reflux-like symptoms in children and adolescents, retrospectively.

Material and Methods

Pediatric gastroenterology outpatient files were searched between October 2013 to July 2014 by using ICD code K21.0 for GER. Search results were examined in order to detect the patient complaints, history and the treatments provided. Treatment naive patients older than 2 years of age with symptoms suggestive of GER such as heartburn and nausea were selected and included if they were given empiric treatment with a PPI with or without on demand alginate. Patients with alarm symptoms such as bloody vomiting, growth deficiency, weight loss, night time abdominal pain or patients who received any form of anti-reflux drug treatment before admission and patients with respiratory symptoms were excluded from the study⁹.

Treatment protocol

As a clinic protocol, patients eligible for empiric treatment were given, once-daily, PPI with or without alginate for 15 days (Gaviscon®). Lansoprazole was usually prescribed at a dose of 15 mg (below 15 kg of body weight), and 30 mg (above 15 mg body weight), taken 30 minutes before the breakfast. Patients were instructed to come back at the 15th day for symptomatic evaluation. If symptoms were decreased or completely resolved patient was considered to be responsive to the treatment. In this case treatment was continued for up to 2 months in order to prevent premature cessation of presumed GER(D) treatment. Alarm symptoms were explained to families and they were instructed to come back if symptoms appear during the treatment or after

cessation of the treatment. If symptoms did not disappear in 15 days or reappear during or after treatment further investigations such as esophago-gastro-duodenoscopy (EGD) with at least two biopsies from esophagus, antrum, corpus and duodenum, were performed. All families were instructed to come back or phone to the clinic 1 month after the discontinuation of treatment in order to report the condition of the child. Along with the medications, lifestyle changes such as dietary modifications, and going to sleep at least 2 to be hours after meal were explained to all patients.

Patient evaluation

From the patient files symptoms were evaluated at the 15th day, 2nd month, and after treatment cessation. If it is discovered that patients did not attend to controls they were inquired by telephone and the last condition of the child was asked. For this study, patients who had no symptoms during the clinical assessments or telephone inquiry were regarded as responders. Others were considered as non-responders.

Results

Through the computer search 151 suitable patients were found. Sixteen of them were eliminated because they were less than 2 years of age. Eleven patients were further excluded from the analysis because their follow-up time is shorter than 2 months. Seven patients were excluded because they did not receive PPI as an empiric treatment. Seventeen patients could not be reached by phone. Data of remaining 100 patients was used for final analysis.

Of the 100 patients, 78 of them were regarded as responders while remaining 22 patients were non-responders. There were 55 girls (55%) and 45 boys (45%) in the study group. Mean age of total patients was 9.4 ± 4.2 years. Follow-up time was 6.8 ± 2.1 months. There were no differences between follow-up times according to the gender. However mean age of girls were significantly higher than the boys (10.5 ± 4.4 vs. 8.2 ± 3.5 respectively, $p=0.007$).

Duration of complaints were 1 year or shorter in 81% of the children. Duration and type of complaints were not related to the treatment response. Likewise, gender did not show any effect on treatment response; 78.2% percent of females and 77.8% of males responded to the

empiric treatment. Age at the time of admission was not different between responders and non-responders. When we divided the group into two according to the age as younger and older than 5 years of age, children younger than 5 years of age tended to respond less to the empiric treatment with respect to children older than 5 years of age (percentage of non-responders were 34.8% [n=8/23] vs. 18.2% [n=14/77] respectively, $p=0.09$).

Of the 100 patients 94 received lansoprazol, 4 received esomeprazol, and 2 received pantoprazole. Of all patients 44 of them received only PPI (43 lansoprazol, 1 esomeprazol) and 56 of them received both PPI and alginate. Response rates to only PPI was 84.1% whereas it was 73.2% to PPI and alginate combination ($p=0.2$).

When we analyzed the gender distribution, duration of symptoms, and the treatment received who were not reached by the phone, they did not show any difference to the patients who were reached by the phone. Moreover, the duration of symptoms did not show any differences between these two.

Of the 22 non-responders, EGD was performed in 9, 24-hr pH monitorization was performed in 1. The results of EGD showed that 7 of the patients had either macroscopic or endoscopic esophagitis, 1 had both esophagitis and duodenal ulcer associated with *H. pylori* infection. In two patients esophagitis was associated with hiatal hernia and gastric heterotopia in distal esophagus. Remaining two patients did not show any pathological findings. Twenty-four hour pH monitorization was normal. Of the patients who had not undergone EGD or pH monitorization, 5 were screened for allergy. Of these, 3 had normal tests (one 3.5 year old patient had cow's milk allergy history during infancy). Two patients (3.7 years, and 12.8 years old) had increased IgE but specific IgE for cow's milk and egg proteins were negative. However parents refused to undergo further testing or challenge tests.

