REVIEW ARTICLE

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Pharmacokinetics of Proton Pump Inhibitors in Children

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Abstract

The use of proton pump inhibitors (PPIs) has become widespread in children and infants for the management of paediatric acid-related disease. Pharmacokinet-

ic profiles of only omeprazole and lansoprazole have been well characterised in children over 2 years of age with acid-related diseases. Few data have been recently published regarding the pharmacokinetics of pantoprazole in children, and none are available for rabeprazole or esomeprazole. The metabolism of PPI enantiomers has never been studied in the paediatric population.

A one-compartment model best describes the pharmacokinetic behaviour of omeprazole, lansoprazole and pantoprazole in children, with important inter-individual variability for each pharmacokinetic parameter. Like adults, PPIs are rapidly absorbed in children following oral administration; the mean time to reach maximum plasma concentration varies from 1 to 3 hours. Since these agents are acid labile, their oral formulations consist of capsules containing enteric-coated granules. No liquid formulation is available for any of the PPIs. Thus, for those patients unable to swallow capsules, extemporaneous liquid preparations for omeprazole and lansoprazole have been reported; however, neither the absolute nor the relative bioavailabilities of these oral formulations have been studied in children. Intravenous formulations are available for omeprazole (in Europe), lansoprazole and pantoprazole.

PPIs are rapidly metabolised in children, with short elimination half-lives of around 1 hour, similar to that reported for adults. All PPIs are extensively metabolised by the liver, primarily by cytochrome P450 (CYP) isoforms CYP2C19 and CYP3A4, to inactive metabolites, with little unchanged drug excreted in the urine. Similar to that seen in adults, the absolute bioavailability of omeprazole increases with repeated dosing in children; this phenomenon is thought to be due to a combination of decreased first-pass elimination and reduced systemic clearance. The apparent clearance (CL/F) of omeprazole, lansoprazole and pantoprazole appears to be faster for children than for adults. A higher metabolic capacity in children as well as differences in the extent of PPI bioavailability are most likely responsible for this finding. This may partly account for the need in children for variable and sometimes considerably greater doses of PPIs, on a per kilogram basis, than for adults to achieve similar plasma concentrations. Furthermore, no studies have been able to demonstrate a statistically significant correlation between age and pharmacokinetic parameters among children. Despite the small number of very young infants studied, there is some evidence for reduced PPI metabolism in newborns. The limited paediatric data regarding the impact of CYP2C19 genetic polymorphism on PPI metabolism are similar to those reported for adults, with poor metabolisers having 6- to 10-fold higher area under the concentration-time curve values compared with extensive metabolisers.

Finally, because a pharmacokinetic/pharmacodynamic relationship exists for PPIs, the significant interindividual variability in their disposition may partly explain the wide range of therapeutic doses used in children. Further studies are needed to better define the pharmacokinetics of PPIs in children <2 years of age.

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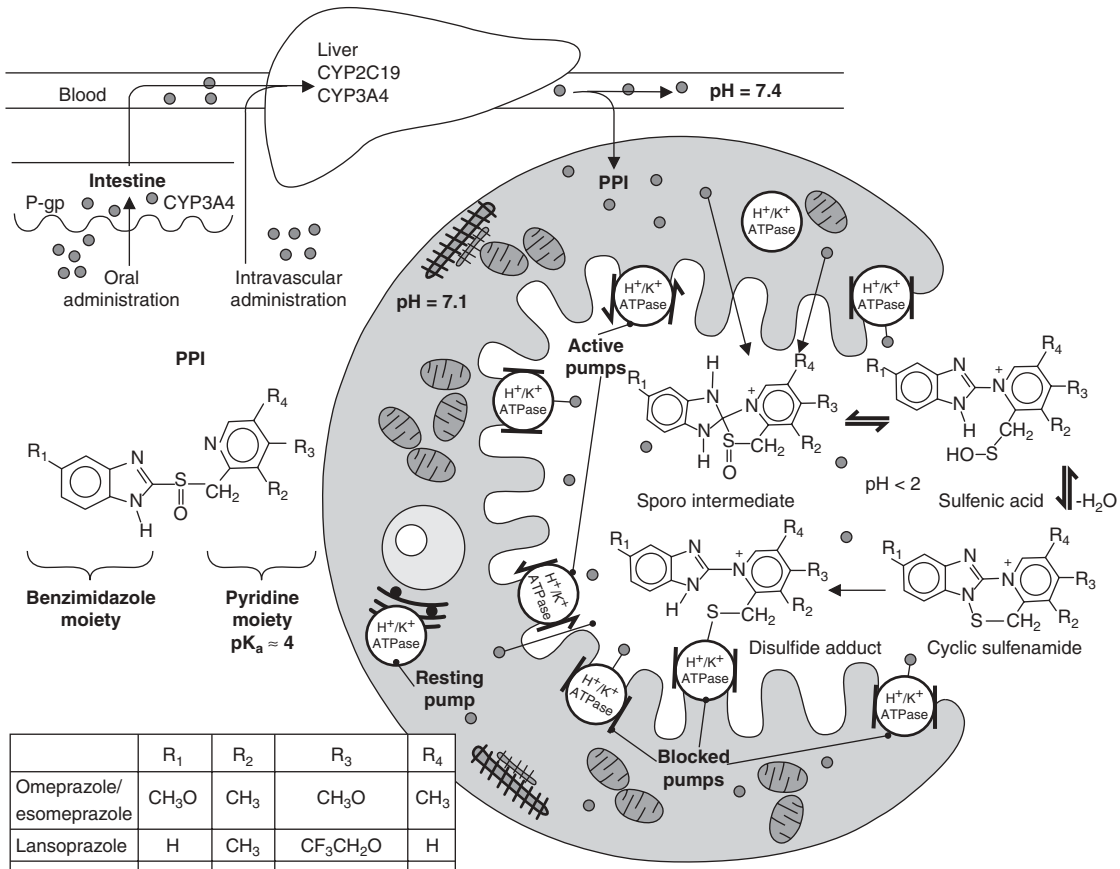

	R_1	R_2	R_3	R_4
Omeprazole/ esomeprazole	CH_3O	CH_3	CH_3O	CH_3
Lansoprazole	H	CH_3	CF_3CH_2O	H
Pantoprazole	CF_2HO	CH_3O	CH_3O	H
Rabeprazole	H	CH_3	$CH_3O(CH_2)_3O$	H

Fig. 1. General chemical structure and mechanism of action of proton pump inhibitors (PPIs). **ATPase** = adenosine triphosphatase; **CYP** = cytochrome P450; **P-gp** = P-glycoprotein; **pK**a = negative logarithm of the acid ionisation constant.

Proton pump inhibitors (PPIs) consist of a group of chemically related compounds (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) that inhibit the final common pathway of acid production of gastric parietal cells.[1] Over the past 20 years, these potent and well tolerated gastric acid suppressing drugs have revolutionised the management of acid-related disorders in adults.[2] In the last decade, PPIs have also dramatically influenced the management of paediatric acid-related disease, and their use has become widespread in infants and children. A thorough understanding of the pharmacokinetic profile of PPIs is of paramount importance, since systemic drug exposure correlates with the degree of gastric acid inhibitory effect.[3-5] This review focuses on available data regarding the pharmacokinetics of PPIs in children, and the impact of developmental changes, genetic constitution and disease on their disposition. Potential drug interactions of PPIs are also discussed.

1. Mechanism of Action

PPIs are all substituted benzimidazole derivatives with a similar mechanism of action (figure 1).[1,6] Being weakly basic compounds (negative

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logarithm of the acid ionisation constant [pK_a] of the pyridine nitrogen is close to 4.0, with the exception of rabeprazole, which has a pK_a of 5), PPIs are not protonated at neutral pH (e.g. in the blood) and become increasingly protonated upon entering an acidic compartment with a pH lower than their pK_a. After oral administration, these prodrugs are absorbed from the small intestine into the systemic circulation and then enter the gastric parietal cell where they diffuse to the extracellular canaliculus. Under the acidic conditions of the canaliculus, protonated PPIs become trapped in this compartment, and are rapidly transformed by an acid-induced, intramolecular rearrangement into the pharmacologically active entity, a cyclic sulphenamide. The cyclic sulphenamide opens and then binds covalently to one or more cysteine thiol groups (-SH) on the luminal surface of the H^+/K^+-adenosine triphosphatase (ATPase) [the proton pump], which leads to irreversible inhibition of this enzyme. Because the H^+/K^+-ATPase represents the final step of gastric acid production by parietal cells, inhibition of this enzyme by PPIs suppresses gastric acid secretion regardless of the primary stimulus.[7]

The requirement for an acidic environment for PPI accumulation and activation provides the basis for selective action against the gastric H^+/K^+-ATPase; such an acidic milieu is found exclusively in the extracellular canaliculi of actively secreting parietal cells and within the stomach cavity. The pH-dependent nature of PPI accumulation and activation is also a possible reason for the significantly shorter period of intragastric pH elevation achieved when a PPI is concomitantly administered with a histamine H_2-receptor antagonist, compared with that obtained with a PPI alone.[8] Elevation of pH in the canaliculus by the H_2-receptor antagonist is thought to prevent accumulation and activation of the PPI in a certain portion of parietal cells.

Due to the covalent nature of the H^+/K^+-ATPase inhibition, restoration of acid production occurs mostly through *de novo* synthesis of the H^+/K^+-ATPase, which has a half-life ($t_{1/2}$) of about 50 hours in the rat.[9] The exact human $t_{1/2}$ is unknown. This accounts for the long duration of antisecretory effect of PPIs (more than 24 hours), which is much longer than expected based on their short plasma elimination half-life ($t_{1/2}\beta$) [about 1 hour], and supports the once-daily administration of these agents.[2] This is also why the restoration of acid secretion upon PPI removal is about 48 hours in humans.[10]

Whether infants and children have an H^+/K^+-ATPase turnover similar to that seen in adults remains to be elucidated. Maturational differences resulting in either faster or slower pump turnover could have important therapeutic consequences, with the need to administer PPIs more or less frequently, respectively. Furthermore, developmental changes in the expression of the human gastric H^+/K^+-ATPase could also influence the dose of PPIs required in children. One study has demonstrated that H^+/K^+-ATPase is present from week 25 of gestation, and its expression increases with gestational age, continuing on through the first 82 days after birth.[11] This is in agreement with data showing that premature infants of 24 weeks gestational age are able to maintain a basal gastric pH below 4 from the first day of life[12-14] and that by 6 months of age, maximal acid output is at about the same level as in older children and adults.[15]

In nonstimulated parietal cells, the H^+/K^+-ATPase is found to be inactive in the cytoplasm as part of a tubulovesicular membrane. Upon stimulation, the H^+/K^+-ATPase is translocated to the canalicular membrane where it becomes active. Only actively secreting pumps are inhibited when effective plasma concentrations of PPIs are reached, sparing the inactive pumps. It is assumed that: (i) about 75% of H^+/K^+-ATPase are active (i.e. on the canalicular membrane) during the time period of systemic bioavailability of PPIs; (ii) full (100%) inhibition of active pumps by PPIs occurs; (iii) the

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half-life of the human proton pump is 50 hours; and (iv) *de novo* synthesis is the main mechanism by which restoration of acid secretion occurs. According to these assumptions, significant gastric acid inhibition is expected after the first dose of PPI, while a steady-state gastric inhibitory effect of PPIs should be reached after a few days with a single-daily dose regimen.[1,16] For circumstances such as active upper gastrointestinal bleeding, for which higher sustained pH is warranted, a greater systemic bioavailability is needed.[7] This is best achieved with a continuous intravenous infusion of PPI, since the plasma $t_{1/2}\beta$ is very short (about 1 hour).[17]

A meal is considered the strongest physiological event inducing the translocation of the H^+/K^+-ATPase from the cytoplasm to the membrane of the secretory canaliculus,[16] emphasising the recommendation that PPIs be administered just before meals.[18]

Finally, although PPIs share the same general mechanism of action, they also differ, with distinct patterns of binding to the H^+/K^+-ATPase and slight variation of pK_a, implying different rates of accumulation and chemical activation.[1,6] However, whether these differences have any pharmacological and/or clinical significance remains to be proven.[19,20]

2. Overview of Therapeutic Use

The therapeutic use of PPIs in children has been summarised recently,[21,22] and is therefore only briefly reviewed here. Gastro-oesophageal reflux disease (GORD) and related oesophageal disorders, peptic ulcer disease and *Helicobacter pylori* infection are the most common conditions for which PPIs are given in children. So far, published paediatric studies that have evaluated the efficacy of PPIs in the management of these gastric acid-related disorders have not been comparative and were limited to omeprazole or lansoprazole, with the exception of one recent report on pantoprazole. In addition, most patients included in these studies were older than 1 year of age. Only four randomised controlled studies have been published and they are further discussed.[23-26]

Lansoprazole is the only PPI with a US FDA labelled paediatric indication (GORD) for infants aged 1 year or older, while in Europe omeprazole is the only PPI approved for use in children.

