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Proton Pump Inhibitors in Pediatrics: Evaluation of Efficacy in GERD Therapy

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Abstract: Gastroesophageal reflux (GER) is defined as the passage of gastric contents into the esophagus. It occurs in healthy infants and can be considered physiological process. Uncomplicated GER can present with recurrent vomiting or regurgitation without any other symptoms and is usually managed by educating, reassuring, and guiding the parent without other intervention. GER disease (GERD) refers to the appearance of troublesome symptoms or complications (erosive esophagitis, ulceration, Barrett's esophagus) and may warrant acid suppression. Proton Pump Inhibitors (PPIs) are the most effective pharmacologic agents available for the treatment of children with GERD. In the pediatric practice only omeprazole, lansoprazole and esomeprazole are available over the first year of life. The empiric use in infants with nonspecific symptoms (excessive crying, regurgitation, feeding refusal, chronic cough) is frequent without randomized controlled study. Our paper will focus on the correct indications, dosages, duration of treatment and safety of PPI use in pediatric population.

Keywords: Proton Pump Inhibitors, GERD, children.

INTRODUCTION

The definition of Gastroesophageal Reflux Disease (GERD), especially in infants, is still uncertain. Recently, the new definition proposed is that GERD occurs when reflux of gastric contents is the cause of troublesome symptoms and/or complications [1]. In infants, many symptoms such as excessive crying or irritability, failure to thrive, food refusal and apnea are often considered as being suggestive of GERD, but these symptoms may also be due to other causes such as colic, constipation, infection or food intolerance. In most cases, conservative management, reassurance of the parents and non-pharmacological measures may improve symptoms and obviate pharmacologic therapy. Medical therapy can include proton pump inhibitors (PPIs) or histamine 2-receptor antagonist (H_2RA) use. These options are effective for healing erosive esophagitis (EE) in children and adolescents. Optimal doses of PPIs approved for pediatric patients (OME, ESO in Europe, OME, LANSO and ESO in USA) range from 0.3 mg to 3.5 mg/kg/day (maximum 80 mg; age range 3 weeks to 18 years) [2]. For LANSO, also in the formulation of orally disintegrating tablet (LADT), the dosage approved by Health Canada for the treatment of GERD in those aged 1 to 11 years is 15 mg (<30 kg) or 30 mg (>30 kg) once daily for up to 12 weeks [3]. A dose of 7.5 mg once daily in those weighing <10 kg has also been recommended. In conclusion, higher doses for some PPIs are needed in infants and children than in adolescents and adults, to treat acid-related disorders (Table **1**).

In our opinion, empiric use of PPIs in infants and children, without specific diagnostic testing, is also becoming prevalent and the prescriptions and/or overuse are increasing. Therefore, correct indications for the use of PPI molecules and pediatric peculiarities regarding pharmacodynamics, pharmacokinetics and bioavailability should be carefully followed.

Table 1. PPI Dosage in Children

	mg/kg/day	Approved Use in Pediatric Population
OMEPRAZOLE	0.7-3.5	Europe-USA
LANSOPRAZOLE	0.7-1.44	USA
ESOMEPRAZOLE	0.2-1	Europe-USA

PATHOPHYSIOLOGY OF GERD IN CHILDREN AND ADOLESCENT

A community-based survey in the United States reported that 19.8% of adults experience heartburn or regurgitation at least once, weekly [4]. A retrospective population-based cohort study in Rochester found that the incidence of GER in children aged < 5 years was 0.9/1.000 person-years [5]. GER can be considered a normal physiological process in infants and children but regurgitation is perceived as a "problem" by parents. Recurrent regurgitation occurs in 50% of infants in the first three months of life, in 67% in 4 months old infants, and in 5% of 10 to 12 months olds. In infants, regurgitation, crying, arching of the back during feeding, and irritability can be classified as GER-plus syndrome [6, 7]. Only a small minority of infants develop GERD or EE, with symptoms such as anorexia, dysphagia (difficulty in swallowing), hematemesis, anemia or failure to thrive. In contrast, the pre-

