Original article

Effect of proton pump inhibition on acid, weakly acid and weakly alkaline gastro-esophageal reflux in children

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Background: **The effect of proton pump inhibitors on the characteristics of gastroesophageal reflux (GER) in children and adolescents was evaluated.**

Methods: **Twenty-one children and adolescents with symptoms suggesting GER disease (GERD) underwent upper endoscopy and a 24-hour multichannel intraluminal impedance/pH (MII-pH) monitoring before and at the end of 2 months of therapy with proton pump inhibitors (PPIs).**

Results: **Fourteen (67%) patients reported clinically relevant symptom improvement after 2 months of PPIs intake. At the first endoscopy, 8 (38%) patients had macroscopic signs of reflux esophagitis; after two months of therapy, 6/8 (75%) patients had a complete mucosal recovery. There was a significant reduction in the total percentage of mean acid reflux time (from 13.1% to 3.8%), and the De Meester score dropped to normal (from 46.4 to 13.1). The mean number of acid refluxes decreased significantly from 48 to 15 per 24 hours, while inversely, the mean number of weakly acid refluxes increased significantly from 26 to 64 per 24 hours. PPI therapy did not affect the total number of reflux episodes, the number of liquid and mixed refluxes, the duration of esophageal bolus exposure and proximal extent of the reflux.**

Conclusions: **In children and adolescents with GERD, PPIs do not affect the total number of reflux episodes. PPIs only decrease the acidity of refluxate. Nevertheless, the majority of patients with typical reflux symptoms may report symptom improvement. Esophagitis can be healed after PPI treatment. The treatment of weakly acid and weakly alkaline reflux remains a challenge for physicians in the future.**

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Introduction

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus with or without regurgitation and vomiting occurring in every individual several times daily.[1] It usually consists of a brief, asymptomatic passage of gastric contents into the distal esophagus, particularly after meals. GER-disease (GERD) is a pathologic condition in which the reflux of gastric contents causes troublesome symptoms and/or complications.[1,2] According to the pH of the refluxed material, GER can be divided into acid (pH<4), weakly acid (pH between 4 and 7.0) and weakly alkaline (pH>7.0) reflux.[3]

Acid is traditionally considered as the major cause of GERD.[4] However, weakly acid and weakly alkaline reflux episodes have been related to respiratory symptoms, such as apnea, irregular breathing in infants, apparent life-threatening events, coughing and wheezing.[5-8] Weakly acid and weakly alkaline reflux episodes more often than acid reflux episodes cause symptoms in patients, which are refractory to acid-suppressive therapy.[9-13]

Acid-suppressive agents and life-style changes are considered standard methods in the treatment of acid-related GERD. Among these agents, proton pump inhibitors (PPIs) are preferred to histamine H_2-receptor antagonists due to their greater efficacy and lack of tachyphylaxis.[14] As a consequence, the question arises if PPIs decrease all reflux episodes or if these drugs only decrease acid reflux. Therefore, we investigated the effect of PPIs on acid, weakly acid, weakly alkaline, liquid and mixed reflux episodes, their proximal extent and the bolus exposure time before and at the end of 2 months of PPI therapy (while still on therapy) measured by 24-h multichannel intraluminal impedance/pH (MII/pH) monitoring in children and adolescents with GERD.

Methods

Patient demographics

The study design was approved by the National Medical Ethics Committee of the Republic of Slovenia and the local Ethical Committee of the UZ Brussels in Belgium. Written informed consent was obtained from each patient (or the patient's parent) prior to the enrolment into the study. A total of 21 children and adolescents were included (10 boys, 11 girls, median age of 10.5 years, range 3.5-18 years) with symptoms suggesting GERD who were referred to the Department of Gastroenterology, Hepatology and Nutrition of Children's Hospital at University Medical Centre in Ljubljana, Slovenia, and to the University Children's Hospital in Brussels, Belgium. Three children (14%) were otherwise healthy, while 18 (86%) had medical conditions that predisposed them to severe GERD: 7 children had cystic fibrosis, 6 cerebral palsy and 5 esophageal atresia.

