REVIEW ARTICLE

Proton Pump Inhibitors in Pediatrics

Mechanism of Action, Pharmacokinetics, Pharmacogenetics, and Pharmacodynamics

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Abstract Proton pump inhibitors (PPIs) have become some of the most frequently prescribed medications for treatment of adults and children. Their effectiveness for treatment of peptic conditions in the pediatric population, including gastric ulcers, gastroesophageal reflux disease (GERD), and *Helicobacter pylori* infections has been established for children older than 1 year. Studies of the preverbal population of neonates and infants have identified doses that inhibit acid production, but the effectiveness of PPIs in the treatment of GERD has not been established except for the recent approval of esomeprazole treatment of erosive esophagitis in infants. Reasons that have been proposed for this are complex, ranging from GERD not occurring in this population to a lack of histologic identification of esophagitis related to GERD to questions about the validity of symptom scoring systems to identify esophagitis when it occurs in infants. The effectiveness of PPIs relates to their structures, which must undergo acidic activation within the parietal cell to allow the PPI to be ionized and form covalent disulfide bonds with cysteines of the H^+–K^+-adenosine triphosphatase (H^+–K^+-ATPase). Once the PPI binds to the proton pump, the pump is inactivated. Some PPIs, such as omeprazole and rabeprazole bind to cysteines that are exposed, and their binding

can be reversed. After irreversible chemical inhibition of the proton pump, such as occurs with pantoprazole, the recovery of the protein of the pump has a half-life of around 50 h. Cytochrome P450 (CYP) 2C19 and to a lesser degree CYP3A4 clear the PPIs metabolically. These enzymes are immature at birth and reach adult levels of activity by 5–6 months after birth. This parallels studies of the maturation of CYP2C19 to adult levels by roughly the same age after birth. Specific single nucleotide polymorphisms of CYP2C19 reduce clearance proportionally and increase exposure and prolong proton pump inhibition. Prolonged treatment of pediatric patients with PPIs has not caused cancer or significant abnormalities.

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1 Introduction

Treatment of all ages of pediatric patients with proton pump inhibitors (PPIs) has expanded dramatically during the last 3 decades as concerns about peptic acid diseases in adults and children have increased. Based on data from four geographically diverse commercial healthcare claims databases including 12.9 million members and 1,308,126 infants <12 months of age, prescriptions for PPIs increased 7.5-fold from 1999 to 2004 [1]. PPIs gained popularity for acid suppression because they inhibit the last step in gastric acid secretion regardless of the stimulus for acid secretion and can be dosed once a day in most patients. Effective treatment with PPIs requires an understanding of the physiology of gastric acid secretion, the need for activation of the PPI for it to bind to the proton pump and cause inactivation, the pharmacokinetics of PPIs, the pharmacogenetics of PPIs, and the results of pharmacodynamics studies of PPIs. This paper will cover those aspects of PPIs in the pediatric population.

1.1 Physiology of Gastric Acid Secretion

The pharmacodynamics and pharmacokinetics of PPIs are integrally linked to the physiology and structure of the enzyme responsible for gastric acid secretion by the parietal cell, the H^+–K^+-adenosine triphosphatase (H^+–K^+-ATPase). This extraordinary acid pump creates a 1 million-fold gradient in H^+ concentration from inside the parietal cell to the gastric lumen in return for inward transport of K^+ [2]. Without stimulation, the H^+–K^+-ATPase enzyme resides in the parietal cell cytoplasm in a relatively inactive tubulovesicle form, as diagrammed by Litalien et al. [3] in Fig. 1. This ATPase can be stimulated to secrete gastric acid by the binding of different ligands, such as acetylcholine, histamine, or gastrin [4]. Histamine can be released by the enterochromaffin-like cells directly or after stimulation of these cells by gastrin, which is released after a meal. Histamine then binds to the histamine H_2 receptor and stimulates the H^+–K^+-ATPase to release intracellular

second messengers, cyclic adenosine monophosphate (cAMP), and Ca^{2+}, leading to acid release.

Regardless of the stimulus, gastric acid secretion occurs through a single common pathway after activation by ligand binding (Fig. 1) [3–5]. Secretion of acid into the gastric lumen requires a conformational change in the H^+–K^+-ATPase to exchange H^+ for K^+ on the enzyme while basolateral secretion of HCO_3^- maintains intracellular electroneutrality. After ligands bind to the parietal cell and activate intracellular second messengers, H^+–K^+-ATPase binds magnesium adenosine 5'-triphosphate (MgATP), which provides the energy to fuse with the apical microvilli on the luminal membrane of the parietal cell's expanded secretory canaliculus [2, 6–8]. This ATPase binds hydronium (H_3O^+) internally with the enzyme in the E1 position while K^+ is bound in the lumen. As K^+ binds, Pi is released internally, which changes the enzyme to an E2K formation from which K^+ cannot be easily released. Binding of MgATP rotates the enzyme so K^+ is inside and
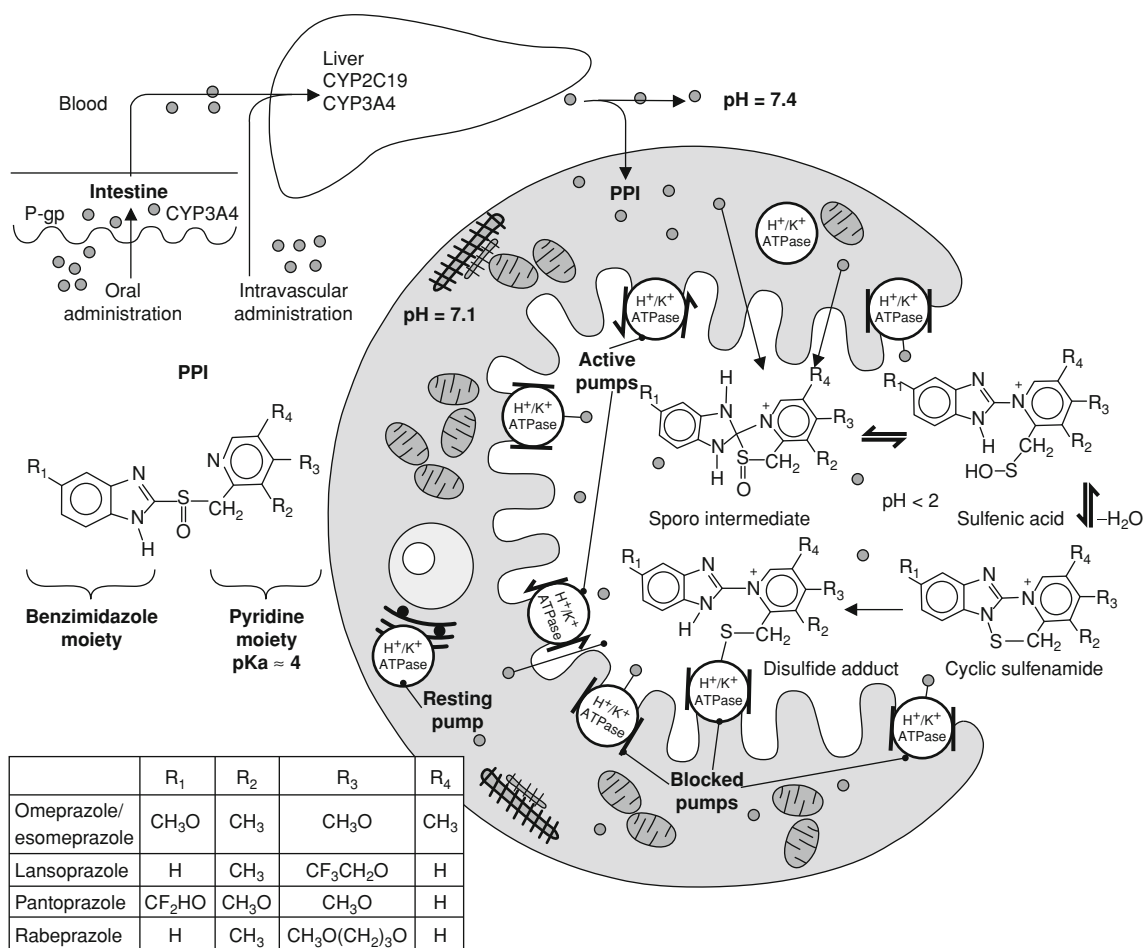
Fig. 1 General chemical structure and mechanism of action of proton pump inhibitors (PPIs). Reproduced from Litalien et al. [3], with permission from Springer International Publishing AG (© Adis Data

