Guide to Informed Decision-Making About PPIs: Research on Side Effects

The following research gives information on potential side effects of PPIs:

"A randomized prospective observational study was performed on 37 critically ill children aged from 1 month to 14 years of age who required prophylaxis for gastrointestinal bleeding. Of these, 19 received intravenous omeprazole 0.5mg/kg every 12 hours, and 18 received intravenous omeprazole 1mg/kg every 12 hours. Heart rate, systolic, diastolic and mean arterial blood pressure, central venous pressure and ECG were recorded at baseline, and at 15, 30, 60 and 120 minutes of the infusion. **There were no significant changes in the electrocardiogram, heart rate, blood pressure and central venous pressure. No patients required inotropic therapy modification. There were no differences between the two doses of omeprazole. Intravenous omeprazole administration of 0.5mg/kg and 1mg/kg is a hemodynamically safe drug** in critically ill children."

Solana MJ, López-Herce J, Botrán M, Urbano J, Del Castillo J, Garrido B. Efectos hemodinámicos del omeprazol por vía intravenosa en niños en estado crítico [Hemodynamic effects of intravenous omeprazole in critically ill children]. *An Pediatr (Barc)*. 2013

"We undertook a prospective randomized clinical trial in critically ill children at risk of gastrointestinal bleeding. The effect of 2 intravenous omeprazole regimens (0.5 or 1 mg/kg every 12 hours) on the gastric pH and incidence of gastrointestinal hemorrhage was compared. **No toxic adverse effects were detected, and there was no clinically significant bleeding."**

Solana MJ, López-Herce J, Sánchez A, et al. 0.5 mg/kg versus 1 mg/kg of intravenous omeprazole for the prophylaxis of gastrointestinal bleeding in critically ill children: a randomized study. *J Pediatr*. 2013

"Omeprazole is recognized as a safe and effective treatment of gastroesophageal reflux in older children, at an initial dosage of 0.7 mg x kg(-1) x day(-1)...The majority respond to a dosage of 0.7 mg x kg(-1) x day(-1), but increased dosages up to 2.8 mg x kg(-1) x day(-1) may be required."

Bishop J, Furman M, Thomson M. Omeprazole for gastroesophageal reflux disease in the first 2 years of life: a dose-finding study with dual-channel pH monitoring. *J Pediatr Gastroenterol Nutr*. 2007

"Omeprazole has been shown to be effective in the treatment of acid-related diseases. Marketed and extemporaneous formulations of omeprazole have been administered to children aged 2 months to 18 years for the treatment of erosive esophagitis, gastric ulcer, duodenal ulcer, HP infection, and related conditions at dosages of 5 to 80 mg/d (0.2-3.5 mg/kg/d) for periods ranging from 14 days to 36 months with a low incidence of adverse effects...**In uncontrolled clinical trials and case reports to date, omeprazole has been effective and well tolerated for the acute and chronic treatment of esophageal and peptic ulcer disease in children,** particularly those who had failed to respond to previous treatment with histamine2-receptor antagonists."

Zimmermann AE, Walters JK, Katona BG, Souney PE, Levine D. A review of omeprazole use in the treatment of acid-related disorders in children. *Clin Ther*. 2001

"**Omeprazole is well tolerated, highly effective, and safe for treatment** of erosive esophagitis and symptoms of gastroesophageal reflux in children, including children in whom antireflux surgery or other medical therapy has failed." (Reporting data on ages 1-16)

Hassall E, Israel D, Shepherd R, et al. Omeprazole for treatment of chronic erosive esophagitis in children: a multicenter study of efficacy, safety, tolerability and dose requirements. International Pediatric Omeprazole Study Group. *J Pediatr*. 2000

"Clinical manifestations of GOR in children range from regurgitation, food refusal, irritability, failure to thrive, hematemesis, wheezing and aspiration pneumonia, apnoea and apparent life threatening events in infants to clinically silent reflux...**Omeprazole has been shown to be effective in treating GOR-esophagitis resistant to H2 antagonist therapy even in high risk patients."**