In all patients, signs and symptoms of GERD were evaluated by taking a thorough history with a standardized questionnaire.[15] All patients underwent esophago-gastro-duodenoscopy, during which absence or presence and grade of reflux esophagitis were noted . After the endoscopy, a MII-pH catheter was inserted for a 24-hour monitoring.

All patients were treated with PPIs (omeprazole) with an approximate daily dose of 1 mg/kg per day, given once daily 30 minutes before breakfast, for a minimum of 2 months. Patients with other chronic conditions continued the therapy they were on. Drugs with an effect on gastrointestinal motility or other acid reducing medications such as alginates were not allowed.

After 2 months, still on PPI therapy, GER-symptoms were reassessed using the same questionnaire. The patients or their parents were asked to evaluate the degree of change induced by PPIs, offering five possibilities: worsened, remained unchanged, slightly better, significantly better (or minimal symptoms not affecting daily activity), symptom-free. The treatment was considered a success when none or only minimal symptoms persisted (the last two categories). All the other possibilities were considered as treatment failure.

Endoscopy

All patients underwent upper endoscopy under general anesthesia. Reflux esophagitis was graded using the Los Angeles classification (Table 1).[16] At least two biopsies were obtained from 3 to 5 cm above the gastroesophageal junction. Biopsies were assessed by a trained gastrointestinal pathologist; other (non-GERD) esophageal pathologies were excluded. To define the severity of esophagitis, endoscopic (macroscopic, not histological) grades were used since endoscopic view offers a better insight into the severity of the esophageal disease.[17] For obvious ethical reasons, follow-up endoscopy was performed (by the same endoscopist) only in those with reflux esophagitis.

MII-pH monitoring

Before the beginning of PPI-treatment and after 2 months of continuous therapy, all patients underwent a 24-hour MII-pH monitoring. A combined MII-pH catheter (pHTip Unisensor AG, Switzerland) was calibrated and inserted transnasally with the esophageal pH sensor positioned between the 2nd and 3rd vertebra above the diaphragm, and controlled by fluoroscopy.[18] An age (size and weight) adapted impedance catheter with 7 impedance rings (which establishes 6 impedance channels) was used. Patients or their parents were instructed to keep a diary to record symptoms, timing of meals and changes in body position. Data from the MII-pH electrodes were sampled at a frequency of 50 Hz and stored in a portable data recorder (MMS Ohmega, Enschede, The Netherlands). After a 24-hour period, the data were transferred and analyzed automatically using commercially available software (MMS Database). MII-pH monitoring allowed identification of the content of the refluxate (gas, liquid or mixed) and pH (acid, weakly acid, weakly alkaline). Acid reflux episodes were counted when the pH dropped below 4; when the pH was above 4 but less than 7.0, the reflux episode was regarded as weakly acid and when pH was over 7.0, the reflux episode was counted as weakly alkaline. Liquid reflux episodes were identified by a retrograde drop of impedance by 50% from the baseline in at least two consecutive distal channels. Gas reflux episodes showed an increase in impedance to more than 3000 ohms in two consecutive impedance sites (with one site having a value of over 7000 ohms). Mixed refluxes showed typical characteristics of both, liquid and gas reflux, one preceding or following another.

The pH sensor was allowed to measure total, upright and supine acid reflux times. The De Meester scores were calculated. The 24-hour bolus exposure time (i.e. the duration that the bolus is present at the

Table 1. Los Angeles classification of esophagitis

Grade A	One or more mucosal breaks not exceeding 5 mm in length and not bridging the tops of mucosal folds
Grade B	One or more mucosal breaks longer than 5 mm but not continuous between the tops of two mucosal folds
Grade C	One or more mucosal breaks bridging the tops of mucosal folds, involving less than 75% of the esophageal circumference
Grade D	Mucosal breaks involving at least 75% of the esophageal circumference

impedance channel) during the total recording time, in upright and supine position, and its proximal extent (% of refluxes that reached the highest electrode) was also calculated.

The association between reflux episodes and symptoms was evaluated by calculation of the symptom index (SI) and symptom association probability (SAP) for acid reflux (pH-monitoring) and bolus reflux (MII-monitoring) both before and during therapy. The absolute values and percentages in the results section are taken as mean values of the 21 children.