Information BV [2005]. All rights reserved.) *ATPase* adenosine triphosphatase, *CYP* cytochrome P450, *P-gp* P-glycoprotein, *pKa* negative logarithm of the acid ionization constant

the H_3O^+ is now in the lumen. To maintain an adequate supply of K^+ in the lumen requires K^+ transport, which occurs through the KCNQ1 channel, a voltage-gated potassium channel originally associated with the Long QT syndrome. For the KCNQ1 channel to transport potassium, its KCNE2 subunit must function at pH 1 on the extracellular side of the parietal cell where acid is being transported. In this extremely acidic environment, the channel is activated by the acid, loses its gating function, and remains open. To balance the secretion of H^+ from the parietal cell into the gastric lumen, HCO_3^- is secreted from the basolateral portion of the cell, which prevents the cell from developing a negative charge.

1.2 Structure of the H^+–K^+-ATPase Enzyme, Parietal Cell Proton Pump

The H^+–K^+-ATPase must be activated to the microvilli location for the PPI to bind and cause inactivation, and the enzyme's structure is a key element of that inactivation (Fig. 1). The gastric H^+–K^+-ATPase belongs to the P_2 family of ATPases and, like the extensively studied Na^+–K^+-ATPase, is a heterodimer with an alpha and beta subunit [7, 9]. Like Na^+–K^+-ATPase, the H^+–K^+-ATPase alpha subunit contains 1,033 amino acids in a heterodimer configuration with ten transmembrane or membrane-inserted segments (TMs). A cluster of carboxylic amino acids in the intra-membrane segments of TM4–6 and TM8 help to form the ion binding domain [5, 10]. The alpha subunit is highly conserved, with 98 % homology among enzymes from the hog, rabbit, dog, and human [6]. The smaller beta subunit contains 190 amino acids, with its N-terminus in the cytoplasm. This beta subunit includes only one transmembrane segment with 6 or 7 external N-linked glycosylation sites that are important for the structure of the enzyme and the conformational changes involved in acid secretion. This ATPase contains 28 cysteine (CYS) molecules, ten of which are accessible for binding by activated PPIs [5, 11]. These CYSs are located at different regions of the enzyme, some within the proton transporting portions (CYS321, 813, and 822) and others outside the proton pump on the luminal side

of the enzyme (CYS892) [5, 12]. The locations are important to the reversibility of the binding of the PPIs and their pharmacodynamics.

1.3 Activation of the Proton Pump Inhibitors (PPIs) for Binding to the H^+–K^+-ATPase

PPIs must be activated to bind to the CYSs of the ATPase, and the rate of this activation varies with their structures [5]. These PPIs are weak bases that are acid labile and must be formulated with an enteric coating to resist gastric acid degradation and allow absorption in the more alkaline environment of the small intestine. Currently approved PPIs have a very similar basic structure that combines a benzimidazole ring and a pyridine ring through a sulfinyl linkage as shown in Fig. 1 [12]. The first PPI discovered was timoprazole, which lacked any substitutions on these rings in contrast to currently approved PPIs with various substitutions that affect their chemistry. For the sulfinyl to chemically bind to the CYSs of the ATPase, it has to gain energy from the acidic environment inside the parietal cell [5].

Activation of the PPI occurs by addition of two protons to the nitrogens on either side of the sulfinyl group (Fig. 1) [5, 6]. Once it is activated, the PPI can inactivate the proton pump by binding to CYS molecules on the ATPase to form disulfide bonds. The chemistry of these reactions has been thoroughly described by Roche [5] and Shin et al. [6]. The PPIs have two pKa (negative logarithm of the acid ionization constant) values that influence their activation (Table 1; Fig. 1) [3, 5, 12]. The first pKa ranges from 3.83 to 4.53 and leads to ionization and accumulation in the acidic region of the parietal cell canaliculus where acid is being secreted, with pH around 1.0. This is the most acidic cytoplasm of any cell within the body [12]. The second pKa of approved drugs ranges from 0.11 to 0.79. This second protonation on the benzimidazole causes rearrangement of the sulfinyl into a cationic sulfenic acid or a sulfenamide, which has the energy to react with the cysteine sulfhydryls to form one or more covalent disulfide bonds (Fig. 1) [3, 4].

