

## Pharmacological Options Beyond Proton Pump Inhibitors in Children with Gastroesophageal Reflux Disease

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### Abstract

Pharmacological treatment of gastroesophageal reflux (GER) disease is mostly based on acid control. However, different molecules have been proposed both for patients with persisting symptoms and to limit adverse effects of proton pump inhibitors (PPI). This paper focuses on other acid inhibitors, alginate, prokinetics, drug acting on lower esophageal sphincter and esophageal hypersensitivity. Mechanism of action, indications, efficacy, limits and recent advances are reported. Pediatric data and possible adverse effects are also considered.

**Keywords:** Reflux; Ranitidine; Alginate; Prokinetics; Baclofen

### Abbreviations:

ASIC: Acid-sensitive ion channels; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition; GABA:  $\gamma$  aminobutyric acid; GER: Gastroesophageal reflux; GERD: Gastroesophageal reflux disease; NASPGHAN: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; NICE: National Institute for Health and Care Excellence; PPI: Proton pump inhibitors; PCABs: Acid-inhibitor acting on potassium; SSRIs: Serotonin selective re-uptake inhibitors; TLESRs: Transient lower esophageal sphincter relaxation; TRPV: Transient receptor potential vanilloid.

### Introduction

Proton pump inhibitors (PPI) are the treatment of choice both for children and adolescents with heartburn, reflux esophagitis, pathological acid exposure or significant association with symptoms related to acid gastroesophageal reflux (GER) detected by (impedance) pH-monitoring [1]. Persisting symptoms on PPI may be related to several factors such as: insufficient drug dosage (e.g., in neurological patients), incorrect intake (e.g., not before the first meal of the day), major effect of the non-acid component (or currently classified as weakly acid reflux with  $\text{pH}>4$ ) or of the volume of reflux (esophageal distention) in the generation of symptoms, esophageal hypersensitivity, primary motor disorders or other diagnosis (non GER disorder).

The pathogenesis of GER disease (GERD) is complex and include several contributing factors such as inappropriate lower esophageal sphincter (LES) relaxations, abnormal esophageal motility and clearance, delayed gastric emptying, increased both acid and non-acid GER, impaired esophageal resistance and esophageal hypersensitivity.

Physiologic GER and infantile regurgitation do not need medical treatment although they frequently cause parental distress and anxiousness [1]. Management in these patients should be based on parental education and reassurance, dietary and, eventually, positional treatment.

Pharmacological therapy used to treat GERD encompass antisecretory agents, antacids, surface barrier agents, prokinetics, agents reducing LES relaxations and, more recently in adult patients, anti-depressant drugs. From the pathophysiologic point of view, prokinetic drugs are the most logic therapeutic approach to treat GERD because they improve the motility of both esophagus and stomach, reducing the time of the esophageal contact with refluxate and accelerating gastric emptying. However, there is no effective and safe prokinetic agent on the market.

Appropriate treatment of GERD is important to reduce GER related symptoms and possible esophageal (e.g., esophagitis) and extra-esophageal (e.g., respiratory manifestations, sleeping or feeding disturbances) complications and to improve quality of life of the patients.

This article focuses on current therapeutic pharmacological options beyond PPI in GERD and updates the current pediatric data of other acid-inhibitors, "barrier agents", prokinetics, and drugs that act on the inferior esophageal sphincter or on the "symptomatic sensitivity" (Table 1). Neither non-pharmacological therapies (e.g., postural, dietetic ones) nor endoscopic and surgical treatments will be herein discussed.

### Other acid-inhibitors except PPI

Ranitidine is often (too much) administered, especially in infants, on clinical basis without a proven diagnosis of GERD. The preference towards ranitidine compared to PPI is mostly related to its availability as a syrup and off-label use of PPI in the first year of life. Ranitidine (at an oral dose of 5-10 mg/kg/die divided in 2-3 doses) suppresses the gastric acid secretion less (partially) and for a shorter period (about 4-8 hours) of time compared to PPI, and is often associated with tachyphylaxis, which cannot be solved with an increase of the dosage.

In 2006 Pfefferkorn evaluated the possible benefit of ranitidine (4 mg/kg), as add-on therapy to PPI, to cover the night-time acid secretion (nocturnal acid breakthrough) in children with reflux esophagitis. There was no evidence of any decrease in the symptomatic score, in the acid exposure detected by pH-monitoring or in the esophageal mucosal lesions compared to placebo [2].