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dominant symptoms in older children (6-17 years) can be epigastric pain or heartburn [8]. Sherman P. *et al*. [9], in a symptoms-based classification, have defined the "Typical Reflux Syndrome" as a condition characterized by heartburn, with or without regurgitation, that can be diagnosed on the basis of the characteristic symptoms, without any additional diagnostic testing. In pediatric patients, esophageal complications of GERD include EE, stricture, Barrett's Esophagus and, rarely, adenocarcinoma [9]. These complications occur more frequently in patients with significant neurological impairment [10], and often, in addition to neonatal esophageal surgery, hiatal hernia [11] and obesity [12]. Numerous small observational studies as well as clinical practices have shown that GERD is prevalent among patients with chronic lung disease such as cystic fibrosis [13]. Positive family history for GERD or its complications are considered predisposing conditions. With regard to extraintestinal manifestation, it is known that GERD may be associated with sleep disorders, chronic cough, chronic laryngitis, asthma, chronic sinusitis, hoarseness and Apparent Life- Threatening Events (ALTE), but a cause and effect relationship with these events has not yet been proved [9, 14]. The only conditions reported in association are dental erosion [15] and Sandifer's syndrome [16]. All infants, including premature infants from 24^{th} gestational week, are able to maintain an intragastric pH below 4 from the first day of life [17]. Parietal cell mass is a variable in the production of gastric acid and increases with fetal weight and age [18]. Acid secretion normalizes after around 6 months of life, with a production of acid approximately 0.2 mEq/kg/h; the same values that occur in young adults. Gastric acid secretion is under nervous and hormonal influence. Multiple factors interact to regulate gastric acid production [19]. The structural development of the stomach is completed by the $14\text{-}15^{th}$ week of gestation, and cells appear to contain the components necessary for specific function [20]. The recognition that H+, K+-ATPase was the final step of acid secretion culminated in the development of a class of drugs, proton pump inhibitors (PPIs), which are targeted at inhibiting this enzyme [21]. Ontogenic development of hepatic microsomal systems, especially CYP2C19 and CYP3A4 systems, are involved in the metabolism of PPIs. It has a low enzymatic capacity in the first weeks of life and then, an activity similar to that of adults around 6-12 months of life. During the period of 1-6 years this activity is greater than in adults, to later return to adult levels at the end of puberty [22].

PHARMACOKINETICS OF PPIs IN PEDIATRICS

PPIs such as omeprazole (OME), esomeprazole (ESO), lansoprazole (LANSO), pantoprazole (PANTO) and rabeprazole (RABE), are substituted benzimidazoles that suppress acid by inhibiting the enzyme hydrogen-potassium adenosine triphosphatase (H+, K+- ATPase, or gastric proton pump), the final step of gastric acid secretion. ESO, the S-isomer of OME, is the only single-isomer PPI available. Although similar in structure, PPIs exhibit differences with regard to metabolism. PPIs are metabolized to varying degrees by the hepatic cytochrome P450 (CYP) enzyme system, principally the CYP2C19 enzyme. It has been demonstrated that the expression of CYP2C19 is under genetic control, and that individuals can be classified as rapid extensive metabolizer (RM), intermediate metabolizer (IM) and poor metabolizer (PM) based on their CYP2C19 genotype. The pharmacokinetics and pharmacodynamics of PPIs depend on CYP2C19 genotype status. In comparison to individuals who have a rapid extensive metabolizer (RM) phenotype for CYP2C19, PMs have a substantially higher exposure (i.e. increased plasma concentrations and area under plasma concentrations AUC) from a therapeutic dose of a PPI [23]. These differences do, however, not warrant routine genotyping in clinical practice [24]. In neonates, there is a reduced metabolic capacity of OME and LANSO in combination with reduced clearance [25]. The increased metabolic capacity, instead, is present in children (1- 6 years), so an increased dose of PPIs according to weight should be considered [26]. Moreover, several studies have shown that preterm infants and term neonates present an immaturity of drug-metabolizing enzyme pathways (CYP2C19, CYP3A4) [27, 28], and this could explain the higher systemic exposure to PPIs in this population than in older children [29-31].