Table 1 Chemical properties and the presence (indicated by +) of specific cysteine (CYS) binding sites of proton pump inhibitors [3, 5, 12]

Proton pump inhibitor	pKa1	pKa2	CYS321	CYS813	CYS822	CYS892
Omeprazole	4.06	0.79		+		+
Lansoprazole	3.83	0.62	+	+		
Pantoprazole	3.83	0.11		+	+	
Rabeprazole	4.53	0.62		+		
Tenatoprazole	4.04	−0.12		+	+	

Not enough pharmacokinetic data on esomeprazole could be obtained for inclusion in the table

pKa negative logarithm of the acid ionization constant

The PPI can bind to several different CYSs on the proton pump. The speed with which these two activation reactions occur influences which CYS(s) it will bind [3, 5]. All the PPIs bind to CYS813 located on the acidic luminal side within the proton transporter, which stops proton transfer. This location is easily accessible to the PPIs for binding, but it is also accessible to reducing agents, such as glutathione and dithiothreitol, which can release the PPI and reactivate the transporter [12]. In contrast, the CYS at position 822 located deep within the sixth transmembrane segment of the ATPase reacts with the PPIs that are activated more slowly, such as pantoprazole and tenatoprazole. CYS822 is relatively inaccessible to reducing agents so the disulfide bonds created by the PPI permanently inactivate the proton pump [12]. This difference in binding sites accounts for some of the dynamic differences among PPIs according to those with reversible binding and those that are inaccessible to reduction of the disulfide bonds. Before inactivation of the proton pump can occur, the PPI must reach the acidic site of action within the parietal cell while the proton pump is active for it to undergo the acidic activation described above. The concentration at the site of action is determined by the PPI's pharmacokinetics, beginning with absorption in an inactive form, distribution, metabolism by cytochrome P450 (CYP) 2C19 or CYP3A4, and elimination. The rate of metabolism is under developmental as well as genetic control, which confounds accurate prediction of these rates.

2 Pharmacokinetics and the Disposition of PPIs in Infants and Children

2.1 Biotransformation

As previously reviewed by Gibbons and Gold [4], all of the PPIs are polyfunctional substrates for a variety of phase I and phase II drug metabolizing enzymes. The relative contribution of these enzymes to the biotransformation of omeprazole, lansoprazole, rabeprazole, and pantoprazole is illustrated in Fig. 2. Of the four predominantly used PPIs within this class, two different CYP isoforms are responsible for the majority of their biotransformation: CYP2C19 and CYP3A4 [4]. In contrast, the metabolism of ilaprazole, a new PPI, is also catalyzed by CYP3A5 [13], which along with CYP3A4, is predominantly located in the liver and small intestine. While functionally important polymorphic expression has been described for both CYP3A4 and CYP3A5 [14], none of the allelic variants of the genes controlling their expression has been shown to be quantitatively important with regard to the biotransformation of the PPIs, with the possible exception of the impact of the

CYP3A5*3/*3 genotype on ilaprazole clearance, as reported from a cohort of Chinese subjects [13]. This is not the case for CYP2C19 where genetic polymorphism has been shown not only to produce large variation in the pharmacokinetics of the PPIs but also to be associated with their pharmacodynamics (i.e., concentration-effect relationships) and drug-interaction potential [15, 16]. Pharmacogenomic variability in the constitutive expression of the enzymes responsible for PPI biotransformation also has potential implications regarding the stereospecificity of their metabolism, as has been demonstrated for omeprazole [17] and lansoprazole [18]. Finally, given the quantitative predominance of CYP3A and CYP2C19 isoforms in the liver, hepatic insufficiency significantly prolongs the plasma clearance of the drug and as a result, increases systemic exposure (i.e., increased area under the concentration–time curve [AUC]) [19].

2.2 Ontogeny and PPI Disposition

As all of the PPIs are extensively metabolized, differences in their biotransformation associated with polymorphism of drug metabolizing enzymes, ontogeny, and concomitant disease states are the primary drivers for their disposition characteristics in pediatric patients. A comprehensive review of PPI pharmacokinetics in children has been previously published and reflects a synthesis of data available before 2005, much of it available in older children and adolescents [3]. In order to supplement these data, we have summarized the pharmacokinetic data for PPIs obtained from clinical investigations conducted in neonates (Table 2) [20–22], infants (Table 3) [23–26], and children (Table 4) [26–34]. With the exception of omeprazole, the pharmacokinetics of available PPIs are not concentration (or dose) dependent. Consequently, any observed differences in their pharmacokinetics across the continuum of development would be expected to occur consequent to the impact of ontogeny on the activity of enzymes responsible for PPI biotransformation and, in the case of CYP2C19, the influence of genetic polymorphism on enzyme activity. An example resides with pantoprazole, the PPI that most extensively relies upon CYP2C19 (as opposed to CYP3A4) for its biotransformation (Fig. 2).

Figure 3 illustrates the apparent oral clearance (CL/F) of pantoprazole in patients from the neonatal period through adolescence [35]. These data were derived from a series of clinical trials submitted to the US FDA for approval and depict information from subjects whose CYP2C19 genotype would predict an extensive metabolizer phenotype. As predicted from previous work examining the developmental expression of human hepatic CYP2C19, which demonstrated extremely low levels of enzyme activity in
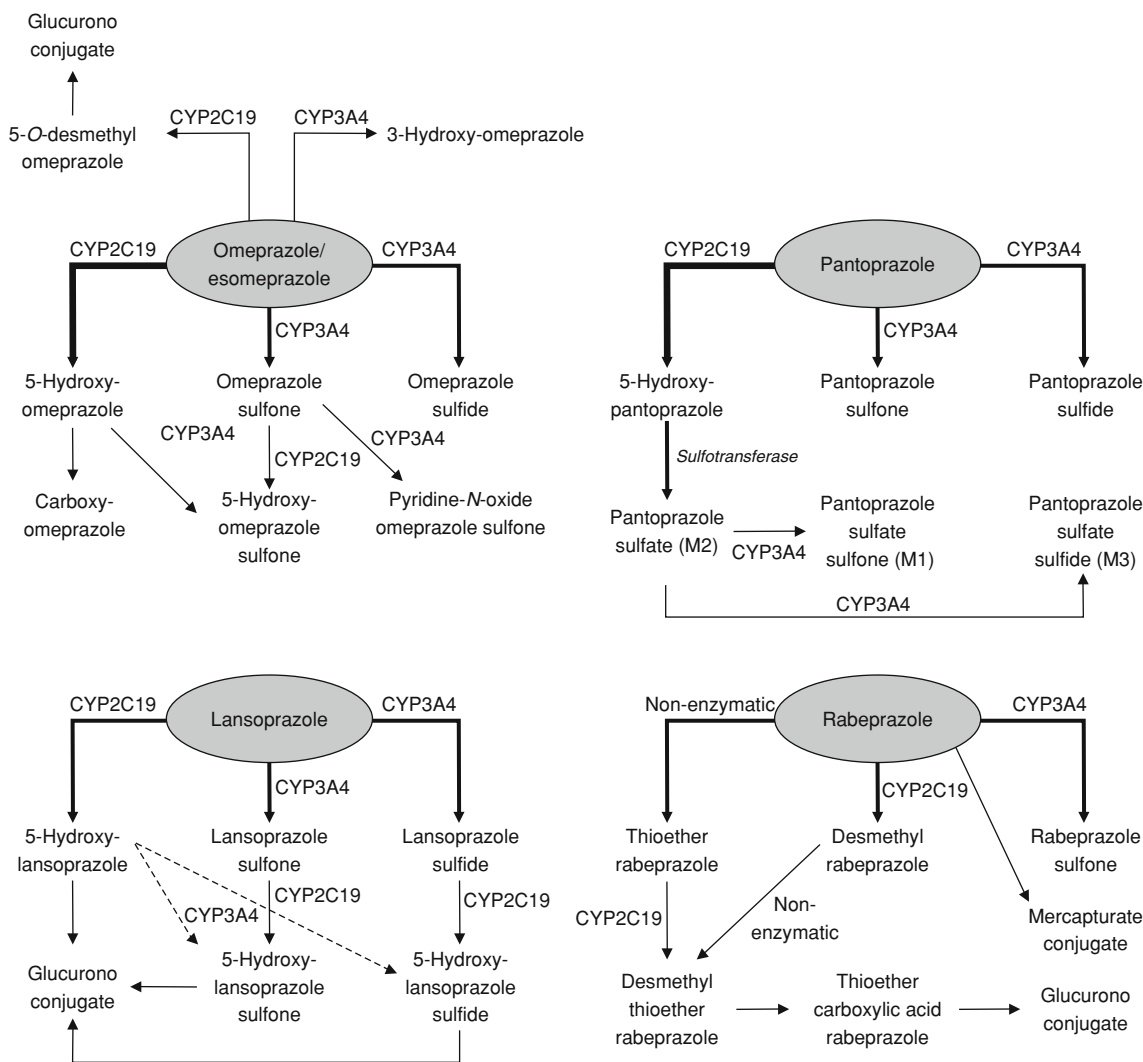
Fig. 2 The metabolic pathways of the proton pump inhibitors and the major cytochrome P450 (CYP) isoenzymes involved. The thicker the *arrow*, the larger the contribution of the CYP isoforms to the metabolic pathway. Reproduced from Litalien et al. [3], with permission from Springer International Publishing AG (© Adis Data Information BV [2005]. All rights reserved.)

