

# Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review

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Gastroesophageal reflux (GER) is commonly observed in children, particularly during the first year of life. Pharmacological therapy is mostly reserved for symptomatic infants diagnosed with GER *disease* (GERD), usually as defined in a recent consensus statement. The purpose of the present article was to review the reported adverse effects of pharmacological agents used in the treatment of paediatric GERD. We conducted this review using the electronic journal database Pubmed and Cochrane database systematic reviews using the latest 10-year period (1 January 2003 to 31 December 2012). Our search strategy included the following keywords: omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, ranitidine, cimetidine, famotidine, nizatidine, domperidone, metoclopramide, betanecol, erythromycin, baclofen, alginate. We used Pubmed's own filter of: 'child: birth–18 years'. All full articles were reviewed and we only included randomized controlled trials retrieved from our search. We addressed a summary of our search on a drug-by-drug basis with regard to its mechanism of action and clinical applications, and reviewed all of the adverse effects reported and the safety profile of each drug. Adverse effects have been reported in at least 23% of patients treated with histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs) and 34% of those treated with proton pump inhibitors (PPIs), and mostly include headaches, diarrhoea, nausea (H<sub>2</sub>RAs and PPIs) and constipation (PPIs). Acid suppression may place immune-deficient infants and children, or those with indwelling catheters, at risk for the development of lower respiratory tract infections and nosocomial sepsis. Prokinetic agents have many adverse effects, without major benefits to support their routine use.

## Introduction

Gastroesophageal reflux (GER) is commonly observed in children, particularly during the first year of life. Up to 65% of infants regurgitate stomach contents at least once a day at the age of 3–6 months [1]. Most cases resolve spontaneously, with complete resolution in 95% of babies by 1 year of age [1]. The efficacy of anti-GER medications in reducing GER symptoms is debatable and there is mounting evidence that these medications are not without adverse effects (AEs). Thus, pharmacological therapy is mostly reserved for symptomatic infants diagnosed with

complicated GER, or GER *disease* (GERD), usually as defined in a recent consensus statement [2].

The purpose of the present article was to review reported AEs of pharmacological agents commonly used in the treatment of paediatric GERD.

## Search strategy

We conducted the present review using the electronic journal database Pubmed and Cochrane database systematic reviews, using the latest 10-year period (1 January 2003 to

31 December 2012). Our search strategy included the following keywords: omeprazole, esomeprazole, lansoprazole, pantoprazole, ranitidine, cimetidine, famotidine, nizatidine, domperidone, metoclopramide, betanecol, erythromycin, baclofen and alginate. For each search and for each pharmacological agent we used the term: 'AND GERD' in order to retrieve only the side effects of these agents when used to treat GERD (and no other therapeutic indication). In order to limit our search to articles related to the paediatric population, we used Pubmed's own filter of: 'child: birth-18years', 'humans only', published in English. We also scrutinized the citations of the retrieved articles for any references not identified by our search. All full articles were reviewed and included only randomized controlled trials retrieved from our Pubmed search, or from our search of the references found in the articles. All AEs reported were recorded by drug and by article, without exception. Below is a summary of our search, on a drug-by-drug basis.

## Results

### Proton pump inhibitors (PPIs)

PPIs are the most frequently prescribed medications for the treatment of adults and children with GERD. Their effectiveness for the treatment of peptic conditions in the paediatric population is well established [3]. The effectiveness of PPIs relates to their structure, which must undergo acidic activation within the parietal cell to allow the PPI to be ionized and form covalent disulfide bonds with cysteine residues of the H<sup>+</sup>-K<sup>+</sup>-adenosine triphosphatase (H<sup>+</sup>-K<sup>+</sup>-ATPase). Once the PPI binds to the proton pump, the pump is inactivated [3]. Table 1 shows the results of the search, in terms of the number of publications identified and selected, and the cumulative patient number.

