

Dosing Proton Pump Inhibitors (PPIs) in Infants and Young Children

This document is intended to be a bridge between parents and physicians to improve the treatment of acid-related disorders in children by optimizing pediatric dosing of PPIs. We encourage parents to read the following information and share it with their child's physician.

Introduction

The use of all medicines in children and adults is simply the combination of a dose and a dosage interval. This combination makes up the *drug regimen*. Most of the drug regimens that we use in children are based on adult information. For example, a common drug regimen for an adult suffering from acid reflux in the esophagus would be Prevacid® (lansoprazole) 30 mg twice per day. In this case the dose is 30 mg and the dosage interval is twice per day. This adult dosing information is important because we rarely have specific dosing information on children.

With PPI drugs - How much is enough?

PPI drugs, such as Prevacid®, have an effect on the production of acid that is related to the amount of drug that is absorbed into the body. Your doctor should know this amount of drug as the *AUC* or *area under the curve*. So, when planning out a drug regimen with a PPI drug, the best thing to do is to try to achieve the AUC that is known to inhibit enough acid in 24 hrs to reduce damage and reduce symptoms. In other words, you have to give enough PPI--and frequently enough--to get the desired effect. ***If you don't give enough PPI, the child will continue to suffer from the acid reflux and the doctor might think something else is causing the symptoms.***

Is it possible to give too much PPI?

The short answer is no. Fortunately, PPI drugs are very specific in where they work in the body. They are only active in a very specific place – that is the acid secreting cell, *parietal cell*. Since PPI drugs only work on the acid secreting cell the chance of side effects is very, very low—even if you give 3 times more than your child needs. In fact, PPI drugs are known as *prodrugs* because they are *not* active as they pass through the body. PPIs become active only when they pass into the acid secreting cell where the pH drops to less than 3.

What is the correct drug regimen for my child?

Remember that a drug regimen is made up of a dose and a dosage interval. For example, an adult might take Prevacid (lansoprazole) 30 mg twice per day—30 mg is the dose and the interval is twice per day. So, we need to calculate a dose and an interval for your child.

Determining the drug regimen can be done in two ways.

The first way is to have your child take the medicine (such as lansoprazole or omeprazole) and then measurements of the drug in the bloodstream are taken. This process is called *pharmacokinetics*. From this measurement you will learn **two** primary pieces of information (we call them *pharmacokinetics variables*, because they vary a little from person to person), the *half-life* ($t_{1/2}$) and the *volume of distribution* (V_d).

Half-life is time required for the drug concentration in the bloodstream to drop by $\frac{1}{2}$. Half-life is used to determine the dosage interval (number of doses per day) and is measured in minutes or hours.

Volume of distribution relates to how the drug moves into the tissues of the body. It is used to determine the dose and is measured in L/kg.

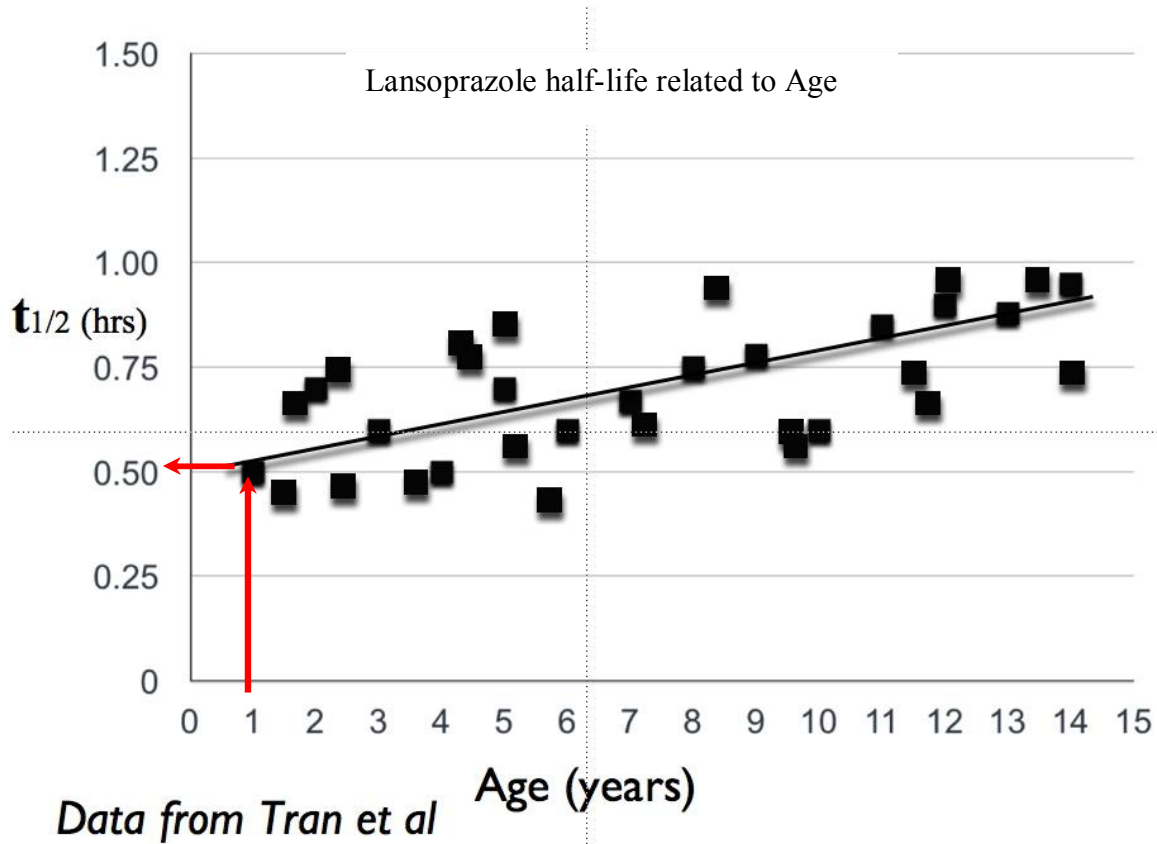
The second way to determine the correct drug regimen for your child is to find a study that has already evaluated the pharmacokinetics of children and reported the half-life and the volume of distribution for various ages of children. The MARCI-Kids dosing page is based on pharmacokinetics studies that have been evaluated and converted into a drug regimen table by Drs. Phillips and Bothwell. Determining a drug regimen this way is much easier since you don't have to get blood draws from your child after they have taken a dose of their medicine.