DOSAGE REGIMENS OF PPIs IN PEDIATRICS

In children, PPIs are rapidly absorbed after oral administration and are also rapidly metabolized similarly to adults; but clearance is apparently faster in children than in adults because of the increased metabolic capacity and differences in bioavailability [32]. In 27 children with GERD aged 1–11 years, the pharmacokinetic properties of ESO were both dose (between 5–20 mg) and age-dependent. Younger children (1–5 years) showed a more rapid metabolism compared with the older children (6–11 years) [33]. In 28 adolescent patients with GERD aged 12–17 years, the mean AUC and Cmax values of ESO were 3.5-fold higher with the 40 mg dose as compared to the 20 mg dose with single-and repeated-dose administration, confirming nonlinear pharmacokinetics [34]. The pharmacokinetics of LANSO (15 mg/day) in children with GERD aged 13–24 months was comparable to older children and adults [35]. In a study conducted in 12–16 year old adolescents, the pharmacokinetic properties of RABE were similar to adults [36].

PPI USE IN CHILDREN AND INFANTS

Infants

No PPI has been approved for use in infants (0-12 months aged) younger than 1 year of age, and there are special concerns pertaining to prescription of PPIs in infants [13]. Nevertheless, the number of PPI prescriptions written for infants has increased many folds in recent years despite the absence of evidence for acid-related disorders [7, 37, 38]. However, results from studies of various available PPIs in infants aged <1 year, including preterm infants and newborns (aged 0-1 month) are currently being reported [39-42]. A double-blind placebo-controlled trial of OME in irritable infants who either had esophagitis or a Reflux index (RI) > 5% found no difference in crying between treated and placebo groups despite highly effective acid suppression in the treated group [43]. A large double-blind study of 162 infants randomized to 4 weeks of placebo or LANSO showed an identical 54% response rate in each group, using an endpoint of >50% reduction of measures of feeding-related symptoms (crying, irritability, arching) and other parameters of the I-

GERQ-questionnaire [42]. Studies in infants with PANTO and ESO have also demonstrated similar negative results; symptoms improved during the open-label run in period, but the PPI group failed to separate from the placebo group during the withdrawal phase [41, 44, 45]. Symptoms in infants could be related to immaturity and physiologic reflux, which does not need pharmacologic therapy, but improves with time as the infant matures and relies more on solid food. The available evidence does not support an empiric trial of acid suppression in infants with unexplained crying, irritability, or sleep disturbance [14]. Many infants with a clinical diagnosis of GERD can have physiologic reflux, which does not require pharmacologic therapy [6]. In a similar study in infants and preterm infants who were enrolled on the basis of GERD symptoms, Springer *et al*. [40] assessed the effect of LANSO on pH-metry parameters, and the effects on gastric pH were similar in both treated and placebo group. Omari *et al*. [29] have studied the effect of OME on pH-metry parameters and symptoms in 10 preterm infants who were enrolled on the basis of symptoms and a reflux index > 5%. The patients have received a treatment with OME and placebo for 7 days each in a crossover fashion. OME provided statistically significant improvements over placebo in the reflux index, as well as the percentage of time with gastric pH < 4, and other parameters. The authors were surprised to see no improvement in symptoms despite the normalization of the reflux index, confirming the dissociation between esophageal pHmetry and symptoms [13, 40, 46]. Di Fiore *et al*. [47] found that 59% of reflux events underlined by ph-metry in neonates are not detected when impedance-based monitoring criteria are used to detect reflux, especially among younger neonates. Many of these studies focused on symptoms as the key outcome measures for efficacy, although they all also assessed the pharmacodynamic indicator of esophageal (with or without gastric) pH monitoring.