2.1 Gastro-Oesophageal Reflux Disease

2.1.1 Peptic Oesophagitis

Most paediatric studies have been performed to determine the efficacy of omeprazole and lansoprazole for healing peptic oesophagitis. Ten case series have been published to date with omeprazole[27-36] and four with lansoprazole.[4,37-39] For both PPIs, current available data show that in children with adequate acid suppression (i.e. receiving appropriate dosage), the endoscopic healing rate of peptic oesophagitis is more than 75% after 4–8 weeks of treatment, with parallel improvement in clinical symptoms. However, considering only the initial dose used in these trials (i.e. 0.7–1 mg/kg), the response rate is lower, around 50%.[4,36] Furthermore, these studies revealed a significant variability in the therapeutic dosage regimen of PPIs in children, with the required dose for omeprazole varying between 0.3 mg/kg[35] and 3.5 mg/kg,[36] and for lansoprazole between 0.5 mg/kg and 1.8 mg/kg.[4,38,39]

Only one trial has compared the efficacy of PPIs and H_2-receptor antagonists in the paediatric population. An 8-week therapeutic trial in 25 children with severe reflux oesophagitis revealed that omeprazole (40 mg/1.73m^2/day) was comparable to high dose ranitidine (20 mg/kg/day) for the healing of oesophagitis and relief of symptoms.[23]

In a recent study, oral pantoprazole 20mg daily given to 15 paediatric patients aged 6–13 years with reflux oesophagitis provided healing of the oesophagitis in 52% of patients.[40]

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2.1.2 Extra-Digestive Manifestations of Gastro-Oesophageal Reflux

Gastro-oesophageal reflux may account for multiple nondigestive respiratory, laryngeal and neurological manifestations in children.[41-43] In adults, although some open-label studies have suggested a benefit of PPI therapy for the management of laryngeal symptoms,[44] a recent meta-analysis of 11 randomised controlled trials (six of them with PPIs) did not find any improvement in asthma following treatment for GORD.[45] In children, with the exception of one open-label study,[46] there are no data available on the efficacy of PPIs for asthma or laryngeal symptoms. One randomised, double-blind, placebo-controlled, crossover trial evaluated the efficacy of omeprazole in irritable infants with gastro-oesophageal reflux, defined as oesophageal acid exposure (pH <4 for over 5% of the time monitoring 24-hour pH) and/or abnormal oesophageal histology.[26] Compared with placebo, omeprazole significantly reduced acid exposure but did not improve irritability, as measured by diary or a visual analogue scale.

2.2 Peptic Ulcers

Omeprazole has been used in children and adolescents (n = 10) for the treatment of gastric and duodenal ulcers refractory to H_2-receptor antagonists.[29,47] Daily doses of 0.3–0.7 mg/kg have produced complete healing after 4–8 weeks of treatment.

2.3 *Helicobacter pylori* Infection

Omeprazole and lansoprazole have been widely used in the treatment of *H. pylori* infection in children. Noncomparative trials – conducted with children – evaluating the efficacy of triple therapy that associates two antimicrobials (amoxicillin, metronidazole or clarithromycin) with omeprazole[48-53] or lansoprazole[54-56] have shown an eradication rate between 54% and 93%. Combination therapies consisting of metronidazole, amoxicillin and either proprietary omeprazole, generic omeprazole or ranitidine were compared in an open-label randomised trial.[25] All three regimens produced effective eradication of *H. pylori* and ulcer healing in children with peptic ulcer disease, with proprietary omeprazole being more effective than the two other antisecretory agents studied. In a prospective, randomised, double-blind, multicentre study, Gottrand et al.[24] compared the efficacy of the combination of omeprazole, amoxicillin and clarithromycin with that of amoxicillin and clarithromycin for the treatment of *H. pylori* gastritis in 73 children (mean age 10.8 years; range 3.3–15.4 years). In an intent-to-treat analysis (n = 63), eradication rates were 74.2% (95% CI 58.7, 89.6) in the omeprazole, amoxicillin and clarithromycin group and 9.4% (95% CI 0, 19.5) in the amoxicillin and clarithromycin group. Guidelines for the treatment of *H. pylori* infection in children have been published recently by paediatric gastroenterology societies.[57,58] These recommendations are summarised as follows.

- Eradication treatment is recommended for children who have a duodenal ulcer or gastric ulcer identified at endoscopy, and *H. pylori* documented by histopathology. Eradication is also clearly recommended in children with mucosa-associated lymphoid tissue lymphoma associated with *H. pylori* infection.
- Eradication therapy is not recommended for children with *H. pylori* infection and either nonulcer dyspepsia or functional recurrent abdominal pain.
- Finally, eradication treatment should be offered if a child undergoes endoscopy and *H. pylori* is identified.

2.4 Others

PPIs are sometimes used as adjuvant therapy in cystic fibrosis to improve the efficacy of pancreatic enzymes and fat absorption. A few studies have

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evaluated the efficacy of PPIs for this indication, with controversial results. One case series[59] and one crossover trial[60] found a positive effect of PPIs on fat absorption while no such improvement could be demonstrated in a double-blind, placebo-controlled, crossover study.[61] PPIs are also used as premedication for general anaesthesia, since both lansoprazole[62] and omeprazole[63] have been shown to reduce preoperative gastric acidity and volume in children.

There is very limited data regarding the use of PPIs for the prevention of stress ulceration in critically ill patients. For this indication, the goal is to maintain gastric pH >4 for >80% of the time, the threshold shown to prevent stress-induced gastrointestinal haemorrhage in adult intensive care unit patients. To date, three paediatric studies have evaluated the efficacy of omeprazole in achieving such a level of gastric acid suppression in this setting.

Two studies[64,65] were performed in paediatric recipients of liver and intestinal transplantation receiving omeprazole 0.5 mg/kg given orally every 12 hours as a suspension in sodium bicarbonate (8.4%). One study[64] showed that omeprazole was able to maintain gastric pH >4 for 78.8% (range 43.2–99.6%) and 97.8% (range 85.6–100%) of the first and multiple dosage intervals (48 hours), respectively. Omeprazole disposition was also assessed and showed that such level of efficacy was achieved with a higher drug exposure, as reflected by the area under the plasma concentration-time curve (AUC), and a longer $t_{1/2}\beta$ in this specific population compared with noncritically ill children receiving omeprazole at similar dosages (table I). Similarly, in the second study[65] the time that gastric pH exceeded 4 was 86% ± 7% in liver allograft recipients and 81% ± 8% in intestinal allograft recipients after 2 days of therapy. Among the 22 patients studied, the dosing interval had to be shortened to every 8 hours in two patients and to every 6 hours in two other patients. No pharmacokinetic study was performed.[65] A recent trial challenges these results. It showed that omeprazole 1 mg/kg (maximum 20mg) given orally as a suspension in sodium bicarbonate (8.4%), failed to achieve an adequate rise in gastric pH for stress ulcer prophylaxis in 50% of the 18 critically ill children studied (aged 1–16 years).[66] Again, no pharmacokinetic parameters were measured.

3. The Pharmacokinetic/ Pharmacodynamic Relationship

In adults, the efficacy of PPIs appears to correlate with the AUC.[3,67,68] This pharmacokinetic/pharmacodynamic relationship appears to be best described by the maximum effect (E_{max}) model, with an upper AUC limit above which no further increase in intragastric pH can be expected.[69,70] Recently, the existence of such systemic exposure-response relationships for PPIs have been further supported by recognition that individuals with slower PPI clearance (cytochrome P450 [CYP] 2C19 poor metabolisers [see section 4.3.4]) and higher plasma drug concentrations experience superior acid suppression.[71-76] Although controversial results have been published, there is also some evidence for a correlation between PPI AUC and gastric acid inhibition in paediatric patients;[4,5,64,77,78] however, the therapeutic target AUC is not known.

4. Pharmacokinetic Properties

While the disposition of PPIs has been extensively studied in healthy adult volunteers and adults with acid-related disorders,[7,79-94] only the pharmacokinetic profiles of omeprazole and lansoprazole have been well characterised in children over 2 years of age with acid-related diseases.[4,5,29,39,47,64,77,78,95-100] Little recent information has been published regarding the pharmacokinetics of pantoprazole in children, and none is available for rabeprazole and esomeprazole.[101-103]

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Table I. Pharmacokinetic parameters[a] of omeprazole, lansoprazole and pantoprazole in children

Study	No. of subjects	Age[b]	Study design	Dose (mg/kg)[c], route of administration	C_{max} (μg/mL)	t_{max} (h)	AUC (μg • h/mL)	CL/F (L/h/kg)	Vd/F (L/kg)	$t_{½β}$ (h)
Omeprazole										
Kato et al.[47]	2	4/10	SD	0.5/0.7, PO[d]	0.37/1.85	1.5/1.5	0.56/3.16	NR	NR	1.0/1.4
		4/10	MD[e]	0.5/0.7,PO[d]	0.36/1.82	1.5/1.5	0.92/3.67	NR	NR	1.1/1.1
Jacqz-Aigrain et al.[95]	4	4–20	SD	59.4 [55.0–62.5][f], IV	NR	NA	3.81 [1.08–8.28]	0.59 [0.16–1.39]	0.5 [0.4–0.7]	1.1 [0.4–2.7]
	9	0.3–15	MD	53.1 [36.9–138.8][f,g], IV	NR	NA	6.78 [1.48–21.43]	0.26 [0.11–0.58]	0.4 [0.2–0.7]	1.4 [0.6–2.8]
Kato et al.[29]	7	3–13	MD[e]	0.6 [0.5–0.7], PO[d]	0.85 [0.07–1.94]	1.5 [1.0–2.0]	1.87 [0.11–5.30]	NR	NR	0.9 [0.5–1.4]
Andersson et al.[96]	7	1.6–6.1	MD[e]	1.6 [0.6–3.6], PO[d]	1.01 [0.04–1.90]	2.4 [0.5–6.0]	1.93 [0.10–4.15]	NR	NR	0.9 [0.7- 1.2][h]
	9	6.7–12.5	MD[e]	1.4 [0.6–3.3], PO[d]	1.09 [0.07–1.59]	2.3 [0.5–6.0]	2.96 [0.10–6.91]	NR	NR	1.6 [0.6–2.6][i]
	9	12.6–16.2	MD[e]	1.1 [0.7–1.5], PO[d]	1.32 [0.31–2.76]	2.6 [1.0–4.2]	4.05 [0.45–7.60]	NR	NR	1.5 [0.6–2.2][j]
Faure et al.[5]	4	0.5–2.3	MD	0.56 [0.52–0.61], IV	NR	NA	0.94 [0.55–1.64]	0.68 [0.37–1.01]	NR	NR
	5	0.4–1.3	MD	1.17 [1.09–1.3], IV	NR	NA	3.94 [1.43–7.71]	0.42 [0.16–0.8]	NR	NR
Olsen et al.[64]	11[k]	0.35–14	SD	0.5 q12h, PO[l]	0.81 (0.41)	1.2 (0.8)	4.96 (3.31)	NR	NR	4.9 (3.5)
			MD	0.5 q12h, PO[l]	1.26 (0.29)	1.3 (0.5)	7.62 (2.74)	NR	NR	5.1 (2.4)
Andersson et al.[97]	24	0–2	SD	1.0, PO	0.45	<1	0.66	NR	NR	1
				1.5, PO	0.35	<1	0.58	NR	NR	1
Andersson et al.[98]	3	<10 days	MD	[0.4–1.2] bid, IV	NR	NA	NR	[0.12–0.20]	NR	[1.6–2.1]
Kearns et al.[99]	23	2–16	SD	0.41 [0.16–0.91], PO[d]	0.45 [0.04–1.45][m]	2.2 [1.0–6.0]	0.81 [0.24–1.33]	1.76 [0.29–5.8]	2.6 [0.4–12.2]	1.0 [0.7–1.5]
Marier et al.[100]	12	0.5–13	MD[e]	0.69 [0.56–0.83], PO[d]	NR	NR	NR	0.51 (0.34)	0.7 (0.3)	1.1 (0.4)
Stedman et al.[68]		Adults		20mg, PO	[0.08–8.00]	[1–3]	[0.2–1.2]	0.45	[0.31–0.34]	[0.6–1.0]
Omeprazole sulphone										
Jacqz-Aigrain et al.[95]	3	12–20	SD	58.4 [55.0–60.2][f], IV	0.7 [0.23–1.03]	2.4 [1.4–4.4]	6.12 [0.92–12.28]	NR	NR	4.0 [2.1–6.9]
	8	0.3–15	MD	52.2 [36.9–138.8][f,g], IV	0.7 [0.39–1.66]	1.8 [1.0–2.2]	8.67 [1.20–39.46]	NR	NR	5.4 [2.0–13.9]
Andersson et al.[98]	3	<10 days	MD	[0.4–1.2] bid, IV	NR	NA	NR	NR	NR	[11-25]
	5	0.4–1.4	MD	[0.4–1.2] bid, IV	NR	NA	NR	NR	NR	[2.1–3.5]

