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REVIEW ARTICLE

Treatment of gastroesophageal reflux disease

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Abstract

Objective: To review the literature on the treatment of gastroesophageal reflux disease (GERD) with emphasis on pharmacological aspects. To identify particularities of pharmacological treatment of esophageal and extraesophageal manifestations of the disease.

Sources: Electronic search of the PubMed/MEDLINE and Cochrane Collaboration databases. Controlled and randomized studies published since 2000 and reviews representing consensus positions and directives published within the last 10 years were identified.

Summary of the findings: The drugs currently available for the treatment of GERD do not act in the primary mechanism of the disease, i.e., transitory relaxation of the lower esophageal sphincter. Pharmacological treatment of GERD with symptoms or with esophageal injury is based on the suppression of acid secretion, particularly with proton pump inhibitors. When the hyperreactivity of the lower airways coexists with esophageal GERD symptoms, suppression of acid secretions should be of benefit in managing the respiratory disease in the presence of a causal relationship; however, this is not usual. When esophageal symptoms are not present, esophageal 24-hour pH study should be carried out prior to starting pharmacological treatment for GERD. Improvement of respiratory symptoms may be delayed with relation to esophageal symptoms. It is common for GERD to recur and pharmacological treatment should be repeated or continued indefinitely, depending on clinical presentation of the disease.

Conclusions: The strategies that have been proposed for the pharmacological treatment of GERD in children are primarily based on studies of case series or on studies with adults. There have been very few controlled and randomized studies in children. Undertaking a greater number of these studies might reinforce existing aspects or establish new aspects of management.

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Research strategy

Searches were run on the PubMed/MEDLINE and Cochrane Collaboration databases for the following keywords: gastroesophageal reflux and drug therapy, gastroesophageal reflux and ommeprazole/lansoprazole/ pantoprazole/ranitidine/cisapride/domperidone/ metoclopramide/ erythromycin; gastroesophageal reflux and esophagitis; gastroesophageal reflux and Barrett esophagus; gastroesophageal reflux and respiratory tract diseases, gastroesophageal reflux and cough; gastroesophageal reflux and asthma. From these results, controlled and randomized treatment studies, blind or otherwise, of children (< 18 years), published from 2000 onwards and reviews that represent consensus positions or directives published during the last 10 years were selected. Other articles judged to be of relevance, such as uncontrolled treatment studies and citations found in the selected articles were also consulted and included when appropriate. When the pediatric literature was considered to be scarce or nonexistent, the literature on adults was also consulted. This review was limited to articles published in English.

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Gastroesophageal reflux and gastroesophageal reflux disease: background

Gastroesophageal reflux (GER) is the movement of the stomach contents back up to the esophagus. The prevalence during the first year of life is around 67% at 4 to 5 months, 61 to 21% at 6 to 7 months and less than 5% at 12 months.[1] Gastroesophageal reflux disease (GERD) is commonly defined as the presence of GER symptoms or complications, which are not restricted to regurgitations or vomiting.[2-5] The term GERD has been used in many ways. It has been used as either a synonym of esophagitis or altered esophageal pH or to name conditions associated with atypical symptoms, i.e. respiratory symptoms. Recently, the consensus conference of Montreal, in which Brazil and France participated, published a definition and classification of gastroesophageal reflux disease. The group thereby reached a definition of GERD as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications". Thus, the definition enhanced the negative aspects of the symptoms whose impact could vary from patient to patient.[6]

The symptoms of GERD are less common than the symptoms of GER, but, even so, are very prevalent. A prevalence study reported weekly heartburn sensation and acid regurgitation in approximately 2% of children aged 3 to 9 years and in 5% to 8% of 10 to 17 year-olds. Heartburn alone was identified in 17.8% of the children in the older age group.[7] In the Western world, the prevalence of GERD among adults has been estimated from 10% to 20%.[5]

The refluxate may be exclusively acidic or mixed with duodenum-gastric reflux. Acid reflux is easier to identify and consequently the pathophysiology, diagnosis and treatment are better known. The bile reflux is little understood, but it has been related to severe esophagitis.[8] The case of mixed reflux diagnosis is highly problematic, and is one of the limitations of pH studies. There are no specific clinical trials on mixed reflux in the literature. Therefore, conclusions drawn about the therapeutic management of GERD refer to situations in which acid reflux was identified. The treatment of clinical conditions that are probably only related to mixed pattern reflux remains undefined.

GERD may be suspected following careful anamnesis and physical examination. The most common complaints in childhood are abdominal pain, highly suggestive when associated with meals, regurgitation or repeated vomiting, heartburn, morning pharyngodynia and early satiety and rarely dysphagia. Irritability and frequent crying during the feeding, decrease in feeding, a failure to thrive, anemia, malaise and apnea in small infants and premature newborns are suggestive of GERD and should lead to further investigation. Sandifer syndrome, characterized by a failure to thrive, anemia, arching of the back and lateral rotation of the head is associated with severe esophagitis. The most common extradigestive symptoms are related to the respiratory tract: bronchial hyperreactivity, chronic cough, laryngitis, hoarseness, repeated pneumonia, otitis and sinusitis.

In clinical trials that assessed the management of GERD, the most frequent primary outcomes were symptom control and normalization of the pH reflux index (percentage of the total time during which esophageal pH is < 4) during 24 hour pH monitoring. Infants aged less than 11 months can exhibit physiologic reflux indices close to 12% while values equal to or greater than 12% are abnormal.[8] For children over 11 months, reflux indices ≥ 6% are considered as abnormal.[2] In clinical trials, patients have been enrolled based on a reflux index greater than 5%.[9,10]

Treatment of GERD

The treatment of GERD should be different from that of common infantile GER. There is evidence that GERD is a lifelong condition.[11] Treatment of GERD aims to improve quality of life during the first years of life and has potential for impact on adult life, since GERD complications have been associated with disease duration.

