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Clinical Pharmacology of Omeprazole in Infants and Children

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Abstract

Omeprazole is a proton pump inhibitor it is a prodrug and requires activation in acid environments. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. Here, it is activated by proton-catalysed formation of a tetracyclic sulfenamide trapping the drug so that it cannot diffuse back across the canalicular membrane. The activated form of omeprazole binds covalently with sulfhydryl groups of cysteine in the H+, K+-ATPase, irreversibly inactivating the pump molecule. Prescription of omeprazole is used to promote healing of gastric, duodenal ulcers, and to treat gastroesophageal reflux disease. Omeprazole is used to suppress gastric secretion when endoscopically-proven oesophagitis or peptic ulceration persists despite treatment with ranitidine and omeprazole is used in short-term treatment of duodenal reflux. In infants, the initial oral treatment consists in 0.7 mg/kg once-daily and the intravenous treatment consists in 0.5 mg/kg once-daily. In children, the dose of omeprazole varies with the child age or with child body-weight. Omeprazole is extensively metabolised by CYP3A4 and CYP2C9 and the metabolites are omeprazole sulfone and 5-hydroxyomeprazole. The pharmacokinetics of omeprazole have been studied in infants and children and the elimination half-life is 56 and 58 min in infants and children respectively. Omeprazole interacts with drugs and poorly migrates into the breast-milk. The aim of this study is to review omeprazole dosing, pharmacokinetics, and treatments in infants and children and omeprazole metabolism and migration into breast-milk.

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- Children

INTRODUCTION

Proton pump inhibitors (PPIs)

The most potent suppressors of gastric acid secretion are inhibitors of the gastric H^+, K^+-ATPase or proton pump. These drugs diminish the daily production of acid (basal and stimulated) by 80 to 95% [1].

Mechanism of action and pharmacology of PPIs

Six PPIs are available for clinical use: omeprazole, dexlansoprazole, rabeprazole, prazole, lansoprazole and its R-enantiomer, dexlansoprazole, rabeprazole, and pantoprazole. All PPIs have equivalent efficacy at comparable doses. PPIs are prodrugs that require activation in acid environments. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. Here, it is activated by proton-catalysed formation of a tetracyclic sulfenamide trapping the drug so that it cannot diffuse back across the canalicular membrane. The activated form then binds covalently with sulfhydryl groups of cysteine in the H^+, K^+-ATPase, irreversibly inactivating the pump molecule. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prolonged (up to 24 to 48 hours) suppression of acid secretion, despite the much shorter plasma elimination half-life of about 0.5 to 3 hours of the parent compounds. Because they block the final step in acid production, the PPIs effectively suppress stimulated acid production, regardless of the physiological stimulus, as well as basal acid production. The amount of H^+, K^+-ATPase increases after fasting; therefore PPIs should be given before the first meal of the day. In most individuals, one-daily dosing is sufficient to achieve an effective level of acid inhibition, and a second dose, which is occasionally necessary, can be administered before an evening meal. Rebound acid hypersecretion occurs following prolonged treatment with PPIs, and clinical studies suggest that rebound after ceasing treatment can provoke symptoms such as dyspepsia. To prevent degradation of PPIs by acid in the gastric lumen and improve oral bioavailability, oral dosage forms are supplied in different formulations: (1) enteric-coated pellets with gelatin capsules (omeprazole, dexlansoprazole, esomeprazole, lansoprazole, and rabeprazole), (2) delayed-release tablets (omeprazole formulations), (3) delayed release capsules (dexlansoprazole, esomeprazole formulations), (4) enteric-coated microgranules in orally disintegrated tablets (lansoprazole), (5) enteric-coated tablets (pantoprazole, rabeprazole, and omeprazole), (6) powered omeprazole combined with sodium bicarbonate (capsules and oral suspension). The delayed release and enteric-

coated tablets dissolve only at alkaline pH, whereas admixture of omeprazole with sodium bicarbonate simply neutralizes stomach acid; both strategies substantially improve the oral bioavailability of these acid-labile drugs. Patients for whom the oral route of administration is not available can be treated parenterally with omeprazole sodium or pantoprazole [1].

