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REVIEW

Delayed-release oral suspension of omeprazole for the treatment of erosive esophagitis and gastroesophageal reflux disease in pediatric patients: a review

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Abstract: Omeprazole is a proton-pump inhibitor indicated for gastroesophageal reflux disease and erosive esophagitis treatment in children. The aim of this review was to evaluate the efficacy of delayed-release oral suspension of omeprazole in childhood esophagitis, in terms of symptom relief, reduction in reflux index and/or intragastric acidity, and endoscopic and/or histological healing. We systematically searched PubMed, Cochrane and EMBASE (1990 to 2009) and identified 59 potentially relevant articles, but only 12 articles were suitable to be included in our analysis. All the studies evaluated symptom relief and reported a median relief rate of 80.4% (range 35%–100%). Five studies reported a significant reduction of the esophageal reflux index within normal limits (<7%) in all children, and 4 studies a significant reduction of intra-gastric acidity. The endoscopic healing rate, reported by 9 studies, was 84% after 8-week treatment and 95% after 12-week treatment, the latter being significantly higher than the histological healing rate (49%). In conclusion, omeprazole given at a dose ranging from 0.3 to 3.5 mg/kg once daily (median 1 mg/kg once daily) for at least 12 weeks is highly effective in childhood esophagitis.

Keywords: proton pump inhibitors, children, ranitidine, H2-blockers

Introduction

Gastroesophageal reflux disease and erosive esophagitis in pediatric patients: symptoms and therapeutic approaches

Gastroesophageal reflux disease (GERD) is defined as the presence of regurgitation of the gastric contents into the esophagus (gastroesophageal reflux) associated with troublesome symptoms and/or complications.[1] Although different abnormalities in motility variables, such as lower esophageal sphincter function, esophageal peristalsis and gastric motor activity can contribute to the development of GERD, the degree of esophageal acid exposure represents the key factor in its physiopathology. GERD is the most common esophageal disorder in childhood and the most frequent reason why infants are referred to the pediatric gastroenterologist, affecting as much as 1.8% to 8.2% of the pediatric population.[2] Presenting features of GERD in infants and children are quite variable and follow patterns of gastrointestinal and extra-intestinal manifestations that may vary according to age. Patients may be minimally symptomatic, or may exhibit severe esophagitis, bleeding, failure to thrive, or severe respiratory problems. Symptoms of GERD may include: regurgitation, persistent vomiting, anorexia/feeding refusal, hypersalivation, arching, irritability, persistent crying, abdominal and epigastric pain, heartburn, chest

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pain, sleep disturbances,[3,4] Sandifer's syndrome (head turning episodes to lengthen the esophagus, repetitive stretching and arching, which gives the appearance of seizure/dystonia),[5] dental erosion,[6] and many other extra-intestinal manifestations, mainly respiratory symptoms such as stridor, recurrent wheezing, cough, chronic laryngitis, hoarseness, asthma.[7–9] In the more severe forms of GERD esophageal complications like erosive or ulcerative esophagitis,[10] hemorrhage, stricture, Barrett's esophagus[11,12] may be diagnosed.

The main aims of the treatment of GERD in children are to relieve symptoms, promote normal growth and prevent the afore-mentioned complications. Conservative measures include parent reassurance, positioning and altering feed consistency. Treatment options include decreasing intra-gastric acidity with antacids, histamine H_2 receptor blockers and proton pump inhibitors (PPI) and correcting gut motility with prokinetics, such as metoclopramide and domperidone. Surgical approaches like fundoplication are typically reserved to children with severe GERD refractory to medical treatment.