Therapeutic management

General measures

Lifestyle changes are indicated in patients with GER and in those with GERD. Guidance and reassurance to parents are extremely important in the case of infants with regurgitations and no other alteration. In these cases of GER without GERD, guidance associated with changes in lifestyle such as different infant positioning and thickening of feeding are sufficient. Depending on the clinical status, patients with GERD may take advantage of changes in lifestyle with or without drug treatment. Twenty-four hour esophageal pH monitoring studies have demonstrated that prone decubitus is related to lower rates of GER episodes.[3] In contrast, population studies demonstrated a strong link between this position and sudden infant death syndrome, leading to recommend supine decubitus in all newborns and infants.[12-13] This position, with a 30° inclination, appears to offer no advantages over horizontal positioning. Bagucka performed a randomized crossover study, monitoring 10 infants in horizontal and inclined supine decubitus with 48 hour esophageal pH monitoring.[14] Comparison of median reflux indices revealed a statistically significant difference favoring horizontal supine decubitus.[14] Tobin assessed four different positions (prone, supine, right lateral and left lateral) and the infants were monitored with and without the head raised. There were statistical differences in reflux index between prone and

left lateral and supine and right lateral decubiti, favoring the first two positions, whereas there was no difference between horizontal and inclined positions.[15]

Therefore, the recommendation of prone decubitus for infants under 1 year old should only be considered if the risks related to GERD outweigh the risk of the sudden infant death syndrome. In clinical practice, this recommendation is restricted to a very small number of cases. Left lateral decubitus is, however, an alternative.

There are no published studies involving children older than 1 year. Some authors consider that like adults, children would benefit from sleeping in left lateral decubitus with the head raised.[2]

Thickening of infant formula and the introduction of solid foods reduce GER-related regurgitations. However, this effect is probably only associated with reductions in episodes of non-acid reflux.[16] A systematic review of eight randomized studies concluded that thickened diet reduced the clinical symptoms of GER but not the reflux index assessed by pH monitoring. In other words, the esophagus continues to be exposed to acid reflux. Furthermore, some infants may exhibit coughing or diarrhea as a consequence of thickened diets.[3]

The recommendations for older children and adolescents are based on those defined for adults. In terms of dietary restrictions, substances causing an increased frequency of transitory lower esophageal sphincter relaxation or able to exacerbate symptoms should be avoided: caffeine, chocolate, spicy foods and alcohol. In addition, control of obesity, abstention from tobacco and the suspension of passive smoking are all recommended.[2]

Pharmacological treatment of GERD

The Montreal Consensus[6] has classified GERD, characterizing its manifestations as esophageal and extraesophageal syndromes. Esophageal syndromes were divided into symptomatic syndromes and syndromes with esophageal injury; extraesophageal syndromes were divided into established and proposed associations. This classification rationalizes pharmacological management and accounts for a balance in terms of cost/risk/benefit, since a precise diagnosis is not necessarily required to start treatment. In this context, therapeutic tests are often adopted, requiring rigorous patient follow-up. The Montreal Consensus[6] has not specified the classification by age group, and most of the definitions proposed are applicable to adult patients. Notwithstanding, an analogy with pediatric clinical situations can be made. We will therefore approach the pharmacological treatment of GERD from this classification, with a small modification. The few data on children are not sufficient for a differentiation between extraesophageal syndromes with established associations and those with proposed associations. Thus, these categories will be discussed together.

Esophageal symptomatic syndrome

The infant who does not gain weight and exhibits frequent vomiting

Worthy of attention is the fact that these symptoms could suggest various disorders, such as metabolic diseases, food allergies, conditions of the central nervous system and anatomic abnormalities of the gastrointestinal tract.[2] These diagnoses should be ruled out before a diagnosis of GERD is established.

In younger infants, there is no advantage in performing endoscopy before starting drug therapy, because in general the findings are negative. Endoscopy may be useful in older infants, in whom positive findings are more common. Although there are many doubts concerning the efficacy of prokinetics, these are recommended in association with H2-receptor antagonists. Clinical observation is essential. If the outcome is poor, esophageal pH monitoring should be carried out to regulate acid inhibition. The next step could be the use of proton inhibitors, which have the additional advantage of decreasing gastric secretion volume and consequently vomiting.

The infant who cries excessively

Excessive crying and irritability are common causes of medical consultations for infants less than 3 months old. At this age, 50% of infants exhibit GER and therefore the coexistence of these findings does not in itself demonstrate a causal relationship.[3] While the correlation is unclear, pediatricians frequently consider gastroesophageal reflux to be the cause of such crying.[17] The importance of this symptom increases if it occurs during or after the feeding. However, cow's milk allergy is also a cause of esophagitis.[18] One possible initial strategy would be a therapeutic trial replacing the dietary cow's milk protein with hydrolyzed formula, for at least 2 weeks. Although some authors recommend a therapeutic trial with gastric acid suppressants for infants with irritability,[2] to date published data do not offer evidence favoring this measure.

In 30 infants aged 3 to 10 months, with proven diagnosis of GERD, Moore et al. have shown that omeprazole (1.0 to 2.0 mg/kg/day) reduces irritability and crying without any relation to treatment sequence. The authors concluded that irritability improved over time and was not associated with pharmacological treatment for GERD.[9]

The child with sporadic or cyclic vomiting

Sporadic or cyclic vomiting can be related to many different systemic or digestive diseases. In these cases, it

is important to emphasize the importance of functional alterations, unrelated to GERD.[19] It is important to evaluate the relationship with diet. If contrast examination of the upper digestive tract does not reveal abnormalities, treatment with prokinetic can be begun, with duration of treatment defined by patient response.[2] In the event of clinical improvement it is difficult to assess whether this improvement results from activity affecting the mechanisms of reflux or gastric emptying. It is also important to consider the possibility of a placebo effect.