Therapeutic uses of PPIs

Prescriptions PPIs are primarily used to promote healing of gastric and duodenal ulcers and to treat gastroesophageal reflux disease, including erosive esophagitis, which is either complicated or unresponsive to treatment with H_2 receptor antagonists. They are also used in conjunction with antibiotics for the eradication of pathological hyper-secretory conditions, including the Zollinger-Ellison syndrome. Lansoprazole, pantoprazole, and esomeprazole are approved for treatment and prevention or recurrence of nonsteroidal anti-inflammatory drugs-associated gastric ulcers in patients who continue nonsteroidal anti-inflammatory drugs use. It is not clear if PPIs affect the susceptibility of nonsteroidal anti-inflammatory drug-induced damage and blending in the small and large intestine. All PPIs are approved for reducing the risk of duodenal ulcer recurrence associated with Helicobacter pylori infection. Over-the-counter omeprazole, esomeprazole, and lansoprazole are approved for the self-treatment of acid reflux [1].

Therapeutic use of omeprazole

Omeprazole is used to suppress gastric secretion when endoscopically-proven oesophagitis or peptic ulceration persists despite treatment with ranitidine. Use is not of benefit in most young children and infants with simple gastro-oesophageal reflux [2]. Omeprazole is used in short-term (less than 8 weeks) treatment of duodenal reflux oesophagitis or duodenal ulcer refractory to conventional therapy. Omeprazole inhibits gastric acid secretion by inhibition of K^+-ATPase, the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell ("proton pump"). Onset of action is within one hour of administration, maximal effect is at approximately 2 hours. Inhibition of acid secretion is approximately 72 hours [3].

Administration, distribution, metabolism and elimination of PPIs

The H_2 receptor antagonists are rapidly absorbed after oral administration, with peak serum concentrations within 1 to 3 hours. Absorption may be enhanced by food or decreased by antacids, but these effects probably are unimportant clinically. Therapeutic levels are achieved rapidly after intravenous dosing and are maintained for 4 to 5 hours (cimetidine), 6 to 8 hours (ranitidine). The elimination half-life values of these agents, after oral administration to adults, range from 1 to 3.5 hours. Cimetidine clearance is faster in children and reduces its elimination half-life by about 30%. Only a small fraction of these drugs is protein bound. The kidneys excrete these drugs and their metabolites by filtration and renal tubular secretion, and it is important to reduce drug doses in patients with decreased creatinine clearance. Neither haemodialysis nor peritoneal dialysis clears significant amounts of these drugs. Hepatic metabolism accounts for a small fraction of clearance (from < 10% to about 35%), but liver disease per se is generally not an indication for dose adjustment [1]. (Figure 1)

Literature search

The literature search was performed electronically using PubMed database as search engine and the following key words were used: "omeprazole dosing infants, children", omeprazole efficacy, safety infants, children", "omeprazole metabolism", "omeprazole pharmacokinetics infants, children", "omeprazole drug interactions", "omeprazole treatment infants, children", and "omeprazole breast-milk". In addition, the books: The Pharmacological Basis of Therapeutics [1], Neonatal Formulary [2], NEOFAX® by Young and Mangum [3], and The British National Formulary for Children [4] have been consulted.

RESULTS

Administration schedules of omeprazole to infants and children

Administration to infants [2]: Administration by mouth: Start by giving 0.7 mg/kg once-daily half an hour before breakfast. Double this after 7 to 14 days if this does not inhibit gastric acid production. A few infants may need as much as 2.8 mg/kg a day nut progressive drug accumulation might occur if an infant is aged < 3 months is given more than 1.4 mg/kg. Sustained treatment is hard to justify unless 3 continuing evidence of active oesophagitis.

Intravenous administration: Give: 0.5 mg/kg once-daily over 5 min (a dose that can be tripled if acid production persists).

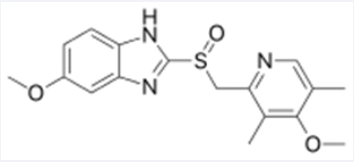

Figure 1 Omeprazole molecular structure (molecular weight = 345.4 grams/mole).

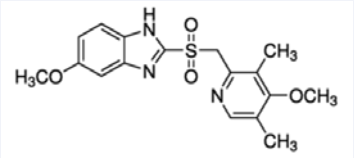

Figure 2 Omeprazole sulfone molecular structure (molecular weight = 361.42 grams/mole).