A recent systematic review about the pharmacological management of GERD in children[13] suggested the only safe and effective medications are ranitidine and omeprazole and probably lansoprazole, being able to promote symptomatic relief, and endoscopic and histological healing of esophagitis. In particular, omeprazole is reported to be effective in children with GERD refractory to ranitidine treatment and should be a first-line treatment in severe esophagitis.[13]

Omeprazole pharmacology and pharmacokinetics

Omeprazole is a PPI blocking the final common pathway of acid secretion at the luminal surface of the parietal cell by binding to H^+K^+-ATPase, the so-called "acid pump" or "proton pump" thereby providing potent suppression of gastric acid output. The pro-drug omeprazole is rapidly and almost completely absorbed, with peak plasma levels occurring 1 to 3 hours after ingestion. It is highly (95%) protein-bound and rapidly distributed in plasma. The pro-drug is rapidly metabolized by hepatic cytochrome P-450 isoenzyme CYP2C19, resulting in a very short plasma half-life of 40 to 60 minutes.[14] Despite its relatively short plasma half-life, clinically adequate suppression of acid secretion lasts 12 to 15 hours after a single morning dose, because of the covalent binding of omeprazole with the parietal cell proton-pumps exposed toward the gastric lumen. Thus, the anti-secretory effect of omeprazole is not dependent on its plasma concentration at any given time but it is directly proportional to the area under the plasma concentration curve (AUC).[14] Omeprazole pharmacokinetic studies in children shows that younger ones tend to have a higher metabolic capacity, resulting in a shorter half life of the drug. This may explain the need for higher doses of omeprazole on a per kilogram basis in children as compared to adults, and even higher in children younger than 6 years of age.[15]

Omeprazole formulations

Omeprazole is approved for the treatment of GERD and erosive esophagitis in children ≥2 years both by European and US indications.

Omeprazole is commercially available in capsules containing enteric-coated, delayed-release granules that should not be chewed or crushed because of their acid liability. For children who have difficulty in swallowing them, the capsules may be opened and the granules sprinkled on applesauce or yogurt or dispersed in fruit juice or swallowed immediately with water. However, if the child accidentally chews the granules, their bitter taste may result in non-compliance with refusal of subsequent doses.[16] In two studies[17,18] omeprazole granules have been dissolved in an alkaline vehicle (8.4% bicarbonate at a concentration of 2 mg/mL) or in milk. The pharmacodynamic resulting from these alternative methods of omeprazole administration has been reported to be the same as for the intact capsule.[19] Use of an extemporaneously prepared flavored omeprazole suspension may increase compliance and palatability in pediatric patients. However, the oral bioavailability of omeprazole in non-proprietary formulations has not been accurately assessed yet.

Omeprazole safety and tolerability

The safety and tolerability of omeprazole in both short- and long-term use is demonstrated by the scarcity of adverse effects in spite of extensive use reported in several studies. Most common reported adverse effects have been nausea, vomiting, diarrhea, epigastric pain, skin rash, and irritability[17,20–22] but generally no severe enough for patient to discontinue the drug. Only one case of anaphylactic reaction due to omeprazole has been reported, in a 14-year-old boy.[23] One recent study reported the association of omeprazole and an increased risk of acute gastroenteritis and community-acquired pneumonia in children.[24] Hypergastrinemia,[22,25–27] parietal cell hyperplasia,[28] and occasionally gastric polyps[29,30] have also been described in children receiving long-term omeprazole therapy. These changes are usually histologically benign. No statistically significant differences in gastrin level according to omeprazole dosage, dosing frequency or treatment duration has been reported.[21] And no correlation between the degree or duration of hypergastrinemia and the

presence of polyps or parietal cell changes. A mild elevation in transaminase levels has been reported.[25] Therefore, both short- and long-term omeprazole therapy appears to be safe and well tolerated in children despite some biochemical, endoscopic, and histologic changes.[20,21]

Drug interactions

Omeprazole appears to interact with only one P-450 isoenzyme, CYP2C19.[31] Thus it is expected to have a narrow spectrum of interaction limited to drugs metabolized by this enzyme. However, interactions with diazepam, phenytoin, warfarin, digoxin, or methotrexate are reported as not clinically significant.[31–36] There is no effect of omeprazole on metabolism of several other drugs tested like theophylline,[37,38] propranolol[39] or cyclosporine.[40]