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Table I. Contd

Study	No. of subjects	Age[b]	Study design	Dose (mg/kg)[c], route of administration	C_{max} (μg/mL)	t_{max} (h)	AUC (μg • h/mL)	CL/F (L/h/kg)	Vd/F (L/kg)	$t_{½β}$ (h)
5′-Hydroxyomeprazole										
Andersson et al.[98]	3	<10 days	MD	[0.4–1.2] bid, IV	NR	NA	NR	NR	NR	[3–10]
	5	0.4–1.4	MD	[0.4–1.2] bid, IV	NR	NA	NR	NR	NR	[0.75–1.2]
Lansoprazole										
Tran et al.[77]	18	0.2–13.5	SD	30.8 [21.1–37.5][f], PO[d]	1.02 [0.018–3.44][n]	1.83 [0.97–3.93]	3.50 [0.45–25.49][n]	0.57 [0.03–1.79]	0.6 [0.3–1.7]	1.5 [0.4–8.9]
	22	0.05–14.1	MD[e]	30.3 [20.1–41.2][f], PO[d]	0.75 [0.08–1.77][n]	1.84 [0.88–4.02]	2.35 [0.40–14.92][n]	0.71 [0.08–1.76]	0.9 [0.2–3.6]	1.2 [0.4–4.8]
Gremse et al.[78]	28	1–9	MD	0.95 [0.51–1.77], PO[d]	0.79 (0.44)	1.5 (0.7)	1.71 (1.69)	NR	NR	0.7 (0.2)
	31	5–12	MD	0.79 [0.43–0.99], PO[d]	0.90 (0.44)	1.7 (0.7)	1.88 (1.16)	NR	NR	0.7 (0.2)
Gunasekaran et al.[39]	30	11–17	MD	15mg, PO[d]	0.41 (0.22)	1.6 (0.7)	1.02 (1.74)	NR	NR	0.8 (0.3)
	29	12–17	MD	30mg, PO[d]	1.01 (0.60)	1.7 (0.7)	2.49 (2.52)	NR	NR	1.0 (0.3)
Faure et al.[4]	23	0.3–13.3	MD[e]	0.73 [0.54–0.91], PO[d]	0.46 (0.36)	NR	1.18 (1.30)	1.85 (2.33)	NR	0.8 (0.4)
Stedman and Barclay[68]		Adults		30mg, PO	[0.6–1.2]	[1.3–2.2]	[1.7–5.0]	[0.20–0.28]	[0.39–0.46]	[0.9–1.6]
Pantoprazole										
Kearns et al.[101]	21 EMs	6–16	SD	20 or 40mg, PO	3.6 (1.5)[o]	NR	4.29 (2.08)[o]	0.30 (0.19)	0.2 (0.1)	0.6 (0.2)
	3 PMs	6–16	SD	20 or 40mg, PO	7.0 (4.0)[o]	NR	45.5 (19.25)[o]	0.03 (0.01)	0.2 (0.1)	5.8 (0.7)
Ferron et al.[102]	14[p]	2–16	SD	0.8 or 1.6, IV	NR	NA	NR	NR	NR	1.1 (0.5)
Litalien et al.[103]	4 no SIRS	3.4–14.6	MD	1.08 [0.47–1.88], IV	NR	NA	2.36 (1.09)[q]	0.34 (0.27)	NR	0.9 (0.3)
	4 SIRS	2.4–16.4	MD	0.98 [0.82–1.25], IV	NR	NA	29.48 (19.43)[q]	0.03 (0.02)	NR	8.2 (4.0)
Stedman and Barclay[68]		Adults		40mg, PO	[1.1–3.3]	[2–4]	[2–5]	[0.08–0.13]	[0.13–0.17]	[0.9–1.9]

a Mean values (standard deviation) or [range] are given.

b Age range (y), unless specified otherwise.

c PPIs were given once daily unless specified otherwise.

d PPI was administered as intact capsules or enteric-coated granules with fruit juice, soft food (yoghurt or apple sauce) or water.

e Pharmacokinetics were assessed after at least 7 days of PPI therapy.

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Table I. Contd

f Denotes dose as mg/1.73m^2 of body surface area.

g One patient received an erroneous high dose of 138.8 mg/1.73 m^2.

h Elimination half-life could be estimated in four patients.

i Elimination half-life could be estimated in three patients.

j Elimination half-life could be estimated in five patients.

k Paediatric intensive care unit patients in the immediate postoperative period after liver and/or intestinal transplantation (<12h post-transplantation).

l Omeprazole was administered nasogastrically in a sodium bicarbonate solution.

m C_{max} normalised for a dose of 1 mg/kg.

n C_{max} and AUC normalised for a dose of 30 mg/1.73m^2, the recommended adult dose of lansoprazole.

o C_{max} and AUC normalised for a dose of 1 mg/kg.

p Paediatric intensive care unit patients with stable liver, kidney and cardiovascular indices.

q AUC normalised for a dose of 0.57 mg/kg, the recommended dose of pantoprazole for a 70kg adult.

AUC = area under the plasma concentration-time curve; **bid** = twice daily; **CL/F** = apparent clearance; $\mathbf{C_{max}}$ = maximum plasma concentration; **EMs** = extensive metabolisers; **IV** = intravenous; **MD** = multiple-dose study; **NA** = not applicable; **NR** = not reported; **PMs** = poor metabolisers; **PO** = oral; **PPI** = proton pump inhibitor; **q12h** = every 12 hours; **SD** = single-dose study; **SIRS** = systemic inflammatory response syndrome; $\mathbf{t_{1/\beta}}$ = elimination half-life; $\mathbf{t_{max}}$ = time to reach C_{max}; **Vd/F** = apparent volume of distribution.

The pharmacokinetic behaviour of omeprazole, lansoprazole and pantoprazole in children is best described by a one-compartment model. Studies that have evaluated their disposition after oral and intravenous administration of single or repeated doses in infants and children are summarised in table I. Two facts are striking: (i) the paucity of data in infants under 2 years of age; and (ii) the important inter-individual variability for each pharmacokinetic parameter, also seen in adults. The pharmacokinetics of PPI metabolites in the paediatric population have been evaluated for omeprazole only (table I).[95,98] Comparison of the results of paediatric studies with each other and with studies in adults should be made with caution, since pharmacokinetic studies in children have been performed at different weight-normalised doses administered both orally (using different oral formulations) and intravenously for a variable number of days, and in single and multiple doses.

4.1 Absorption

In adults as well as in children, PPIs are rapidly absorbed in the gastrointestinal tract following oral administration. The mean time to reach maximum plasma concentration for omeprazole and lansoprazole in infants and children varies between 1 and 3 hours, similar to that observed in adults.[68] The effect of food on PPI absorption in children has not been evaluated, but food intake delays the absorption of omeprazole, lansoprazole and pantoprazole in adults. Although it does not affect the amount of omeprazole and pantoprazole absorbed, it decreases by 50% the extent of lansoprazole absorption.[104-106]

Since these agents are acid labile,[107] their oral formulations are designed to avoid contact with acid in the stomach. Their enteric coating dissolves only at a pH higher than 6, allowing release of PPIs in the alkaline duodenum, where they are mostly absorbed. Unfortunately, no liquid formulation is

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Table II. Absolute and relative bioavailabilities of the oral formulations of omeprazole, lansoprazole and pantoprazole in adults

Drug/formulation	Absolute bioavailability	Relative bioavailability
Omeprazole		
Available oral formulations		
Hard gelatin capsule containing enteric-coated granules	SD: 30–40% MD: 65%[109]	
Capsule containing 1000 acid-protected micropellets (Losec® MUPS®)[a]	Unknown	Bioequivalent to capsule[110]
Extemporaneous oral liquid formulations		
Enteric-coated granules suspended in a slightly acidic medium (pH 4) such as apple, orange or cranberry juice, yoghurt or apple sauce	Unknown	Unknown[b]
Enteric-coated granules mixed in 8.4% sodium bicarbonate	Unknown	MD: 58.4% of that of the capsule[112]
Lansoprazole		
Available oral formulations		
Hard gelatin capsule containing enteric-coated granules	SD: 81–91%[88]	
Disintegrating tablet	Unknown	SD: bioequivalent to capsule[113]
Extemporaneous oral liquid formulations		
Enteric-coated granules suspended in a slightly acidic medium (pH 4) such as apple, orange or cranberry juice, yoghurt or apple sauce	Unknown	SD: bioequivalent to capsule[c][114]
Enteric-coated granules mixed in 8.4% sodium bicarbonate	Unknown	MD: 84.7% of that of the capsule[112]
Pantoprazole		
Available oral formulation		
Enteric-coated tablet	SD: 77%[91]	
Extemporaneous oral liquid formulation		
Crushed tablet mixed in 8.4% sodium bicarbonate	Unknown	SD: 75% of that of the tablet[108]

a The use of trade names is for product identification purposes only and does not imply endorsement.

b One pharmacodynamic study involving 11 healthy adult volunteers has shown that enteric-coated granules mixed with orange juice, water with aspirin-free Alka-Seltzer® antacid tablets dissolved in it, or apple sauce achieve gastric acid suppression comparable to that of omeprazole capsules.[111]

c Enteric-coated granules in either orange juice, tomato juice or strained pears was bioequivalent to an intact capsule.

MD = multiple doses; **MUPS** = multiple unit pellet system; **SD** = single dose.

available for any of the PPIs. For those unable to swallow capsules or tablets, such as infants and young children, neurologically impaired patients or those with swallowing disorders, extemporaneous oral liquid preparations for omeprazole, lansoprazole and pantoprazole[108] have been reported (table II). These consist of suspensions of the enteric-coated granules removed from the capsule in media that prevent the dissolution of the protective coating. Neither the absolute nor the relative bioavailability of any of these oral formulations or extemporaneous liquid formulations have been studied in children. Adult data regarding the absolute and relative bioavailability of these different formulations are summarised in table II.[88,91,109-114]

Two important issues need to be addressed regarding PPI bioavailability. First, the absolute bioavailability of omeprazole (capsule) increases with repeated dosing. As shown in table I, this is also observed in children after multiple doses of omeprazole, with AUC values increasing by between 16% and 64% compared with those obtained after a single dose.[47,64] The reason for such behaviour is discussed in section 4.3.2. Thus, for omeprazole, studies performed after repeated doses (at least 7 days) provide the most accurate pharmacokinetic data, while results from single oral dose

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studies are difficult to interpret. This may explain some of the variability observed between paediatric studies evaluating the disposition of omeprazole.

Second, the relative bioavailability of the two extemporaneous oral liquid formulations of omeprazole is either unknown (enteric-coated granules suspended in a slightly acid medium) or poor (enteric-coated granules mixed with 8.4% sodium bicarbonate).[112] This certainly contributes to the wide interindividual variability observed between studies evaluating the disposition of omeprazole in children, since these formulations were often used. In contrast, the relative bioavailability of the two extemporaneous oral liquid formulations of lansoprazole and pantoprazole is higher.[112,114]

An intravenous formulation is only available for omeprazole (Europe), lansoprazole and pantoprazole. Also, very recently, lansoprazole has been available in the US as delayed-release orally disintegrating tablets and microganules for delayed-release oral suspension. To date, no data regarding the bioavailability of this new formulation are available in children.

4.2 Distribution

PPIs are highly bound to plasma proteins (>95%), primarily albumin. Two paediatric studies have evaluated the apparent volume of distribution (Vd) of omeprazole in children. In one study involving nine very sick children in whom a pharmacokinetic analysis was performed after multiple doses of omeprazole given intravenously, the mean Vd was 0.4 L/kg, similar to that of adults (0.31–0.34 L/kg).[95] In contrast, after a single oral dose of omeprazole given to 23 children, the mean Vd was much larger (2.6 L/kg) in the other study.[99] As explained in section 4.1, the bioavailability of omeprazole is at its lowest after a single oral administration, and the Vd reported by Kearns et al.[99] is most likely an overestimation of the true Vd of omeprazole in children. The mean Vd of lansoprazole in children is somewhat larger than that reported in adults (0.6–0.9 L/kg vs 0.39–0.46 L/kg).[77] Finally, the Vd of pantoprazole in children is comparable to that of adults (0.13–0.17 L/kg).[101]

4.3 Metabolism

4.3.1 General Considerations

Like adults, children rapidly metabolise PPIs, with a short $t_{1/2}\beta$ of around 1 hour. The main metabolic pathways of PPIs are shown in figure 2. All PPIs are extensively metabolised by the liver – primarily by CYP isoforms CYP2C19 and CYP3A4 – to inactive metabolites, with little unchanged drug excreted in the urine.[83,94,115] Also, a non-enzymatic pathway seems to be involved in rabeprazole metabolism. Although some investigators have advocated that the latter was the main metabolic route of this PPI,[116] the decreased clearance of rabeprazole in cirrhotic patients (38% of that in healthy volunteers) indicates that hepatic metabolism contributes significantly to rabeprazole disposition.[117] Also, the degree to which PPIs rely on CYP2C19 compared with CYP3A4 varies from one PPI to another (figure 2).[118-121]

Since all PPIs depend significantly on CYP2C19 for their elimination, changes in the level of CYP2C19 activity will affect their clearance and systemic drug exposure. The pharmacokinetic consequences of factors known to modify CYP2C19 activity are discussed below in sections 4.3.2, 4.3.3 and 4.3.4.