Sandhu BK, Sawczenko A. Gastroesophageal reflux in children. *Indian J Pediatr*. 1999

"Following failure of conventional therapy for reflux oesophagitis, 15 children were treated with omeprazole 20 mg daily for a period of up to three months initially...**No complications from the use of omeprazole were recorded and some children have continued long-term treatment."**

Martin PB, Imong SM, Krischer J, Noblett HR, Sandhu BK. The use of omeprazole for resistant oesophagitis in children. *Eur J Pediatr Surg*. 1996

"As reported previously, our results suggest that omeprazole fails to prevent the morphological transition of parietal cells to an actively secreting phase, although it strongly inhibits acid secretion. **There were no adverse morphological changes in mitochondria and nuclei in any of the groups. Moreover, if omeprazole is administered at a pharmacologically effective dosage for a short period of time, it may not have serious effects on the ultrastructure of human parietal cells."**

Kato S, Fujii T, Nakano K, Naganuma H, Nakagawa H. The effects of omeprazole on the ultrastructure of gastric parietal cells. *J Pediatr Gastroenterol Nutr*. 1994

"Many of the studies considered had significant methodological flaws, although based on available evidence the following statements can be made. **For infant GERD, ranitidine and omeprazole and probably lansoprazole are safe and effective medications, which promote symptomatic relief, and endoscopic and histological healing of esophagitis.** There is less evidence to support the use of domperidone or metoclopramide. More evidence is needed before other anti-reflux medications can be recommended. The largest evidence base supports the early use of H(2) receptor antagonists or proton pump inhibitors."

Tighe MP, Afzal NA, Bevan A, Beattie RM. Current pharmacological management of gastro-esophageal reflux in children: an evidence-based systematic review. *Paediatr Drugs*. 2009

"Oral treatment with esomeprazole 0.25 mg/kg and 1 mg/kg was well tolerated and provided dose-related acid suppression, dose-related exposure to esomeprazole, and decreased esophageal acid exposure in infants 1-24 months old with GERD."

Omari T, Davidson G, Bondarov P, Nauclér E, Nilsson C, Lundborg P. Pharmacokinetics and acid-suppressive effects of esomeprazole in infants 1-24 months old with symptoms of gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr*. 2007

"Gastroesophageal reflux, common in infants, usually resolves spontaneously by 12 to 18 months. Gastroesophageal reflux disease (GERD) contributes to certain respiratory symptoms, but is reported to be due to other causal diseases, such as tracheolaryngeal anomaly, congenital esophageal hiatal hernia, and cerebral palsy, in pediatric patients. Their case histories (much belching and hiccups) and findings for the posterior glottitis, etc., suggested that symptoms might be induced by GERD, but, barium esophagography and esophagoscopy provided no conclusive proof. We could not monitor their ph because of the excessive physical and psychological stress involved. **After therapeutic trials with a proton pump inhibitor (lansoprazole 10-15 mg) for 8 weeks, all had recovered almost completely without side effects."**

Saigusa H, Niimi S, Saigusa U, Yagi T. Laryngeal Manifestations of Gastroesophageal Reflux Disease GERD in Pediatric Patients the Usefulness of Therapeutic Proton Pump Inhibitor PPI Trials. *Nihon Jibiinkoka Gakkai Kaiho*. 2001

"This prospective study enrolled children with EoE and histological remission to an 8-week esomeprazole trial (1 mg/kg/dose, twice daily). Esomeprazole was maintained at 1 mg/kg/day for 1 year. Fifty-seven children were included...Forty-nine children (86%) remained asymptomatic...**Mild and transient side effects without requiring PPI avoidance were observed in 5 children."**

Gutiérrez-Junquera C, Fernández-Fernández S, Cilleruelo ML, et al. Long-term Treatment With Proton Pump Inhibitors Is Effective in Children With Eosinophilic Esophagitis. *J Pediatr Gastroenterol Nutr*. 2018

"There is no causal association between treatment with esomeprazole and the occurrence of community-acquired respiratory tract infections, including pneumonia."