The young child with abdominal pain

Abdominal pain is a common manifestation of GERD.[7] Ashorn et al. found that recurrent abdominal pain was the most common symptom of GERD among children.[20] On the other hand, GERD is far from being the most common cause of abdominal pain in children. Empirical therapeutic trials, particularly with proton pump inhibitors, are acceptable as a diagnostic criterion in children with histories consistent with GERD.[21] In this situation, the presence of epigastric or burning pain (more often observed in older children) is an important finding, in addition to previous history of esophageal or extraesophageal GERD symptoms. Proton pump inhibitors (PPI) should be used for 4 to 6 weeks and the efficacy assessed in terms of clinical improvement. Initial clinical improvement followed by recurrence of the pain after the medication is interrupted supports the clinical suspicion and helps select patients for digestive endoscopy with greater accuracy. It is important to consider the noninvasive character of this strategy and the great safety related to PPI. Nevertheless, this conduct is not suitable for infants, and is based on studies undertaken with adults.[22]

The child with heartburn

Children and adolescents complaining of heartburn can be treated in the same manner as adults.[2,23] In addition to lifestyle changes, therapeutic testing with H2-receptor antagonists or proton pump inhibitors for 2 to 4 weeks is acceptable. If clinical improvement is observed, the treatment can be continued for 12 weeks. If symptoms return or it is not possible to withdraw pharmacological treatment, digestive endoscopy is necessary. One should be alert to the possibility of the more severe forms of esophagitis and Barrett's esophagus.

Symptomatic relief from episodes of retrosternal burning can be obtained with isolated doses of H2-receptor antagonist. Orenstein et al. evaluated the pharmacokinetic and pharmacodynamic parameters of low doses of ranitidine (75 mg/day) administered to children aged 4 to 11 years with esophageal GERD syndromes. After the drug was administered, a significant increase in intragastric pH was observed for 5 to 6 hours, in addition to adequate pharmacokinetic and pharmacodynamic profiles. Therefore, as with adults, this dosage of ranitidine can be used to control symptoms of burning sensations in older children.[24]

Syndromes with esophageal injury

Erosive esophagitis

Faced with an unequivocal diagnosis of erosive esophagitis, important aspects must be considered. Treatment aims at achieving improvement of symptoms, healing of the esophageal mucosa, resolution and prevention of complications and maintenance of clinical remission. It is possible that inadequate or delayed treatment of GERD increases the risk of other disease manifestations, such as esophageal stricture. Pharmacological treatment of esophagitis is founded on gastric acid suppressants.

The current knowledge on children with GERD is mainly drawn from countless case series reports about H2-receptor antagonists date, cimetidine[25] and nizatidine[26,27] are the only H2-receptor antagonists (H2RA) that have been evaluated in controlled and randomized trials with children in terms of GERD outcome. Cimetidine has been known to present a large number of drug interactions. The clinical experience with ranitidine in children is superior to that with any other H2RA. The use of ranitidine in children is based on several case reports in childhood and on controlled and randomized trials in adult.[28,29]

In a study with 24 children with mild or moderate esophagitis, Simeone et al. showed that nizatidine (10 mg/kg/day) was more effective than placebo to relieve symptoms and heal esophagitis.[26]

In a randomized, open multicenter study, nizatidine was administered to 210 children aged 5 days to 18 years with clinical diagnoses of GERD. Thirty two percent of patients achieved complete relief from symptoms after 8 weeks of treatment.[27] Despite the large number of patients involved, the study suggests either a limited efficacy of the drug or most likely the difficulty to assess GERD based on clinical symptoms. Furthermore, regarding drug safety, several adverse effects, such as upper respiratory tract infections, vomiting, diarrhea, pneumonia, dermatitis, fatigue and tremor were recorded. On the other hand, studies on adults have confirmed the superiority of PPI over H2RA for healing severe esophagitis.[30,31] Studies with this class of drugs in children have primarily selected patients based on treatment failure with H2RA, achieving high rates of symptom relief and esophageal mucosa healing.[32-35]

Cucchiara et al. compared both drugs in children. Patients who did not respond to ranitidine (4 mg/kg/day two times a day) and cisapride (0.2 mg/kg/day, three

times a day) for 8 weeks were randomized to receive omeprazole 40 mg/1.73 m^2 or high dose of ranitidine (20 mg/kg/day) for a further 8 week period[33]. The authors found no significant difference in the observed healing rates of 75% and 83% and symptom relief of 62 and 69% for patients treated with omeprazole and ranitidine, respectively. Further studies demonstrated however that a significant number of patients with esophagitis did not heal with the dose of omeprazole used by Cucchiara et al.[32] Nevertheless, the ranitidine dose given was very high and there are no studies that could confirm its safety with children.

Omeprazole at doses from 0.7 mg/kg/day contributes to the healing of esophageal erosion. Hassal et al. studied 57 children aged 1 to 16 years with erosive esophagitis and pH study reflux index over 6%. Fifty percent of the patients were suffering from neurological problems or atresia of the esophagus. An esophageal pH study was performed every 5 to 14 days to obtain a reflux index less than 6%, and then treatment was maintained for 3 months after the healing dose had been determined. The identified healing doses ranged from 0.7 to 3.5 mg/kg/day. A 0.7 mg/kg/day dose cured the esophagitis in 44% and 1.4 mg/kg/day in 28% of the patients. Cure occurred 90±30 days after the healing dose had been reached. Symptoms improved during the first 2 weeks of treatment.[32] Three patients underwent a second course of treatment, requiring up to 325 days to cure. Despite the need for more randomized and controlled trials of PPI, the clinical experience with omeprazole keeps on growing. Treatment courses may be repeated.