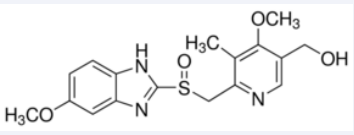

Figure 3 5-Hydroxyomeprazole molecular structure (molecular weight = 361.42 grams/mole).

Administration to children [4]: Oral administration for Helicobacter pylori eradication in combination with amoxicillin and clarithromycin; or in combination with amoxicillin and metronidazole; or in combination with clarithromycin and metronidazole.

Children aged 1 to 5 years. Give: 1 to 2 mg/kg once-daily (maximum per dose = 40 mg).

Children aged 6 to 11 years. Give: 1 to 2 mg/kg once-daily (maximum per dose = 40 mg).

Children aged 12 to 17 kg. Give: 40 mg once-daily.

Oral treatment of duodenal ulcers including those complicating nonsteroidal anti-inflammatory drugs therapy. Treatment of beginning gastric ulcers including those complicating nonsteroidal anti-inflammatory drugs therapy.

Children aged 1 month to 1 year. Give: 700 µg/kg once-daily, increase the dose if necessary to 3 mg/kg once-daily (maximum per dose = 20 mg).

Children aged 2 to 17 years (body-weight of 10 to 19 kg). Give: 10 mg once-daily, increase the dose if necessary to 20 mg once-daily.

Children aged 2 to 17 years (body-weight of 20 mg and above). Give: 20 mg once-daily, increase the dose if necessary to 40 mg once-daily.

Administration by injection or by intravenous infusion: Children aged 1 month to 11 years. Give initially 500 µg/kg once-daily (maximum per dose = 20 mg), increase the dose if necessary to 2 mg/kg once-daily (maximum per dose = 40 mg).

Children aged 12 to 17 years. Give: 40 mg once-daily, the injection should be given over 5 min.

Oral treatment of Zollinger-Ellison syndrome: Children aged 1 month to 1 year. Give: 700 µg/kg once-daily, increase the dose if necessary to 3 mg/kg once-daily (maximum per dose = 20 mg).

Children aged 2 to 17 years (body-weight of 10 to 19 kg). Give: 10 mg once-daily, increase the dose if necessary to 20 mg once-daily.

Children aged 2 to 17 years (body-weight of 20 kg and above). Give: 20 mg once-daily, increase the dose if necessary to 40 mg once-daily.

By intravenous injection or by intravenous infusion: Children aged 1 month to 11 years. Give initially 500 µg/kg once-daily (maximum per dose = 20 mg) increase the dose if necessary to 2 mg/kg once-daily (maximum per dose = 40 mg), the injection should be given over 5 min.

Children aged 12 to 17 years. Give: 40 mg once-daily, the injection should be given over 5 min.

Oral treatment of gastro-oesophageal reflux disease: Children aged 1 month to 1 year. Give: 700 µg/kg once-daily, increase the dose if necessary to 3 mg/kg once-daily (maximum per dose = 20 mg).

Children aged 12 to 17 years (body-weight of 10 to 19 kg). Give: 10 mg once-daily, increase the dose if necessary to 20 mg once-daily, in severe ulcerating reflux oesophagitis the maximum is 12 weeks at higher dose.

Children aged 12 to 17 years (body-weight of 20 kg and above). Give: 20 mg once-daily, increase the dose if necessary to 40 mg once-daily, in severe ulcerating reflux oesophagitis the maximum is 12 weeks at higher dose.

By intravenous injection or by intravenous infusion: Children aged 1 month to 11 years. Give initially 500 µg/kg once-daily (maximum per dose = 20 mg), increase the dose if necessary to 2 mg/kg once-daily (maximum per dose = 40 mg), the injection should be given over 5 min.

Children aged 12 to 17 years. Give: 40 mg once-daily, the injection should be given over 5 min.

Oral treatment of acid-related dyspepsia: Children aged 1 month to 1 year. Give: 700 µg/kg once-daily, increase the dose if necessary to 3 mg/kg once-daily (maximum per dose = 20 mg).

Children aged 2 to 17 years (initiated by a specialist) (body-weight of 10 to 19 kg). Give: 10 mg once-daily, increase the dose if necessary to 20 mg once-daily.