Estborn L, Joelson S. Frequency and time to onset of community-acquired respiratory tract infections in patients receiving esomeprazole: a retrospective analysis of patient-level data in placebo-controlled studies. *Aliment Pharmacol Ther*. 2015

"In otherwise healthy community-dwelling infants, current use of a PPI does not appear to increase the risk of CAP[Community-Acquired Pneumonia] or other LRTIs [Lower Respiratory Tract Infections]."

Blank ML, Parkin L, Zeng J, Barson D. Proton Pump Inhibitors and Infant Pneumonia/Other Lower Respiratory Tract Infections: National Nested Case-control Study. *J Pediatr Gastroenterol Nutr*. 2018

"Prolonged treatment of pediatric patients with PPIs has not caused cancer or significant abnormalities."

Ward RM, Kearns GL. Proton pump inhibitors in pediatrics : mechanism of action, pharmacokinetics, pharmacogenetics, and pharmacodynamics. *Paediatr Drugs*. 2013

"Patients were initially given omeprazole at 10 to 20 mg; the dose was titrated upward until results of a subsequent 24-hour intraesophageal pH study was normal. Symptoms and signs abated and evidence of esophagitis diminished in all patients. Omeprazole was given for periods of 5.5 to 26 months (mean, 12.2 months). The effective total dose was 20 to 40 mg (0.7 to 3.3 mg/kg) in 11 patients, 10 mg (0.7 mg/kg) in 1 patient, and 60 mg (1.9 to 2.4 mg/kg) in 3 patients. The dosage range was 0.7 to 3.3 to mg/kg per day (mean, 1.9 mg/kg). **Omeprazole appears to be safe for short-term use, but further studies are needed to assess long-term safety because the significance of chronically elevated gastrin levels in children is unknown."**

Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *J Pediatr*. 1993

"Lansoprazole was generally well tolerated in children and adolescents, with the most common treatment-related adverse events being gastrointestinal events and headache."

Croom KF, Scott LJ. Lansoprazole: in the treatment of gastro-oesophageal reflux disease in children and adolescents. *Drugs*. 2005

"Forty children (age range, 18 days-14 years) with gastric acid-related disorders entered an open study and received lansoprazole in a single dose of 17 mg. m(-2) (group A) or in multiple doses (17 mg. m(-2) per day) for 7 to 14 days (group B)... **Lansoprazole was well tolerated in children."**

Tran A, Rey E, Pons G, et al. Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. *Clin Pharmacol Ther*. 2002

"Infants with symptom improvement were randomized to esomeprazole...**Esomeprazole was well tolerated."**

Winter H, Gunasekaran T, Tolia V, Gottrand F, Barker PN, Illueca M. Esomeprazole for the Treatment of GERD in Infants Ages 1-11 Months. *J Pediatr Gastroenterol Nutr*. 2015

"The mean number of acid reflux episodes of >5 minutes duration decreased from 6 at baseline to 3 and 2 with esomeprazole 0.25 mg/kg and 1 mg/kg, respectively. **Both esomeprazole dosages were well tolerated."**

Omari T, Davidson G, Bondarov P, Nauclér E, Nilsson C, Lundborg P. Pharmacokinetics and Acid-suppressive Effects of Esomeprazole in Infants 1-24 Months Old With Symptoms of Gastroesophageal Reflux Disease. *J Pediatr Gastroenterol Nutr*. 2015

"In children ages 1 to 11 years with endoscopically proven GERD, **esomeprazole** (at daily doses of 5, 10, or 20 mg) **was generally well tolerated."**

Gilger MA, Tolia V, Vandenplas Y, Youssef NN, Traxler B, Illueca M. Safety and Tolerability of Esomeprazole in Children With Gastroesophageal Reflux Disease. *J Pediatr Gastroenterol Nutr*. 2015

"In this randomized, double-blind, placebo-controlled multicenter study, neonates (premature to 1 month corrected age; n = 52) with signs and symptoms of GERD received esomeprazole 0.5 mg/kg or placebo once daily for up to 14 days. **Esomeprazole was well tolerated** and reduced esophageal acid exposure and the number of acidic reflux events in neonates."