**Esomeprazole** Esomeprazole is the *s*-isomer of omeprazole, with less first-pass metabolism than omeprazole, resulting in higher bioavailability; this provides more effective and longer lasting inhibition of gastric acid secretion over the 24-h period [4].

A total of 69 articles on esomeprazole were retrieved. Only 12 were found to be relevant, in that they addressed a paediatric population treated for GERD [5–16]. All other

articles were excluded because of mislabelling (dealing with an adult population), because the indication for therapy was not GERD, because they were not original articles (reviews mostly) or because they did not report AEs.

The cumulative sample size of all these studies was 764 paediatric patients, ranging in age from 0 to 17 years (five studies dealt with patients < 1 year). The studies were difficult to combine as the doses used ranged from 0.5 mg kg<sup>-1</sup> to 1 mg kg<sup>-1</sup>, or were empirically 5, 10, 20 or 40 mg per dose (depending on the weight of the patients), and because of patients' heterogeneity (outpatients or inpatients). The proportion having at least one AE was 266/764 (34.8%). However, these AEs were usually mild, and included: diarrhoea in 25 (3.2%); abdominal pain in 21 (2.7%); fever in 17 (2.2%); eczema in one (0.1%); nausea, vomiting or regurgitation in 31 (4%); pharyngitis in 17 (2.2%); irritability in three (0.4%); flatulence in one (0.1%); somnolence in three (0.4%); constipation in six (0.8%); arthralgia in three (0.4%); and headache, the most commonly reported AE, in 34 patients (4.4%). In one study of 57 patients who received esomeprazole parenterally, six patients (10%) suffered from catheter-related infection [6]. The proportion of serious AEs reported in these series (and which included the six patients with catheter-related infection) was 7/764 (0.9%).

**Omeprazole** A total of 133 articles on omeprazole were retrieved but only 10 were relevant [17–26]. The cumulative sample size of these studies was 318 paediatric patients, ranging in age from 0 to 16 years (four studies dealt with patients < 1 year). The doses used ranged from 0.25 mg kg<sup>-1</sup> to 3.5 mg kg<sup>-1</sup>, or were empirically 20 mg per dose (in one study), and patients were outpatients or inpatients. The proportion having at least one AE was 108/318 (34%). However, this percentage could not be firmly established as the reporting of AEs was not consistent from one study to the next. For instance, in one study [18], 43 out of 46 children aged 1–16 years and receiving doses of 0.7–35 mg kg<sup>-1</sup> day<sup>-1</sup> were reported as having at least one AE, while in another study [17], none of the 35 children aged 1–181 months were reported as having at least one AE. Overall, the AEs reported were usually mild: abdominal pain in two (0.6%); eczema in one (0.3%); nausea, vomiting or regurgitation in 31 (9.7%); pharyngitis in 17 (5.3%); irritability in three (0.9%);

**Table 1**

Proton pump inhibitors

	Esomeprazole	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole
Number of articles identified	69	133	54	34	39
Number of paediatric articles	12	10	9	6	2
Sample size	764	318	620	340	52
Placebo controlled studies	309	295	207	128	52

flatulence in one (0.3%); somnolence in three (0.9%); constipation in six (1.9%); arthralgia in three (0.9%); and headache in one patient (0.3%).

**Lansoprazole** Fifty-four articles on lansoprazole were retrieved from the search but only nine were found to be relevant [27–35]. The cumulative sample size of the nine studies was 620 paediatric patients, ranging in age from 0 to 18 years (three studies dealt with patients < 1 year). The doses used ranged from 0.3 mg kg<sup>-1</sup> to 2 mg kg<sup>-1</sup>, or were empirically 15, 30 or 60 mg per dose, depending on the weight of the patients (outpatients or inpatients). The proportion having at least one AE was 271/620 (43.7%). Serious AEs were reported in 14 (2.3%) patients. Ten children had asthma exacerbations [27], and four had pneumonia that was diagnosed as serious by the authors [31]. Overall, the AEs were usually mild and included upper respiratory tract infection (URTI) in 93 (15%); pharyngeal pain in 77 (12%); sinusitis in 16 (2.6%); otitis media in 12 (1.9%); bronchitis in 10 (1.6%); asthma exacerbation in 10 (1.6%); abdominal pain in nine (1.5%); pneumonia in nine (1.5%); headache in seven (1.1%); pharyngitis in six (1%); nausea, vomiting or regurgitation in six (1%); diarrhoea in three (0.5%); dizziness in three (0.5%); liver enzyme elevation in two (0.3%); flushing in two (0.3%); and anorexia, anaemia, chest tightness, hair loss or constipation in one (0.2%).