The main aspects of the use of PPI in infants can be summarized as: a) the symptoms presented by infants may be difficult to quantify accurately; b) it is often difficult to confirm a relationship between symptoms and reflux of gastric contents into the esophagus; c) the symptoms may be nonspecific and unrelated to reflux disease, but can be secondary to functional conditions without organic pathology (happy spitter) [48, 49], or secondary to cow's milk allergy. This condition may be excluded with empiric 2-weeks trial of extensively hydrolyzed or amino acid–based formula [14]. In these clinical conditions there is no indications for PPI use.

Children

Non-pharmacologic or conservative therapy for GER in children nearly always begins with lifestyle modifications (obesity, positioning during and after feedings, quantity and type of feeding [50]. The value of these approaches is well documented and can be considered a proper first-line therapy [51]. For children who remain symptomatic or develop EE or complications (hematemesis, dysphagia), treatment with acid suppressant may be warranted. In the late 1970s, the efficacy of histamine 2-receptor antagonists (H_2 RA), such as cimetidine and ranitidine, which are active drugs available to block receptors within 1-2 hours after absorption, was demonstrated [52]. One disadvantage of H_2RA is that tolerance, or tachyphylaxis, often develops and the effect of the drug is diminished within a few days [53].

In children, as in adults, PPIs are highly efficacious for the treatment of symptoms due to GERD and the healing of erosive disease [14]. Other clinical indications include peptic ulcer disease and related complications such as gastrointestinal bleeding, Helicobacter Pylori disease and Barrett's Esophagus [54]. The most important indication is the treatment of EE or, according to the new classification of Sherman *et al*. [9], the "Typical Erosive Reflux Syndrome". This condition is detectable in more frequency in children aged up to 8 years. PPIs are more effective than H_2RAs for healing and relief of GERD symptoms. Both medications are more effective than placebo [55]. Most children require a daily dose of PPI to obtain symptomatic relief and heal esophagitis [56]. The optimum dosage regimen is 15 to 30 minutes before breakfast. However, improvement of heartburn, following treatment, does not confirm a diagnosis of GERD as symptoms may improve spontaneously or respond to a placebo effect [14]. In children and adolescents (> 8 yrs), expert opinions suggest lifestyle changes (diet changes, weight loss, sleeping position, no late night eating) and an empiric trial of PPIs for up to 4 weeks [57, 58]. In some patients, abrupt discontinuation of treatment may result in acid rebound that precipitates symptoms; therefore, it is recommended that antisecretory therapy be weaned slowly [59, 60]. With regard to maintenance therapy, in a prospective study of children where EE had healed following 3 months of OME therapy, only half maintained remission of symptoms and endoscopic disease in a maintenance phase during which they received half the healing dose of PPI [61]. In another study, where EE healed after 3 months of OME treatment (1.4 mg/kg/day) patients underwent double-blind randomization into 3 groups, receiving either maintenance therapy with OME at half the healing dose, ranitidine, or placebo for 6 months. In all 3 groups, few patients had a relapse of symptoms during or after the maintenance therapy [62]. Patients who require higher PPI doses to control symptoms and produce healing are those with conditions (neurological impairment) that predispose to severe-chronic GERD and those with higher grades of esophagitis or Barrett's Esophagus [14] (Table **2**). In patients with asthma who also have heartburn, reflux may be a contributing factor to the asthma, but, as has been shown, acid suppression did not change respiratory symptoms [63]. The majority of these studies are conducted in prevalence adult population with limited evidence about pediatric population.

Table 2. Our Indications to PPI Use in Infants (0-1 Years Aged) and Children (1-12 Years Aged)

1. Healing of acute erosive esophagitis
2. Mantaining remission in patients with erosive esophagitis
3. Symptomatic relief of nonerosive reflux disease
4. Nocturnal acid secretion and relevant reflux
5. Supraesophageal symptoms of GERD

ARE ALL PPIs CURRENTLY AVAILABLE IN PEDIATRICS ?