Davidson G, Wenzl TG, Thomson M, et al. Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. *J Pediatr*. 2013

"Remission of erosive oesophagitis is maintained with omeprazole treatment for at least 21 months in most children aged 1-16 years, and **the drug is well tolerated**.To maintain remission, some 60% of patients require more than half the dose required for healing. In children with GERD-predisposing conditions, GERD is often chronic and relapsing, and requires long-term management."

Hassall E, Shepherd R, Koletzko S, Radke M, Henderson C, Lundborg P. Long-term maintenance treatment with omeprazole in children with healed erosive oesophagitis: a prospective study. *Aliment Pharmacol Ther*. 2012

"Patient databases were screened for long-term PPI use, defined as more than 9 months of continuous prescription, between 1989 and 2004. The median duration of PPI use in the 166 patients in the study group was 3 years (range, 0.75 to 11.25 years). Omeprazole was used in 90% of the patients; lansoprazole, in 7%. **Six adverse reactions seen in 4 patients were potentially related to PPI (nausea and diarrhea, skin rash, agitation, and irritability).** Children with underlying GERD-predisposing disorders compose the majority of long-term PPI users. **Few adverse reactions to these drugs occur, and discontinuation of the drug is seldom indicated. These preliminary data suggest that PPIs may be efficacious and safe for continuous use for up to 11 years' duration in children."**

Hassall E, Kerr W, El-Serag HB. Characteristics of children receiving proton pump inhibitors continuously for up to 11 years duration. *J Pediatr*. 2007

"Gastroesophageal reflux disease (GERD) has a prevalence of 10% to 20% in the pediatric population...Omeprazole is the elective drug for a proper treatment...**No adverse events were observed in infants and the suspension flavor was palatable...The taste of the solution was well accepted by all the babies, which is a very important finding for this age group.**"

Orsi M, Donato G, Busoni V, Naisberg G, Caruso N. Eficacia acidosupresora del omeprazol en polvo en lactantes con reflujo gastroesofágico. Estudio piloto [Gastric acid suppression of a new oral powder omeprazole suspension for infants with gastroesophageal reflux disease. A pilot study]. *Acta Gastroenterol Latinoam*. 2011

"The effect of PPIs on this developing microbiome has never been studied...In this prospective longitudinal study 12 infants with proven GERD received oral PPIs for a mean period of 18 weeks (range 8-44). Stool samples were collected before ("before PPI") and 4 weeks after initiation of PPI therapy ("on PPI"). A third sample was obtained 4 weeks after PPI discontinuation ("after PPI")...**PPI treatment has only minor effects on the fecal microbiome. After discontinuation of PPI treatment the fecal microbiome correlated to patients' age and nutrition."**

Castellani C, Singer G, Kashofer K, et al. The Influence of Proton Pump Inhibitors on the Fecal Microbiome of Infants with Gastroesophageal Reflux-A Prospective Longitudinal Interventional Study. *Front Cell Infect Microbiol*. 2017

"The results of this small study suggest that, in children aged 1 to 11 years who had GERD, the PK properties of esomeprazole may be both dose and age dependent and that younger children might have a more rapid metabolism of esomeprazole per kilogram of body weight compared with older children. **Esomeprazole was well tolerated at doses of 5, 10, and 20 mg in the pediatric patients studied."**

Zhao J, Li J, Hamer-Maansson JE, et al. Pharmacokinetic properties of esomeprazole in children aged 1 to 11 years with symptoms of gastroesophageal reflux disease: a randomized, open-label study. *Clin Ther*. 2006

"Most patients who had any upper gastrointestinal symptoms at baseline were asymptomatic at the end of the study. Thirty-three patients (66%) reported ≥1 adverse events, including three patients who reported serious adverse events not judged to be causally related to esomeprazole. Conclusions: **Oral esomeprazole, at 10 mg or 20 mg once daily, had a similar safety, efficacy, and pharmacokinetic profile in Japanese pediatric patients to that previously seen in adults and Caucasian children."**

Shimizu T, Nakayama Y, Ishii E, et al. Oral esomeprazole in Japanese pediatric patients with gastric acid-related disease: Safety, efficacy, and pharmacokinetics. *Pediatr Int*. 2019

"Lansoprazole, when administered on the basis of body weight in children between 1 and 11 years of age, is safe and well-tolerated."