Statistical analysis

Each patient served as his own control since data (symptoms, endoscopy results, pH-impedance data) from before and while on therapy were compared. The effects of PPI therapy on symptoms were assessed by rating the degree of change by the patient or the parents, and the effects of therapy on mucosal healing were evaluated by comparison of severity of reflux esophagitis (endoscopic grade) before and during treatment. For paired parameters (results of pH-impedance monitoring) the Wilcoxon's signed-rank test was used. Significance was established by a P value <0.05.

Results

Symptom evaluation

At inclusion, all patients presented with symptoms suggestive of GERD (Table 2). After two months of PPI treatment, 9 (43%) patients became symptom-free and 5 (24%) had only minimal residual symptoms that did not interfere with daily activities. Symptoms improved only slightly in 4 (19%) patients, and remained unchanged in 3 (14%). Thus, failure of therapy occurred in 7 patients (33%). No patient reported that symptoms got worse.

Evaluation of reflux esophagitis

The endoscopic findings were normal in 13 (62%) children. In 8 (38%) patients, signs of reflux esophagitis were found: grade A in 3 (14%) patients, grade B in 2 (10%) and grade D in 3 (14%). In none of the patients, the endoscopic appearance suggested Barrett's esophagus. Histological findings confirmed the absence of Barrett and ruled out non-reflux causes of esophagitis. A follow-up endoscopy was performed after two months of PPI therapy in the 8 patients with endoscopic esophagitis. Complete remission occurred in 6 patients, but esophagitis grade A was still present in 2 patients.

Acid reflux evaluation (pH metry)

Before therapy, children with reflux esophagitis had slightly higher mean values of both total acid reflux time and De Meester score than those without esophagitis, but the differences were not statistically significant (Table 3). During treatment with PPIs, the total acid reflux time was reduced from 13.1% to 3.8% (P<0.01). Upright reflux time was reduced from 14.0% to 4.2% (P<0.05) and supine reflux time was reduced from 12.5% to 2.8% (P<0.01). The De Meester score dropped from 46.4 to 13.1 (P<0.01), which is within the normal range.

Evaluation of all reflux episodes (impedance)

According to impedance criteria, children with reflux esophagitis had slightly higher mean values of both total number of reflux episodes and a number of acid reflux episodes before treatment than those without esophagitis, but the differences were not statistically significant (Table 3). During therapy with PPIs, there was a significant decrease in the number of acid refluxes, from 48 to 15 (P<0.01). But, the number of weakly acid refluxes rose from 26 to 64 (P<0.05). There was an insignificant decrease in the number of weakly alkaline refluxes, from 6 to 4. The total number of all reflux episodes remained equal since the mean number of reflux episodes was 80 at inclusion and 83 during PPI treatment (Table 4, Fig).

Evaluation of refluxate composition

The total number of liquid and mixed reflux episodes did not change before and during treatment. The mean number of liquid refluxes rose from 28 to 31 and the

Table 2. Evolution of symptoms during treatment with a proton pump inhibitor

Symptoms	Before treatment *n* (%)	During treatment *n* (%)	*P* value
Patients with symptoms	21 (100)	12 (57)	<0.005
Heartburn	16 (76)	0	<0.0005
Regurgitation	13 (62)	9 (43)	NS
Vomiting	10 (48)	0	<0.0005
Dysphagia	5 (24)	0	<0.05
Belching	4 (19)	0	<0.05
Odynophagia	2 (10)	0	NS
Cough	2 (10)	0	NS

NS: not significant.

Table 3. pH/MII results at inclusion of patients with and without esophagitis

Variables	Esophagitis (*n*=8)	Non-erosive reflux disease (*n*=13)
Acid reflux time (%)	16.20 ± 6.30	10.20 ± 7.20
DeMeester Score	47.54 ± 51.13	35.67 ± 23.76
All episodes	87.82 ± 91.63	68.54 ± 23.24
Acid episodes	57.69 ± 89.99	39.09 ± 22.25
Weakly-acid episodes	21.26 ± 19.73	24.16 ± 16.44
Weakly-alkaline episodes	8.87 ± 10.93	5.35 ± 9.13
Bolus exposure time (%)	2.23 ± 3.24	1.18 ± 0.55

All data were described as mean ± SD.

total number of mixed refluxes increased from 51 to 54 (both with NS) (Table 4).