**Pantoprazole** Thirty-four articles on pantoprazole were retrieved but only six were found to be relevant [36–41]. The cumulative sample size was 340 ambulatory patients, ranging in age from 0 to 16 years (four studies dealt with patients < 1 year). The doses used ranged from 0.3 mg kg<sup>-1</sup> to 1.5 mg kg<sup>-1</sup>, or were empirically 40 mg per dose, depending on the weight of the patients. The proportion having at least one AE was 135/340 (40%). This was probably an underestimate of the real number because one large study of 128 children [41] did not report AEs. For all the other studies combined, the average proportion of patients having AEs was 63.7%, ranging from 44% (*n* = 43) and 100% (*n* = 1). Only one serious AE was reported (one case report of acute pancreatitis) [36]. All other reported AEs were mild and included fever in 23 (17%); abdominal pain in 13 (10%); diarrhoea or gastroenteritis in 26 (19%); headache in 12 (9%); nausea, vomiting or regurgitation in 20 (15%); pharyngeal pain or pharyngitis in seven (5%); eczema or rash in 12 (9%); viral infection in six (4.5%); constipation in five (4%); URTI in 74 (55%); anaemia in four (3%); and tooth discoloration in two patients (1.5%). Overall, there were 11 cases of accidental injuries (8%).

**Rabeprazole** Rabeprazole has a greater antisecretory potency relative to equivalent doses of the above-mentioned PPIs [42]. We retrieved 39 articles on

rabeprazole but only two were paediatric RCTs and were retained for analysis [43, 44]. The cumulative sample size was 52 outpatients, ranging from 1 to 16 years of age; doses used ranged from 0.14 mg kg<sup>-1</sup> to 1 mg kg<sup>-1</sup>, or were empirically 10 mg or 20 mg per dose, depending on the weight of the patients. The proportion having at least one AE was 32/52 (61.5%). However, these AEs were usually mild, and included: diarrhoea in three (5.7%); abdominal pain in three (5.7%); fever in two (3.8%); pharyngitis and pharyngolaryngeal pain in three (5.7%); headache in four (7.7%); cough in three (5.7%); and asthma exacerbation in two (3.8%). The following AEs were each reported once (1.9%): URTI, proteinuria, dysmenorrhoea, fatigue, periorbital oedema, increase in urine output, mild hypergastrinaemia, increase in blood uric acid, heart murmur, chills, toothache and pancreatitis; the most common AE reported was nausea, vomiting or regurgitation, in seven patients (13.4%). Serious AEs were reported in only one individual (1.9%), who was diagnosed as having moderate viral gastritis on Day 4, severe intestinal volvulus on Day 7 and moderate hepatitis on day 19 (all of which we considered as unlikely to be related to the study drug) [44].

### *H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs)*

H<sub>2</sub>RAs act by reducing histamine-induced gastric acid secretion and pepsin output. They are well absorbed from the gastrointestinal tract but, due to high first-pass metabolism, the bioavailability of oral doses is only 50%. Intravenous dosing provides better bioavailability [45]. Table 2 shows the results of the search in terms of the number of publications identified and selected, and the cumulative patient number.