Materials and methods

Literature search

We systematically searched PubMed, Cochrane and EMBASE (1990 to 2009) to identify studies evaluating the efficacy of delayed release oral suspension of omeprazole for the treatment of erosive esophagitis and gastroesophageal reflux in children. The search terms used included: "omeprazole", "gastroesophageal (or gastro-oesophageal) reflux", "erosive esophagitis (or oesophagitis)", "child$" (or "infant$") and "drug$" or "therapy" or "treatment". These terms were combined in various ways to generate a wide search. In addition, we checked references of eligible articles for further papers that were not captured by our search strategy and corresponded with authors when a full-length article was not available directly on-line or when relevant information was missing in the paper.

Inclusion criteria

We included articles that met the following pre-determined criteria: a) clinical trials performed in pediatric patients reporting on efficacy of omeprazole for the treatment of erosive esophagitis and gastroesophageal reflux in children, b) only delayed release omeprazole as oral suspension: ie, powder for oral suspension (Prilosec) or capsule content in liquid vehicle or non-encapsulated intact enteric-coated granules administered with fluids, c) studies in English language, d) studies with adequate data about number and age of treated children, endoscopic diagnosis, total daily dose and duration of treatment.

Data extraction and synthesis

A form was generated to register whether individual studies met eligibility criteria and collect data regarding study design and methodological quality. Two investigators independently reviewed and extracted data from the papers according to the pre-determined criteria. Any differences in opinion about the studies were resolved by discussion between them.

Outcomes

Our analysis focused on the following measures of therapeutic efficacy: GERD symptom relief/resolution, reduction in reflux index, endoscopic and/or histological healing of esophagitis.

Analysis

Selection bias and lack of common outcome measures were some of the problems preventing a proper metanalysis. Therefore, we defined subgroups for the analysis by dividing studies into 3 groups according to the outcome measures considered in each paper: a) GERD symptom relief/resolution, b) reduction in reflux scores as documented by 24-hour esophageal and/or gastric pH-monitoring, and c) endoscopic and/or histological healing of esophagitis.

Results

Our literature search identified 59 potentially relevant articles. After reviewing the titles and abstracts and the full-length articles, 12 articles were selected for closer assessment and then included in our analysis.[17,18,22,25–27,41–46] They are summarized in Table 1.

Of the 12 selected studies, 10 were controlled trials, 2 were randomized controlled trials (1 was placebo-controlled[41] and the other compared omeprazole to ranitidine[27]). Ten were single-center studies, 2 were multi-center studies (1 of them was multinational[42]). Overall, data from a total of 262 children were reported. Children's age showed a wide range of variability ranging from 1.25 months to 18 years. The treatment duration varied widely, ranging from 2 to 24 weeks, but after 2 weeks only intra-esophageal and/or gastric pH was evaluated in 2 studies[17,41] and in 1 study also endoscopy was performed as early as within 2 weeks.[22] The median dose of omeprazole was 1 mg/kg once daily (range 0.26–3.5 mg/kg). In all studies omeprazole was administered as a capsule or as the capsule content dispersed in a weakly acid vehicle, except for 2 studies[17,18] where granules were dispersed in non-acid vehicles.

In general all the studies had similar aims, but some had different approaches, and consequently slightly different results. In the study by Cucchiara et al[27] omeprazole decreased clinical score by 83%, improved histological and endoscopic degree of esophagitis by 75% and 82%,