4.3.2 Effects of Dose

For lansoprazole,[86] pantoprazole[122] and rabeprazole,[123] there is a linear relationship between dose and plasma concentration. In contrast, the pharmacokinetics of omeprazole are dose dependent, with nonlinear increases in plasma concentration with increasing doses. One possible reason for this behaviour is the saturation of CYP2C19 metabolism with high doses.[124] Interestingly, the lowest

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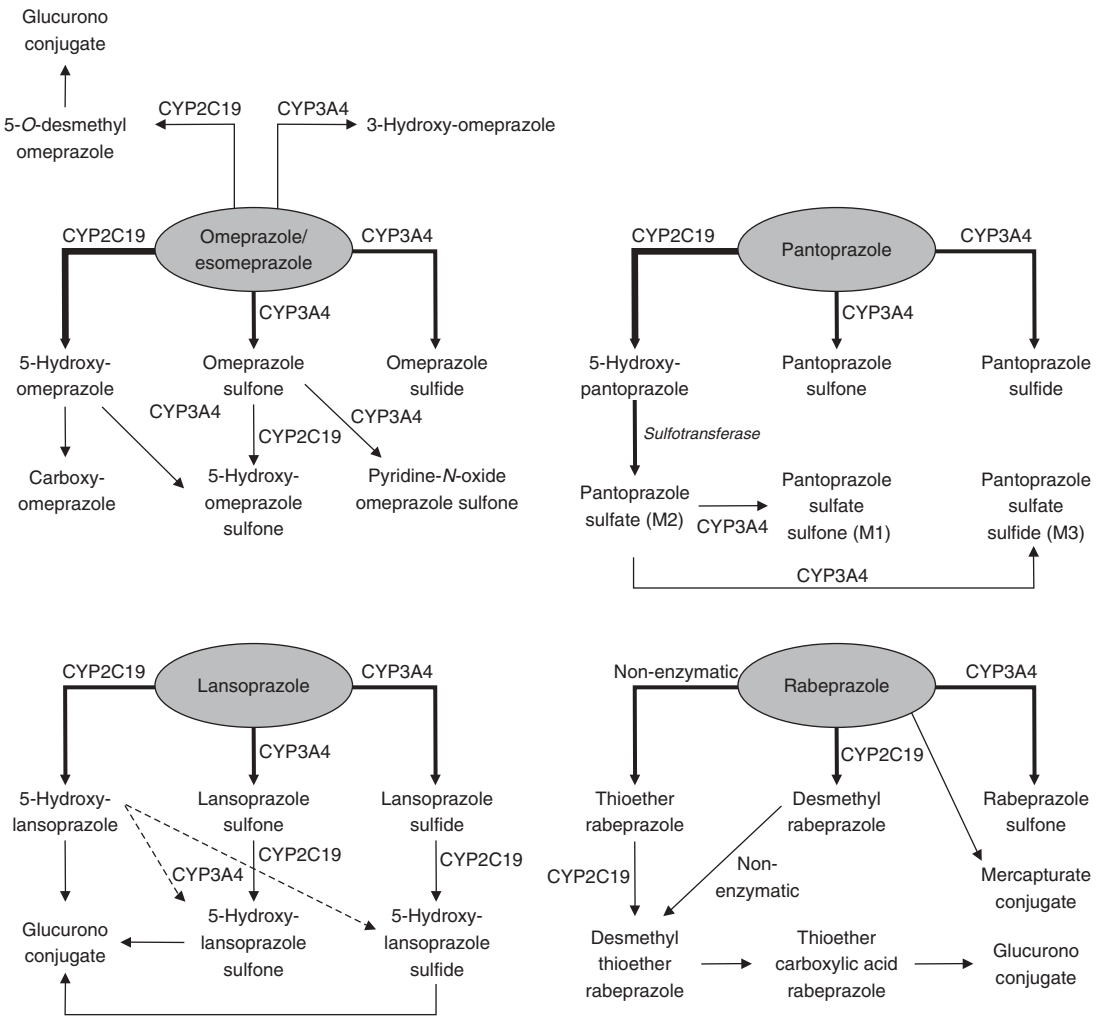

Fig. 2. The metabolic pathways of the proton pump inhibitors (PPIs) and the major cytochrome P450 (CYP) isoenzymes involved. The thicker the arrow, the larger the contribution of the CYP isoforms to the metabolic pathway.[121]

omeprazole clearance reported in children (0.11 L/h/kg) was observed in a 15-year-old adolescent who had received an erroneous high dose of omeprazole (114mg).[95]

While the pharmacokinetics of lansoprazole and pantoprazole after single and multiple doses are similar, the absolute bioavailability of omeprazole increases with repeated dosing.[109] This is thought to be secondary to both decreased first-pass elimination and reduced systemic clearance due to inhibition of CYP2C19 by omeprazole.[83,94,115] This is consistent with the known inhibition of this enzyme by omeprazole.[125-128] This phenomenon is also encountered with esomeprazole.[115,129]

4.3.3 Effects of Age

The ontogenic development of CYP2C19 and CYP3A4 is such that their activities are expected to be low in the first weeks of life, reaching adult activity by 6–12 months of age, then exceeding adult levels between 1 and 4 years of age and returning

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gradually to adult levels by the end of puberty.[130] Thus, there is reason to suspect age dependence in the disposition of PPIs. Some paediatric studies have tried to assess the impact of age on omeprazole and lansoprazole pharmacokinetics; however, very few patients <2 years of age were included, preventing any definite conclusion for this younger age group. Nevertheless, there is some evidence for:

- reduced metabolism of PPIs in newborns. In this age group, omeprazole clearance is slower than that of older children and adults (0.12–0.20 vs 0.45 L/h/kg), with longer $t_{1/2}\beta$ values for omeprazole, omeprazole sulphone, and 5-hydroxyomeprazole (1.6–2.1, 11–25 and 3–10 hours, respectively, vs 0.5–1, 2.1–3.5 and 0.75–1.2 hours, respectively).[98] Also, Tran et al.[77] found that the only newborn (18 days of age) in their study had the longest lansoprazole $t_{1/2}\beta$ value (4.8 hours) and the largest AUC value normalised to the recommended adult dose (14.9 μg • h/mL);
- a trend towards an increasing PPI (omeprazole and lansoprazole) metabolic rate with decreasing age in childhood;[77,96] however, no studies have been able to demonstrate a statistically significant correlation between age and pharmacokinetic parameters among children;[77,78,95,96,99,100]
- a faster apparent clearance (CL/F) of PPIs in children compared with adults (table II). A higher metabolic capacity in children as well as differences in the extent of PPI bioavailability may be responsible for this finding, and partly account for the need for considerably greater doses of PPIs in children than adults on a per kilogram basis, to achieve similar plasma concentrations;[96]
- an apparent shorter delay and faster rate of drug absorption in children with GORD compared with healthy adults.[100] The investigators attributed this to the younger children in their study receiving omeprazole as granules mixed into orange juice, instead of receiving intact capsules.

4.3.4 Effects of Cytochrome P450 (CYP) 2C19 Polymorphism

CYP2C19, the *S*-mephenytoin hydroxylase, is polymorphically expressed in man[131] and is characterised by three phenotypes of varying metabolic capacity determined by the presence of one or more mutant alleles. The wild type allele (wt) confers the highest metabolic capacity. Individuals homozygous for the wild type allele (wt/wt) demonstrate the greatest degree of CYP2C19 activity and are termed homozygous extensive metabolisers (hom EMs), or rapid metabolisers. Individuals homozygous for the mutant allele (mut/mut) demonstrate the lowest level of CYP2C19 activity and are termed poor metabolisers (PMs). Finally, heterozygous individuals for the wild type allele (wt/mut) are termed heterozygous extensive metabolisers (het EMs), or intermediate metabolisers, and demonstrate a CYP2C19 activity that falls between those of hom EMs and PMs, but closer to that of hom EMs. As such, both hom EMs and het EMs are often grouped together and termed extensive metabolisers (EMs). The frequency of PM phenotype varies significantly, based on ethnicity: 1% of African Americans, 2–6% of Caucasians, 13% of Koreans, 15% of Chinese and 19–23% of Japanese.[132]

Since CYP2C19 is a major metabolic pathway for all PPIs, the genetic polymorphism of CYP2C19 is expected to result in significant differences in the pharmacokinetic parameters of this class of drug. In fact, adult studies have shown that AUC values of omeprazole are about 6- to 8-fold higher, and that of lansoprazole and pantoprazole 4- to 5-fold higher in PMs compared with those of EMs,[94,133-139] whereas those of esomeprazole[94] are about 3-fold higher. The pharmacokinetic disposition of rabeprazole in relation to CYP2C19 polymorphism is somewhat controversial, with AUC ratios of PM/EM ranging from 1.2 (i.e. no difference between PMs and

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EMs)[135] to 5.3.[134,136,137,140] Those studies that have shown significantly higher AUCs in PMs compared with EMs further support the importance of hepatic metabolism in rabeprazole degradation.[136,137,140] Also, there is some evidence that significant pharmacokinetic differences exist between het EMs and hom EMs, with AUC values of omeprazole 3.7-fold higher in het EMs compared with those in hom EMs.[71]

The relationship between genetic polymorphism of CYP2C19 and PPI efficacy has been studied primarily with omeprazole. Clinically, PMs have been shown to experience superior gastric acid suppression compared with EMs,[71,73] consistent with the known correlation between AUC and the acid suppressive effect of the PPIs. Studies have demonstrated a superior cure rate for *H. pylori* infection in PMs compared with EMs, without greater incidence of adverse effects.[72,74,75] The differences between the het EM and hom EM phenotypes also seem to affect PPI pharmacodynamics. In one study, the percentage of time with intragastric pH >4 at day 8 was significantly higher in the het EMs than the hom EMs.[76] Furuta et al.[72] showed that the cure rates for *H. pylori* eradication were 28.6%, 60% and 100% in the hom EMs, het EMs and PMs, respectively.

To date, two paediatric studies have examined the impact of CYP2C19 genotype on PPI elimination. One study involved 37 children who had received a single oral dose of omeprazole.[99] None of the 23 patients included in the complete pharmacokinetic analysis had a PM phenotype; 11 children were het EMs and 12 were hom EMs. In contrast to the adult population, no significant pharmacokinetic differences were found between these two phenotypes, with mean normalised AUC values (corrected for an omeprazole dose of 1 mg/kg) of 1.0 ± 0.8 μg • h/mL and 0.9 ± 0.9 μg • h/mL in het EMs and hom EMs, respectively. The investigators also reported one patient with a PM phenotype with an AUC value 6-fold higher than the mean value reported for the 23 EMs (4.6 μg • h/mL compared with 0.8 μg • h/mL), although the dose of omeprazole received by this PM was not specified. The second study included 21 EMs and 3 PMs who had received a single oral dose of pantoprazole.[101] The mean normalised AUC value (corrected for a pantoprazole dose of 1 mg/kg) in PMs was 10-fold higher than that of EMs (45.5 ± 19.25 vs 4.29 ± 2.08 μg • h/mL; $p < 0.05$).

In summary, all PPIs depend significantly on CYP2C19 for their elimination in both adults and children, and genetic polymorphisms of CYP2C19 account to a large extent for the interindividual variation in PPI elimination. Further work is needed to determine the pharmacokinetic impact of the het EM phenotype in children.

4.3.5 Effects of Intestinal CYP3A4 and P-glycoprotein

CYP3A4 is abundantly and constitutively expressed in hepatic and intestinal epithelium, intestinal CYP3A4 playing a major role in limiting oral absorption of many drugs.[141] P-glycoprotein (P-gp), the product of *ABCB1* (also known as *MDR1*) gene, is a transporter expressed at the apical surface of mature enterocytes in the small intestine. It prevents the absorption of drugs from the intestinal lumen by active extrusion from the cell. Since PPIs are substrates of both CYP3A4 and P-gp,[142] variable intestinal expression of these may contribute to differences in the extent of PPI bioavailability in paediatric patients.

Very few data are available regarding the ontogeny of CYP3A4 and P-gp in the small intestine. One study evaluating the level of expression of enterocytic CYP3A4 in the paediatric population demonstrated that CYP3A4 expression and activity increase with age, starting with relatively low levels in neonates.[143] The ontogeny of P-gp in the small intestine of children is currently unknown. In the mouse intestine, P-gp was present in limited

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amounts at birth and increased significantly with maturation.[144] These data argue against reduced PPI bioavailability in children compared with adults.

To date, no studies have evaluated whether genetic polymorphisms of the *CYP3A4*[145] and *ABCB1*[146] genes affect the disposition of PPIs.

4.3.6 Effects of Hepatic Impairment

Since PPI elimination relies mostly on hepatic metabolism, liver insufficiency is expected to result in impaired metabolism of these drugs. In adults with hepatic impairment, reduced clearance of PPIs[117,147-150] was observed, the metabolic rate being substantially lower in patients with severely impaired hepatic function. In such patients, the dosage of PPI should be reduced by 50%.