Examples

Let's start with half-life to tell us the ***number of doses per day***. Physicians need to look at adult data because of a lack of data available for children. The average adult with acid reflux disease takes a PPI drug 1 or 2 times per day. About $\frac{1}{3}$ of adults need 2 doses per day. The average number of doses per day is then 1.33 times per day. ***This average is our baseline for the number of doses per day.*** Now compare how the half-life of children differs from adults and modify the number of doses per day accordingly.

1. Find the child's age at the bottom of the graph.
2. Draw a line straight up until you intersect the slanted line drawn on the graph.
3. Plot over to the left where you see the half-life in hrs.

Example: a one-year-old taking lansoprazole (see below the red lines with arrows).



Data from Tran et al
Tran A., Rey E., Pons G, Pariente-Khayat, d'Athis P, Sallerin V, Dupont C. Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. 2002;71-359-367.

Based on this process, the estimated half-life for this child would be 0.5 hrs. Published data indicates that the normal adult has a half-life of 1.5 hrs for lansoprazole. By dividing the adult half-life of 1.5 hours by this child's half-life of 0.5 hours (as indicated on the table above), we know this child would eliminate the lansoprazole 3 times faster than the adult.

The average adult takes 1.33 doses per day (*baseline from above*) to achieve good acid control, so this one-year-old would be expected to need 3 x 1.33 = 4 doses per day. Now we know that this child will need 4 doses per day.

How much PPI per each dose?

The amount of PPI is determined by multiplying the volume of distribution and the child's weight. For lansoprazole and omeprazole, it has been shown that the V_d is 3 to 4 times larger in children than in adults. The average adult dose is approximately 0.5 mg/kg therefore,

$3 \times 0.5 \text{ mg/kg} = 1.5 \text{ mg/kg}$ per dose and
 $4 \times 0.5 \text{ mg/kg} = 2 \text{ mg/kg}$ per dose.

We generally start with the higher amount (2mg/kg per dose) since giving a little too much will not cause any side effects and giving enough to control the acid is the ultimate priority.

Dr. Jeffrey Phillips
Associate Professor and Director of Research
School of Medicine
University of Missouri – Columbia
Columbia MO 65212

For more information contact MARCI-Kids (info@marci-kids.com).

Here's a list of citations that may be helpful in learning more about dosing PPIs in children:

Clinical studies showing that higher PPI doses are required to achieve healing in pediatric patients

Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. *The Journal of Pediatrics* 1993;123:148-154.

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. *The Journal of Pediatrics* 2000; 137:800-807.

Iarocci TP, Tan H, Singer, J, Barron J, Pilzer E, Patel D, Bakst A. Proton pump inhibitors in infants. [Abstract] *American Journal of Gastroenterology*. 2005;100 (suppl.):S273.

Clinical study of pharmacokinetics of omeprazole in children

Andersson T, Hassall E, Lundborg P, et al. Pharmacokinetics of orally administered omeprazole in children. *American Journal of Gastroenterology* 2000; 95:3101-3106.

Pharmacokinetic study showing the relationship between lower age and higher dosing requirements in pediatric patients: younger children require higher and/or more frequent doses due to shorter PPI half-life. The first author is employed at Astra (company that makes Prilosec.)

Reviews of PPI use in children: pharmacokinetics, safety, efficacy, and dosing information

Israel DM, Hassall E. Omeprazole and other proton pump inhibitors: pharmacology, efficacy, safety, with special reference to use in children. *Journal of Pediatric Gastroenterology and Nutrition*. 1998; 27:568-579.

Specifically states that on a per kilogram (weight) basis, children require higher doses of omeprazole than adults due to different pharmacokinetics of omeprazole in children. Discusses at length the use of buffered PPI suspensions in children as a preferred dosage form.

Litalien C, Theoret Y, Faure C. Pharmacokinetics of proton pump inhibitors in children. *Clinical Pharmacokinetics* 2005;44:441-466.

Abstracts by Jeffrey Phillips, Pharm.D., describing use of ChocoBase and CaraCream in pediatric patients; includes some dosing information

Phillips JO, Bettag ME, Parsons DS, Wilder B, Metzler MH. Use of flavored lansoprazole or omeprazole suspensions in pediatric GERD. [Abstract A1292] *Gastroenterology* 2000; 118: 5904.

Phillips JO, Parsons DS, Fitts SW. Flavored lansoprazole suspension in pediatric GERD. [Abstract] *Journal of Pediatric Gastroenterology and Nutrition* 2000;31:S181. [Abstract No. 707].