Table 1 Clinical trials testing delayed-release omeprazole in children

Author	Study design	Trial data (country, center)	No of treated children	Age	Formulation	Dosage	Duration of therapy	Measured parameters
Cucchiara[27]	RCT	Italy, single-center	12	6 mo–13.4 y	capsule content or capsule	40 mg/1.73 m^2/die	8 wk	symptoms, esophageal and gastric pH monitoring, endoscopic and histological degree of esophagitis
Moore[41]	RCT, double-blind, placebo controlled, crossover	Australia, multi-center	15	3–12 mo	microspheres in apple juice	5–10 kg: 10 mg/die; >10 kg: 10 mg/bid	2 wk	symptoms, esophageal pH monitoring
Hassal[42]	CT, open-label	Multinational, multi-center	57	1–16 y	capsule or granules in weakly acid vehicle for children unable to swallow intact capsule	0.7–3.5 mg/kg/die	12 wk	symptoms, endoscopic degree of esophagitis
Alliët[18]	CT, open-label	Belgium, single-center	12	2–3.8 mo	capsule content in milk or water	0.5 mg/kg/die = 20 mg/1.73 m^2/die	6 wk	symptoms, gastric pH monitoring, endoscopic and histological degree of esophagitis
Bishop[17]	CT, open-label	UK, single-center	10	1.25–20 mo	multiple unit pellet system dissolved in alkaline vehicle	0.7–2.8 mg/kg/die	2 wk	symptoms, esophageal and gastric pH monitoring
Cucchiara[43]	CT, open-label	Italy, single-center	22	19 mo–12 y	content of the capsule in acid vehicle as grapefruit or orange juice	1 mg/kg/die = 40 mg/1.73 m^2/die	8 wk	symptoms, endoscopic degree of esophagitis
Kato[22]	CT, open-label	Japan, single-center	5	3–18 y	enteric coated preparation	0.3–1.6 mg/kg/die	2–8 wk	symptoms, gastric pH monitoring, endoscopic degree of esophagitis
De Giacomo[44]	CT, open-label	Italy, single-center	10	2–9 y	capsule content	<30 kg: 20 mg/die; >30 kg: 40 mg/bid	12 wk	symptoms, esophageal pH monitoring, endoscopic and histological degree of esophagitis
Karjoo[45]	CT, open-label	USA, single-center	38	6–18 y	capsule content	20–60 mg/die	8 wk	symptoms
Gunasekaran[25]	CT, open-label	Canada, single-center	15	0.8–17 y	capsule or granules in weakly acid vehicle for children unable to swallow intact capsule	0.7–3.3 mg/kg/die = 10–60 mg/die	24 wk	symptoms, esophageal pH monitoring, endoscopic degree of esophagitis

(*Continued*)

Table 1 (*Continued*)

Author	Study design	Trial data (country, center)	No. of treated children	Age	Formulation	Dosage	Duration of therapy	Measured parameters
Boccia[46]	CT, open-label	Italy, single-center	48	2.7–14.2 y	capsule or granules in weakly acid vehicle for children unable to swallow intact capsule	1.4 mg/kg/die	12 wk	symptoms, endoscopic degree of esophagitis
Strauss[26]	CT, open-label	USA, single-center	18	2–17 y	capsule content	0.26–1.35 mg/kg/die	8–12 wk	symptoms, endoscopic and histological degree of esophagitis

Abbreviations: CT, controlled trial; die, once daily; RCT, randomized controlled trial.

respectively, and reduced esophageal acid exposure by 61.9% and intra-gastric acidity by 29%. Moore et al[41] reported significant reduction in reflux index without a significant reduction in irritability, which was the only evaluated symptom. In the study by Hassal et al[42] omeprazole healed endoscopic esophagitis in 95% of children and improved reflux symptoms in 91.5% even in the unhealed children. Alliet et al[18] reported symptom improvement in 67%, endoscopic healing in 100% and histological healing in 67% of children and a significant reduction of intra-gastric acidity. Bishop et al[17] reported a significant improvement both in reflux index and intra-gastric acidity and a significant improvement in clinical score in children younger than 2 years. In another study Cucchiara et al[43] reported symptom resolution or improvement in all patients and improvement in the endoscopic degree of esophagitis in 76% of cases. Kato et al[22] reported symptom improvement in all children, endoscopic healing of esophagitis in 80% of children and significant reduction of intra-gastric acidity. De Giacomo et al[44] showed endoscopic, but not histological, healing of esophagitis in 90% of treated children, symptoms improvement in 100% and a significant reduction in reflux index. Karjoo et al[45] reported symptom improvement in 87% of treated children. Gunasekaran et al[25] reported symptom resolution, esophageal acid exposure within normal range and endoscopic healing of esophagitis in 100% of children by 6 months of treatment. Boccia et al[46] reported endoscopic healing of esophagitis in 96% of children and symptom resolution in 35%. Strauss et al[26] showed symptom resolution or improvement in 100%, histological healing of esophagitis in 37.5% and endoscopic healing in 100% of children.