Target	Molecule	Results	Notes	Latest Pediatric Studies
Reduction of reflux	Alginate	Viscous gel in stomach	Consider the content of sodium, aluminum and antacid	[9-12]
		Reduction of regurgitations, heartburn, acid and proximal GER		
Effect on LES	Baclofen	Reduction of TLESR, GER and symptoms, increase of LES pressure, accelerate gastric emptying	Possible neurological effects, dizziness, dyspnoea, decreased seizure threshold	[20,21,23]
Mucosal protection	Sucralfate	In an acid environment, it creates a gel over the eroded mucosa	Only one pediatric RCT in 1989	None
Prokinetic	Domperidone	Unclear efficacy Increased incidence of GER, reduction of its duration	Possible extrapyramidal and cardiological serious effects	[14,15]
Reduction of esophageal sensitivity	Antidepressants, SSRIs	Pain modulation both in the CNS and in the esophagus	Useful in adults with esophageal hypersensitivity and functional heartburn	None

**Table 1:** Pharmacological therapy of GERD beyond acid-inhibitors: molecules and mechanisms

A systematic review analysing 8 studies (276 children treated) have recently reported a limited evidence of effectiveness and safety in pediatric age and a lack of good quality data. Conversely, adverse effects similar to PPI have been shown, including increased infections, variation of the intestinal microbiota and an increased risk of necrotizing enterocolitis in premature babies [3].

Cimetidine has seldom been used as acid-inhibitor in children and is not recommended for its side effects on cytochrome P450, on the metabolism of vitamin D and on the endocrine function.

Other drugs have been proposed for adult patients with GERD, e.g., Vonoprazan (a new acid-inhibitor acting on potassium, PCABs), which seems to have a stronger and more lasting effect of acid suppression compared to PPI [4,5].

Current available information about antacids (based on potassium/sodium bicarbonate, aluminum and magnesium hydroxide or calcium salts) in children with GERD are too limited to recommend their use and concern about the prolonged use of aluminum has been raised, especially in young children and in patients affected by kidney diseases [1].

## Alginate

Alginate is a polysaccharide derived from brown seaweed and it can absorb water or react with gastric enzymes like pepsin, thus increasing the viscosity of the gastric content.

Alginate based drugs can act on GERD both physically, through a mechanic effect in the stomach and chemically, reducing acid content. Alginate precipitates in an acidic environment and quickly creates, a few minutes after administration, a viscous gel or “rafting” in the upper part of the stomach, thus reducing reflux. Besides, some commercial alginate compounds may decrease acid GER because of the concomitant presence of antacids (e.g., bicarbonate, with a “foam” effect over gel and gastric content) thus reducing the “backwash” of the acid pocket located in the gastric fundus. However, alginate is not currently recommended for the treatment of esophagitis for less evidence of efficacy compared to ranitidine and PPI, but only for heartburn in older children and for regurgitations associated to other distressing symptoms in infants [6,7].

In 2000 a review evaluated the effect of alginate based specific formulations (Gaviscon and Gaviscon Infant) and included 6 pediatric studies for a total amount of 303 treated children or infants. Only one double-blind trial was available. The authors reported a significant effect of alginate in reducing regurgitation/vomiting and heartburn, a possible benefit on the pH-monitoring parameters (in one study with a concurrent presence of thickening agents), and less effectiveness compared to H2-antagonists in the treatment of esophagitis. Tolerance was satisfactory in all patients and the only report assessing side effects showed diarrhea or constipation in few patients, with a similar rate compared to placebo [8]. A double-blind pediatric trial which enrolled 20 infants with random administration (3+3) of milk formula on/off an alginate formulation (Gaviscon Infant) without antacids, showed a decrease of all reflux parameters, assessed by impedance-pH monitoring, with a significant effect of alginate only for the height (esophageal extension) of reflux [9].

In 32 preterm newborns Corvaglia et al. confirmed a significant reduction of proximal, gaseous, and acid reflux and of the acid esophageal exposure after the 4 meals with alginate (Gaviscon 0.25 ml/kg/dose) compared with the other 4 drug-free meals [10]. Another trial of the same year which have analysed only one postprandial period with alginate, reported the decrease of acid GER without a concurrent effect on the reflux related apneas in 28 preterm newborns. No adverse effect occurred [11]. In 2015 a clinical study comparing 3 groups of infants showed a greater reduction of GER related symptoms in the group (25 infants) treated for 2 months with a magnesium plus simeticone alginate based formulation (Gastrotuss Baby) (2.5 to 5 mls three times per day) compared to the other two groups (one treated with a thickened milk formula and the other one with parental reassurance). Only one infant reported constipation as a possible side effect of the treatment [12].