the first 2 months of postnatal life [36], the CL/F of pantoprazole was also lower than that observed in older infants, children, and adolescents. These data corroborate previously summarized findings of reduced omeprazole and lansoprazole plasma clearance in neonates [3]. Previous studies have reported a trend towards increasing PPI (omeprazole and lansoprazole) clearance with decreasing age in childhood and no correlation between age and PPI pharmacokinetic parameters among children [3]. The CL/F data from the pediatric studies of pantoprazole (Fig. 3) do not suggest significant age association, with the exception of the first 4–5 months of postnatal life, a time where the correlation between CL/F and age is direct, linear, and statistically significant (Fig. 4b). It should be noted that the relationship between pantoprazole CL/F and age over the

first 20 weeks of postnatal life (Fig. 4b) [22] corresponds dimensionally to the ontogeny of CYP2C19 over this same period (Fig. 4a) [36]. Thus, the ontogeny of CYP2C19 and the apparent oral plasma clearance of pantoprazole 'mirror' each other and, thereby, validate the predominant role for this particular CYP isoform in the metabolism of this PPI.

As mentioned previously, polymorphic expression of all enzymes responsible for catalyzing the biotransformation of the PPIs can markedly influence their dose versus exposure versus response relationships. It is now widely recognized that the CYP2C19 polymorphism is responsible for the marked variability in the pharmacokinetics, pharmacodynamics, and drug interaction potential for the PPIs in adults [15]. Likewise, in pediatric patients, we have previously demonstrated that patients with a CYP2C19

Table 2 Pharmacokinetics of proton pump inhibitors in newborn patients from birth to 44 weeks adjusted age (gestational age at birth + chronologic age after birth)

	Esomeprazole [20]	Lansoprazole [21]	Pantoprazole [22]
No. of newborns	26	12, 12	19, 21
Gestational age at birth (weeks)	33.3 (23–41)		29 (23.5–40.0), 28 (23.0–41.0)
Fixed dose (mg)			1.25, 2.5
Dose (mg/kg)		0.5, 1.0	0.6 approx., 1.2 approx.
Chronologic age (weeks)		4.1 (1–19), 3.3 (<1–12)	7.7 (1.3–17.7), 8.0 (1.3–19.6)
Adjusted age at study (weeks)	39.8 (35.6–44)	40.4 (35–43), 38.7 (30–44)	37.8 (34.1–43.9), 36.4 (33.3–43.6)
Weight at study (g)		3,339 ± 763, 2,690 ± 926	2,661 ± 586 (2,060–4,100), 2,636 ± 623 (2,018–4,550)
$AUC_{0-\infty}$ (μg·h/mL)		5.09 ± 2.61, 9.37 ± 4.79	
AUC (μg·h/mL)			3.54 ± 2.82 (80 % CV), 7.27 ± 5.30 (73 % CV)
AUC_{τ} (μmol·h/mL)	2.5 (0.2–6.6)		
t_{max} (h)	1.65 (0.65–2.25)	3.1 ± 2.2, 2.6 ± 1.5	
C_{max} (ng/mL)		831 ± 381, 1,672 ± 809	
C_{max} (μmol/L)	0.74 (0.1–1.5)		
CL/F (L/kg h)		0.16 ± 0.18, 0.16 ± 0.15	0.21 ± 0.12 (59 % CV), 0.23 ± 0.21 (92 % CV)
V/F (L)			1.63 (19 % RSE)
Terminal $t_{1/2}$ (h)		2.8, 2.0	3.1 ± 1.5, 2.7 ± 1.1

All values are mean ± standard deviation and/or (range) unless otherwise indicated

Approx. approximately, *AUC* Area under the concentration–time curve from zero to the last time point measured, $AUC_{0-\infty}$ area under the concentration–time curve from time zero to infinity, AUC_{τ} area under the concentration–time curve from time zero to a specified time, *CL/F* apparent oral clearance, C_{max} maximum plasma drug concentration, *CV* coefficient of variation, *RSE* relative SE (100 × SE/estimate), *SE* standard error, $t_{1/2}$ elimination half-life, t_{max} time to maximum concentration, *V/F* apparent volume of distribution