For the purpose of our analysis, the studies were divided in subgroups according to the outcome parameters measured. Table 2 shows esophageal and gastric pH-monitoring, Table 3 shows endoscopic and histological results, and Figure 1 shows percentage of asymptomatic children after treatment.

All studies evaluated symptom relief/resolution, even if the symptoms considered and the scores used to graduate their presence/intensity were not homogeneous. GERD symptom improvement or disappearance were reported as percentage of asymptomatic children in 10 studies[18,22,25–27,42–46] and showed symptomatic response in 189 out of 235 treated children (80.4%) but rate of symptom relief widely varied ranging from 35% to 100% (Figure 1). In 2 studies[17,41] the clinical score only was reported, and was significantly decreased in 1 study.[17]

Five studies[17,25,27,41,44] evaluated reduction of esophageal reflux index, 4 studies[17,18,22,27] measured reduction of intra-gastric acidity (2 of them monitored both the esophageal and the gastric pH). Out of these 5 studies analyzing the esophageal 24-hour pH profile, 4 were comparable since they reported homogeneous data, ie, the median percentage of time of esophageal pH $<$ 4 (reflux index) before and after omeprazole treatment. In all studies reflux index was significantly decreased and was always within normal limits (ie, $<$7%) ranging from 1% to 5.4%. Out of the 4 studies measuring reduction of intra-gastric acidity, 3 were comparable since they homogeneously reported the median percentage of time of gastric pH $<$ 4 both before and after treatment. Percentage of time of gastric pH $<$ 4 significantly decreased from 20% to 69%.

Table 2 Studies evaluating esophageal and/or gastric pH-monitoring

Author	No of treated children	Esophageal pH-monitoring % of time of esophageal pH < 4	Gastric pH-monitoring % of time of gastric pH < 4
Cucchiara[27]	12	before treatment 9 after treatment 3.1 Δ –5.9	before treatment 90.3 after treatment 60.3 Δ –30
Moore[41]	15	before treatment 9.9 after treatment 1 Δ –8.9	
Alliët[18]	12		before treatment 90.3 after treatment 21.3 Δ –69
Bishop[17]	10	before treatment 18.5 after treatment 1.6 Δ –16.9	before treatment 71.9 after treatment 13.2 Δ –58.7
Kato[22]	5		after treatment 72.2
De Giacomo[44]	10	before treatment 17 after treatment 5.4 Δ –11.6	
Gunasekaran[25]	15	before treatment range 11–88 after treatment ≤6	

Nine studies evaluated the rate of healing of esophagitis in term of endoscopic healing[18,22,25–27,42–44,46] and in 4 of them histological healing was also evaluated.[18,26,27,44] For the purpose of our analysis, we considered as endoscopically healed a macroscopically normal esophageal mucosa, corresponding to grades 0 and 1 of Hetzel and Dent scale.[47] According to this criterion, patients presenting a grade 1 esophagitis at baseline were excluded from the calculation for the healing rate. The majority of children where endoscopic healing was reported were treated for 12 weeks or longer and healing tended to be better than in children treated for 8 weeks or less ($P = 0.053$). Histological healing was defined according to different criteria, so results were non comparable and we analyzed only the percentage of children reported as histologically healed. Overall the histological healing rate was significantly lower than the endoscopic healing in these 4 studies (49% vs 91%, $P = 0.0001$).

Discussion

In this review evidences about the efficacy of omeprazole treatment for esophagitis in children have been systematically reviewed. Efficacy has been evaluated in terms of symptom relief, normalization or improvement of gastric and/or esophageal acidity, and endoscopic and/or histological healing of esophagitis.