Currently, the evidence of effectiveness of alginate in GER is limited in the pediatric age, whereas it's more validated in the adults. Considering the lack of information, NASPGHAN and ESPGHAN guidelines published in 2009 did not recommend alginate in GER(D) treatment [1]. More recently, NICE guidelines have considered alginate as first pharmacological approach in GER, with a 1-2 weeks trial (to extend in case of benefit) in infants with severe reflux symptoms (regurgitations and “marked distress”), persisting after parental reassurance, postural treatment and diet changes [7]. It's recommended to use formulations without aluminum and to consider the sodium

content (variable according to the different commercial products) for a prolonged use particularly in preterm newborns and in children with kidney diseases.

The heterogeneity of age of the populations, of commercial alginate formulations and outcomes, does not allow a proper meta-analysis of the results.

In a trial recruiting 16 adults affected by GERD, an alginate-antacid based product (Gaviscon Double Action Liquid) proved to be located into the postprandial “acid pocket” (an upper stomach area not buffered by meal) right under the diaphragm and close to LES, thus reducing the postprandial acid reflux [13].

### Prokinetics

From a pathogenetic point of view prokinetics should be one of the most rational therapeutic approach in patients with GERD, especially in case of non-acid reflux disease. Nevertheless, prokinetics are not recommended as GERD treatment in infants and children because of the limited evidence of efficacy and their known neurological and cardiological adverse events.

No recent trials using erythromycin (a macrolide that promotes peristalsis and gastric emptying binding to motilin receptors) or metoclopramide (a molecule with an alfa sympathomimetic effect with dopamine and serotonin receptor antagonism) as GERD treatment in children are available. Moreover, metoclopramide should not be administered because of its high rate of serious side effects like lethargy, irritability, gynaecomastia, galactorrhoea and extrapyramidal reactions with possible permanent dyskinesia.

Domperidone is a dopamine receptor antagonist (D2) with a gastric prokinetic effect. A systematic review on domperidone published in 2005 identified only 4 controlled randomized trials in children and no one of them showed a significant evidence of efficacy supporting its use in pediatric GERD [14]. In 2008 Cresi et al. assessed the effect of domperidone in 13 neonates with symptoms of GERD using impedance-pH monitoring. The number of reflux episodes increased although the duration of each GER events decreased [15]. Furthermore, domperidone may cause extrapyramidal effects, increase of prolactin, unpredictable increase of QTc on ECG and serious ventricular arrhythmias with possible sudden death [16].

No pediatric studies have been published so far and limited data are available in adult patients treated for GERD with other prokinetic molecules like mosapride, itopride, prucalopride, levosulpiride, revexepride and renzapride, or motilin agonists [17].

Bethanechol, a choline carbamate with para sympathomimetic action selectively stimulating muscarinic receptors as a cholinergic agonist, showed a doubtful effectiveness and a high rate of side effects in children affected by GERD [1].

### Drugs acting on LES

Inappropriate (because not triggered by swallowing) transient LES relaxations (TLESRs) are one of the most important mechanism in reflux genesis at any age and are mediated by a vasovagal reflex stimulated by gastric distention. This reflex can be blocked by an interaction with 5 metabotropic Glutamate receptors (mGluR5), A and B alfa-aminobutyric acid receptors (GABA (A, B)) and cannabinoid ones (CB 1,2). The above receptors recently proved to be widely expressed (except GABA(A) receptors) in the neurons of LES

myenteric plexus, of cellular bodies and of nerve fibers of the nodose ganglion (except GABA(A) ones), in the dorsal motor and in the solitary tract nuclei [18]. Pharmacological molecules which interact with these receptors may thus determine a reduction of GER through a peripheral action but may, concurrently, also cause central side effects.

Gamma-aminobutyric acid type B receptor agonist baclofen is often used to reduce spasticity in neurological patients. Moreover, in adult patients with GER baclofen reduced TLESRs of 40-60%, both acid and nonacid (postprandial) GER and a symptomatic score, increased LES basal pressure and accelerated gastric emptying [19]. Because of its passage through the blood-brain barrier, several side effects have been reported in patients treated with baclofen, such as headache, fatigue, tiredness, drowsiness, lethargy, confusion, unsteadiness, dizziness, hypotension, “memory lapses”, dyspnoea sensation, weakness, tremor and reduction of seizure threshold.