Although similar findings are expected in the paediatric population, the impact of liver dysfunction on PPI disposition in children has never been studied; however, elimination of omeprazole in a 5-year-old child with impaired hepatic function was found to be delayed, with a slower clearance (0.16 L/h/kg) and longer $t_{1/2}\beta$ (2.76 hours).[95]

4.3.7 Effects of Renal Impairment

Renal insufficiency is not expected to alter PPI elimination, since little unchanged parent drug is excreted in the urine; the kidney is responsible for most excretion of inactive PPI metabolites. Adult studies have shown that the pharmacokinetics of PPIs in patients with renal impairment do not differ from those observed in healthy individuals.[148,151-153] In the study by Jacqz-Aigrain et al.,[95] four children had impaired renal function, and the pharmacokinetic parameters of omeprazole in three of them were in the range of those seen for the nine who had normal renal function (the fourth renally impaired child had concomitant hepatic impairment). Thus, no dosage adjustment appears necessary for patients with renal impairment.

4.3.8 Effects of Concomitant Diseases

Inflammation and infection are known to alter drug biotransformation and elimination, mainly by downregulation of CYP isoforms by cytokines,[154,155] and could therefore possibly modify PPI pharmacokinetics. This has been suggested recently by the results of a paediatric study evaluating the disposition of intravenous pantoprazole.[103] Children presenting with systemic inflammatory response syndrome (SIRS), as defined by accepted criteria,[156] were found to have similar pharmacokinetic parameters to those observed in PMs, with a statistically significant slower clearance, higher AUC values and longer $t_{1/2}\beta$ compared with children without SIRS (all $p = 0.029$) and healthy adults. However, one cannot exclude the contribution of drug interactions and genetic constitution to explain part of these results, although the latter is less likely since most of the patients ($n = 7$) were Caucasian. Ferron et al.[102] also evaluated the pharmacokinetics of intravenous pantoprazole in paediatric intensive care unit patients. Unfortunately, their data are not reported per kilogram, preventing any comparison or conclusion.

In critically ill paediatric patients in the immediate postoperative period after liver and/or intestinal transplantation, omeprazole elimination was slower, and had a longer mean $t_{1/2}\beta$ (4.9 ± 3.5 and 5.1 ± 2.4 hours after single and multiple doses, respectively) compared with healthy children and adults.[64] Although the investigators attribute their results partially to slower metabolism secondary to residual effects of pre-transplant hepatic failure, inflammation and cytokine production may also serve as a possible explanation for these findings. Further studies are ongoing to better define the impact of SIRS on drug metabolism in critically ill children.

4.3.9 Stereoselective Metabolism

Omeprazole, lansoprazole, pantoprazole and rabeprazole share a pyridinyl sulphinyl benzimidazole backbone with a chiral centre on the sulphur of

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the sulphoxide functionality, and are administered as racemates. From a pharmacodynamic point of view, there is no reason to expect differences in pharmacological activity between the racemate and the optical enantiomers (*R*- and *S*-enantiomers), since all PPIs are prodrugs that are transformed into a common achiral active form, the cyclic sulphenamide. In fact, the two enantiomers of omeprazole[157] and lansoprazole[158] proved to be equipotent either *in vitro* or *in vivo* in rat. However, since PPI metabolism relies mostly on enzymes that are either genetically determined or can be induced or inhibited, determination of the disposition of the enantiomers could reveal pharmacokinetic differences in favour of one enantiomer over the racemate. Thus, both *in vitro* and *in vivo* studies have evaluated the metabolism of the enantiomers of omeprazole, lansoprazole and pantoprazole (*in vivo* only).

In vitro experiments using human liver microsomes and *in vitro* expressed human CYP isoforms have shown that the total metabolic clearance of *S*-omeprazole is approximately three times slower than that of *R*-omeprazole.[159] *In vivo*, similar results were found, the clearance of *S*-omeprazole being 1.4 times slower than that of *R*-omeprazole, resulting in higher plasma levels of *S*-omeprazole in EMs.[160] In PMs, the AUC values of both *S*- and *R*-omeprazole were significantly higher compared with those of EMs (3.1- and 7.5-fold higher, respectively). The metabolism of *R*-omeprazole was impaired to a greater extent, with a mean AUC value 1.5-fold higher than that of *S*-omeprazole.

Although the *in vitro* metabolism of pantoprazole enantiomers has not been elucidated yet, the stereoselective disposition of pantoprazole was evident *in vivo* and resembled that of omeprazole, though marked only in PMs.[161] Like omeprazole, the AUC values of *S*- and *R*- pantoprazole were significantly higher in PMs than those seen in EMs (2.5- and 10.7-fold higher, respectively) and the metabolism of *R*-pantoprazole was impaired to a greater extent in PMs, with a mean AUC value 3.59-fold greater than that of *S*-pantoprazole.

Even though the clearance of *S*- and *R*-enantiomers of omeprazole and pantoprazole depends on CYP2C19, as shown by the increase in AUC values of both enantiomers in PMs, the decrease in clearance was more pronounced for the *R*-enantiomer.[160,161] This indicates that the *R*-enantiomer is metabolised to a higher extent than the *S*-enantiomer by CYP2C19 and is, therefore, more influenced by CYP2C19 genetic polymorphism. Thus, since the *S*-enantiomer of omeprazole was cleared more slowly than the *R*-enantiomer in EMs and more rapidly than the *R*-enantiomer in PMs, less overall interindividual variability in the disposition of the *S*-enantiomer is expected compared with the *R*-enantiomer or the racemic form. These findings have led to the development of the first enantiomeric PPI drug, esomeprazole, the *S*-enantiomer of omeprazole. As expected, the AUC values of esomeprazole in EMs and PMs are closer than those of *R*-omeprazole and the racemate, omeprazole.[94] The real clinical significance of the theoretical pharmacokinetic advantages of esomeprazole is not clear and remains a matter of debate. Some investigators are convinced that the unique metabolic properties of esomeprazole translate into clinical advantages,[162] while others view its development as a marketing ploy.[163] According to a recent meta-analysis, studies demonstrating an important therapeutic benefit of esomeprazole compared with omeprazole and other PPIs are still lacking.[164]

In contrast to omeprazole and pantoprazole, *S*-lansoprazole was cleared approximately four times faster than *R*-lansoprazole,[165] resulting in lower AUC levels of *S*-lansoprazole in both EMs and PMs when given as the racemate.[138] Like omeprazole and pantoprazole, the AUC values of *S*- and *R*-lansoprazole in PMs were significantly higher than those in EMs (2.5- and 10.7-fold higher, respective-

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Table III. Drug interactions with proton pump inhibitors (PPIs)

Drug	Mechanism	Effects	Clinically significant	References
Omeprazole	Inhibition of CYP2C19	Decreases clearance of diazepam	Yes	79,168
		Decreases clearance of moclobemide in CYP2C19 extensive metabolisers	Yes	127
		Decreases clearance of proguanil	Yes	169
		Decreases clearance of phenytoin	No	170-172
		Decreases clearance of carbamazepine	Yes	173
	Probable inhibition of CYP3A4	Decreases clearance of dapsone	Yes	125
	Elevation of gastric pH	Increases absorption of nifedipine	No	174
		Increases absorption rate of salicylate administered as enteric-coated tablets	Unknown	175
Lansoprazole	Inhibition of CYP2C19	Decreases clearance of tacrolimus in CYP2C19 poor metabolisers	Yes	176
Ketoconazole	Inhibition of CYP3A4	Increases omeprazole plasma levels	Unknown	177
Clarithromycin	Inhibition of CYP3A4	Increases omeprazole, esomeprazole and lansoprazole plasma levels	Unknown	178-180
All PPIs	Elevation of gastric pH	Decreases absorption of ketoconazole, itraconazole	Unknown	20,116
		Increases absorption of digoxin	No	181

CYP = cytochrome P450.

ly). However, compared with omeprazole and pantoprazole, the metabolism of both enantiomers was impaired to a similar extent in PMs. This suggests that the enantioselective disposition of lansoprazole is influenced less significantly by CYP2C19 genetic polymorphism than that of omeprazole and pantoprazole. Different sites of hydroxylation (the methyl carbon of the pyridinyl moiety for omeprazole and pantoprazole, and carbon 5 of the benzimidazole moiety for lansoprazole),[166] as well as enantioselective protein binding of lansoprazole,[138] may account for these observed differences between the disposition of the enantiomers of lansoprazole and those of omeprazole and pantoprazole.

The pharmacokinetics of PPI enantiomers has not been studied in children, nor have the effects of CYP2C19 and CYP3A4 induction or inhibition on the stereoselectivity of PPI metabolism.

4.4 Excretion

PPIs are completely metabolised by the liver into inactive metabolites that are excreted in faeces, primarily by biliary excretion, and in urine, in different proportions.[86,91,94,116,167]

5. Drug Interactions

Alteration of drug absorption by an increased gastric pH, competition for the same metabolising pathway, and induction or inhibition of drug metabolising enzymes represent the three main mechanisms by which PPIs could interact with other drugs in a clinically significant fashion. Table III summarises pharmacokinetic changes induced by PPIs, along with their clinical consequences.[20,79,116,125,127,168-182] Very few drug interactions have been shown to be clinically relevant.

Among PPIs, omeprazole is the most associated with known drug interactions. The most important interaction is an increase in AUC values of diazepam by 27% (20 mg/day)[79] or 41% (40 mg/

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day)[168] due to competitive inhibition of CYP2C19. Other clinically relevant interactions include: (i) a decrease in carbamazepine clearance requiring close drug monitoring when this antiepileptic drug is coadministered with omeprazole;[173] (ii) an increase in moclobemide AUC by 121% in CYP2C19 EMs, with no remarkable changes in the pharmacokinetics of this antidepressant in PMs;[183] and (iii) an increase in proguanil AUC by 32%.[169] Also, omeprazole was shown to decrease the excretion of dapsone, a CYP3A4 substrate, by 40% in White subjects but not in Chinese subjects.[125] Finally, the levels of *S*-warfarin, the more active isomer of warfarin, was not significantly increased when coadministered with omeprazole.[184,185]

Even though lansoprazole was shown to induce CYP1A activity with a decrease in theophylline AUC values by 13%,[186] no significant changes in theophylline concentrations were reported in several studies where it was coadministered with lansoprazole.[187-189] Pantoprazole has been shown to have a lower potential for drug interactions than omeprazole or lansoprazole.[119]

CYP2C19 phenotype may also play a role in the predisposition for and type of drug interactions. While CYP2C19 is the main metabolic pathway of PPIs in CYP2C19 EMs, the major route of elimination in PMs is CYP3A4. Thus, CYP2C19 EMs are at increased risk for drug interactions with inhibitors or inducers of CYP2C19, whereas PMs are at greater risk for interactions with drugs that modulate CYP3A4 activity. The coadministration of moclobemide, an antidepressant and inhibitor of CYP2C19, doubles the AUC of omeprazole in EMs without affecting that in PMs.[183] Also, CYP2C19 PMs, with their higher plasma PPI levels, are theoretically more likely to experience drug interactions. For example, omeprazole (40 mg/day) has been shown to induce CYP1A2 activity in CYP2C19 PMs, with minor inducing effects in EMs.[190] Significant induction was also observed in EMs receiving high doses of omeprazole (120 mg/day). A recent study has revealed a drug interaction between tacrolimus and lansoprazole that is clinically significant only in subjects with *CYP2C19* mutant alleles (PMs and het EMs). They experienced an 81% change in tacrolimus AUC values compared with a 29% change in CYP2C19 EMs.[176]

Finally, the ATP-dependent efflux transporter P-gp is another potential target for drug interactions because the PPIs (omeprazole, lansoprazole and pantoprazole) are both inhibitors and substrates for P-gp.[142]

6. Dosage and Administration

The optimal dosage of PPI may be very different from one child to another, as demonstrated by efficacy trials where the therapeutic doses vary over a wide range. The significant interindividual variability of PPI disposition in children may contribute to this variability in dosage regimen, since a pharmacokinetic/pharmacodynamic relationship exists for PPIs.

Table IV summarises paediatric dosage recommendations for the initiation of oral omeprazole and lansoprazole therapy. For both drugs, it should again

Table IV. Recommended oral dosages of proton pump inhibitors (PPIs) in children

Drug	Indication	Starting dose	Maximum daily dose (mg)
Omeprazole	GORD	1 mg/kg/day od or bid	60–80
	Helicobacter pylori infection	1 mg/kg/day bid	
Lansoprazole	GORD	≤30kg bodyweight: 15mg od	30
		>30kg bodyweight: 30mg od	60
	H. pylori infection	1 mg/kg/day bid	

bid = twice daily; **GORD** = gastro-oesophageal reflux disease; **od** = once daily.

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be emphasised that the optimal dosage varies among patients, and in case of treatment failure one must remember that almost 25% of patients may require double dosage. In the absence of a clinical response to the starting recommended dosage, it is suggested that the mode and timing of administration of PPIs be verified. Due to the activation of proton pumps in the pre- and postprandial period, PPIs should be given just before or during meals. If both the mode and timing are correct, it is recommended that the dose be doubled, to the maximum daily dose.

With children who are unable to swallow capsules or tablets, the enteric-coated granules can be removed from the capsule and suspended in an acidic medium such as fruit juice, yoghurt or apple sauce. The granules or tablets should not be crushed, chewed or dissolved, since gastric acid secretion may alter the drugs. A homemade liquid formulation, produced by dissolving the enteric-coated granules in an 8.4% sodium bicarbonate solution, has also been used.[191] As seen in table II, the relative bioavailability of lansoprazole administered this way is good, close to that of the capsule, while the omeprazole relative bioavailability is low. Consequently, it is not recommended that omeprazole be administered in an 8.4% sodium bicarbonate solution.