**Ranitidine** Ranitidine is the most commonly used H<sub>2</sub>RA. Twenty-eight articles on ranitidine were retrieved but only four were found to be relevant [17,24,46, 47]. The cumulative sample size was 245 patients, ranging in age from 0 to 15 years (two studies dealt with patients < 1 year), with doses used ranging from 2 mg kg<sup>-1</sup> to 15 mg kg<sup>-1</sup>, or empirically 45 mg per dose, depending on the weight of the patients (outpatients in three studies and inpatients in one). The proportion having at least one AE was 58/245 (23.7%) but this percentage could not be

**Table 2**

H<sub>2</sub> receptor antagonists

	Ranitidine	Cimetidine	Famotidine	Nizatidine
Number of articles identified	28	0	7	3
Number of paediatric articles	4	0	0	1
Sample size	245	0	0	210
Placebo- controlled studies	17	0	0	210

firmly established as in one large study of 91 children [24] the proportion having at least one AE was 59%, while in another large study of 102 patients the proportion was 4% [46]. There were no serious AEs reported in any of the studies. All other reported AEs were mild, and included abdominal pain in one (1.7%); diarrhoea or gastroenteritis in 43 (74%); headache in two (3.4%); somnolence in one (1.7%); and pneumonia in 11 (19%).

Canani *et al.* [24] reported on 186 subjects, aged 4–36 months, consisting of 95 controls and 91 patients with GERD. The GERD patients were treated with ranitidine (10 mg kg<sup>-1</sup>) or omeprazole (1 mg kg<sup>-1</sup>) for 4 months. The rates of pneumonia and gastroenteritis were significantly higher in the patients receiving either of the drugs (12% vs. 2%, and 47% vs. 20%, respectively). The study was not placebo controlled or randomized.

**Cimetidine** Cimetidine is rarely used clinically as there are concerns about its effect on cytochrome P450 and consequent multiple drug interactions, as well as interference with vitamin D metabolism and endocrine function [48]. We could not find any prospective studies of paediatric patients with GERD exposed to cimetidine reporting AEs.

**Famotidine** Famotidine is an alternative H<sub>2</sub>RA; it is not licensed for use in children in the UK but is licensed in the US. Seven articles on famotidine were retrieved but only one dealt with paediatric patients with GERD; the focus of this article [49] was on the pharmacokinetics of famotidine and AEs were not reported systematically.

**Nizatidine** Nizatidine is a competitive, reversible, H<sub>2</sub>RA. It has a much lower drug interaction potential than cimetidine and a lower risk of drug-associated pancreatitis than either cimetidine or ranitidine [50]. Three articles were retrieved in our search but only one [51] dealt with ambulatory paediatric patients (*n*=210), ranging from 0 to 18 years of age. The dose used was 2.5–5 mg kg<sup>-1</sup> day<sup>-1</sup>. The proportion having at least one AE was 115/210 (54.7%). A total of 292 AEs occurred in these 115 patients. Four (1.4%) serious AEs were reported, of which only one (worsening sickle cell anaemia) was considered as possibly related to the study drug. The other AEs were considered as mild or moderate, and included fever in

12/292 (4%), diarrhoea in nine (3%), pharyngitis in 12 (4%), cough or URTI in 40 (14%), vomiting in nine (3%), somnolence in one (0.3%) and eczema in one (0.3%).

**Prokinetics** Table 3 shows the results of the search in terms of the number of publications identified and selected, and the cumulative patient number.

**Metoclopramide** Metoclopramide blocks dopamine and serotonin receptors, and has sympathomimetic activity. Twenty-eight articles on metoclopramide were retrieved but only two were relevant [52, 53]. They were both single case reports of dystonia (*n*=1) and galactorrhoea (*n*=1) and therefore were excluded from analysis. As a result of our search method (using a recent 10-year period), we did not find any recent studies of this relatively 'old' drug. However, we were able to retrieve a systematic study of metoclopramide for the treatment of GERD in infants [54], published in 2006. Briefly, AEs were reported in only four of 12 studies. The AEs that were reported consisted of dystonic reactions, oculogyric crisis, irritability, drowsiness, emesis and apnoea, present in 9–15% of the patients [54–56].