A 1-week small trial in 8 neurologically impaired children with GERD treated with baclofen showed a reduction in the number of acid reflux episodes and in the frequency of emesis (in 6 children), whilst the percentage of esophageal acid exposure (reflux index) didn't decrease and the esophageal clearance time increased (in 4 out of 8 patients) [20]. The efficacy of 0.5 mg/kg baclofen has been evaluated in the only randomised, placebo controlled trial in 30 children affected by resistant GERD. Measurement of esophageal motility and pH during the 2 hours' test period showed a significant reduction of the incidence of TLESR and a significant acceleration of gastric emptying [21]. No important adverse effect occurred during the first 48 hours post treatment. More recently, a retrospective analysis including 53 children with proven GERD or GERD related symptoms (such as heartburn, regurgitation, vomiting, abdominal pain, weight loss, dyspepsia, lack of appetite, coughing, dental erosion) treated with 0.5 mg/kg/day (or 30 mg/die maximum) of baclofen in 3 divided doses showed a significant reduction in symptoms in 2/3 (35) of patients at their first follow-up evaluation and in 22 patients after 12 months, respectively. In 3 patients the treatment was stopped because of sleepiness [22].

Prospective studies are needed to validate these preliminary results and assess baclofen safety.

Arbaclofen placarbil has only been studied in adults without significant efficacy compared to placebo in reducing symptoms of GERD [23,24].

In another trial in adult patients, Lesogaberan, another GABA-B receptor agonist with a peripheral action, showed an important reduction of both TLESR and of acid and postprandial non-acid reflux [25].

Preliminary analysis in adults with GERD treated with mGluR5 selective receptor antagonists (AZD2066, ADX10059) reported a reduction TLESRs and of acid reflux with adverse events like instability (in 3 out of 13) and attention disorders (in 3 out of 13) or an increase of liver enzymes [18].

### “Esophageal hypersensitivity” therapy and future perspective

In the last ten years, it has been clearly demonstrated that many patients suffering from GERD present non-erosive reflux disease, that both esophageal symptoms and mucosal injuries can occur with nonacid GER (pH>4) and that several “sensory” receptors are located in the esophagus and respond to different pH (transient receptor potential vanilloid receptor (TRPV) type 1 and TPRV4 at pH<6, acid-sensitive ion channels (ASIC) between pH 6 and 7 and p2X at pH<7).

However, the manifestation of pain, heartburn or other symptoms, are dependent on many components (chemical, physical and mechanical ones, related to pH, to volume and content of GER, or to esophageal distention, clearance and mucosal defense) and, particularly, on the individual threshold of perception of one or more stimuli.

Neither enough information nor current studies on mucosal protective drugs, such as sucralfate, are available in pediatric patients and they are not recommended by the current guidelines on GERD treatment [1]. Sucralfate is a sucrose, sulphate and aluminium compound that, in an acid environment, creates a gel binding to the mucosa with peptic erosions. The only pediatric randomized controlled study available was published in 1989 and proved that sucralfate was as effective as cimetidine in the treatment of esophagitis [26].

Serotonin selective re-uptake inhibitors (SSRIs) have been proposed in adult patients with esophageal hypersensitivity (negative endoscopy and acid exposure at pH-monitoring but positive symptom association with GER in the (impedance)pH-monitoring) [27]. Analgesic drugs and low doses of tricyclic antidepressants have been suggested in case of functional heartburn (symptoms of GER but normal endoscopy and (impedance)pH-monitoring) [27].

Pain modulators like tricyclic antidepressants, trazodone, serotonin-norepinephrine re-uptake inhibitors or SSRIs can act as gut analgesics both through central nervous system effects and/or sensory nerve fibers afferents.

A systematic review has recently analysed the efficacy of antidepressants in adults with GERD or esophageal functional disorders with symptoms like heartburn or chest pain, dysphagia or pharyngeal globus, caused by possible esophageal visceral hyperalgesia. Overall 378 articles and 15 randomised controlled trials eligible for the inclusion criteria were identified. After antidepressant therapy the esophageal pain threshold raised from 7 to 37%, with a reduction of pain from 18 to 67% and a reduction of heartburn, in patients with GERD, from 23 to 61%, highlighting that antidepressants can ease esophageal symptoms in a subgroup of patients with GERD [28]. Further controlled trials are needed to evaluate their effects on esophageal functional disorders [28].

No study evaluates the prevalence of esophageal functional disorders in children and analgesics or antidepressants effect in pediatric patients with GERD.

## Conclusion

As reported by a recent Cochrane review on pharmacological treatment of children with GERD, analyzing 24 randomized controlled trials, for an amount of 1201 children, there is no enough evidence of the efficacy of prokinetics, there is some evidence of benefit using H2 antagonists, and there's a moderate evidence of a specific alginate formulation in improving infant's symptoms [6]. Data about GABA receptor agonists are still too limited and there are no pediatric data on pain modulators or mucosal protective agents in patients with GERD. Several adverse effects have been shown for all categories of drugs. A proper diagnostic work-up and an adequate assessment of the safety profile of the molecule are fundamental before starting any pharmacological treatment in infants and children with only symptoms or evidence of GERD.

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