Lansoprazol was the second PPI to be cleared for pediatric use by the Food and Drug Administration (FDA). Nevertheless, treatment studies of the drug in children remain even less common than for omeprazole. In a case series, 35 patients aged 3 to 15 years with esophagitis refractory to H2RA underwent digestive endoscopy and 24-hour esophageal pH monitoring and were treated with lansoprazol for 12 weeks. Doses were adjusted in reference to the pH study. Digestive endoscopy was repeated at the end of treatment. Twelve patients were initially treated with 1.3 to 1.5 mg/kg/day and 23 with of 0.8 to 1.0 mg/kg/day. The dose given to the first group was effective for most patients (75%), but just 53.5% of the patients in the second group exhibited healed esophageal erosion.[36] In a multicenter study, 64 adolescents with non-erosive GERD and 22 with erosive esophagitis were given 15 mg of lansoprazol daily for 8 weeks. Reflux symptoms significantly reduced from 91% to 51% among the patients without erosive esophagitis and 95% patients with erosive esophagitis healed.[37]

Recently, similar results were demonstrated again. Twenty and 40 mg doses were effective in reducing endoscopically proven GERD symptoms in children as early as 1 week. The same was not observed with a 10 mg dose.[38]

Thus, omeprazole is recommended at a dosage of 0.7 to 3.5 mg/kg, for an average period of 3 months. Lansoprazole from the dose of 15 mg/day partially improves symptoms of non-erosive esophagitis and a dose of 1.5 mg/kg/day or 30 mg/day appears to be effective for healing esophageal erosion.

It is important to point out that the most common error when prescribing proton pump inhibitors is sub-therapeutic dosage. In case of limited response the prescribed dose should be reviewed, compliance with treatment verified and diagnosis revisited. Eosinophilic esophagitis is an entity that should always be borne in mind in such cases.

It is usual for GERD to relapse when treatment has been withdrawn. Approximately 80% of adult patients relapse after 6 to 12 months, requiring gastric acid suppressants over the long term.[39]

Non-erosive esophagitis

Most children whose esophagitis only exhibits histological abnormalities benefit from H2RA courses of 8 to 12 weeks.[2] Many adult patients with non-erosive esophagitis despite lesser exposure to acid esophageal contents than patients with erosive esophagitis have a worse response to acid inhibition with PPI. The pathophysiologic mechanism postulated is that PPI have a reduced effect on postprandial gastric acidity in patients without erosive esophagitis. This was the conclusion of Gardner et al. after performing a study involving 26 adults with reflux indices > 10%, 18 of them with and 8 without erosive esophagitis.[40] This finding possibly explains the postprandial heartburn that many patients with non-erosive esophagitis present since the volume of acid secreted after eating is greater. Thus, while using PPI, treatment for many GERD patients without erosive esophagitis may require greater reductions in gastric acidity than with erosive esophagitis. It is not known whether this is also applicable to older children and adolescents.

Peptic stricture and Barrett's esophagus

Peptic stricture is the most common complication of reflux esophagitis. Acid inhibition with PPI prevents progress of the stricture and reduces the need for endoscopic dilatation.[2,32]

Barrett's esophagus is a pre-malignant condition in which the normal squamous epithelium of the distal esophagus is replaced with specific intestinal metaplasia, and predisposes to adenocarcinoma. The risk of adenocarcinoma in these patients was 0.5% per year. It occurs as a consequence of excessive and prolonged

exposure of the esophagus to acidic and non-acidic material. The therapeutic objective of Barrett's esophagus treatment is to reduce esophageal exposure to refluxate in order to improve symptoms and prevent progression to adenocarcinoma. Treatment consists of deep and prolonged inhibition of acid with PPI, surgery (fundoplication) and ablative endoscopic techniques.

Treatment with PPI must be lifelong. Patients with Barrett's esophagus require frequent monitoring to assess the effectiveness of acid suppression and progress of the dysplasia. There are several clinical trials in the literature on Barrett's esophagus, however very few were randomized controlled studies. Just two of them have compared pharmacological treatment with surgery. Faybush et al. reviewed randomized and controlled studies, concluding that treatment with PPI does not result in complete regression of Barrett's esophagus. A combination of PPI with ablative techniques appears to be promising.[41,42]

Extraesophageal syndromes with established or proposed associations

Apnea

The causal relationship between apnea and GERD is still not completely understood. The difficulties in understanding the characteristics of this relationship rest primarily on two points: the occurrence of apnea episodes and reflux are most likely to occur during the postprandial period; and in newborns reflux is predominantly non-acid.[43] Orenstein considers it improbable that episodes of apnea during sleep, when the infant is in prone position, are related to reflux episodes.[44] However, some authors have identified clinical characteristics of apnea that should lead to GERD testing: apnea while awake, obstructive apnea,[2] apnea with vomiting or cyanosis.[43] In these cases, left lateral decubitus should be adopted, along with dietary changes such as thickening of foods, lower intake volume and more frequent feeds. Additionally, prokinetics and acid suppressants can be tried, with H2RA being the first option, later replaced with PPI if necessary.[2,43,45]

Recurrent pneumonia

Reflux of the gastric contents into the respiratory tree can cause recurrent pneumonia and, possibly, pulmonary fibrosis.[2] However, macroaspirations are relatively rare and occur more often in children with impaired neuropsicomotor development and structural abnormalities, such as occur with corrected esophageal atresia.[44] In such situations, clinical status and X-ray findings are clear and leave no doubts as to the diagnosis.[43] When reflux occurs in children without these abnormalities, the integrity of physical airway protection mechanism should be investigated. This scenario requires the use of propaedeutic methods familiar to pediatric pneumologists.[2] These patients may benefit from prokinetic medication. Gastric acid suppressants, in particular PPI, by reducing the volume of gastric secretion, may be of benefit to some patients. In certain severe and recurrent cases fundoplication is an option.[2,44]

