Guide to Informed Decision-Making About PPIs: Research on PPI Dosing

The following research gives information about PPI dosing for infants and young children:

"GERD that is refractory to proton pump inhibitor (PPI) medications may be related to CYP2C19 variants. **Current PPI dosing practices in children do not take into account CYP2C19 allelic variants, which may lead to underdosing and subsequently to a misperception of PPI therapy failure."**

[This is extremely interesting and fairly recent research that genetics play a major factor in how individual patients metabolize PPIs.]

Franciosi JP, Mougey EB, Williams A, et al. Association Between CYP2C19*17 Alleles and pH Probe Testing Outcomes in Children With Symptomatic Gastroesophageal Reflux. *J Clin Pharmacol*. 2018

"The half-life of the drug in each of the six patients was much lower than in other studies involving adults; furthermore, almost no variability was evident. When this data is compared with previously published data in pediatrics, it becomes clear that **lansoprazole half-life increases with age.** Conclusion: These results explain why **many clinicians find a need for larger daily doses of PPIs in children** and the consideration of such factors is critical in the effort to control Gastroesophageal Reflux Disease in children."

[PPIs are metabolized more quickly by younger patients, so they leave the system faster.]

Pediatric Patients Have Shorter *Lansoprazole Half-Life* Than Previously Reported 1188. Phillips, Jeffrey O. PharmD; Burnett, Jane E.; Siddiqi, Shan H.; Bothwell, Marcella R. MD. American Journal of Gastroenterology: September 2007 - Volume 102 - Issue - p S552

"We investigated the pharmacokinetics, pharmacodynamics, and tolerability of lansoprazole in children after single and multiple administrations. 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 plasma concentrations were measured by HPLC. A 24-hour intragastric pH monitoring assessed the antisecretory effect. Lansoprazole was well tolerated in children. After a single oral dose of 30 mg per 1.73 m(2), **there was a trend for the elimination to be higher in infants than in adults and the antisecretory effect appeared to be higher in infants younger than 6 months than in older children and adults."**

[More evidence that PPIs are metabolized more quickly in infants. The younger the child, the faster the drug leaves the system.]

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

"Nine children (three girls), aged 4.5 to 27 months, with normal liver and renal functions requiring intravenous omeprazole were studied. Patients in group 2 had a significantly higher median pH (6.99 vs. 3.35; P = 0.01) and percent of monitored time with gastric pH >4 than children given 20 mg/1.73 m2 (90.6% vs. 44.8%; P < 0.01). Systemic clearance was not different between the two groups: median values were 0.68 and 0.42 L. kg-1. h-1 (P = 0.22). In critical situations, intravenous administration of omeprazole may be required in infants. **The authors demonstrate that the dose of 20 mg/1.73 m2 is not effective in maintaining 24-hour gastric pH of more than 4 and that a dose of 40 mg/1.73 m2 is required."**

[High doses of omeprazole may be needed in some instances.]

Faure C, Michaud L, Shaghaghi EK, et al. Intravenous omeprazole in children: pharmacokinetics and effect on 24-hour intragastric pH. *J Pediatr Gastroenterol Nutr*. 2001

"A marked discordance between the disposition of proton pump inhibitors (PPIs) in plasma and the kinetics of effect suggests the need for new approaches to characterize the clinical pharmacology of PPIs in infants and children. An assessment of pharmacokinetics and pharmacodynamics must take into account the genetic polymorphism of CYP2C19 and the impact of ontogeny on the activity of this and other enzymes (e.g., CYP3A4) which affect the biotransformation of the PPIs and, thus, their plasma clearance. **In addition, the potential effects of extemporaneous formulations of the drugs on their rate and extent of absorption must be considered.** Because of the apparent safety of PPIs and a well-demonstrated dose-response-effect relationship in adults, pediatric pharmacokinetic data and an exposure correlate, such as the dose-area-under-the-plasma-concentration-versus-time-curve relationship, can be used as a bridge to determine pediatric dosing."

[There are many factors that affect how drugs are metabolized in the body, and adult studies should not be used to determine pediatric dosing.]

Kearns GL, Winter HS. Proton pump inhibitors in pediatrics: relevant pharmacokinetics and pharmacodynamics. *J Pediatr Gastroenterol Nutr*. 2003

"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)...We recommend a starting dose of 0.7 mg/kg as a single morning dose; the adequacy of reflux control is then determined by follow-up 24-hour intraesophageal pH studies."

[Correct dose needs to be worked up to if the initial dose is not effective, and needs to keep being increased until pH is under control.]

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

"Effective treatment of the esophagitis and prevention of stenosis consisted in high doses of omeprazole (1.9 to 2.5 mg/kg/d). After this treatment, the need for esophageal dilatation disappeared, and nutritional status normalized." (The age group for this study was 11 to 14 months.)

Van Biervliet S, Van Winckel M, Robberecht E, Kerremans I. High-dose omeprazole in esophagitis with stenosis after surgical treatment of esophageal atresia. *J Pediatr Surg*. 2001

"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). To our knowledge, no dose-finding studies have been carried out in children under 2 years of age. Omeprazole is an effective treatment for gastroesophageal reflux in children younger than 2 years. **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

"Furthermore, within the group as a whole, these values showed a gradation from lowest in the children 1-6 yr of age to higher in the older age groups. **The doses of omeprazole required were substantially higher doses per kilogram of body weight than in adults.** Values of the pharmacokinetic parameters of omeprazole were generally within the ranges previously reported in adults. **The pharmacokinetics of omeprazole in children showed a trend toward higher metabolic capacity with decreasing age, being highest at 1-6 yr of age. This may explain the need for higher doses of omeprazole on a per kilogram basis, not only in children overall compared with adults but, in many cases, particularly in younger children."**

Andersson T, Hassall E, Lundborg P, et al. Pharmacokinetics of orally administered omeprazole in children. International Pediatric Omeprazole Pharmacokinetic Group. *Am J Gastroenterol*. 2000

"On a per-kilogram basis, the **doses of omeprazole required to heal erosive esophagitis are much greater than those required for adults."** (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

"The results of this small study suggest that, in children aged 1 to 11 years who had GERD, the **PK [pharmacokinetic] 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

"However, the pharmacokinetics of PPIs have not been studied in children less than two years old. **In general children, under 4 months had higher omeprazole levels and an immature metabolism.** Studies in children older than 2 years old have showed similar pharmacokinetics to adults."

Hoyo-Vadillo C, Venturelli CR, González H, et al. Metabolism of omeprazole after two oral doses in children 1 to 9 months old. *Proc West Pharmacol Soc*. 2005

"Rapid responders required 0.72 mg/kg per day omeprazole suspension to achieve adequate gastric pH elevation for stress ulcer prophylaxis. **Late responders required 1.58 mg/kg per day.** Nasogastric administration of omeprazole suspension has variable efficacy in critically ill pediatric patients. **Half of the studied subjects either required significant dose titrations to achieve gastric acid suppression** or did not respond to nasogastric administration of omeprazole suspension."

[Doses are a bit lower because the study was on older children, but it indicates that different metabolisms require different doses.]

Haizlip JA, Lugo RA, Cash JJ, Vernon DD. Failure of nasogastric omeprazole suspension in pediatric intensive care patients. *Pediatr Crit Care Med*. 2005

"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...Neither of the 2 omeprazole regimens achieved adequate alkalinization of the gastric pH during the first 24 hours. Between 24 and 48 hours, the 1 mg/kg dose maintained the gastric pH greater than 4 for a greater percentage of the time."

[This study stated that 0.5 mg/kg twice a day and 1 mg/kg twice a day was not sufficient in controlling acid.]

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