**Betanechol** Bethanechol is a muscarinic receptor agonist that has been shown to increase the tone of the lower oesophageal sphincter. No paediatric studies on this molecule were reported in the 10-year study period.

**Domperidone** Domperidone is a prokinetic agent [57], through its action as a peripheral dopamine-2 receptor antagonist, but, unlike metoclopramide, it does not readily cross the blood–brain barrier and reports of AEs on the central nervous system are rare. Fifteen articles on domperidone were retrieved but only four were found to be relevant [58–61]. The cumulative sample size was 120 patients, ambulatory and hospitalized, ranging in age from 0 to 12 months, with the doses used ranging from 0.5 mg kg<sup>-1</sup> day<sup>-1</sup> to 1.8 mg kg<sup>-1</sup> day<sup>-1</sup>. None of the four studies systematically addressed AEs, focusing only on whether or not domperidone prolonged the QT interval on the electrocardiogram. Two of the studies reported no change in the QT interval (*n*=43 and 45, respectively), while the other two reported an increase in the QT interval (*n*=31 and *n*=1, respectively).

**Table 3**

Prokinetics

	Metoclopramide	Betanechol	Domperidone	Erythromycin	Baclofen
Number of articles identified	28	0	15	8	7
Number of paediatric articles	0	0	4	0	2
Sample size	0	0	120	0	38
Placebo-controlled studies	0	0	28	0	30

**Erythromycin** Erythromycin is a macrolide antibiotic that increases gastrointestinal motility by acting as a motilin receptor agonist [62]. Eight articles on erythromycin were retrieved but none was relevant, in that they were either reviews or did not deal with paediatric subjects.

**Cisapride** Cisapride is a prokinetic agent but, as of 14 July 2000, it has been withdrawn from the market because of at least 341 reports of heart rhythm abnormalities, including 80 deaths [63].

**Baclofen** Gamma-amino-butyric acid (GABA) plays an inhibitory role in the transient lower oesophageal sphincter relaxation reflex mediated via GABA(B) receptors. We retrieved seven articles on the use of baclofen but only two were relevant [64, 65], with a cumulative sample size of 38 paediatric patients, aged 0.2–17.4 years. Doses ranged from 0.5 mg kg<sup>-1</sup> day<sup>-1</sup> to 0.7 mg kg<sup>-1</sup> day<sup>-1</sup>. No AEs were reported.

### Thickening agents (Alginate)

Alginate contains sodium and magnesium alginate; it acts as a feed thickener by increasing the viscosity of feeds and, together with sodium/potassium bicarbonate in the presence of gastric acid, forms a 'foam raft' to neutralize gastric acid (providing symptomatic relief) and to reduce oesophageal irritation [66]. We retrieved 20 articles on the use of alginate but only two were found to be relevant [67, 68]. The cumulative sample size was 73 preterm infants, ranging in age from 0 to 30 days, with doses ranging from 0.25 ml kg<sup>-1</sup> dose<sup>-1</sup> to 1.0 ml kg<sup>-1</sup> dose<sup>-1</sup>. No AEs were reported.

## Discussion

Many studies have shown that H<sub>2</sub>RAs and PPIs are effective in suppressing gastric acid production and relieving oesophagitis in children. The current review has allowed us to determine the relative safety of anti-GERD drug therapy in children. Out of the list of AEs reported for the various drugs considered, it is not always clear which were truly related to the drug, as opposed to the disease itself or a randomly acquired illness. For instance, it is difficult, in a patient with GERD, to determine whether an episode of vomiting, regurgitation or abdominal pain is related to the drug used for GERD, or to GERD. It has been reported that in ill patients with a compromised immune system, the use of acid suppression, which is likely to decrease the natural immune barrier of gastric acidity, has been associated with an increased rate of nosocomial sepsis [69]. Within this context, it is not possible, for instance, to determine whether or not the use of esomeprazole was a contributory factor in the six reported cases of catheter-related sepsis in the study by Sandström [6]. It is also difficult, in a patient with GERD, to determine whether

pharyngeal pain or pneumonia is related to GERD (directly or indirectly) or to lansoprazole [31].