Children aged 2 to 17 years (initiated by a specialist) (body-weight of 20 kg and above). Give: 20 mg once-daily, increase the dose if necessary to 40 mg once-daily.

By intravenous injection or by intravenous infusion: Children aged 1 month to 11 years. Give initially 500 µg/kg once-daily (maximum per dose = 20 mg), increase the dose if necessary to 2 mg/kg (maximum per dose = 40 mg), the injection should be given over 5 min.

Children aged 12 to 17 years. Give: 40 mg once-daily, the injection should be given over 5 min.

Oral treatment of fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis: Children aged 1 month to 1 year. Give: 700 µg/kg once-daily, increase the dose if necessary to 3 mg/kg once-daily (maximum per dose = 20 mg).

Children aged 2 to 17 years (body-weight of 10 to 19 kg). Give: 10 mg once-daily, increase the dose if necessary to 20 mg once-daily.

Children aged 2 to 17 years (body-weight of 20 kg and above). Give: 20 mg once-daily, increase the dose if necessary to 40 mg once-daily.

By intravenous injection or by intravenous infusion: Children aged 1 month to 11 years. Give initially 500 µg/kg once-daily (maximum per dose = 20 mg), increase the dose if necessary to 2 mg/kg once-daily (maximum per dose = 40 mg), the injection should be given over 5 min.

Children aged 12 to 17 years. Give: 40 mg once-daily, the injection should be given over 5 min.

Efficacy and safety of omeprazole in infants and children: Thirty infants received ranitidine and 30 infants received omeprazole and ranitidine and omeprazole are efficacy and safe in these infants [5]. The efficacy and safety of omeprazole was assessed in 15 infants and children and the optimal dose of ome-

prazole is 0.7 to 3.3 mg/kg [6]. Omeprazole has been effective and well tolerated for the acute and chronic treatment of oesophageal and peptic ulcer disease in children [7]. Omeprazole is well tolerated, highly effective, and safe for treatment of erosive esophagitis and symptoms of gastroesophageal reflux in children [8]. Omeprazole is highly effective for all grades of esophagitis in intellectually disabled children, without adverse-effects [9]. Long-term omeprazole therapy up to 11 years is highly effective and safe for control of reflux esophagitis in children [10]. Omeprazole is highly effective in children with severe esophagitis and the optimal dose of omeprazole is 0.7 mg/kg once-daily [11].

Metabolism of omeprazole: The sulfoxidation of S-omeprazole into omeprazole sulfone is metabolized by CYP3A4 and CYP2C19 exclusively metabolizes R-omeprazole to hydroxyomeprazole, which is hydrophilic and can be easily excrete, whereas CYP3A4 metabolizes S-omeprazole to lipophilic sulfone [12]. (Figure 2&3)

The omeprazole sulfone formation is catalysed by CYP3A4 and is 10-fold higher for S-omeprazole than for R-omeprazole, which may contribute to their stereoselective disposition. Both CYP2C19 and CYP3A4 exhibit a stereoselective metabolism of omeprazole. CYP2C19 favours 5-hydroxylation of the pyridine group of R-omeprazole, whereas the same enzyme mainly 5-O-demethylates S-omeprazole into benzimidazole group [13].

Pharmacokinetics of omeprazole in infants: Bestebreurtje et al. [14] studied the pharmacokinetics of omeprazole in infants with gastroesophageal reflux disease due to oesophageal atresia or with congenital diaphragmatic hernia. Infants were aged 6 to 12 weeks with a body-weight of > 3 kg. Infants received omeprazole orally (N = 1) or rectally (N = 4) and omeprazole was administered at a dose of 1 mg/kg. (Table 1).

The comparison of pharmacokinetic parameters between rectal and oral administration of omeprazole is difficult because there is only one date after oral administration. Omeprazole is rapidly absorbed following rectal administration as Tmax is 96.5 min and the distribution volume of omeprazole is larger than the water volume. Following rectal dosing of omeprazole, the AUC_{0-t} of omeprazole is similar to that 5-hydroxyomeprazole whereas that of omeprazole sulfone is lower than that of omeprazole. The peak concentration of omeprazole is similar to that of 5-hydroxymeprazole whereas that of omeprazole sulfone is lower than that of omeprazole. Tmax of omeprazole is similar to that of 5-hydroxyomeprazole whereas that of omeprazole sulfone is greater than that of omeprazole. Following rectal administration of omeprazole, there is a remarkable interindividual variability of the pharmacokinetic parameters of omeprazole and its metabolites. In infants, omeprazole is preferentially metabolized into 5-hydroxyomeprazole and omeprazole sulfone is a minor metabolite of omeprazole.