Discussion

In this study, we found that 78% of the children with GER-like symptoms have responded to a short course of empiric reflux treatment and this effect was sustained at the 6th month.

Also a significant fraction of investigated non-responder children have shown GERD findings.

Proton pump inhibitors are effective in treatment of erosive esophagitis or non-erosive reflux disease in children and adolescents^{11,12}. In an empiric treatment, Gold et al.¹⁰ have demonstrated that reflux related symptoms were decreased in 52 to 67% of children receiving esomeprazole either 20 or 40 mg/day for 8 weeks. Symptoms such as heartburn have already decreased on day 8 of treatment and physician global assessment scores were also decreased at the 2nd week of treatment. In children between 5-11 years of age with endoscopically proven GERD, pantoprazole (20 or 40 mg) significantly decreased symptoms with 8 weeks of treatment¹¹. Significant decreases in symptom scores were noted even at the 1st week of study. Both studies show that symptom improvement starts earlier in the course of PPI treatment and increases toward the 2nd month of study. Although optimal duration of empiric treatment is debatable, expert opinion from ESPGHAN and NASPGHAN consensus justifies up to 4 weeks of empiric treatment. In the light of these studies and opinions, we chose 2 weeks for the first assessment point and 2 months for the total treatment time in order to prevent premature cessation of therapy.

However empiric treatment is not without side effects; a recent review indicated that acid suppressive medications (namely, ranitidine, famotidine, omeprazole and lansoprazole) are related to necrotizing enterocolitis, sepsis, pneumonia in newborns, nosocomial infection and ventilator associated pneumonia in pediatric intensive care unit patients, and pneumonia and gastroenteritis in outpatients between 1 to 36 months of age^{13,14}. However in older children and adolescents, side effects are less prominent. In a recent Cochrane review on the outpatient pharmacological treatment of children with GER, PPIs were associated with headache, pharyngitis, and diarrhea¹⁵.

Expert opinion from ESPGHAN and NASPGHAN consensus states that there is no evidence to support an empiric trial of acid suppression as a diagnostic test for GERD in infants and young children⁹. In this study we included children older than 2 years of age who do not show the signs of GERD. We found that children

between 2-5 years of age tended to respond less to empiric treatment in comparison to children above 5 years of age. Risk of organic diseases might increase as the age of patient decreases so children below 5 years of age must be carefully evaluated before commencing empiric treatment and closely followed-up.

We did not find any predictive factor to indicate treatment response. In a pooled analysis of three studies involving 2458 adult patients, authors have found that response on first week might be a better predictive factor of heartburn resolution at 4 weeks⁸. Determination of predictive factors for pediatric patients' response to empiric treatment will be an important task for the future.

In a recent systematic review, empiric therapy as the initial treatment was found to be more cost-effective than other approaches¹⁶. Short course test and treatment approaches seem to be effective in adults. However there is no data about this approach in children. However, given the lower prevalence of erosive esophagitis in children compared to adults, test and treat strategy might also be cost-effective and acceptable in carefully selected children.

Lastly, we showed that a significant proportion of investigated non-responders had either endoscopic or histological findings of esophagitis, anatomical problems such as hiatal hernia, and duodenal ulcer. So patients undergoing empiric treatment must be closely followed-up and any treatment failures must be investigated promptly.

One of the important limitations of this study is that all the treatments were started on the basis of symptoms (and the absence of alarm symptoms). So it was impossible to know how many patients had functional diseases, GER or GERD at the start of the therapy. Even though 22 patients did not benefit from empiric treatment actual number of GERD patients might be higher than this number. Given the relapsing nature of esophagitis, follow-up time for empiric therapy responders must be long enough to detect any relapse of symptoms¹⁷. Moreover 17 patients could not be reached during follow-up. Although demographic characteristics of these patients did not differ from study patients in terms of age, gender or symptom duration, their latest condition might have an impact on the results

of our study. Also we did not formally check adherence to treatment. Lack of adherence in non-responsive group might be an important problem. Use of different drugs might have affected our results. However 94% of the study population had used lansoprazole as the single PPI which minimizes this complication. Moreover, no clear superiorities of PPIs over each other were shown in different trials¹⁸. We also did not ask for the side effects of the treatment. Because this was not a prospective study, asking the side effects some months after the treatment might have created a recall bias.

In conclusion, treatment of children and adolescents with GER-like symptoms with a PPI might significantly decrease the need for extensive evaluations. However, it is important to investigate non-responders to empiric therapy as it seems there might be high probability of pathological findings in evaluated patients. Responders might also be followed-up for signs of relapse. Further studies might be performed in order to detect which patients are likely to benefit from empiric PPI treatment and also about the optimal duration of this treatment.

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