Table 3 Pharmacokinetics of proton pump inhibitors in infants 1–24 months of age

	Omeprazole [23]	Esomeprazole [24]	Lansoprazole [25]	Pantoprazole [26]
Chronologic age (months)	4–27	1–24	13–24	1–11
No. of infants	4, 5	26, 24	5	21, 21
Dose (mg/kg)	0.56 ± 0.04, 1.17 ± 0.08[a]	0.25, 1	1.4 ± 0.19	0.6 approx., 1.2 approx.
Dose (mg/1.73 m^2)	20, 40			
Fixed dose (mg)			15	2.5–5, 5–10
$AUC_{0-\infty}$ (ng·h/mL)				1,046 ± 1,043, 3,602 ± 3,269
$AUC_{0-\infty}$ (μg·h/mL)	0.94 ± 0.48, 3.94 ± 2.53[a]			
AUC_{0-24} (ng·h/mL)			1,906 ± 770	
AUC_{τ} (μmol·h/mL)		1.34 ± 1.52, 5.31 ± 5.47		
t_{max} (h)		2.2 ± 1.0, 3.4 ± 1.9	1.4 ± 0.9	1.03 (0.98–11.83), 1.02 (0.5–4.08)
C_{max} (ng/mL)			894 ± 345	503 ± 506, 1,318 ± 1,307
C_{max} (μmol/L)		0.39 ± 0.48, 1.43 ± 2.15		
CL/F (L/kg h)	0.68 ± 0.27, 0.42 ± 0.28[a]			1.54 ± 2.35, 0.87 ± 1.36
Terminal $t_{1/2}$ (h)		0.9 ± 0.5, 1.0 ± 0.4	0.66 ± 0.30	1.78 ± 1.30, 1.42 ± 0.78

All values are mean ± standard deviation or mean (range), unless otherwise indicated

Approx. approximately, $AUC_{0-\infty}$ area under the concentration–time curve from time zero to infinity, AUC_{τ} area under the concentration–time curve during a dosing interval, AUC_{0-24} area under the concentration time for 24 h on treatment day 5, *CL/F* apparent oral clearance, C_{max} maximum plasma drug concentration, $t_{1/2}$ elimination half-life, t_{max} time to maximum concentration

[a] Recalculated from data in Faure et al. [23], Table 2

genotype predictive of a poor-metabolizer phenotype have significantly higher systemic drug exposure (i.e., AUC) and prolonged plasma drug clearance for both omeprazole [27] and pantoprazole [31] as compared with individuals with an extensive and/or intermediate metabolizer phenotype. Concordance between genotype and phenotype for

Table 4 Pharmacokinetics of proton pump inhibitors in children, most 1–16 years of age. Values are reported after multiple doses whenever available

	Omeprazole [27]	Omeprazole [28][a]	Esomeprazole [29][b]	Lansoprazole [30]	Pantoprazole [26]	Pantoprazole [31]	Pantoprazole [32]	Pantoprazole [32]	Pantoprazole [32]	Rabeprazole [33]	Rabeprazole [34][c]
Chronologic age (years)	(2–16)	4.2, 9.6, 15.0 (1.6–16.2)	(12–17)	(0.25–13.33)	3.2 ± 1.6	(5–16)	(2–14)	(6–11)	(12–16)	(1–11)	(12–16)
Dose (mg/kg)	0.41 ± 0.21 (0.16–0.91)	1.3, 0.7, 1.1 (0.6–3.6)		0.73 ± 0.11 (0.54–0.91)	0.6 approx., 1.2 approx.	0.82 ± 0.51	0.8 IV, 1.6 IV			0.14, 0.5, 1	
Fixed dose (mg)	10, 20		20, 40		5.0–10, 15–20			20, 40	20, 40		10, 20
No. of children	23	7, 9, 9	12–14, 12–14	23	7, 10	24	9, 10	11, 13	11, 11		12, 12
AUC (mg·h/L normalized to 1 mg/kg)	0.810 ± 0.894					9.44 ± 15.16	8.95 ± 7.03	3.9 ± 3.1, 3.1 ± 1.4	4.8 ± 2.7, 6.9 ± 3.4		
AUC$_{0-\infty}$ (μg·h/mL)					0.293 ± 0.146, 2.448 ± 2.170			2.5 ± 2.1, 3.8 ± 1.8	1.3 ± 0.6, 4.3 ± 3.1	0.157 ± 0.050[d], 0.429 ± 0.232, 0.884 ± 0.579	0.250 ± 0.032, 0.828 ± 0.176
AUC$_{0-\infty}$ (μmol·h/L)		5.8, 8.3, 9.9	3.65 ± 54 %, 13.86 ± 39 %								
t_{max} (h)	2.15 ± 1.21	2.0, 1.5, 2.0	1.96 ± 0.77, 2.04 ± 0.97 arithmetic mean ± SD		5.8 (1.0–6.0), 3.0 (1.0–6.0)	2.54 ± 0.72	0.34 ± 0.12	2.0 (1.0–4.0), 2.0 (1.0–4.0)	1.5 (1.0–3.0), 2.0 (1.0–12.0)	1.90 ± 0.97, 1.52 ± 0.53, 1.74 ± 1.03	3.4 ± 0.52, 4.1 ± 0.45
C_{max} (ng/mL)	446 ± 402 (normalized to 1 mg/kg)			464 ± 357	229 ± 196, 653 ± 645					50.7 ± 34.5, 200 ± 149, 439 ± 298	184.1 ± 26.58[d], 460.4 ± 85.82
C_{max} (μg/mL)			1.45 ± 123 %, 5.13 ± 45 %			2.97 ± 1.51	8.04 ± 3.21	1.6 ± 1.2, 2.1 ± 1.3	0.9 ± 0.5, 2.2 ± 1.4		
C_{max} (μmol/L)		3.7, 3.0, 2.7									
CL/F (L/kg h)	1.76 ± 1.38			1.85 ± 2.33	2.08 ± 1.27, 1.28 ± 1.16	0.26 ± 0.20	0.20 ± 0.23	0.41 ± 0.30, 0.40 ± 0.22	0.28 ± 0.17, 0.18 ± 0.08		0.755 ± 0.110[d], 0.608 ± 0.12
CL/F (L/h)			15.88 ± 54 %, 8.36 ± 39 %								
V/F (L/kg)	2.60 ± 2.66					0.24 ± 0.09	0.22 ± 0.14	0.43 ± 0.30, 0.40 ± 0.27	0.32 ± 0.22, 0.21 ± 0.06		
Terminal $t_{1/2}$ (h)	0.98 ± 0.22	0.85, 1.74, 1.58	0.82 ± 40 %, 1.22 ± 17 %	0.82 ± 0.43	5.34 ± 7.39, 1.7 ± 0.6	1.27 ± 1.29	1.22 ± 0.68	0.8 ± 0.2, 0.7 ± 0.2	0.8 ± 0.3, 0.9 ± 0.3	1.3 ± 0.4, 1.9 ± 1.0	

Mean values are given as ± SD, unless otherwise indicated

Approx. approximately, *AUC* area under the concentration–time curve, *AUC$_{0-\infty}$* AUC from time zero to infinity, *CL/F* apparent oral clearance, *C$_{max}$* maximum plasma drug concentration, *CV* coefficient of variation, *IV* intravenous, *SD* standard deviation, *t$_{1/2}$* elimination half-life, *t$_{max}$* time to maximum concentration, *V/F* apparent volume of distribution