Kearns et al. [15] investigated the pharmacokinetics of omeprazole in 23 children aged 2 to 16 years and omeprazole was orally administered at a single dose. Subjects weighing ≥ 20 kg received 10 mg of omeprazole and those weighing > 20 kg received 20 mg of omeprazole. (Table 2)

This table shows that omeprazole is rapidly absorbed as the median Tmax is 2 hours, the distribution volume is larger than the water volume, and the elimination obtained in children is similar to that in infants following rectal administration (for comparison to infants see table 1).

Interaction of omeprazole with drugs: Simultaneous prescription of amlodipine and omeprazole to patients with arterial hypertension and acid-dependent disease enhances the antihypertensive effect of amlodipine because amlodipine and omeprazole are metabolised by CYP3A4 and omeprazole inhibits CYP3A4 [16]. Omeprazole is metabolised by CYP3A4 and this CYP metabolises also caffeine and theophylline thus omeprazole increases the blood concentrations of caffeine and theophylline because omeprazole inhibits CYP3A4 [17]. Omeprazole impairs clopidogrel-induced antiplatelet effects in the maintenance phase of treatment irrespective of timing of their administration [18]. Raltegravir is a HIV-1 integrase inhibitor and has pH-dependent solubility. Raltegravir plasma concentration increases with the co-administration of omeprazole in healthy subjects and

Table 1. Pharmacokinetic parameters of omeprazole which are obtained in infants. Omeprazole was administered rectally or orally to a dose of 1 mg/kg. Figure are the median and (range), by Bestebreurtje et al. [14].

	Omeprazole		5-hydroxyomeprazole		Omeprazole sulfone	
Parameter	Rectal (N = 4)	Oral (N = 1)	Rectal (N = 4)	Oral (N = 1)	Rectal (N = 4)	Oral (N = 1)
AUC_{0-t} (µg/ml*min)	57.4 (13.1-79.8)	49.8	63.9 (15.7-108)	69.3	11.5 (2.1-27.8)	14.9
$AUC_{0-\infty}$ (µg/ml*min)	57.7 (13.3-64.8)	50.5	68.2 (18.5-114)	73.6	NA	NA
TBC/F (L/min/kg)	0.016 (0.009-0.08)	0.020	---	---	---	---
DV/F (L/kg)	2.0 (0.9-2.1)	1.2	---	---	---	---
$T_{0,5}$ (min)	65.2 (18.7-138)	38.5	63.8 (42.4-83.0)	58.4	117 (77.3-156)	118
Peak conc. (µg/ml)	0.3 (0.3-0.4)	1.0	0.4 (0.2-0.7)	0.7	0.05 (0.02-0.1)	0.1
Tmax (min)	96.5 (60-167)	123	75.5 (60-167)	123	209 (60-247)	123
*Half-life (min)	56 (19-137)	38	---	---	---	---

AUC_{0-t} = AUC from the time zero to the last sampling time point. **$AUC_{0-\infty}$** =AUC from time zero to infinity. **TBC/F** = apparent serum total body clearance. **DV/F** = apparent distribution volume. **Tmax** = time to reach the peak concentration. **NA** = not available.

Table 2: Pharmacokinetic parameters of omeprazole which are obtained in 23 children. The study is conducted by Kearns et al. [15].