Most studies of PPIs in children are open-label and uncontrolled. Empirical studies show that the off-label use of drugs in pediatrics is connected with a significantly increased risk of an adverse drug reaction [64, 65]. This is due to the fact that these drugs are only tested in, and licensed for, adult patients and the transfer of knowledge to the pediatric population is sometimes doubtful. There is a high incidence of off-label use both in out-patient and in-patient settings, which ranges from 10.5% up to 90% [66-68]. In Europe, over 50% of drugs used in children are off-label [69]. The use of these drugs in neonatal intensive care unit (NICUs) seems to be far greater than in other pediatric settings. It has been reported that at least 30% of neonates received treatment with gastric acidity inhibitors at the time of discharge from NICU [70]. With regard to PPIs, through a study conducted by Tafuri *et al.* [71], after upgrading EUDRANET databases and FDA web-site, 19 pediatric studies involving the use of PPIs in GERD were selected. Available data of pharmacokinetics, efficacy and profile safety were analyzed. Data on OME can be found in 6 trials (3 RCT) for a total of 282 children treated; data on LANSO, from 6 studies (1 RCT), for a total of 257 children; data on PANTO, from 2 trials (1 RCT), for a total of 68 children; data on RABE , from only 1 trial, for a total of 24 children. OME, LANSO and ESO have been assessed as appropriate on the basis of substantial evidence available on pharmacokinetics, efficacy and security, and these PPIs, at present, are being approved by the US Food and Drug Administration for use in children (1–17 years). In Europe, only OME and ESO have been approved. No PPI has been approved for use in infants younger than 1 year of age [14]. The use of other molecules is considered off-label.

WHEN ARE WE TALKING ABOUT OVERUSE OF PPI IN CHILDREN?

PPIs are one of the most frequently prescribed classes of drugs in the world as they combine a high level of efficacy with low toxicity [72]. Already data in adult populations show that PPIs are being overprescribed worldwide in both primary and secondary care [73-77]. Between 25% and 70% of patients taking these drugs have no appropriate indication.

Although it might be assumed that overprescribing occurs mainly in primary care, some surveys in Australia [73], Ireland [74] and UK [75] have shown that between 33%-67% of hospitalized patients did not meet the criteria for taking PPI drugs. In a series of hospital inpatients in Michigan, USA, 20% of patients were taking PPIs on admission and another 40% were prescribed the drug during their hospital stay (mostly for prophylaxis). At discharge, half the patients were taking PPIs- more than double the number who were taking the drug when admitted [76].

Also in pediatric populations, especially in infants, in recent years, there has been a remarkable increase in the use of PPIs. Barron *et al.*, in a retrospective study, found that the prevalence of use of PPIs increased 4-fold from 2000 to 2003, with a suggested 7.5-fold increase from 1999 to 2004 for infants younger than 12 months [37]. The most common diagnoses identified, in this retrospective analysis, through medical claims, included gastroesophageal reflux (59%), feeding problems (23%), upper respiratory infections (23%), pain from gas (20%) and esophagitis (21%). This review of treatment patterns for this infant population showed that PPIs were not first-line therapy in most patients, but "step-up" strategy was common. Almost 60% of infants received a trial of H_2 blocker before a PPI was given. Khoshoo *et al.* [38], have shown that the majority of infants enrolled (64 infants with persistent regurgitation) who were prescribed antireflux drugs did not meet the diagnostic criteria for GERD. Only 20% of the infants in the study had evidence of an underlying pathology to explain their symptoms, such as GERD, pyloric stenosis, or renal tubular acidosis. In conclusion, overdiagnosis of acid-related disorders and over-prescription are the major problems that can limit the efficacy of PPI use (Table **3**).