[a] Values in the column are medians with or without range

[b] Values in the column are geometric mean ± CV (%), unless otherwise indicated

[c] Values in the column are mean ± standard error, unless otherwise indicated

[d] Recalculated to similar units used by other studies
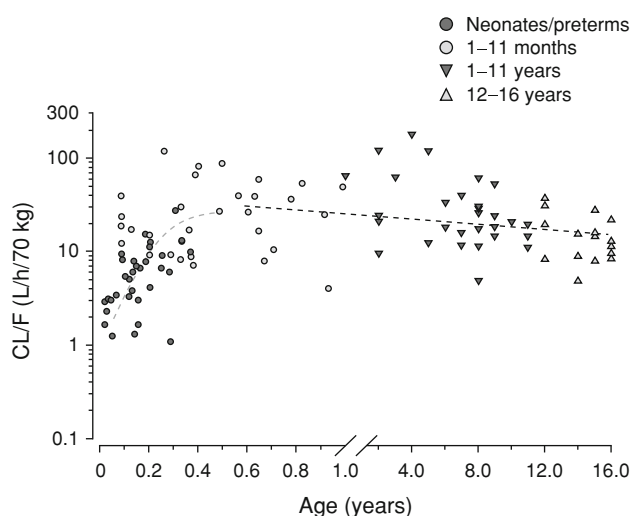
Fig. 3 Association between age and the weight-normalized apparent oral clearance (CL/F) of pantoprazole in neonates, infants, children, and adolescents. *Dashed lines* represent apparent 'best fit' from non-linear (for subjects from birth through 0.5 years of age) and linear (for subjects from 0.5 to 16 years of age) regressions of the data and are provided to illustrate association between CL/F and age. Data were obtained from a series of labeling studies conducted by the study sponsor and subjected to a population-based pharmacokinetic analysis to explore age-associated effects on disposition [35]

CYP2C19 would be expected in children where CYP2C19 has reached adult activity (6–12 months after birth). This would be reflected in concordance between pharmacokinetics and pharmacodynamics for pantoprazole, which is seen with pantoprazole CL/F (Fig. 3). In contrast, low constitutive activity of CYP2C19 observed in the first 2 months of life (Fig. 4a) produces a discordance between genotype and phenotype, as reflected by examination of pantoprazole CL/F (Fig. 4b).

Finally, interpretation of the intersection of ontogeny and the CYP2C19 genotype must consider that for this drug metabolizing enzyme and selected PPIs, an apparent gene–dose effect exists. In a recent study designed to examine the impact of the *CYP2C19**17 allele on PPI pharmacokinetics [37], a gene–dose effect was apparent for pantoprazole when the apparent plasma elimination rate constant (a pharmacokinetic parameter that should be independent of absorption) was examined as a function of CYP2C19 genotype. This same relationship was absent for omeprazole (Fig. 5). It is possible that this difference resides with the relative contributions of CYP2C19 and CYP3A4 in the overall biotransformation of omeprazole as compared with pantoprazole [38]. Thus, an ontogenic relationship has been demonstrated for some PPIs, but not for others. Consequently, even within this relatively homogeneous drug class, genotype does not always predict drug disposition.
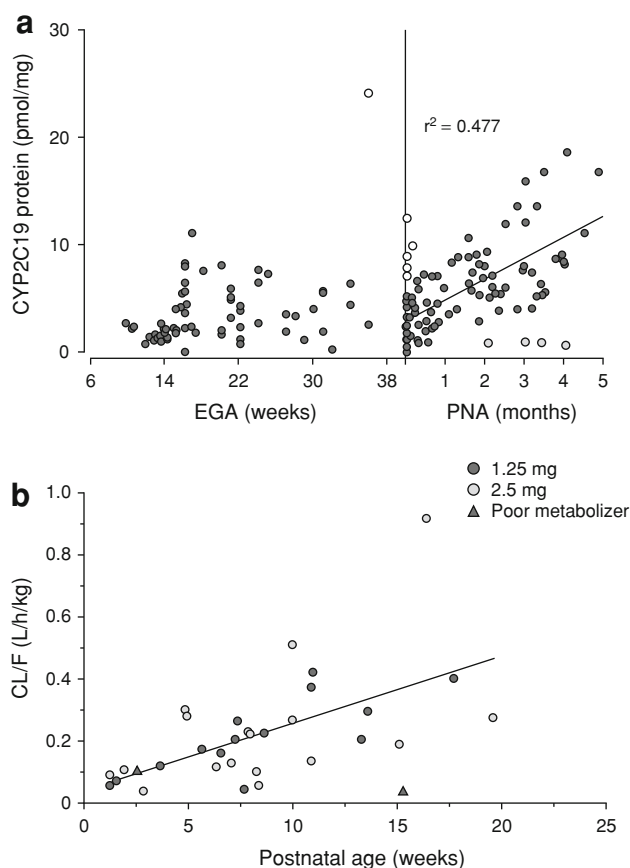

Fig. 4 a Association between cytochrome P450 (CYP) 2C19 protein expression in the human fetus and neonate, shown by *dark circles*. *Open* and *grey circles* represent outliers based on analysis of residuals that were not used in the regression analysis [36]. Reproduced from Koukouritaki et al. [36], © The American Society for Pharmacology and Experimental Therapeutics 2004, with permission. *EGA* estimated gestational age, *PNA* postnatal age. **b** The association between postnatal age and the apparent oral clearance (CL/F) of pantoprazole following a single oral dose of either 1.25 mg (*dark circles*) or 2.5 mg (*grey circles*). *Triangles* denote patients with a CYP2C19 genotype that would be predictive of a poor-metabolizer phenotype. A regression line ($p < 0.05$ for r^2) is shown to illustrate the association between CL/F and age. Reproduced from Ward et al. [22], © Springer-Verlag 2010, with the kind permission of Springer Science + Business Media