Parameter	$AUC_{0-\infty}$ (ng/ml*h)	Peak conc. (ng/ml)	Tmax (h)	TBC/F (L/h/kg)	DVss/F (L/kg)	*half-life (h)	*Half-life (min)
Mean	809	446	2.15	1.76	2.60	0.98	58.5
SD	±893	±402	±1.21	±1.38	±2.66	±0.22	±13.2
Median	624	218	2.0	1.59	2.14	1.04	62.4
Minimum	236	42.1	1.0	0.29	0.43	0.67	40.2
Maximum	1,330	1,449	6.0	5.80	2.16	1.45	87.0

$AUC_{0-\infty}$ = AUC extrapolated from zero to the infinity. **Tmax** = time to reach the peak concentration. **TBC/F** = apparent total body clearance. **DVss** = apparent distribution volume at the steady-state. *Elimination half-life.

this is due to increase of gastric pH [19]. The use of omeprazole simultaneously with phenprocoumon during hospital admissions increases the anticoagulant effect of phenprocoumon [20]. The increased anticoagulant activity of phenprocoumon, when it is co-administered with omeprazole, is due to competitive inhibition of omeprazole degradation [21]. The combination of clarithromycin and tinidazole results in 76% inhibition of omeprazole metabolism, while the combination of amoxicillin and metronidazole results in 48% inhibition of omeprazole metabolism. Both combinations of drugs inhibit the metabolism of omeprazole by inhibiting CYP2C19 which is the CYP that metabolises omeprazole [22]. Lansoprazole is at least 5 times more potent than omeprazole as an inhibitor of CYP2D6-mediated conversion of dextromethorphan to dextrorphan [23]. Omeprazole interacts with the hepatic microsomal cytochrome P-450 enzymes and the clearance of both diazepam and phenytoin are decreased and their terminal half-lives are increased during concomitant omeprazole treatment [24].

Treatment of infants and children with omeprazole: In literature there is only one study on the treatment of infants and children with omeprazole and it has been reported by Bishop et al. [25]. Omeprazole is an effective treatment for gastroesophageal reflux in infants and children and the majority of subjects respond to a dosage of 0.7 mg/kg daily but an increased dosage up to 2.8 mg/kg daily may be required.

Migration of omeprazole into the breast-milk: In literature there is only one study on the migration of omeprazole into the breast-milk and it has been reported by Marshall et al. [26]. Omeprazole was administered to lactating women at a dose of 20 mg daily and the concentration of omeprazole is 20 ng/ml, after 3 hours of maternal treatment, and it is less than 7% of the peak serum concentration, indicating that omeprazole poorly migrates into the breast-milk.

DISCUSSION

Six proton pump inhibitors are available for clinical use: omeprazole, dexlansoprazole, rabeprazole, prazole, lansoprazole and its R-enantiomer, dexlansoprazole, rabeprazole, and pantoprazole. Proton pump inhibitors are prodrugs that require activation in acid environments. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. Here, it is activated by proton-catalysed formation of a tetracyclic sulfenamide trapping the drug so that it cannot diffuse back across the canalicular membrane. The activated form then binds covalently with sulfhydryl groups of cysteine in the H^+, K^+-ATPase, irreversibly inactivating the pump molecule. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prolonged (up to 24 to 48 hours) suppression of acid secretion, despite the much shorter plasma elimination half-life of about 0.5 to 3 hours. The proton pump inhibitors effectively suppress stimulated acid production regardless of the physiological stimulus as well as the basal acid production. Proton pump inhibitors are primarily used to promote healing of gastric and duodenal ulcers and to treat gastroesophageal reflux disease including erosive esophagitis which is either complicated or unresponsive to treatment with H_2 receptor antagonists [1]. Omeprazole is used to suppress gastric secretion when endoscopically-proven oesophagitis or peptic ulceration persists despite treatment with ranitidine [2]. Omeprazole is used in short-term (less than 8 weeks) treatment of duodenal reflux oesophagitis or duodenal ulcer refractory to conventional treatment [3]. Omeprazole may be administered orally or intravenously and after oral administration it is rapid absorbed. In infants, the initial oral dosing consists in 0.7 mg/kg once-daily and following intravenous administration the treatment consists in 0.5 mg/kg once-daily [2]. In children, omeprazole is used for the eradication of Helicobacter pylori, for treatment of duodenal and gastric ulcers, for treatment of Zollinger-Ellison disease, for treatment of acid-related dyspepsia, and for treatment of fat malabsorption in cystic fibrosis and omeprazole may be administered orally or intravenously and the omeprazole dose varies according to the child age or the child body-weight [4]. Omeprazole has been found efficacy and safe in infants and children [5-11]. Omeprazole and ranitidine are efficacy and safe in infants [5], an omeprazole dose of 0.7 to 3.3 mg/kg is efficacy and safe in infants and children [6], omeprazole is effective and well tolerated in children with oesophageal and peptic ulcer [7], omeprazole is effective and well tolerated in the treatment of children with erosive esophagitis and gastroesophageal reflux [8], omeprazole is highly effective for all grades of esophagitis and gastroesophageal reflux without cause adverse-effects [9], long-term omeprazole treatment up to 11 years in effective and safe for the control of severe esophagitis in children [10], and the optimal dose of omeprazole is 0.7 mg/kg once-daily in children with severe esophagitis [11]. Omeprazole is metabolized by CYP3A4 and CYP2C19 into omeprazole sulfone, the formation-rate is 10-fold higher for S-omeprazole than R-omeprazole [12], and CYP2C19 catalyses the conversion of omeprazole into 5-hydroxymeorazole