Tolia V, Fitzgerald J, Hassall E, Huang B, Pilmer B, Kane R 3rd. Safety of lansoprazole in the treatment of gastroesophageal reflux disease in children. *J Pediatr Gastroenterol Nutr*. 2002

"The drug [lansoprazole] is generally well tolerated in children with GERD. In the largest study, **the most common treatment-related adverse events occurring during therapy were constipation and headache."**

Scott LJ. Lansoprazole: in the management of gastroesophageal reflux disease in children. *Paediatr Drugs*. 2003

"PPI therapy is associated with higher infection rates in children with normal CYP2C19 function than in those with increased CYP2C19 function, highlighting this adverse effect of PPI therapy and the relevance of *CYP2C19* genotypes to PPI therapeutic decision-making."

Bernal CJ, Aka I, Carroll RJ, et al. CYP2C19 Phenotype and Risk of Proton Pump Inhibitor-Associated Infections. *Pediatrics*. 2019

"It could be interesting to underline that we observed an **increased incidence of intestinal and respiratory infection in otherwise healthy children** taking GA inhibitors for GERD treatment."

[This article studied children 0-36 months who had taken PPIs and calculated the rates of respiratory and gastrointestinal infections. Infection rates seemed to be influenced by genetics and how quickly or slowly patients' bodies metabolize the drug.]

Canani RB, Cirillo P, Roggero P, et al. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics*. 2006

"A high percentage of children (61%) receiving long-term PPI continuously for up to 10.8 years (median 2.84 years) develop minor degrees of ECL [enterochromaffin-like] hyperplasia. **This has no known clinical significance. Children on PPIs for this duration do not appear to develop atrophic gastritis or carcinoid tumours."**

Hassall E, Owen D, Kerr W, Sturby T, Richardson P, El-Serag H. Gastric histology in children treated with proton pump inhibitors long term, with emphasis on enterochromaffin cell-like hyperplasia. *Aliment Pharmacol Ther*. 2011

"Antibiotics, acid suppressants and the combination of multiple medications in the first 2 years of life are associated with a diagnosis of childhood obesity. Microbiota-altering medications administered in early childhood may influence weight gain."

[Only 3.3% of the patients represented in this article are ones who were prescribed a PPI.]

Stark CM, Susi A, Emerick J, Nylund CM. Antibiotic and acid-suppression medications during early childhood are associated with obesity. *Gut*. 2019

"The high use of oral antibiotics, PPI, and H2B among outpatients **may be a contributing factor to the rise of Clostridium difficile infection** in the community."

[The study states that adults were prescribed PPIs FAR more frequently than children.]

Faden HS, Ma CX. Trends in Oral Antibiotic, Proton Pump Inhibitor, and Histamine 2 Receptor Blocker Prescription Patterns for Children Compared With Adults: Implications for Clostridium difficile Infection in the Community. *Clin Pediatr (Phila)*. 2016

"Children with aspiration who are treated with PPI have increased risk of hospitalization compared with untreated patients. These results support growing concern about the risks of PPI use in children."

[All of the patients in this study aspirated. The majority (95%) that used a PPI and were hospitalized also had an enteral feeding tube.]

Duncan DR, Mitchell PD, Larson K, McSweeney ME, Rosen RL. Association of Proton Pump Inhibitors With Hospitalization Risk in Children With Oropharyngeal Dysphagia. *JAMA Otolaryngol Head Neck Surg*. 2018

"Infants prescribed AST [Acid Suppression Therapy] had an earlier median first fracture age (3.9 vs 4.5 years). After adjustment, increased fracture hazard was associated with PPI use (21%) and PPI and H2RA use (30%), but not H2RA use alone. Longer duration of AST treatment and earlier age of first AST use was associated with increased fracture hazard.Conclusions: Infant PPI use alone and together with H2RAs is associated with an increased childhood fracture hazard, which appears amplified by days of use and earlier initiation of ASTs. Use of AST in infants should be weighed carefully against possible fracture."