If omeprazole is administered intravenously, a dose of 1 mg/kg should be given once daily. The paediatric dose for a continuous infusion of omeprazole is unknown. The intravenous formulation of omeprazole or pantoprazole should not be administered enterally because gastric acid secretion alters the drug.

Lack of information regarding the disposition, efficacy and safety of pantoprazole, rabeprazole and esomeprazole in infants and children prevents recommending dosage for these agents for this population.

7. Conclusion

Paediatric pharmacokinetic data are available for omeprazole, lansoprazole and pantoprazole. As seen in adults, important interindividual variability is observed. In children older than 2 years of age, the disposition of PPIs is similar to that of adults. The need for higher doses of PPIs (on a per kilogram basis) for children compared with adults to achieve similar plasma concentrations is most likely secondary to differences in the extent of PPI bioavailability. In children <2 years of age, there are insufficient pharmacokinetic data to conclude dosage recommendations, and the impact of age in this youngest group is unknown. In both children and adults, PPI elimination is greatly affected by CYP2C19 polymorphism, but whether genotyping of CYP2C19 would help in guiding therapy with the PPIs remains a matter of debate. Variability in PPI pharmacokinetics in children may partly explain the wide range of efficacious doses reported, since a plasma concentration-effect relationship exists for PPIs. However, in addition to pharmacokinetic factors, age-related or disease-related differences in the expression and turnover of the H^+/K^+-ATPase may influence the pharmacokinetic/pharmacodynamic relationship of PPIs and consequently affect the optimal PPI dosage regimen for a child. Further studies are warranted to determine the pharmacokinetic profiles of PPIs for children <2 years of age, and those of the newer generation of PPIs, and to better define the PPI plasma concentration-effect relationship in the paediatric population. Finally, an oral liquid formulation with a predictable bioavailability would be more than welcome.

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References

1. Sachs G, Shin JM, Briving C, et al. The pharmacology of the gastric acid pump: the H+,K+ ATPase. Annu Rev Pharmacol Toxicol 1995; 35: 277-305
2. Sachs G. Proton pump inhibitors and acid-related diseases. Pharmacotherapy 1997; 17: 22-37
3. Lind T, Cederberg C, Ekenved G, et al. Effect of omeprazole: a gastric proton pump inhibitor: on pentagastrin stimulated acid secretion in man. Gut 1983; 24: 270-6
4. Faure C, Michaud L, Shaghaghi EK, et al. Lansoprazole in children: pharmacokinetics and efficacy in reflux oesophagitis. Aliment Pharmacol Ther 2001; 15: 1397-402
5. 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; 33: 144-8
6. Kromer W. Similarities and differences in the properties of substituted benzimidazoles: a comparison between pantoprazole and related compounds. Digestion 1995; 56: 443-54
7. Huber R, Kohl B, Sachs G, et al. Review article: the continuing development of proton pump inhibitors with particular reference to pantoprazole. Aliment Pharmacol Ther 1995; 9: 363-78
8. Postius S, Brauer U, Kromer W. The novel proton pump inhibitor pantoprazole elevates intragastric pH for a prolonged period when administered under conditions of stimulated gastric acid secretion in the gastric fistula dog. Life Sci 1991; 49: 1047-52
9. Gedda K, Scott D, Besancon M, et al. Turnover of the gastric H+,K(+)-adenosine triphosphatase alpha subunit and its effect on inhibition of rat gastric acid secretion. Gastroenterology 1995; 109: 1134-41
10. Naesdal J, Bodemar G, Walan A. Effect of omeprazole, a substituted benzimidazole, on 24-h intragastric acidity in patients with peptic ulcer disease. Scand J Gastroenterol 1984; 19: 916-22
11. Grahnquist L, Ruuska T, Finkel Y. Early development of human gastric H,K-adenosine triphosphatase. J Pediatr Gastroenterol Nutr 2000; 30: 533-7
12. Euler AR, Byrne WJ, Meis PJ, et al. Basal and pentagastrin-stimulated acid secretion in newborn human infants. Pediatr Res 1979; 13: 36-7
13. Hyman PE, Clarke DD, Everett SL, et al. Gastric acid secretory function in preterm infants. J Pediatr 1985; 106: 467-71
14. Kelly EJ, Newell SJ, Brownlee KG, et al. Gastric acid secretion in preterm infants. Early Hum Dev 1993; 35: 215-20
15. Grand RJ, Watkins JB, Torti FM. Development of the human gastrointestinal tract: a review. Gastroenterology 1976; 70: 790-810
16. Israel DM, Hassall E. Omeprazole and other proton pump inhibitors: pharmacology, efficacy, and safety, with special reference to use in children. J Pediatr Gastroenterol Nutr 1998; 27: 568-79
17. Brunner G, Luna P, Hartmann M, et al. Optimizing the intragastric pH as a supportive therapy in upper GI bleeding. Yale J Biol Med 1996; 69: 225-31
18. Hatlebakk JG, Katz PO, Camacho-Lobato L, et al. Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. Aliment Pharmacol Ther 2000; 14: 1267-72
19. Kromer W. Relative efficacies of gastric proton-pump inhibitors on a milligram basis: desired and undesired SH reactions: impact of chirality. Scand J Gastroenterol Suppl 2001; 234: 3-9
20. Robinson M, Horn J. Clinical pharmacology of proton pump inhibitors: what the practising physician needs to know. Drugs 2003; 63: 2739-54
21. Gibbons TE, Gold BD. The use of proton pump inhibitors in children: a comprehensive review. Pediatr Drugs 2003; 5: 25-40
22. Zimmermann AE, Walters JK, Katona BG, et al. A review of omeprazole use in the treatment of acid-related disorders in children. Clin Ther 2001; 23: 660-79
23. Cucchiara S, Minella R, Iervolino C, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Arch Dis Child 1993; 69: 655-9
24. Gottrand F, Kalach N, Spyckerelle C, et al. Omeprazole combined with amoxicillin and clarithromycin in the eradication of *Helicobacter pylori* in children with gastritis: a prospective randomized double-blind trial. J Pediatr 2001; 139: 664-8
25. Shcherbakov PL, Filin VA, Volkov IA, et al. A randomized comparison of triple therapy *Helicobacter pylori* eradication regimens in children with peptic ulcers. J Int Med Res 2001; 29: 147-53
26. Moore DJ, Tao BS, Lines DR, et al. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. J Pediatr 2003; 143: 219-23
27. Gunasekaran TS, Hassall EG. Efficacy and safety of omeprazole for severe gastroesophageal reflux in children. J Pediatr 1993; 123: 148-54
28. Karjoo M, Kane R. Omeprazole treatment of children with peptic esophagitis refractory to ranitidine therapy. Arch Pediatr Adolesc Med 1995; 149: 267-71
29. Kato S, Ebina K, Fujii K, et al. Effect of omeprazole in the treatment of refractory acid-related diseases in childhood: endoscopic healing and twenty-four-hour intragastric acidity. J Pediatr 1996; 128: 415-21
30. Martin PB, Imong SM, Krischer J, et al. The use of omeprazole for resistant oesophagitis in children. Eur J Pediatr Surg 1996; 6: 195-7
31. Cucchiara S, Minella R, Campanozzi A, et al. Effects of omeprazole on mechanisms of gastroesophageal reflux in childhood. Dig Dis Sci 1997; 42: 293-9
32. De Giacomo C, Bawa P, Franceschi M, et al. Omeprazole for severe reflux esophagitis in children. J Pediatr Gastroenterol Nutr 1997; 24: 528-32
33. Alliet P, Raes M, Bruneel E, et al. Omeprazole in infants with cimetidine-resistant peptic esophagitis. J Pediatr 1998; 132: 352-4

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34. Bohmer CJ, Niezen-de Boer RC, Klinkenberg-Knol EC, et al. Omeprazole: therapy of choice in intellectually disabled children. Arch Pediatr Adolesc Med 1998; 152: 1113-8
35. Strauss RS, Calenda KA, Dayal Y, et al. Histological esophagitis: clinical and histological response to omeprazole in children. Dig Dis Sci 1999; 44: 134-9
36. 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; 137: 800-7
37. Franco MT, Salvia G, Terrin G, et al. Lansoprazole in the treatment of gastro-oesophageal reflux disease in childhood. Dig Liver Dis 2000; 32: 660-6
38. Tolia V, Ferry G, Gunasekaran T, et al. Efficacy of lansoprazole in the treatment of gastroesophageal reflux disease in children. J Pediatr Gastroenterol Nutr 2002; 35 Suppl. 4: S308-18
39. Gunasekaran T, Gupta S, Gremse D, et al. Lansoprazole in adolescents with gastroesophageal reflux disease: pharmacokinetics, pharmacodynamics, symptom relief efficacy, and tolerability. J Pediatr Gastroenterol Nutr 2002; 35 Suppl. 4: S327-35
40. Madrazo-de la Garza A, Dibildox M, Vargas A, et al. Efficacy and safety of oral pantoprazole 20mg given once daily for reflux esophagitis in children. J Pediatr Gastroenterol Nutr 2003; 36: 261-5
41. El-Serag HB, Gilger M, Kuebeler M, et al. Extraesophageal associations of gastroesophageal reflux disease in children without neurologic defects. Gastroenterology 2001; 121: 1294-9
42. Yellon RF, Goldberg H. Update on gastroesophageal reflux disease in pediatric airway disorders. Am J Med 2001; 111 Suppl. 8A: 78-84S
43. Rudolph CD. Supraesophageal complications of gastroesophageal reflux in children: challenges in diagnosis and treatment. Am J Med 2003; 115 Suppl. 3A: 150-156S
44. Wong RK, Hanson DG, Waring PJ, et al. ENT manifestations of gastroesophageal reflux. Am J Gastroenterol 2000; 95: S15-22
45. Gibson PG, Henry RL, Coughlan JL. Gastro-oesophageal reflux treatment for asthma in adults and children. Cochrane Database Syst Rev 2003; (1): CD001496
46. Khoshoo V, Le T, Haydel Jr RM, et al. Role of gastroesophageal reflux in older children with persistent asthma. Chest 2003; 123: 1008-13
47. Kato S, Shibuya H, Hayashi Y, et al. Effectiveness and pharmacokinetics of omeprazole in children with refractory duodenal ulcer. J Pediatr Gastroenterol Nutr 1992; 15: 184-8
48. Dohil R, Israel DM, Hassall E. Effective 2-wk therapy for *Helicobacter pylori* disease in children. Am J Gastroenterol 1997; 92: 244-7
49. Kato S, Takeyama J, Ebina K, et al. Omeprazole-based dual and triple regimens for *Helicobacter pylori* eradication in children. Pediatrics 1997; 100: E3
50. Moshkowitz M, Reif S, Brill S, et al. One-week triple therapy with omeprazole, clarithromycin, and nitroimidazole for *Helicobacter pylori* infection in children and adolescents. Pediatrics 1998; 102: E14
51. Casswall TH, Alfven G, Drapinski M, et al. One-week treatment with omeprazole, clarithromycin, and metronidazole in children with *Helicobacter pylori* infection. J Pediatr Gastroenterol Nutr 1998; 27: 415-8
52. Tiren U, Sandstedt B, Finkel Y. *Helicobacter pylori* gastritis in children: efficacy of 2 weeks of treatment with clarithromycin, amoxicillin and omeprazole. Acta Paediatr 1999; 88: 166-8
53. Chan KL, Zhou H, Ng DK, et al. A prospective study of a one-week nonbismuth quadruple therapy for childhood *Helicobacter pylori* infection. J Pediatr Surg 2001; 36: 1008-11
54. Kato S, Ritsuno H, Ohnuma K, et al. Safety and efficacy of one-week triple therapy for eradicating *Helicobacter pylori* in children. Helicobacter 1998; 3: 278-82
55. Shashidhar H, Peters J, Lin CH, et al. A prospective trial of lansoprazole triple therapy for pediatric *Helicobacter pylori* infection. J Pediatr Gastroenterol Nutr 2000; 30: 276-82
56. Kocak N, Saltik IN, Ozen H, et al. Lansoprazole triple therapy for Turkish children with *Helicobacter pylori* infections [letter]. J Pediatr Gastroenterol Nutr 2001; 32: 614
57. Drumm B, Koletzko S, Oderda G. *Helicobacter pylori* infection in children: a consensus statement. European Paediatric Task Force on *Helicobacter pylori*. J Pediatr Gastroenterol Nutr 2000; 30: 207-13
58. Gold BD, Colletti RB, Abbott M, et al. *Helicobacter pylori* infection in children: recommendations for diagnosis and treatment. J Pediatr Gastroenterol Nutr 2000; 31: 490-7
59. Tran TM, Van den Neucker A, Hendriks JJ, et al. Effects of a proton-pump inhibitor in cystic fibrosis. Acta Paediatr 1998; 87: 553-8
60. Proesmans M, De Boeck K. Omeprazole, a proton pump inhibitor, improves residual steatorrhoea in cystic fibrosis patients treated with high dose pancreatic enzymes. Eur J Pediatr 2003; Nov; 162 (11): 760-3
61. Francisco MP, Wagner MH, Sherman JM, et al. Ranitidine and omeprazole as adjuvant therapy to pancrelipase to improve fat absorption in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 2002; 35: 79-83
62. Mikawa K, Nishina K, Maekawa N, et al. Lansoprazole reduces preoperative gastric fluid acidity and volume in children. Can J Anaesth 1995; 42: 467-72
63. Nishina K, Mikawa K, Maekawa N, et al. Omeprazole reduces preoperative gastric fluid acidity and volume in children. Can J Anaesth 1994; 41: 925-9
64. Olsen KM, Bergman KL, Kaufman SS, et al. Omeprazole pharmacodynamics and gastric acid suppression in critically ill pediatric transplant patients. Pediatr Crit Care Med 2001; 2: 232-7
65. Kaufman SS, Lyden ER, Brown CR, et al. Omeprazole therapy in pediatric patients after liver and intestinal transplantation. J Pediatr Gastroenterol Nutr 2002; 34: 194-8
66. Haizlip JA, Lugo RA, Cash JJ, et al. Failure of nasogastric omeprazole suspension in pediatric intensive care patients. Pediatr Crit Care Med 2005; 6: 182-7
67. Howden CW. Clinical pharmacology of omeprazole. Clin Pharmacokinet 1991; 20: 38-49
68. Stedman CA, Barclay ML. Review article: comparison of the pharmacokinetics, acid suppression and efficacy of proton pump inhibitors. Aliment Pharmacol Ther 2000; 14: 963-78