24-hour bolus exposure time evaluation

In the upright position, the 24-hour bolus exposure time decreased from 2.2% to 1.5%, the bolus exposure time in supine position increased from 1.3% to 2.3% and the total bolus exposure time rose from 1.7% to 2.0%; all these changes were insignificant. There was an insignificant drop in the percentage of refluxes that reached the highest electrode (19.7% to 15.6%). Four patients were positive for symptom index (≥50%) before PPI therapy, none during PPI therapy with pH analysis, and in 5 and 1 with impedance analysis, respectively. Seven patients were positive for symptom association probability (≥95%) before therapy, none during therapy, and 6 and 4 with impedance analysis.

Table 4. Evolution of number of reflux episodes according to impedance

Reflux episodes		Before treatment	During treatment	*P*	Normal values*
Total	Mean ± SD	80 ± 59	83 ± 71	NS	38.9 ± 9.4
	Median	72	59		
	Range	18-303	12-301		
Acid reflux	Mean ± SD	48 ± 58	15 ± 16	<0.01	23.5 ± 8.4
	Median	37	12		
	Range	2-276	0-65		
Weakly acid reflux	Mean ± SD	26 ± 17	64 ± 61	<0.05	11.3 ± 3.6
	Median	15	51		
	Range	0-51	0-275		
Weakly alkaline reflux	Mean ± SD	6 ± 9	4 ± 7	NS	4.1 ± 2.3
	Median	3	2		
	Range	0-33	0-31		
Liquid reflux	Mean ± SD	28 ± 30	31 ± 43	NS	20.6 ± 7.0
	Median	17	18		
	Range	0-141	0-192		
Mixed reflux	Mean ± SD	51 ± 33	54 ± 40	NS	18.2 ± 6.0
	Median	36	34		
	Range	12-162	9-140		

*: Normal adult values of reflux episodes and their characteristics detected by 24-hour impedance according to Zerbib et al.[19] NS: not significant.

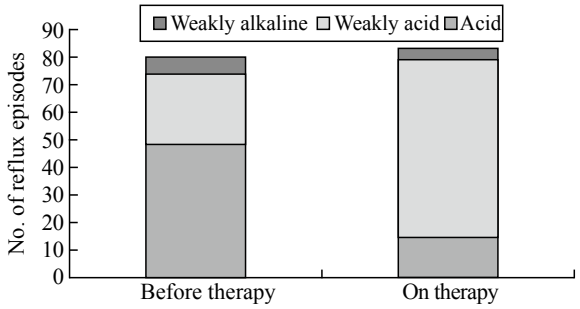

Fig. The proportions of acid, weakly acid and weakly alkaline reflux and the total reflux (average absolute numbers) before and after a continuous proton pump inhibition of a minimum of 2 months (without discontinuation of the therapy). There was a significant decrease of acid reflux episodes (P<0.01) and a significant increase of weakly-acid episodes (P<0.05).

Discussion

Definitions and guidelines for the diagnosis and management of GERD in children have been published.[1,2] To date, endoscopy with histology is the preferred procedure to diagnose "classic" GERD with esophageal symptoms suggesting erosive disease and esophagitis.[1,2] In patients with non-erosive reflux disease and especially in those presenting with extra-esophageal symptoms, MII-pH recording is the preferred diagnostic tool.[2,20,21]

Options for medical treatment of GERD are limited. PPIs have been shown to be efficacious in the treatment of erosive esophagitis as well as acid GERD at any age.[21-24] The challenge remains the treatment of weakly alkaline or weakly-acid reflux.