[This article studied children who were prescribed acid suppressing drugs prior to age 1. It indicates that children may be more susceptible to fractures later in life. It is important to remember, however, that correlation does not prove causation. It is also worth noting that the research isn't saying kids who took PPIs get fractures, while kids who didn't take PPIs do not. It's saying that fractures may be more likely to occur 6 months earlier than they otherwise might have.]

Malchodi L, Wagner K, Susi A, Gorman G, Hisle-Gorman E. Early Acid Suppression Therapy Exposure and Fracture in Young Children. *Pediatrics*. 2019

"Allergic diseases are prevalent in childhood. Early exposure to medications that can alter the microbiome, including acid-suppressive medications and antibiotics, may influence the likelihood of allergy...This study found associations between the use of acid-suppressive medications and antibiotics during the first 6 months of infancy and subsequent development of allergic disease. Acid-suppressive medications and antibiotics should be used during infancy only in situations of clear clinical benefit."

[This article brings up an interesting connection between PPI use and allergic disorders, the highest of which was food allergy. It seems to fail to draw the connection between the fact that some of our children may need PPIs BECAUSE of their allergies or intolerances, and the way those influence the production of acid.]

Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM. Association Between Use of Acid-Suppressive Medications and Antibiotics During Infancy and Allergic Diseases in Early Childhood. *JAMA Pediatr*. 2018

"The use of a PPI is a risk factor for ultra-late onset of Group B Streptococcus meningitis. The use of PPI in infants should be closely monitored in the light of changes in the gut microbiota, in the oropharyngeal and of the respiratory tract colonization, potentially with pathogenic flora."

[This article is about one specific nine-month old child, not a large-scale study.]

Bîrluţiu V, Luca CM, Bîrluțiu RM. Streptococcus agalactiae meningoencephalitis associated with gastroesophageal reflux disease and chronic proton pump inhibitors use, in a 9 month-old infant: a case report. *BMC Pediatr*. 2018

"Data on children (aged 0-18 years) first dispensed esomeprazole, other PPIs or H2RAs between September 2008 and August 2011 was obtained from the Dutch PHARMO Database Network. In total, 504 (2%) children were hospitalized for 762 predefined events: gastroenteritis (246); convulsion/seizure (200); pneumonia (154); failure to thrive (119); acute interstitial nephritis (19); thrombocytopenia (23); and angioneurotic edema (1). **Hospitalization rates for predefined outcomes were low and mostly similar in pediatric first-time users of PPIs and of H2RAs."**

Houben E, Johansson S, Nagy P, Penning-van Beest FJA, Kuipers EJ, Herings RMC. Observational cohort study: safety outcomes in children using proton pump inhibitors or histamine-2 receptor antagonists. *Curr Med Res Opin*. 2018

"Thirty-one children had long-term endoscopic follow-up while receiving omeprazole. Seven of 31 children had gastric polyps and/or nodules, noted between 10 and 48 months (mean = 28 months) of omeprazole therapy. Four had nodules only, one had a sessile hyperplastic polyp, and two had both a polyp (one hyperplastic and one fundic gland polyp) and nodules. All lesions were found in the gastric body. Nodules in four of the six children disappeared spontaneously while the children continued to receive omeprazole. The polyps persisted. There were no dysplastic changes in the gastric mucosa or polyps in any of the patients. There were no significant differences between the 7 children with and the 24 without polyps/nodules with respect to age, gastrin concentrations, or dose and duration of omeprazole therapy."

Pashankar DS, Israel DM. Gastric polyps and nodules in children receiving long-term omeprazole therapy. *J Pediatr Gastroenterol Nutr*. 2002

"Children exposed to PPIs therapy seem to be at higher risk for the development of Clostridium difficile-associated disease."

[No ages were provided in this article.]

Turco R, Martinelli M, Miele E, et al. Proton pump inhibitors as a risk factor for paediatric Clostridium difficile infection. *Aliment Pharmacol Ther*. 2010