3 Pharmacodynamics of PPIs in Pediatric Patients

Inhibition of the H^+–K^+-ATPase proton pump requires activation of the pump before the PPI is removed from the circulation, which in turn relates to the rate of absorption, time to maximum concentration (t_{max}), and rate of elimination of the drug from the circulation, which is influenced by development and genetics. Wide ranges of t_{max} imply variable absorption of PPIs among individuals and likely affect the inhibition of acid secretion. Since gastrin release after a meal is one of the most potent activators of H^+–K^+-ATPase, the PPI should be administered long enough
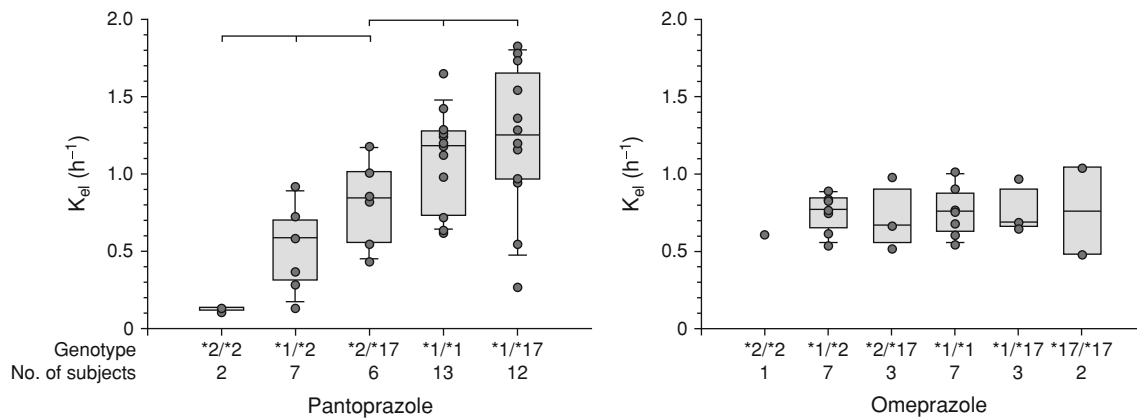
Fig. 5 Relationship between cytochrome P450 2C19 genotype and the apparent terminal elimination rate constant (K_{el}) for pantoprazole in children and adolescents. *Boxes* reflect interquartile range, *lines* in the boxes depict the mean values, and *whiskers* indicate the 10th and 90th percentiles, respectively. For the pantoprazole data, *horizontal lines* above the boxes join genotype groups that are *not* significantly different from each other as determined by Tukey's honestly significant difference test after an initial ANOVA. Reproduced from Kearns et al. [37], © The American Society for Pharmacology and Experimental Therapeutics 2010, with permission

before a meal to be absorbed, but not eliminated, by the time the proton pump is activated. Several pharmacokinetic studies in Tables 2, 3, and 4 show wide ranges of t_{max}, indicating wide variation in absorption, which can lead to variation in response. After the activated PPI binds to the H^+–K^+-ATPase, either reversibly or irreversibly, acid secretion is inhibited long after the PPI is eliminated from the circulation. The pump protein has a half-life of around 54 h in rats, which is similar to that in humans [6]. Acid secretion is inhibited for 24 h after omeprazole and for 46 h after pantoprazole, because of the differences in binding to the CYSs of the proton pump [6]. Not all pumps are active and inhibited after the first dose, so steady state requires around 3 days to develop [7]. Despite this difference between persistence of drug in the circulation and the duration of inhibition of acid secretion, pharmacogenetic studies of serum AUC and acid secretion AUC in patients with allelic variants for CYP2C19 showed a potential relationship between systemic drug exposure and gastric pH (Kearns et al., unpublished data).

3.1 Newborn Gastric Acid Secretion

At birth, premature newborns at 24 weeks gestation have the capacity to secrete enough acid to maintain a basal gastric pH of <4, but the volume of acid secreted does not reach adult levels for 5–6 months after birth [39]. The volume of gastric acid that is released after stimulation relates to the parietal cell mass and does not reach adult levels until 5–6 months after birth [39]. Although it would seem logical that a smaller parietal cell mass would require smaller doses of a PPI for inhibition, that is not the case, or at least that is not current practice. When the current neonatal and infant doses of PPI are compared with the

capacity for acid secretion in milliEquivalents, these doses are 7-fold to 9-fold higher than the doses that are effective for treatment of adults. The dose-related duration of proton pump inhibition in newborns has not been described, but might support lower and less frequent dosing than is currently practiced. The pharmacodynamics among different PPIs needs more study in neonates.

3.2 Treatment of Newborns with PPIs

The pharmacodynamics of PPIs in preterm and term newborns have not received as much study as they have in older pediatric populations, because of the challenges in studying this population. Most of the studies of PPIs in newborns have been stimulated by the *Best Pharmaceuticals for Children Act*, which provides an extension of market exclusivity in return for completion of studies specified in a Written Request by the FDA [40–43]. The Written Request specifies the study design, including the ages of patients, size of study population, and the measurements to be completed. Omeprazole was evaluated in a double-blind, randomized, crossover study that measured the effect of a 0.7 mg/kg dose administered once daily in ten newborns at 34–40 weeks postmenstrual age [44]. Both esophageal pH and gastric pH were increased after 1 week of treatment. The percentage of time that gastric pH was <4 was inversely related to the plasma omeprazole concentration measured 2 h after the dose. Pantoprazole studied in the newborn showed that a 1.2 mg/kg daily dose raised gastric pH, but not esophageal pH, although the normalized AUC of esophageal H^+ was significantly reduced [45]. Just as importantly, the percentage of patients with a normal reflux index of <5 % was not changed significantly. The effects of esomeprazole treatment of

preterm and term newborns at postmenstrual ages of 35.6–44 weeks for 7 days were similar [20]. Esomeprazole raised gastric pH and the percentage of time gastric pH was >4. It reduced the percentage of time the esophageal pH was <4, the number of reflux events, and the number of acid reflux episodes >5 min. Despite this inhibition of acid production and acid reflux, reflux episodes measured by impedance did not decrease. Thus, inhibition of acid production by PPIs for treatment of newborns will only be beneficial if they have acid-related problems, such as esophagitis or upper airway inflammation. Clinicians will recognize that such problems do occur in newborns, but they are difficult to diagnose accurately, and clinical signs such as apnea are not valid indicators of reflux.

3.3 Treatment of Infants <12 Months of Age with PPIs

In infants of 1–11 months of age, PPIs demonstrate significant inhibition of gastric acid secretion and reduce acid reflux. Pantoprazole demonstrated a dose response with significantly more inhibition of acid secretion with 1.2 mg/kg than with 0.6 mg/kg dosing [45]. The 1.2 mg/kg dose reduced gastric H^+ AUC and esophageal H^+ AUC, but this dose paradoxically lowered mean ($\pm$ standard deviation) esophageal pH from 5.2 ± 0.4 to 4.9 ± 0.3. Possibly due to the smaller parietal cell mass in the newborn, pantoprazole doses of 1.2 mg/kg (high dose) raised gastric pH above 4 for 79 % of the day in newborns and for 57 % of the day in infants at 1–11 months of age. Esomeprazole in a larger age range of 1–24 months demonstrated a favorable dose-response from 0.25 mg/kg to 1 mg/kg, with the larger dose increasing the percentage of time the gastric pH was >4 and reducing the percentage of time the intra-esophageal pH was <4 [44].