and the formation-rate of 5-hydroxyomeprazole is stereoselective [13]. The pharmacokinetics of omeprazole have been studied in infants following rectal (N = 4) or oral (N = 1) administration of omeprazole. Following rectal administration, the elimination half-life of omeprazole is 56 min and the distribution volume is larger than the water volume [14]. In these infants, omeprazole is metabolized into 5-hydroxyomeprazole and omeprazole sulfone and the former metabolite is the main metabolite whereas the latter metabolite is a minor metabolite. The pharmacokinetics of omeprazole have been studied in children, the elimination half-life of omeprazole is 58.5 hours and the distribution volume is 2.6 L/kg [15]. Omeprazole interacts with drugs [16-24]. Omeprazole and amlodipine are metabolized by CYP3A4, omeprazole inhibits this CYP and omeprazole enhances the antihypertensive effect of amlodipine [16], as omeprazole is an inhibitor of CYP3A4 omeprazole increases the blood concentrations of caffeine and theophylline which are metabolized by this CYP [17], omeprazole impairs clopidogrel-induced antiplatelet effects [18], raltegravir plasma concentration increases when it is co-administered with omeprazole and this increase is due to increase of gastric pH [19], the anticoagulant activity of phenprocoumon is increased when phenprocoumon is combined with omeprazole and this is due to competitive inhibition of omeprazole degradation [20-21], clarithromycin and tinidazole inhibits the omeprazole metabolism and amoxicillin and metronidazole inhibit the metabolism of omeprazole as both drug combinations inhibit CYP2C19 which is the CYP that metabolizes omeprazole [22], lansoprazole is a more potent inhibitor of omeprazole of CYP2D6-mediated the conversion of dextromethorphan to dextrorphan [23], and omeprazole induces the cytochrome P-450 and reduces the terminal half-lives of diazepam and phenytoin [24]. Omeprazole is an effective treatment of infants and children with gastroesophageal reflux [25], and omeprazole poorly migrates into the breast-milk [26].

In conclusion, omeprazole is a proton pump inhibitor. Omeprazole is used to suppress gastric secretion when endoscopically-proven oesophagitis or peptic ulceration persists despite treatment with ranitidine. Omeprazole is used in short-term (less than 8 weeks) treatment of duodenal reflux oesophagitis or duodenal ulcer refractory to conventional therapy. Omeprazole inhibits gastric acid secretion by inhibiting of K^+-ATPase, the enzyme responsible for the final step in the secretion of hydrochloric acid by the gastric parietal cell. Onset of action is within one hour of administration, maximal effect is at approximately 2 hours and the inhibition of acid secretion is approximately 72 hours. Omeprazole may be administered orally or intravenously. In infants, the initial oral dose is 0.7 mg/kg once-daily and the intravenous dose of omeprazole is 0.5 mg/kg once-daily. In children, the dose of omeprazole varies according to the child age or the child body-weight. Omeprazole has been found efficacy and safe in infants and children and omeprazole is converted by CYP3A4 and CYP2C19 into omeprazole sulfone and by CYP3A4 and CYP2C19 into 5-hydroxyomeprazole and the formation-rate of both omeprazole sulfone and 5-hydroxyomeprazole is stereoselective. The elimination half-life of omeprazole is 56 min in infants and in 58.5 min in children and the distribution volume of omeprazole is larger than the water volume in infants and children. The interaction of omeprazole with drugs has been extensively studied and omeprazole poorly migrates into the breast-milk. The aim of this study is to review the clinical pharmacology of omeprazole in infants and children.

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