Laryngeal stridor

Recurrent laryngeal stridor is relatively common among children. The principal cause of stridor is laryngomalacia. The association between laryngeal symptoms and GERD in children was identified only in case series. Orenstein considers that stridor and reflux can form a vicious circle, each perpetuating and aggravating the other. In older children, laryngospasm may occur secondary to reflux episodes.[44] Studies in adults and children demonstrated that suppression of acid secretion was effective for many patients. However, none of these studies were controlled and randomized. This being so, some authors do not recommend pharmacological treatment for GERD in these situations,[2] whereas others, considering that laryngeal manifestations may be secondary to acid reflux, believe that gastric acid suppressants could be of benefit to some patients.[44] With adults, it is recommended that therapeutic tests be performed with gastric acid suppressants, the treatment should last more than 3 months; shorter periods are not enough to confirm therapeutic failure. It is possible that the same rationale is suited to older children.

Otitis, sinusitis and pharyngitis

The existence of a relationship between these entities and GERD has not been clearly established. Empiric therapy with prokinetics or gastric acid suppressants is often performed with children, even though it is not formally indicated.

Asthma

Asthma is the most common chronic disease in childhood and adolescence. Many studies have demonstrated that GERD and asthma often coexist. Studies employing instillation of acid into the esophagus that were able to demonstrate reflexive bronchoconstriction are used as basis for the argument that these two conditions are related.[46] Studies have shown that children and adolescents with GER often exhibit respiratory symptoms.[20]

The clinical association between these two entities does exist, but any causal relationship remains to be elucidated. Some studies have illustrated this association well. One study observed that the prevalence of reflux was directly related to the severity of asthma. Using 24-hour esophageal pH monitoring, it was observed that GERD was absent in patients with intermittent asthma, in contrast to those with mild, moderate or severe persistent forms,

whose pH study was abnormal for 11%, 23% and 57%, respectively. Moreover, one or more GERD symptoms was present in 53% of patients with reflux and 13% of the patients without reflux, while digestive endoscopy revealed esophagitis in 44% of patients with abnornal pH study and in 9% of patients with normal pH study.[47]

One large study compared the prevalence of respiratory manifestations in neurologically normal children hospitalized with a diagnosis of GERD against that of children without a GERD diagnosis. These manifestations were twice as frequent in children with reflux compared with children without reflux.[48]

Work carried out in Belo Horizonte, Brazil, evaluated 69 children from 1 to 5 years with persistent moderate or severe asthma with 24-hour pH monitoring. GERD was observed in 68.1% of children and was more prevalent among persistent severe asthma cases (82.1%) than moderate ones (58.5%). GERD without esophageal symptoms occurred in 31.8% of cases.[49]

Notwithstanding, even in the absence of definitive conclusions on the causal relationship, it is clinically relevant to enquire whether treating asthmatics for GERD would have positive repercussions for the behavior and control of asthma.

Among studies that have been undertaken with children investigating pharmacological treatment for reflux in asthmatics, the controlled and randomized crossover study carried out by Gustafsson stands out.[50] This study assessed 37 children and adolescents aged 10 to 20 years and with moderate or severe asthma diagnosed on the basis of clinical parameters. Diagnosis of GERD was based on clinical criteria (11 patients did not exhibit esophageal symptoms), 24-hour pH monitoring and the Bernstein test. Patients were given ranitidine at a dose of 150 or 300 mg or a placebo with identical characteristics to the medication. The variables analyzed were forced expiratory volume in one second (VEF_1), peak expiratory flow (PEF), hyperreactivity of the airways and clinical status. None of these variables was useful to identify any superiority of ranitidine in relation to placebo in terms of the progress of asthma.

Controlled and randomized trials on GERD in adults with asthma[50] also failed to identify improvement in pulmonary function test results using H2-receptor antagonist or omeprazole or anti-reflux surgery. However, some of these studies demonstrated improved clinical parameters, such as nocturnal symptoms and wheezing.

Koshoo et al.[45] selected 46 children from 5 to 10 years old with persistent moderate asthma. The children were treated for reflux, irrespective of the presence of GERD diagnosed by pH study. Clinical (lifestyle changes, omeprazole, prokinetics) and surgical management were adopted. Twenty-seven children exhibited GERD on pH study and 19 did not. Eighteen children from the first group and eight from the second received treatment with lifestyle changes, prokinetics and PPI. Among the children treated for GERD, significant reductions were observed in asthma medication requirements in the patients with asthma and GERD and also in two patients with asthma and without GERD. The patients in the group without GERD given treatment for reflux did not exhibit improvement in asthma in relation to those who were not treated.

Recently, Stordal et al. conducted a placebo-controlled, randomized and double-blind study evaluating 38 children aged 7 to 16 years with asthma (a minimum of two episodes requiring medication during the previous 6 months) and GERD. Patients were eligible if they had at least one digestive symptom and a reflux index on pH study greater than 5%. Omeprazole was given for 12 weeks at a dose of 0.25-1 mg/kg/day. Despite the intention being to confirm whether or not acid suppression had been adequate, the pH study was repeated at the end of treatment for less than half of the patients and omeprazole was used in low doses. No difference was observed between groups in relation to asthma symptoms, quality of life or pulmonary function measurements.[51]

The studies that have been carried out to date have major limitations. The use of the clinical parameter alone is flawed for the evaluation of adequate acid suppression and healing of the esophageal mucosa. Just a single study attempted to identify improvements in GERD based on diagnostic test parameters.[51] However, the esophageal pH study was repeated at the end of treatment for just half of the patients. In addition, in all cases the number of subjects enrolled was smaller than that required, and the trials were short. Also, the primary criterion to select patients was the presence of asthma. A study employing laboratory confirmed symptoms of GERD as primary patient selection criterion may find different results.