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69. Hussein Z, Granneman GR, Mukherjee D, et al. Age-related differences in the pharmacokinetics and pharmacodynamics of lansoprazole. Br J Clin Pharmacol 1993; 36: 391-8
70. Pounder RE, Sharma BK, Walt RP. Twenty-four hour intragastric acidity during treatment with oral omeprazole. Scand J Gastroenterol Suppl 1986; 118: 108-17
71. Chang M, Tybring G, Dahl ML, et al. Interphenotype differences in disposition and effect on gastrin levels of omeprazole: suitability of omeprazole as a probe for CYP2C19. Br J Clin Pharmacol 1995; 39: 511-8
72. Furuta T, Ohashi K, Kamata T, et al. Effect of genetic differences in omeprazole metabolism on cure rates for *Helicobacter pylori* infection and peptic ulcer. Ann Intern Med 1998; 129: 1027-30
73. Furuta T, Ohashi K, Kosuge K, et al. CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. Clin Pharmacol Ther 1999; 65: 552-61
74. Aoyama N, Tanigawara Y, Kita T, et al. Sufficient effect of 1-week omeprazole and amoxicillin dual treatment for *Helicobacter pylori* eradication in cytochrome P450 2C19 poor metabolizers. J Gastroenterol 1999; 34 Suppl. 11: 80-3
75. Tanigawara Y, Aoyama N, Kita T, et al. CYP2C19 genotype-related efficacy of omeprazole for the treatment of infection caused by *Helicobacter pylori*. Clin Pharmacol Ther 1999; 66: 528-34
76. Sagar M, Bertilsson L, Stridsberg M, et al. Omeprazole and CYP2C19 polymorphism: effects of long-term treatment on gastrin, pepsinogen I, and chromogranin A in patients with acid related disorders. Aliment Pharmacol Ther 2000; 14: 1495-502
77. Tran A, Rey E, Pons G, et al. Pharmacokinetic-pharmacodynamic study of oral lansoprazole in children. Clin Pharmacol Ther 2002; 71: 359-67
78. Gremse D, Winter H, Tolia V, et al. Pharmacokinetics and pharmacodynamics of lansoprazole in children with gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr 2002; 35 Suppl. 4: S319-26
79. Andersson T, Andren K, Cederberg C, et al. Effect of omeprazole and cimetidine on plasma diazepam levels. Eur J Clin Pharmacol 1990; 39: 51-4
80. Tolman KG, Sanders SW, Buchi KN, et al. The effects of oral doses of lansoprazole and omeprazole on gastric pH. J Clin Gastroenterol 1997; 24: 65-70
81. Benet LZ, Zech K. Pharmacokinetics: a relevant factor for the choice of a drug? Aliment Pharmacol Ther 1994; 8 Suppl. 1: 25-32
82. Blum RA. Lansoprazole and omeprazole in the treatment of acid peptic disorders. Am J Health Syst Pharm 1996; 53: 1401-15
83. Andersson T. Pharmacokinetics, metabolism and interactions of acid pump inhibitors: focus on omeprazole, lansoprazole and pantoprazole. Clin Pharmacokinet 1996; 31: 9-28
84. Andersson T, Regardh CG, Dahl-Puustinen ML, et al. Slow omeprazole metabolizers are also poor S-mephenytoin hydroxylators. Ther Drug Monit 1990; 12: 415-6
85. Hartmann M, Theiss U, Huber R, et al. Twenty-four-hour intragastric pH profiles and pharmacokinetics following single and repeated oral administration of the proton pump inhibitor pantoprazole in comparison to omeprazole. Aliment Pharmacol Ther 1996; 10: 359-66
86. Landes BD, Petite JP, Flouvat B. Clinical pharmacokinetics of lansoprazole. Clin Pharmacokinet 1995; 28: 458-70
87. Spencer CM, Faulds D. Lansoprazole. A reappraisal of its pharmacodynamic and pharmacokinetic properties, and its therapeutic efficacy in acid-related disorders. Drugs 1994; 48: 404-30
88. Gerloff J, Mignot A, Barth H, et al. Pharmacokinetics and absolute bioavailability of lansoprazole. Eur J Clin Pharmacol 1996; 50: 293-7
89. Langtry HD, Wilde MI. Lansoprazole: an update of its pharmacological properties and clinical efficacy in the management of acid-related disorders. Drugs 1997; 54: 473-500
90. Parsons ME. Pantoprazole, a new proton-pump inhibitor, has a precise and predictable profile of activity. Eur J Gastroenterol Hepatol 1996; 8 Suppl. 1: S15-20
91. Huber R, Hartmann M, Bliesath H, et al. Pharmacokinetics of pantoprazole in man. Int J Clin Pharmacol Ther 1996; 34: S7-16
92. Fitton A, Wiseman L. Pantoprazole: a review of its pharmacological properties and therapeutic use in acid-related disorders. Drugs 1996; 51: 460-82
93. Prakash A, Faulds D. Rabeprazole. Drugs 1998; 55: 261-7
94. Andersson T, Hassan-Alin M, Hasselgren G, et al. Pharmacokinetic studies with esomeprazole, the (*S*)-isomer of omeprazole. Clin Pharmacokinet 2001; 40: 411-26
95. Jacqz-Aigrain E, Bellaich M, Faure C, et al. Pharmacokinetics of intravenous omeprazole in children. Eur J Clin Pharmacol 1994; 47: 181-5
96. Andersson T, Hassall E, Lundborg P, et al. Pharmacokinetics of orally administered omeprazole in children. International Pediatric Omeprazole Pharmacokinetic Group. Am J Gastroenterol 2000; 95: 3101-6
97. Andersson T, Anderson G, Dasen S, et al. Pharmacokinetics and pharmacodynamics of oral omeprazole in infants [abstract]. J Pediatr Gastroenterol Nutr 2001; 33: 416
98. Andersson T, Göthberg G, Friberg L, et al. Pharmacokinetics of intravenous omeprazole in neonates and infants [abstract]. J Pediatr Gastroenterol Nutr 2001; 33: 424
99. Kearns GL, Andersson T, James LP, et al. Omeprazole disposition in children following single-dose administration. J Clin Pharmacol 2003; 43: 840-8
100. Marier JF, Dubuc MC, Drouin E, et al. Pharmacokinetics of omeprazole in healthy adults and in children with gastroesophageal reflux disease. Ther Drug Monit 2004; 26: 3-8
101. Kearns GL, Ferron GM, James LP, et al. Pantoprazole disposition in pediatrics [abstract PII-35]. Clin Pharmacol Ther 2003; 73: P38
102. Ferron G, Schexnayder S, Marshall JD, et al. Pharmacokinetics of IV pantoprazole in pediatric patients [abstract PII-30]. Clin Pharmacol Ther 2003; 73: P37
103. Litalien C, Theoret Y, Drouin C, et al. Reduction of IV pantoprazole metabolism in children with systemic inflammatory response syndrome (SIRS) [abstract]. J Pediatr Gastroenterol Nutr 2003; 37: 349

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104. Delhotal-Landes B, Cournot A, Vermerie N, et al. The effect of food and antacids on lansoprazole absorption and disposition. Eur J Drug Metab Pharmacokinet 1991; Spec. No. 3: 315-20
105. Barradell LB, Faulds D, McTavish D. Lansoprazole: a review of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid-related disorders. Drugs 1992; 44: 225-50
106. Prevacid (lansoprazole) product information. Lake Forest (IL): TAP Pharmaceuticals Inc., 2003
107. Larsson H, Carlsson E, Junggren U, et al. Inhibition of gastric acid secretion by omeprazole in the dog and rat. Gastroenterology 1983; 85: 900-7
108. Ferron GM, Ku S, Abell M, et al. Oral bioavailability of pantoprazole suspended in sodium bicarbonate solution. Am J Health Syst Pharm 2003; 60: 1324-9
109. Andersson T, Andren K, Cederberg C, et al. Pharmacokinetics and bioavailability of omeprazole after single and repeated oral administration in healthy subjects. Br J Clin Pharmacol 1990; 29: 557-63
110. Losec MUPS (omeprazole multiple unit pellet system) product information. Luton: AstraZeneca UK Ltd, 2004
111. Mohiuddin MA, Pursnani KG, Katzka DA, et al. Effective gastric acid suppression after oral administration of enteric-coated omeprazole granules. Dig Dis Sci 1997; 42: 715-9
112. Sharma VK, Peyton B, Spears T, et al. Oral pharmacokinetics of omeprazole and lansoprazole after single and repeated doses as intact capsules or as suspensions in sodium bicarbonate. Aliment Pharmacol Ther 2000; 14: 887-92
113. Freston JW, Chiu YL, Mulford DJ, et al. Comparative pharmacokinetics and safety of lansoprazole oral capsules and orally disintegrating tablets in healthy subjects. Aliment Pharmacol Ther 2003; 17: 361-7
114. Chun AH, Erdman K, Chiu YL, et al. Bioavailability of lansoprazole granules administered in juice or soft food compared with the intact capsule formulation. Clin Ther 2002; 24: 1322-31
115. McColl KE, Kennerley P. Proton pump inhibitors: differences emerge in hepatic metabolism. Dig Liver Dis 2002; 34: 461-7
116. Fuhr U, Jetter A. Rabeprazole: pharmacokinetics and pharmacokinetic drug interactions. Pharmazie 2002; 57: 595-601
117. Hoyumpa AM, Trevino-Alanis H, Grimes I, et al. Rabeprazole: pharmacokinetics in patients with stable, compensated cirrhosis. Clin Ther 1999; 21: 691-701
118. Andersson T, Miners JO, Veronese ME, et al. Identification of human liver cytochrome P450 isoforms mediating secondary omeprazole metabolism. Br J Clin Pharmacol 1994; 37: 597-604
119. Meyer UA. Metabolic interactions of the proton-pump inhibitors lansoprazole, omeprazole and pantoprazole with other drugs. Eur J Gastroenterol Hepatol 1996; 8 Suppl. 1: S21-5
120. Chiba K, Kobayashi K, Manabe K, et al. Oxidative metabolism of omeprazole in human liver microsomes: cosegregation with S-mephenytoin 4′-hydroxylation. J Pharmacol Exp Ther 1993; 266: 52-9
121. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors: emphasis on rabeprazole. Aliment Pharmacol Ther 1999; 13 Suppl. 3: 27-36
122. Bliesath H, Huber R, Hartmann M, et al. Dose linearity of the pharmacokinetics of the new H+/K(+)-ATPase inhibitor pantoprazole after single intravenous administration. Int J Clin Pharmacol Ther 1994; 32: 44-50
123. Yasuda S, Ohnishi A, Ogawa T, et al. Pharmacokinetic properties of E3810, a new proton pump inhibitor, in healthy male volunteers. Int J Clin Pharmacol Ther 1994; 32: 466-73
124. Rost KL, Roots I. Nonlinear kinetics after high-dose omeprazole caused by saturation of genetically variable CYP2C19. Hepatology 1996; 23: 1491-7
125. Caraco Y, Wilkinson GR, Wood AJ. Differences between white subjects and Chinese subjects in the in vivo inhibition of cytochrome P450s 2C19, 2D6, and 3A by omeprazole. Clin Pharmacol Ther 1996; 60: 396-404
126. Ko JW, Sukhova N, Thacker D, et al. Evaluation of omeprazole and lansoprazole as inhibitors of cytochrome P450 isoforms. Drug Metab Dispos 1997; 25: 853-62
127. Yu KS, Yim DS, Cho JY, et al. Effect of omeprazole on the pharmacokinetics of moclobemide according to the genetic polymorphism of CYP2C19. Clin Pharmacol Ther 2001; 69: 266-73
128. Furuta S, Kamada E, Suzuki T, et al. Inhibition of drug metabolism in human liver microsomes by nizatidine, cimetidine and omeprazole. Xenobiotica 2001; 31: 1-10
129. Hassan-Alin M, Andersson T, Bredberg E, et al. Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. Eur J Clin Pharmacol 2000; 56: 665-70
130. Leeder JS, Kearns GL. Pharmacogenetics in pediatrics. Implications for practice. Pediatr Clin North Am 1997; 44: 55-77
131. de Morais SM, Wilkinson GR, Blaisdell J, et al. The major genetic defect responsible for the polymorphism of S-mephenytoin metabolism in humans. J Biol Chem 1994; 269: 15419-22
132. Bertilsson L. Geographical/interracial differences in polymorphic drug oxidation: current state of knowledge of cytochromes P450 (CYP) 2D6 and 2C19. Clin Pharmacokinet 1995; 29: 192-209
133. Andersson T, Holmberg J, Rohss K, et al. Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole. Br J Clin Pharmacol 1998; 45: 369-75
134. Yasuda S, Horai Y, Tomono Y, et al. Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephenytoin 4′-hydroxylation status. Clin Pharmacol Ther 1995; 58: 143-54
135. Sakai T, Aoyama N, Kita T, et al. CYP2C19 genotype and pharmacokinetics of three proton pump inhibitors in healthy subjects. Pharm Res 2001; 18: 721-7
136. Shirai N, Furuta T, Moriyama Y, et al. Effects of CYP2C19 genotypic differences in the metabolism of omeprazole and rabeprazole on intragastric pH. Aliment Pharmacol Ther 2001; 15: 1929-37
137. Ieiri I, Kishimoto Y, Okochi H, et al. Comparison of the kinetic disposition of and serum gastrin change by lansoprazole versus rabeprazole during an 8-day dosing scheme in relation to CYP2C19 polymorphism. Eur J Clin Pharmacol 2001; 57: 485-92