In 10 of 12 studies omeprazole was very effective in improving or resolving GERD symptoms, both when evaluated as a percentage of asymptomatic children or as a decreased symptom score. However, in 2 studies efficacy on symptoms was lower, particularly on irritability. Moore et al[41] reported that omeprazole did not significantly reduce irritability score in infants. However, irritability being evaluated by subjective methods, such as a diary of crying and fussing time and a visual analogue score of parental impression of its intensity was the only symptom evaluated. And when efficacy on reducing esophageal pH was assessed even in these infants a significant reduction in reflux index was seen. Similarly Boccia et al[46] reported a low symptom resolution rate of 35%. However, analyzing each reported symptom even in this study irritability was the only non-improving one, whereas frequency of other symptoms like vomiting,

Table 3 Studies evaluating rates of endoscopic and/or histological healing of esophagitis

Author	Duration of therapy	Endoscopic healing	Histological healing
Cucchiara[27]	8 wk	9/11 (82%)	9/12 (75%)
Hassal[42]	12 wk	54/57 (95%)	
Alliët[18]	6 wk	12/12 (100%)	8/12 (67%)
Cucchiara[43]	8 wk	13/17 (76%)	
Kato[22]	2–8 wk	4/5 (80%)	
De Giacomo[44]	12 wk	9/10 (90%)	0/10
Gunasekaran[25]	24 wk	6/6 (100%)	
Boccia[46]	12 wk	46/48 (96%)	
Strauss[26]	8–12 wk	1/1 (100%)	6/14 (43%)

Notes: In 115 of 121 children treated for 12 weeks or longer endoscopic healing rate was 95% (95% CI 89–98). In 38 of 45 children treated for 8 weeks or shorter endoscopic healing rate was 84% (95% CI 71–93).

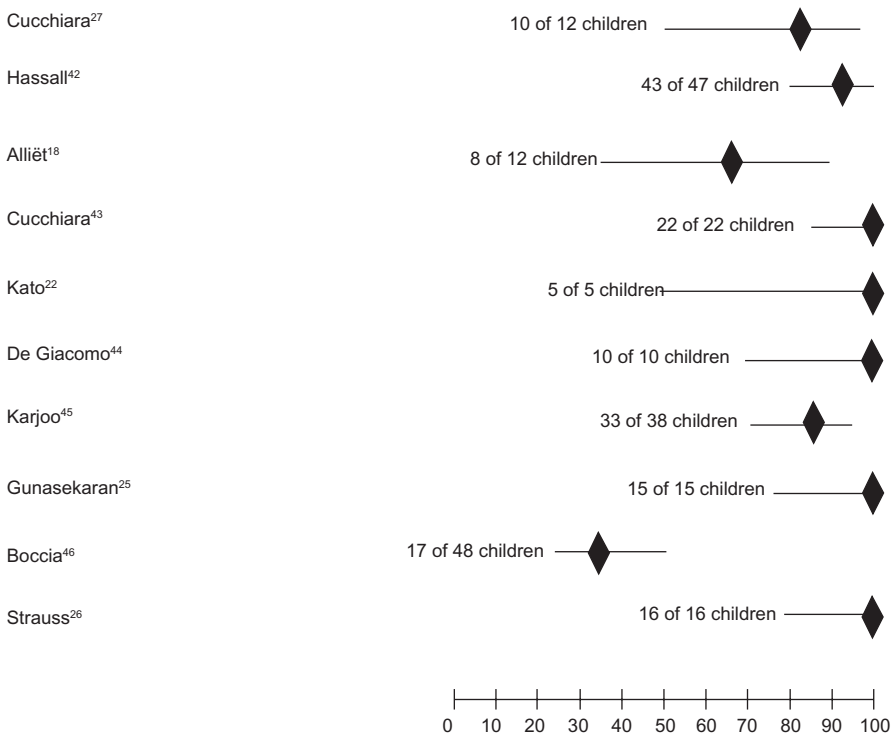

Figure 1 Symptom resolution rates in the 10 studies reporting percentage of asymptomatic children after treatment.

heartburn, epigastric pain, and dysphagia significantly decreased. Therefore, the failure of omeprazole in treating irritability, despite effective acid suppression and significant efficacy on other symptom improvement, may be explained by the hypothesis that some infants/children could be irritable because of non-acid reflux or irritability could be a self-limiting condition tending to improve only over time.