The treatment of asthma patients needs to be rigorously monitored. It is useful to record variables indicative of progress that can be considered when evaluating treatment efficacy, such as coughing, dyspnea, wheezing, frequency and severity of exacerbations, nocturnal symptoms, use of beta-2 agonists and quality of life. Children capable of performing spirometry should do it before and after treatment for reflux. There are recommendations for the selection of asthma patients who could benefit from pharmacological treatment for GERD. Children who present asthma and esophageal symptoms of reflux should undoubtedly be treated for GERD and clinically monitored. GERD is thus associated with asthma and should be consider as a comorbidity and treated as such. No improvement in asthma should be expected. In patients with difficult to treat asthma, that is, with nocturnal asthma more than once a week; patients requiring treatment with continuous oral corticoid, high dose inhaled

corticoid or more than two cycles of oral corticoid per year; patients with persistent asthma who cannot be weaned of drug therapy, irrespective of severity,[2] a predominant role of reflux should be ruled out and 24h pH monitoring performed. These cases are rare. As already stated, this is the case of infants who wheeze or cough during or after the feeding. Therefore, acid suppression therapy should be started using PPI for 3 months at higher doses than normally prescribed.[47] Some authors believe that respiratory symptoms improve later than other symptoms of GERD, taking from 2 to 3 months to respond. It may be necessary to divide the acid-suppression dose into two to control nocturnal symptoms, with the second portion taken after the evening meal.

Nonspecific chronic coughing

As is the case with asthma, GERD may coexist with chronic coughing. However, the number of these cases is overestimated, and the characteristics and timing of the cough are essential for suggesting the diagnosis. To date, randomized and controlled studies evaluating the response to GERD treatment in chronic coughing have only been carried out with adults. In children, the response of nonspecific coughing to pharmacological treatment for reflux has not been studied.

Studies with adults have been evaluated in systematic reviews by the Cochrane Collaboration.[52] The results of these studies did not reveal improvement in chronic coughing with pharmacological treatment for reflux (H2-receptor antagonist, PPI, prokinetic). The reviewers call attention to the large difference between the results of uncontrolled studies when compared with controlled ones. The first type did not consider the placebo effect of treatment or time on the progression of coughing. Furthermore, intense acid suppression, as recommended for asthma, was not employed in any of the controlled studies. Nevertheless, 11 of the studies had employed PPI therapy and the variables monitored allowed their inclusion in a meta-analysis.[53] A certain beneficial effect on coughing could be perceived among adults with GERD. The authors concluded that treatment for adults with nonspecific chronic coughing for 2 to 8 weeks could be considered as an empiric treatment test. In children, other causes of coughing should be exhaustively sought before subjecting them to treatment testing.[52]

We can observe in Table 1 a summary of the treatment for the principal esophageal and extraesophageal syndromes associated with GERD. In cases for which causal links have not been indubitably established, treatment options appear with a question mark ("?").

Table 1 - Summary of treatment for esophageal and extraesophageal GERD syndromes

Clinical condition	Treatment
Infant does not gain weight and exhibits frequent vomiting	Lifestyle changes and prokinetics associated with H2RA
Infant cries excessively	Lifestyle changes (?) and H2RA (?)
Child with sporadic or cyclic vomiting	Lifestyle changes and prokinetics
Child with abdominal pain	Lifestyle changes and PPI
Child with heartburn	Lifestyle changes and H2RA or PPI
Erosive esophagitis	Lifestyle changes and PPI
Non-erosive esophagitis	Lifestyle changes and PPI
Peptic stenosis and Barrett's esophagus	Lifestyle changes and PPI; endoscopic dilatations, ablative endoscopic techniques; surgery
Apnea	Lifestyle changes and H2RA or PPI
Recurrent pneumonia	Lifestyle changes associated with prokinetics and PPI; surgery
Laryngeal stridor	H2RA or PPI
Otitis, sinusitis and pharyngitis	?
Asthma	Lifestyle changes and PPI
Nonspecific chronic coughing	Lifestyle changes (?) and PPI (?)

Considerations on the pharmacology and safety of drugs used to treat GERD in children

Prokinetics

The pathophysiologic mechanism most strongly linked with GERD is increase in the frequency of transient relaxation of lower esophageal sphincter. Studies have demonstrated that the lower esophageal sphincter tonus increases with prokinetic treatment, but that this is not followed by a reduction in the number of reflux episodes.[2]

Cisapride is a serotonergic agent that facilitates acetylcholine liberation at the synapses of the intestinal wall myenteric plexi. Cisapride has proven prokinetic effects on the lower esophageal sphincter and the stomach.[54] Of all the drugs used in GERD treatment with children, it is without doubt cisapride that has been most thoroughly evaluated in controlled and randomized studies. Improvements in clinical symptoms, pH study parameters, esophageal histology and respiratory complications were observed in some studies with the drug,[2,55-57] although a review performed by the Cochrane Collaboration only indicated improvements in reflux indices.[54] Cisapride was never licensed for patients under 12 years old, but was widely used on children in that age group worldwide.[58] Nevertheless, cardiac effects, potentially related to its administration, induced increases in QT interval, arrhythmia and sudden death led to restrictions on the use of cisapride and it was later withdrawn.[59]

Domperidone is a peripheral D2 dopamine receptor antagonist. It reduces the length of postprandial reflux and is used to treat regurgitation and vomiting. Since cisapride was withdrawn, domperidone has come to be widely used. A review study by Pritchard et al. showed only minor evidence for the efficacy of domperidone.[60] Domperidone can cause extrapyramidal symptoms and episodes oculogyric movements in infants. In common with cisapride, domperidone is metabolized by the P450 enzymatic system. Therefore, serum levels can become elevated if there is concomitant use of imidazoline derivatives and macrolide antibiotics. The QT interval may be prolonged if ketoconazole is used in association with domperidone.