SAFETY AND LONG TERM USE

PPIs have demonstrated an excellent safety profile after approximately two decades of clinical use in adults [78]. In children, several trials, in recent years, have shown that these drugs appear to be effective, safe and well tolerated, also for long-term use [42,79-81]. There are potential risks associated with acid suppression resulting from PPI therapy in children. Different categories of adverse effects related to PPIs be include idiosyncratic reactions, drug–drug interactions, drug-induced hypergastrinemia, and drug-induced hypochlorhydria. The most common idiosyncratic side effects are headache, diarrhea, constipation, and nausea, that occur in up to 14% of children taking PPIs [34,81]. It has been shown that PPIs, inducing acid suppression and hypergastrinemia, could determine parietal cell hyperplasia [82, 83] enterochromaffin cell-like (ECL) hyperplasia [61] and occasional fundic gland polyps [84]. A prospective study monitoring patients treated for up to 2 years [61], and retrospective studies of patients treated up to 11 years [81] found only mild grades of ECL hyperplasia [85]. PPIs may increase rates of community-acquired pneumonia in adults and children, and gastroenteritis, candidemia and necrotizing enterocolitis in preterm infants [86-90]. To date, there are no data available to assess the effect of PPI therapy on the flora of infants and children, or the consequences of any alterations. Other adverse effects have been reported in elderly patients undergoing chronic PPI therapy [91], such as deficiency of vitamin B12 and increased incidence of hip fractures [92, 93], but these findings have not been confirmed by recent studies [94, 95]. PPIs are considered to be the most common cause of acute interstitial nephritis in adults [96]. No childhood cases have been described. Animal studies suggest that acid suppression may predispose to the development of food allergy [97], but this remains to be confirmed by human studies. Finally, it is possible to conclude that generally, PPIs, although not yet approved in their entirely in children, are safe and well tolerated drugs [98].

CONCLUSIONS

Recent evidence suggests that empiric use of PPIs in infants with crying symptoms unresponsive to conservative management is both inefficacious and potentially harmful. Not all PPIs have been approved for children who have a

Table 3. Different Pediatric Studies on PPI in Children and Adolescent

Authors	Design Study	Conclusion
Hassall E *et al*., J Pediatr 2000 [56]	Open multicenter study in children aged 1 to 16 years with erosive reflux esophagitis	Omeprazole is a PPI well tolerated and highly efficacy in children
Orenstein SR *et al*., J Pediatr 2009 [42]	Multicenter, DBRPCT in infants with persisting symptoms attributed to GERD.	No difference in efficacy between lansoprazole and placebo for symptoms attributed to GERD in infants age 1 to 12 months.
Heyman MB *et al*., JPGN 2007 [35]	Multicenter prospective study in children between 13 and 24 months of age with GERD.	Lansoprazole pharmacokinetic and pharmacodynamic parameters in children between 13 and 24 months of age that are similar to those results observed in older children as well as adults.
Kearns GL *et al*., JPGN 2003 [23]	Review on pharmacokinetic and pharmacodynamic of PPI in infants and children	The pharmacokinetics and pharmacodynamics of PPIs depend on CYP2C19 genotype status
Hassall E *et al*., J Pediatr 2007 [11]	Retrospective cohort study in children receiving PPI continuously for up to 11 years duration	Children with underlying GERD-predisposing disorders (esophageal atresia) take advantages of long-term PPI use.
Gibbons TE *et al*., Paediatr Drugs 2003 [2]	Review	Optimal doses of PPIs approved for pediatric is ranging from 0.3 mg to 3.5 mg/kg/day (maximum 80 mg; age range 3 weeks to 18 years).

different pharmacokinetic profile from adults. PPI failure in children can be related to clinical and pharmacodynamic factors. Appropriate indications (Table **2**) for use of these drugs may lead to improved efficacy with reduced risk of side effects.

ABBREVIATIONS

PPI = Proton Pump Inhibitors

GER = Gastroesophageal Reflux

GERD = Gastroesophageal Reflux Disease

H_2RA = Histamine 2- receptor antagonist

ALTE = Apparent Life- Threatening Events

EE = Esophagitis Erosive

LES = Lower Esophageal Sphincter

OME = Omeprazole

ESO = Esomeprazole

LANSO = Lansoprazole

PANTO = Pantoprazole

RABE = Rabeprazole

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