However, the most used H<sub>2</sub>RA, ranitidine, is well known for its ability to lead to tachyphylaxis, which seriously restricts its long-term (more than a few weeks) use [70]. PPIs do not appear to lead to tachyphylaxis and might be more appropriate for long-term therapy. A major limitation of acid-suppressant therapy is that it has little efficacy over placebo in reducing symptoms such as irritability [71]. From our search, it appears that AEs have been reported in at least 23% of patients treated with H<sub>2</sub>ARs and 34% of those treated with PPIs. Headaches, diarrhoea and nausea have been reported routinely in trials of H<sub>2</sub>ARs and PPIs, and constipation can be added to this list in patients treated with PPIs. These numbers might greatly underestimate the true incidence of AEs as some of them, such as headaches or nausea, are relatively subjective and cannot be reliably estimated in non-verbal infants. Moreover, as our review was focused on 10 recent years of literature, we may have missed other AEs, published in earlier studies and not reported in recent reviews (that were retrieved and analysed). There is increasing evidence that acid suppression may place susceptible infants and children, particularly those with defective immune systems or with indwelling catheters, at risk for the development of lower respiratory tract infections, gastroenteritis and candidaemia, and in premature infants may increase the risk of necrotizing enterocolitis and nosocomial infections. One report not included in our analysis was a retrospective study of 274 very low birth weight infants who were ( $n=91$ ) or were not ( $n=183$ ) exposed to ranitidine during their hospitalization [72]. The authors reported that the risks of necrotizing enterocolitis, nosocomial infection and mortality were significantly higher in the exposed infants (odds ratio 6.6, 95% confidence interval 1.7–25; odds ratio 5.5, 95% confidence interval 2.9–10.4; mortality rate 9.9% vs. 1.6%, respectively;  $P=0.003$ ). This paper is both provocative and concerning, but its nonprospective, noncontrolled and nonblinded design limits its significance as ranitidine exposure may have been associated in a non-causal manner with the above-mentioned complications. Nevertheless, one should carefully weigh the use of acid-suppressing agents to ameliorate GERD symptoms against the inherent risks of the medications.

A meta-analysis of metoclopramide in children younger than 2 years with GERD confirmed a decrease in GERD symptoms [73]. However, this efficacy comes at the cost of significant AEs that include drowsiness, restlessness and extrapyramidal reactions in 10–20% of patients from our search and up to 34% of patients reported in older studies [73]. Therefore, we support the most recent statement in the American Academy of Pediatrics clinical report on GER, suggesting that: 'there is insufficient evidence to support the routine use of any prokinetic agent for the treatment of GERD in infants or older

children' [74]. At this time, thickening agents have not been studied adequately in the paediatric population, both in terms of efficacy and AEs, so their routine use cannot be recommended as independent agents [70].

The weaknesses of the research carried out in the field of GERD therapy so far include a relatively low number of drug trials conducted in the paediatric age group, as compared with the much larger number of adult studies; and combined sample sizes that were too small in nearly all the included articles, for all medications, that we studied. Finally, the reporting quality of many of the studies retrieved in our search was very poor, which may have significantly affected the results, a phenomenon almost universally described when dealing with AE reporting [75].

Thus, our recommendations are that the *primum non nocere* ('first, do no harm') rule should also apply to paediatric GERD. We suggest that the use of GERD medications should be used only after nonpharmacological measures have been taken with incomplete success, to infants and children with significant symptoms, and that the use of such medications in 'happy spitter' infants should be avoided. The use of the minimum number of acid-suppressant medicines, at the lowest dose, for the shortest period should enable physicians to minimize the rate and the severity of AEs [76]. Continual vigilance by prescribers and the reporting of AEs should be performed in order to improve knowledge and reduce the number of AEs that occur.

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