Metoclopramide is an antidopaminergic agent with cholinergic and serotonergic effects. It acts to increase lower esophageal sphincter tonus, improving esophageal peristalsis and accelerating gastric evacuation. The dosage used in treatment studies of GERD varies from 0.125 mg/kg/course to 0.3 mg/kg/course, split into three to four daily doses of 0.5 to 1.0 mg/kg/day.[3] However, it should be used with caution, since this drug presents significant adverse effects that are not rare.[61] Metoclopramide causes extrapyramidal symptoms, including dystonic reactions and sleepiness. Metoclopramide-induced dyskinesia can be identified years after its use. From 1997 onwards, metoclopramide resurfaced as a prokinetic drug option as a result of the report of cisapride's cardiac side-effects and its withdrawal from the market.[3] There is also minor evidence for the efficacy of this drug in GERD.

It has been recognized during the last 20 years that erythromycin has prokinetic gastric effects.[62] Studies demonstrated that erythromycin exercises its gastrointestinal motor effects by direct activation of motilin receptors. Motilin is a naturally-occurring peptíde, produced by enterochromaffin cells present in duodenal and jejunal mucosa, which is liberated periodically into the circulation between meals. Oral erythromycin salts have been observed to be effective with preterms with food intolerance due to dysmotility, in postoperative gastroparesis and diabetic gastroparesis. In the esophagus, erythromycin appears to increase fasting and postprandial lower esophageal sphincter pressure and the amplitude of esophageal contractions in the organ's most distal portion. These effects have already been observed in patients with GERD,[62] indicating that the drug could have clinical applications with these patients.[63] However, an association has been identified between erythromycin and development of hypertrophic pyloric stenosis in infants.[64] The dose of oral erythromycin recommended to stimulate gastric motility is well below the antibiotic dosage, with 1-3 mg/kg/doses being recommended. The dosage for the treatment of GERD is not known.[62]

Baclofen is a gamma-aminobutyric acid agonist (GABA B) which, despite not being a prokinetic drug, has been shown to inhibit lower esophageal sphincter relaxation in studies with animals and humans. It is expected that, due to its active mechanism, this drug can interfere with episodes of both acid and non-acid reflux. It has not yet been used on children with GERD, but appears promising.[65]

H2-receptor antagonists

H2-receptor antagonists form a reversible bond with parietal cell H2 receptors, inhibiting these receptors' acid secretion response. They offer proven effectiveness and are used by millions of people worldwide. The clinical efficacy of the drug depends on the gastric suppression desired and on aspects inherent to that inhibition. This class of drug is most effective at suppressing baseline acid secretion, particularly nocturnal secretion.[66,67] Cimetidine, ranitidine, famotidine and nizatidine are available on the market. Among them Ranitidine is the most prescribed.

Cimetidine inhibits CYP and, for this reason, can increase the levels of several drugs that are metabolized by these enzymes. Ranitidine interferes to a very small extent with the metabolic action of these enzymes. Famotidine and nizatidine are even safer and do not interact with CYP. Tolerance to H2RA has been described. This is due to the hypergastrinemia which occurs when they are used and which stimulates histamine liberation.[67]

Patients on ranitidine may experience headaches, dizziness, tiredness, irritability, rash, constipation, diarrhea, thrombocytopenia and elevated transaminase levels. However, these occurrences are infrequent and the drug can be used with confidence. Care should be taken with patients with renal insufficiency who should be given reduced doses.[2]

Proton pump inhibitors

This class of drugs selectively inhibits the H^+K^+ ATPase proton pump (proton pump) in the parietal cell membrane and suppress gastric acid secretion in response to all stimulatory agents.

PPI are benzimidazoles that suppress the final phase of acid secretion, completely inhibiting the H^+K^+ ATPase enzyme until new bomb molecules are synthesized. The potent action of PPI, in addition to elevating gastric pH, also results in a reduction in 24-hour intra-gastric volume, facilitating gastric emptying and reducing refluxate volume.

The PPI that are currently in clinical use around the world are omeprazole, lansoprazole , pantoprazole, rabeprazole and esomeprazole. Of these, esomeprazole most reduces intragastric acidity.[68] Only omeprazole and lansoprazole have been approved by the FDA for use with children. None of them have been approved for use with children less than 1 year old.

While they have similar structures, different PPI differ in terms of metabolism. PPI, principally omeprazole, are metabolized to different degrees by the P450 hepatic enzyme system, specifically by the CYP2C19 and CYP3A4 enzymes. Significant features of the pharmacokinetics and pharmacodynamics of PPI relate to these enzymes' genetic polymorphism, which affects the biotransformation and plasmatic elimination of PPI. Genetic polymorphism can lead to major differences in the kinetics of PPI. Individuals who metabolized these drugs poorly may have greater exposure to a treatment dose. Thus, a proportion of the great variation observed in trials of omeprazole with children could be explained by these findings.[69,70]

The degree to which PPI suppress acid correlates with systemic exposure to the drug.[71] Omeprazole is rapidly eliminated from plasma (a half-life of approximately 1 hour), but its effects may last for 24 to 72 hours due to the strength of the bond that its active form makes with the target receptors. The clinical implication of this is major systemic exposure to the drug. Oral bioavailability of omeprazole is clearly inferior to lansoprazol, ranging from 35 to 65% in contrast with 80 to 91%.[71]

Omeprazole is sold in enteric-coated capsules and in the multiple-unit pellet system (MUPS) presentation. The capsule contains delayed-release granules, which should not be chewed or ground up because they are acid labile. There is no liquid preparation. When children are unable to swallow the capsules, they are opened and their contents mixed with acid media, preferably semi-liquid, such as yoghurt. It appears that these alternative forms of administration do not change the drug's pharmacodynamics,[72] but studies have not been conclusive. Omeprazole - MUPS contains individually enteric-coated pellets. The MUPS preparation is protected from intraluminal degradation and offers the advantage of solubility in water. These are important factors when one is dealing with children.