Our patients represented a selected group of children at risk for severe GERD because 7 children had cystic fibrosis, 6 cerebral palsy, and 5 esophageal atresia are included. Since the number of the patients is limited, a subgroup analysis could not be made. Therefore, these patients do not represent the majority of pediatric patients with GERD. Patients with cerebral palsy are likely to have a low resting tone of the lower esophageal sphincter, whereas those with esophageal atresia may have poor motility and peristalsis. No questionnaire has been validated in these selected children at risk for severe GERD.[15]

As far as recording of the reflux episodes is considered, MII is preferred to pH metry because impedance quantifies besides acid, also weakly-acid and weakly alkaline reflux.[2,20,25] Therefore, it is relevant to know what is the effect of proton pump inhibition on total number and extent of reflux episodes. To date, only few studies, and all performed in adults, evaluated the effect of PPIs on acid, weakly acid and weakly alkaline reflux, and their results are not uniform. In three of the studies, a smaller number of subjects (n=6, 12 and 15) were included. Vela et al[26] found that treatment with omeprazole converts postprandial acid to predominantly weakly acid and weakly alkaline reflux. Hemmink et al[27] showed that treatment with PPI reduced acid but increases weakly acid reflux episodes. Similarly, Frazzoni et al[28] observed that during PPI therapy the total number of reflux episodes remains unchanged and only the number of acid episodes diminishes with a compensatory increase of the number of weakly acidic episodes. However, Orr et al[29] found that not only the number of acid but also the total number of reflux episodes was significantly reduced by therapy. Moreover, several studies of duodenogastroesophageal reflux have revealed that bile reflux into the esophagus can be significantly reduced by PPIs, both in adults and in children. The proposed mechanism is a reduction of total reflux due to decreased gastric secretion and fluid content.[30-32] To our knowledge, such study has not

been undertaken in children. In the mean time, PPIs are reported to increase baseline impedance in children and adults.[33,34] Baseline impedance is related to mucosal integrity, and is lower when there is inflammation.[33,34]

In the present study, we confirmed that PPIs are efficacious in treating reflux symptoms and their consequences, especially heartburn and esophagitis. As expected with disappearance or at least amelioration of symptoms, the number of patients with positive symptom index and symptom association probability also decreases during treatment. Moreover, our data showed that PPIs decrease acid reflux, evaluated by the normalization of De Meester score and reflux index, and the healing of esophagitis in most patients.

According to the impedance results, the total number of reflux episodes did not change any more. There was a significant decrease in the number of acid refluxes from a mean of 48 to 15, but a comparable increase in weakly acid reflux episodes from a mean of 26 to 64. Thus, the total number of reflux episodes remained equal as the mean was 80 at inclusion and 83 episodes after a two-month treatment, respectively. PPIs did not change the composition of reflux episodes (air, liquid, mixed) nor the proximal extent reached by the reflux. Therefore, we could demonstrate that PPIs decrease acid reflux but not total reflux.[27,28] Hence, treatment of weakly acid and weakly alkaline reflux remains a challenge.[2,35] The treatment of GERD has greatly improved with the use of PPIs. Despite excellent success, there is a sizeable population of patients who do not have adequate response to therapies directed only at acid suppression.

Based on current evidence, fantasy clearly dominates the facts.[27] If PPIs fail, prokinetic drugs, if available in children, should be considered.[36,37] However, prokinetic medication cannot be generally recommended because the side-effects of each currently available prokinetic agent outweigh the potential benefits.[2] There is insufficient support to justify the routine use of metoclopramide, erythromycin, bethanechol or domperidone for GERD.[2] Newer medications such as GABA(B) receptor agonists (including lesogaberan and arbaclofen placarbil), mGluR5 receptor antagonists, P-CABs, cholecystokinin antagonists and add-on therapies to PPIs including mosapride and rikkunshito are not or insufficiently studied in children to be recommended.[38]

Several studies have confirmed the efficacy of fundoplication when there is a failure of pharmacotherapy. It has been shown that after surgery both acid and non-acid refluxes are significantly reduced.[39,40] In conclusion, in children and adolescents with GERD, PPIs do not alter the total number of reflux episodes, but merely decrease the acidity of the refluxate. Therefore, the treatment of weakly acid and weakly alkaline reflux remains a challenge for the future.

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Ethical approval: This study was approved by the national committee for medical research ethics of Slovenia and Belgium.

Competing interest: Yvan Vandenplas is a consultant for Biocodex and United Pharmaceuticals. The other authors did not report any potential COI.

Contributors: Rok Orel proposed the study, Helena Turk wrote the first draft, all authors contributed to the design and interpretation of the study and to further drafts and all contributed to the intellectual content and approved the final version.

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