Until the recent labeling of esomeprazole for erosive esophagitis in 1–11 month old infants, the effectiveness of the PPIs in infants and newborns for reduction of esophagitis and gastroesophageal reflux disease (GERD) had not been established. Many pediatric clinical studies of the effectiveness of PPIs have occurred in response to Written Requests from the FDA for studies to qualify for Pediatric Exclusivity through the *Food and Drug Administration Modernization Act* of 1997, the *Best Pharmaceuticals for Children Act* of 2002, and the *Food and Drug Administration Amendments Act* of 2007 [46–48]. Some study designs, particularly those relating to infants that involved a 'run-in' treatment period followed by blinded treatment withdrawal have been criticized because of the potential for hypergastrinemia to overstimulate gastric acid secretion when the PPI is stopped. Furthermore, the effectiveness of PPI treatment of newborns remains controversial primarily because of uncertainty about how to measure reflux associated disorders, such as esophagitis, laryngitis, or

aspiration. Endoscopy and biopsies are not routinely performed in neonates suspected of esophagitis, so assessment has relied on symptom assessment.

The initial Written Requests for studies of efficacy of PPIs in neonates issued by the FDA requested analysis of obstructive apnea as an index of symptomatic reflux [40–43]. Unfortunately, pH probe studies combined with measures of apnea have shown a low temporal correlation between gastroesophageal reflux and apnea [49–51]. Furthermore, studies of the rate of apnea before and during treatment with PPIs have not shown a reduction in apnea [52]. This endpoint was later eliminated from the PPI Written Requests, and no efficacy studies were required by the FDA in neonates to qualify for Pediatric Exclusivity [53–56]. Orenstein et al. [57] conducted a randomized, blinded, placebo-controlled study of lansoprazole treatment of gastroesophageal reflux (GER) in newborns. They found no improvement in symptom scores between neonates who received placebo and those treated with lansoprazole, but response was defined as a 50 % reduction in the specific symptom. Treatment was confounded by non-pharmacologic management of GER that was continued in 63 % of patients at the investigator's discretion [57]. Placebo-controlled studies of GERD in newborns and infants without the confounding influence of other simultaneous treatments for GERD are still needed. Until that occurs, the controversies about whether acid-related problems occur in newborns or not will continue [58, 59].

Except for the recent labeling of esomeprazole for 1–11 month old infants, studies of PPIs in infants had also failed to demonstrate efficacy. The study design by Winter et al. [60] for pantoprazole is one recommended by the FDA to qualify for Pediatric Exclusivity. This study enrolled infants with GERD at 31 sites who were identified by a symptom score or endoscopic evidence of esophagitis. For 2 weeks, they received non-PPI therapy of thickened hypoallergenic feedings (if not breast fed), positioning, environmental modification, and antacids as needed. Infants who were still symptomatic after 2 weeks were treated with pantoprazole approximately 1.2 mg/kg/day for 4 more weeks. At that point, a blinded substitution of placebo for pantoprazole began in half of the patients. The endpoint of the study was the percentage of patients with worsening of GERD by symptoms, endoscopic study, or maximal use of antacids during the 4-week, double-blind, randomized withdrawal phase. Although there was a significant decrease in symptom scores during the open-label treatment phase, no differences were detected in the rate of study withdrawal between the pantoprazole-treated and placebo-treated groups during the double-bind PPI withdrawal. Several possible explanations could be considered. It is possible that esophagitis does not occur at these ages, but many pediatric gastroenterologists and pediatricians

find that inaccurate. It might be that only a small percentage of infants with GER develop GERD. It is also possible that the study design was unable to detect a change in esophagitis primarily on the basis of symptoms. Possibly, the esophagitis was healed during the 4-week, open-label treatment. At enrollment, only 35 of 106 symptomatic patients had some type of test performed for GERD. Of those having a test, 66 % were consistent with GERD. The study did not require endoscopy in all patients, and there was no follow-up endoscopy at the end of study, creating uncertainty about the diagnosis.

3.4 Treatment of Children Older than 1 Year of Age with PPIs

In pediatric patients older than 1 year of age, many studies have shown PPIs to be effective for treatment of erosive esophagitis diagnosed by history, endoscopy, and biopsy and for treatment of *Helicobacter pylori*. Extensive reviews of reported pediatric studies of PPIs have been reported. Earlier reviews reported on omeprazole 0.7–3.5 mg/kg/day, lansoprazole 0.73–1.5 mg/kg/day [4] and omeprazole 0.3–3.3 mg/kg/day [61]. Rather than repeat this work, we refer the reader to those reviews along with additional reviews that have expanded the list of PPIs to include pantoprazole, esomeprazole, and rabeprazole [62–66].

4 Prolonged Treatment of Pediatric Patients

Prolonged inhibition of the proton pump has raised concerns among gastroenterologists and regulators at the FDA. Long-term inhibition of gastric acid secretion leads to prolonged hypergastrinemia and concerns for enterochromaffin-like cell hyperplasia, carcinoid formation, vitamin B_{12} deficiency, hypomagnesemia, necrotizing enterocolitis, osteoporosis, atrophic gastritis, and increased infections [67]. These concerns have been raised in adults, but pediatric studies are limited. Tolia and Boyer [67] reported the outcomes of 32–47 months of treatment with PPIs in 133 pediatric patients ranging in age from 0.1 to 17.6 years at the start of treatment. The frequency of use of PPIs was lansoprazole > omeprazole > pantoprazole > esomeprazole > rabeprazole. Most patients were dosed twice a day. Parietal cell hyperplasia was observed in 0–16 % of patients during follow-up, but interestingly, the gastric histology was normal significantly more often when treatment continued for longer than 48 months and when patients were treated with higher doses. Gastrin levels were elevated to >90 pg/mL in 73 % of the children, but vitamin B_{12} remained normal.

5 Summary

Several aspects of the pharmacology and treatment of children with PPIs should be considered to optimize treatment of pediatric patients with acid-related disorders.

- Without activation through ligand binding by histamine, gastrin, acetyl choline, or other mediators, the parietal cell acid pump (H^+–K^+-ATPase) is inactive and cannot be inhibited.
- H^+–K^+-ATPase must be activated to secrete gastric acid, which is needed for the PPI to be activated in order to bind to the enzyme to cause inhibition.
- The pharmacokinetics of the PPIs, especially the absorption rate and t_{max}, must be considered in the dosing schedule for a PPI so it is present in the circulation when the proton pump is active. This usually requires administration of the PPI 60–90 min before a meal.
- The site of binding of the different activated PPIs to different CYSs in the H^+–K^+-ATPase influence the reversibility of the proton pump inactivation and the duration of inhibition.
- For children older than 1 year, the pharmacodynamics of PPIs for treatment of peptic acid disorders, such as erosive esophagitis and peptic ulcer disease, are similar to that in adults.
- Except for the recent labeling of esomeprazole, efficacy of PPI treatment of newborns and infants through 11 months of age for GERD has not been demonstrated, despite inhibition of gastric acid secretion. This may relate to difficulties in determining what clinical signs relate to esophagitis and which do not in this preverbal population or to a lack of gastric acid-mediated disease. Clinicians are divided on this last issue between those who believe gastric acid-mediated disease does occur in newborns and infants and those who do not.

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