The ideal regime for PPI is one dose a day, before the first meal, since that is when proton pumps are generated and can be effectively blocked. A second dose may be indicated with the evening meal in the presence of severe esophagitis, peptic stricture, esophageal motility disorders, persistent nocturnal reflux and extraesophageal GERD. Data on this last entity are inconclusive and studies are needed to assess treatment regimes.[4]

In adults omeprazole has been demonstrated as safe even when used for 11 years or more.[69] In children omeprazole appears to be safe for more than two years.[4] Additional data on the safety of long term omeprazole treatment in children are necessary. To date, records on the use of lansoprazol relate only to 12-week courses.

Adverse effects related to omeprazole include headaches, diarrhea, abdominal pains, nausea, skin rash, constipation and vitamin B12 deficiency. Lansoprazol can cause headaches, diarrhea, abdominal pain, nausea, elevated transaminase levels, proteinuria, angina and hypotension. Hypergastrinemia and parietal cells hyperplasia have been observed with omeprazole. This hypergastrinemia may have prokinetic effects. Beyond this, these findings do not have clinically relevant implications.[70]

PPI can be involved in many drug interactions. As a result of the intense reduction in gastric acidity, PPI can reduce the bioavailability of drugs that require lower pH values to be absorbed, such as ampicillin, cyanocobalamin, iron, digoxin and ketoconazole.

As has already been pointed out, PPI can inhibit or induce P450 system CYO enzymes. They therefore have the potential effect of interaction with drugs that are metabolized by this enzymatic pathway. In humans interactions have been identified between omeprazole and phenytoin, benzodiazepines, diazepam, carbamazepine, clarithromycin, methrotrexate and warfarin.[70,71] Lansoprazol is less capable of inhibiting or inducing CYP, and it has less propensity to interact with other drugs.

Table 2 summarizes the main drugs used for the clinical treatment of GERD.

Table 2 - Main drugs used for treatment of GERD

Drug	Mechanism of action	Dose
Cimetidine	H2-receptor antagonist	20-40 mg/kg/day QID or BID
Ranitidine	H2-receptor antagonist	5-10 mg/kg/day BID
Nizatidine	H2-receptor antagonist	10 mg/kg/day BID
Famotidine	H2-receptor antagonist	1-1.2 mg/kg/day TID or BID
Omeprazole	Protein pump inhibitor	0.7-3.5 mg/kg/day, once a day or BID
Lansoprazole	Protein pump inhibitor	1.4 mg/kg/day or 15 to 30 mg/kg/day, once a day or BID
Metoclopramide	Antidopaminergic, cholinergic and serotonergic effects. Increases lower esophageal sphincter tonus; improving esophageal clearance; accelerates gastric emptying.	0.1-0.2 mg/kg/day QID
Domperidone	Peripheral dopamine D2 receptor antagonist. May have some effect on reducing the duration of postprandial reflux.	0.3 mg/kg/dose TID

Surgical treatment for GERD

Some time ago, before the effectiveness and safety of PPI was known about for the treatment of children with hydrochloric-peptic disease, surgery had a larger part to play in managing children with GERD. Although surgery is still widely employed, its indiscriminate use is not compatible with current knowledge about the effectiveness of pharmacological treatment or with the high rates of surgical failure and morbidity.[73] Before surgery is indicated, GERD must be characterized as chronic and recurrent and the patient defined as needing lifelong PPI therapy. Thus the choice is between years and years of drug therapy or surgical intervention. The chance that repeat surgery may be necessary and also the possibility of having to return to PPI should be taken into account.

Anti-reflux surgery should be considered for children with respiratory problems when there are life-threatening complications, such as aspiration, laryngospasm, apnea; in situations where there is no response to drug therapy due to a esophageal motor disorder, with chronic aspirations; and in children with side effects that will not tolerate medication.[47] A good predictor of success with surgery is improving symptoms with PPI and the experience of the surgeon.[4]

Final remarks

When considering treatment for GERD great value should be given to the fact that the disease is likely to last many years, if not lifelong. Pharmacological treatment for GERD has already achieved major advances. Proton pump inhibitors are the most effective drugs for suppression of acid secretion and safe treatment of acid reflux. However, none of the drugs currently in use is effective at treating the primary mechanism of GERD, that is, transient, pathological relaxation of the lower esophageal sphincter. One other aspect is that little is known about the magnitude of the role that non-acid reflux plays in the presentation of this disease and in partial improvements and treatment failures when GERD is treated with gastric acid suppressants. The treatment of non-acid reflux has only been investigated in clinical trials a few times. Despite the high prevalence of GER in asthmatic patients, these patients do not require anti-reflux treatment. Randomized controlled trials concerning patients with difficult to treat asthma should be encouraged, since GERD can have a role. The recognition of the clinical conditions and treatment modalities that could be given to patients, particularly those with recurrent pneumonia, difficult to treat asthma and chronic coughing need to be established for pediatric patients.

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