The efficacy of omeprazole in suppressing acid output has been demonstrated by esophageal[17,25,27,41,44] and/or gastric[17,18,22,27] pH monitoring or both.[17,27] In particular, all the studies analyzing esophageal pH-monitoring showed an effective acid suppression by omeprazole, reducing the percentage of time of esophageal pH <4 to less than 6%, a reflux index $>7\%$ being considered abnormal according to recent guidelines of North American and European Society for Pediatric Gastroenterology.[48]

Omeprazole resulted to be very effective in healing esophagitis in children. Although data are analyzed in different way from studies performed in adults, and so results are not completely comparable, efficacy in children seems to be better than in adults. Indeed, a recent systematic review[49] reported the overall endoscopic healing for omeprazole in adults of 73.8% (95% CI 71–76) and in our children treated for 8 weeks or less was similar (84%, 95% CI 71–93) but in those treated for 12 weeks or longer healing rate was significantly higher (95%, 95% CI 89–98). The possible better efficacy of omeprazole in children might be due to the higher dosage used in children, in whom doses of omeprazole are given on a per kilogram basis; or, alternatively, to a lesser severity of the inflammatory changes due to a shorter duration of the reflux disease in the younger population. However, when analyzed, the histological healing even in children was significantly lower, and in 2 studies[26,44] histological parameters did not correlate with endoscopic healing or symptomatic relief.

Comparing omeprazole with other most common drugs or surgical approaches used for GERD and esophagitis treatment in children, omeprazole seem to be more effective. Most of the children successfully treated with omeprazole included in this review were unresponsive to previous medical treatments with anti-acids, H2-receptor blockers, pro-kinetic agents or surgery. However, when looking more carefully at the data presented the higher efficacy of omeprazole compared to ranitidine is not proven. Karjoo et al[45] initially treated children with 8 mg/kg once daily ranitidine, increasing to 12 mg/kg once daily if no symptomatic improvement was observed after 2 weeks, but this apparent failure of ranitidine could be due to a too short period of observation or, more probably, to a too low dosage of ranitidine. Indeed, when Cucchiara et al[27] directly compared omeprazole 1 mg/kg once daily to ranitidine at the dose of 20 mg/kg once daily efficacy was similar in symptom relief, endoscopic and

histological healing, and in reducing esophageal and gastric acidity, whereas the same children previously treated with ranitidine at the dosage of 8 mg/kg once daily had not responded. Dosage of ranitidine is known to correlate with the esophageal reflux index and a dose lower than 10 mg/kg dail is indeed ineffective to heal esophagitis.[50] However, data on the similarity of ranitidine and omeprazole efficacy in the treatment of childhood esophagitis are insufficient and other head-to-head studies are necessary, particularly because in adults omeprazole was reported to have a superior efficacy to H2-receptor blockers in treating esophagitis.[51]

Similarly, data on usefulness of maintenance therapy or in-demand therapy for prevention of recurrence in children are insufficient. Only in 1 study[46] were children followed after healing and maintenance therapy for longer enough to assess prevalence of relapse and found symptoms recurrence only in 6.8% of children even after maintenance discontinuation, unsupporting the necessity of maintenance therapy.

Conclusion

In conclusion, delayed-release oral suspension of omeprazole given at a median dosage of 1 mg/kg once daily for a median duration of 12 weeks showed high efficacy in treating GERD and esophagitis in children. Moreover, thanks to its safety and tolerability omeprazole use in childhood can be extended to clinical settings. The need for a long-term maintenance therapy, however, is still to be assessed in the pediatric population.

Disclosures

The authors report no conflicts of interest in this work.

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