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138. Kim KA, Shon JH, Park JY, et al. Enantioselective disposition of lansoprazole in extensive and poor metabolizers of CYP2C19. Clin Pharmacol Ther 2002; 72: 90-9
139. Tanaka M, Ohkubo T, Otani K, et al. Metabolic disposition of pantoprazole, a proton pump inhibitor, in relation to S-mephenytoin 4′-hydroxylation phenotype and genotype. Clin Pharmacol Ther 1997; 62: 619-28
140. Horai Y, Kimura M, Furuie H, et al. Pharmacodynamic effects and kinetic disposition of rabeprazole in relation to CYP2C19 genotypes. Aliment Pharmacol Ther 2001; 15: 793-803
141. Wacher VJ, Silverman JA, Zhang Y, et al. Role of P-glycoprotein and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics. J Pharm Sci 1998; 87: 1322-30
142. Pauli-Magnus C, Rekersbrink S, Klotz U, et al. Interaction of omeprazole, lansoprazole and pantoprazole with P-glycoprotein. Naunyn Schmiedebergs Arch Pharmacol 2001; 364: 551-7
143. Johnson TN, Tanner MS, Taylor CJ, et al. Enterocytic CYP3A4 in a paediatric population: developmental changes and the effect of coeliac disease and cystic fibrosis. Br J Clin Pharmacol 2001; 51: 451-60
144. Mahmood B, Daood MJ, Hart C, et al. Ontogeny of P-glycoprotein in mouse intestine, liver, and kidney. J Investig Med 2001; 49: 250-7
145. Sata F, Sapone A, Elizondo G, et al. CYP3A4 allelic variants with amino acid substitutions in exons 7 and 12: evidence for an allelic variant with altered catalytic activity. Clin Pharmacol Ther 2000; 67: 48-56
146. Hoffmeyer S, Burk O, von Richter O, et al. Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity in vivo. Proc Natl Acad Sci U S A 2000; 97: 3473-8
147. Andersson T, Olsson R, Regardh CG, et al. Pharmacokinetics of [14C]omeprazole in patients with liver cirrhosis. Clin Pharmacokinet 1993; 24: 71-8
148. Delhotal-Landes B, Flouvat B, Duchier J, et al. Pharmacokinetics of lansoprazole in patients with renal or liver disease of varying severity. Eur J Clin Pharmacol 1993; 45: 367-71
149. Ferron GM, Preston RA, Noveck RJ, et al. Pharmacokinetics of pantoprazole in patients with moderate and severe hepatic dysfunction. Clin Ther 2001; 23: 1180-92
150. Sjovall H, Bjornsson E, Holmberg J, et al. Pharmacokinetic study of esomeprazole in patients with hepatic impairment. Eur J Gastroenterol Hepatol 2002; 14: 491-6
151. Naesdal J, Andersson T, Bodemar G, et al. Pharmacokinetics of [14C]omeprazole in patients with impaired renal function. Clin Pharmacol Ther 1986; 40: 344-51
152. Lins RL, De Clercq I, Hartmann M, et al. Pharmacokinetics of the proton pump inhibitor pantoprazole in patients with severe renal impairment [abstract]. Gastroenterology 1994; 106: A126
153. Keane WF, Swan SK, Grimes I, et al. Rabeprazole: pharmacokinetics and tolerability in patients with stable, end-stage renal failure. J Clin Pharmacol 1999; 39: 927-33
154. Renton KW. Alteration of drug biotransformation and elimination during infection and inflammation. Pharmacol Ther 2001; 92: 147-63
155. Carcillo JA, Doughty L, Kofos D, et al. Cytochrome P450 mediated-drug metabolism is reduced in children with sepsis-induced multiple organ failure. Intensive Care Med 2003; 29: 980-4
156. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992; 101: 1644-55
157. Erlandsson P, Isaksson R, Lorentzon P, et al. Resolution of the enantiomers of omeprazole and some of its analogues by liquid chromatography on a trisphenylcarbamoylcellulose-based stationary phase: the effect of the enantiomers of omeprazole on gastric glands. J Chromatogr 1990; 532: 305-19
158. Nagaya H, Inatomi N, Nohara A, et al. Effects of the enantiomers of lansoprazole (AG-1749) on (H+ + K+)-ATPase activity in canine gastric microsomes and acid formation in isolated canine parietal cells. Biochem Pharmacol 1991; 42: 1875-8
159. Abelo A, Andersson TB, Antonsson M, et al. Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. Drug Metab Dispos 2000; 28: 966-72
160. Tybring G, Bottiger Y, Widen J, et al. Enantioselective hydroxylation of omeprazole catalyzed by CYP2C19 in Swedish white subjects. Clin Pharmacol Ther 1997; 62: 129-37
161. Tanaka M, Ohkubo T, Otani K, et al. Stereoselective pharmacokinetics of pantoprazole, a proton pump inhibitor, in extensive and poor metabolizers of S-mephenytoin. Clin Pharmacol Ther 2001; 69: 108-13
162. Andersson T. Single-isomer drugs: true therapeutic advances. Clin Pharmacokinet 2004; 43: 279-85
163. Mansfield P, Henry D, Tonkin A. Single-enantiomer drugs: elegant science, disappointing effects. Clin Pharmacokinet 2004; 43: 287-90
164. Klok RM, Postma MJ, van Hout BA, et al. Meta-analysis: comparing the efficacy of proton pump inhibitors in short-term use. Aliment Pharmacol Ther 2003; 17: 1237-45
165. Kim KA, Kim MJ, Park JY, et al. Stereoselective metabolism of lansoprazole by human liver cytochrome P450 enzymes. Drug Metab Dispos 2003; 31: 1227-34
166. Meyer UA. Interaction of proton pump inhibitors with cytochromes P450: consequences for drug interactions. Yale J Biol Med 1996; 69: 203-9
167. Regardh CG, Andersson T, Lagerstrom PO, et al. The pharmacokinetics of omeprazole in humans: a study of single intravenous and oral doses. Ther Drug Monit 1990; 12: 163-72
168. Caraco Y, Tateishi T, Wood AJ. Interethnic difference in omeprazole's inhibition of diazepam metabolism. Clin Pharmacol Ther 1995; 58: 62-72
169. Funck-Brentano C, Becquemont L, Lenevu A, et al. Inhibition by omeprazole of proguanil metabolism: mechanism of the interaction in vitro and prediction of in vivo results from the in vitro experiments. J Pharmacol Exp Ther 1997; 280: 730-8
170. Prichard PJ, Walt RP, Kitchingman GK, et al. Oral phenytoin pharmacokinetics during omeprazole therapy. Br J Clin Pharmacol 1987; 24: 543-5

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171. Gugler R, Jensen JC. Omeprazole inhibits oxidative drug metabolism: studies with diazepam and phenytoin in vivo and 7-ethoxycoumarin in vitro. Gastroenterology 1985; 89: 1235-41

172. Andersson T, Lagerstrom PO, Unge P. A study of the interaction between omeprazole and phenytoin in epileptic patients. Ther Drug Monit 1990; 12: 329-33

173. Dixit RK, Chawla AB, Kumar N, et al. Effect of omeprazole on the pharmacokinetics of sustained-release carbamazepine in healthy male volunteers. Methods Find Exp Clin Pharmacol 2001; 23: 37-9

174. Soons PA, van den Berg G, Danhof M, et al. Influence of single- and multiple-dose omeprazole treatment on nifedipine pharmacokinetics and effects in healthy subjects. Eur J Clin Pharmacol 1992; 42: 319-24

175. Nefesoglu FZ, Ayanoglu-Dulger G, Ulusoy NB, et al. Interaction of omeprazole with enteric-coated salicylate tablets. Int J Clin Pharmacol Ther 1998; 36: 549-53

176. Itagaki F, Homma M, Yuzawa K, et al. Effect of lansoprazole and rabeprazole on tacrolimus pharmacokinetics in healthy volunteers with CYP2C19 mutations. J Pharm Pharmacol 2004; 56: 1055-9

177. Bottiger Y, Tybring G, Gotharson E, et al. Inhibition of the sulfoxidation of omeprazole by ketoconazole in poor and extensive metabolizers of S-mephenytoin. Clin Pharmacol Ther 1997; 62: 384-91

178. Furuta T, Ohashi K, Kobayashi K, et al. Effects of clarithromycin on the metabolism of omeprazole in relation to CYP2C19 genotype status in humans. Clin Pharmacol Ther 1999; 66: 265-74

179. Andersson T, Hassan-Alin M, Hasselgren G, et al. Drug interaction studies with esomeprazole, the (*S*)-isomer of omeprazole. Clin Pharmacokinet 2001; 40: 523-37

180. Ushiama H, Echizen H, Nachi S, et al. Dose-dependent inhibition of CYP3A activity by clarithromycin during *Helicobacter pylori* eradication therapy assessed by changes in plasma lansoprazole levels and partial cortisol clearance to 6β-hydroxycortisol. Clin Pharmacol Ther 2002; 72: 33-43

181. Oosterhuis B, Jonkman JH, Andersson T, et al. Minor effect of multiple dose omeprazole on the pharmacokinetics of digoxin after a single oral dose. Br J Clin Pharmacol 1991; 32: 569-72

182. Gerson LB, Triadafilopoulos G. Proton pump inhibitors and their drug interactions: an evidence-based approach. Eur J Gastroenterol Hepatol 2001; 13: 611-6

183. Cho JY, Yu KS, Jang IJ, et al. Omeprazole hydroxylation is inhibited by a single dose of moclobemide in homozygotic EM genotype for CYP2C19. Br J Clin Pharmacol 2002; 53: 393-7

184. Sutfin T, Balmer K, Bostrom H, et al. Stereoselective interaction of omeprazole with warfarin in healthy men. Ther Drug Monit 1989; 11: 176-84

185. de Hoon JN, Thijssen HH, Beysens AJ, et al. No effect of short-term omeprazole intake on acenocoumarol pharmacokinetics and pharmacodynamics. Br J Clin Pharmacol 1997; 44: 399-401

186. Kokufu T, Ihara N, Sugioka N, et al. Effects of lansoprazole on pharmacokinetics and metabolism of theophylline. Eur J Clin Pharmacol 1995; 48: 391-5

187. Granneman GR, Karol MD, Locke CS, et al. Pharmacokinetic interaction between lansoprazole and theophylline. Ther Drug Monit 1995; 17: 460-4

188. Dilger K, Zheng Z, Klotz U. Lack of drug interaction between omeprazole, lansoprazole, pantoprazole and theophylline. Br J Clin Pharmacol 1999; 48: 438-44

189. Ko JW, Jang IJ, Shin JG, et al. Theophylline pharmacokinetics are not altered by lansoprazole in CYP2C19 poor metabolizers. Clin Pharmacol Ther 1999; 65: 606-14

190. Rost KL, Roots I. Accelerated caffeine metabolism after omeprazole treatment is indicated by urinary metabolite ratios: coincidence with plasma clearance and breath test. Clin Pharmacol Ther 1994; 55: 402-11

191. Phillips JO, Metzler MH, Palmieri MT, et al. A prospective study of simplified omeprazole suspension for the prophylaxis of stress-related mucosal damage. Crit Care Med 1996; 24: 1793-800

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