Newborn Use Only
Omeprazole

2016

Alert	Short- and long-term safety data in infants are limited. There have been several safety concerns with long-term usage in adults. The bioavailability of the in-house pharmacy suspension made from the contents of the capsule may be less (up to 50% less) than that of the capsule itself. Dose may need to be adjusted if no clinical response.
Indication	Treatment of gastroesophageal reflux disease (GORD). Prophylaxis in congenital tracheoesophageal fistula and oesophageal atresia (role unclear).
Action	Omeprazole is a proton pump inhibitor (PPI).
Drug Type	Proton Pump Inhibitor.
Trade Name	APO-Omeprazole Capsules (Apotex) 20 mg Omeprazole Sandoz IV Powder for injection (Sandoz]) 40 mg.
Presentation	20 mg/capsule; 10 mg tablets; 20 mg tablets. Oral suspension of 2 mg/mL prepared in pharmacy. Omeprazole Sandoz IV Powder for injection 40 mg.
Dosage / Interval	PO: 0.5–1.5 mg/kg/dose daily IV: 0.5 mg/kg/dose daily
Maximum daily dose	1.5 mg/kg/dose
Route	PO, IV
Preparation/Dilution	PO: In-house pharmacy can prepare a 2 mg/mL suspension using these capsules as follows: Disperse 100 mg omeprazole in 50 mL of 8.4% sodium bicarbonate solution. 1 mL of omeprazole suspension contains 2 mg omeprazole, 1 mmol sodium and 1 mmol bicarbonate. IV: Reconstitute the vial with 5 mL from a 100 mL bag of sodium chloride 0.9% or glucose 5%. Add the reconstituted solution back into the 100 mL bag to obtain 0.4 mg/mL.
Administration	PO: Administer prior to meals. IV: Infuse over 30 minutes.
Monitoring	Serum magnesium, in patients on prolonged therapy or who use digoxin or drugs that may cause hypomagnesaemia (e.g. diuretics) concomitantly.[20-21] Serum vitamin B_{12} — every 1 to 2 years in patients on prolonged therapy.[20-21]
Contraindications	Hypersensitivity to any component of the product.
Precautions	
Drug Interactions	Concurrent use of ketoconazole may result in decreased ketoconazole exposure. Concurrent use of fluconazole may result in increased plasma concentrations of omeprazole. Concurrent use of iron may result in reduced non-heme iron bioavailability.
Adverse Reactions	Common Dermatologic: Rash Gastrointestinal: Increased risk of *Clostridium difficile*-associated diarrhea (CDAD), Abdominal pain, constipation, diarrhea, flatulence, vomiting Respiratory: Upper respiratory infection (adults) Other: Fever (1 to less than 2 years, 33%) Serious Dermatologic: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis Endocrine: Hypomagnesaemia Gastrointestinal: Atrophic gastritis, *Clostridium difficile* diarrhea, pancreatitis Haematological: Haemolytic anaemia Hepatic: Hepatic encephalopathy, hepatic necrosis, liver failure Immunological: Anaphylaxis

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	Musculoskeletal: Fracture of bone, hip fracture, rhabdomyolysis Renal: Acute interstitial nephritis
Compatibility	
Incompatibility	Oral: No information. IV: No information.
Stability	Prepared suspension is stable for 30 days. Refrigerate. Protect from light. Shake the bottle well before administration. IV reconstituted solution and diluted solution: Stable for 6 hours below 25°C. Protect from light.
Storage	Oral suspension: Refrigerate (2–8°C) the prepared suspension. Injection: Store below 25°C. Protect from light.
Special Comments	
Evidence summary	**Treatment of gastroesophageal reflux disease (GORD)** NICE Guidelines[1] 1. Do not offer acid-suppressing drugs, such as proton pump inhibitors (PPIs) or H_2 receptor antagonists (H_2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom. 2. Consider a 4-week trial of a PPI or H_2RA for those who are unable to tell you about their symptoms (for example, infants and young children, and those with a neurodisability associated with expressive communication difficulties) who have overt regurgitation with 1 or more of the following: Unexplained feeding difficulties (for example, refusing feeds, gagging or choking), distressed behaviour, faltering growth. 3. Consider a 4-week trial of a PPI or H_2RA for children and young people with persistent heartburn, retrosternal or epigastric pain. 4. Assess the response to the 4-week trial of the PPI or H_2RA, and consider referral to a specialist for possible endoscopy if the symptoms: do not resolve or recur after stopping the treatment. 5. When choosing between PPIs and H_2RAs, take into account: The availability of age-appropriate preparations, the preference of the parent (or carer), child or young person (as appropriate) and local procurement costs. 6. Offer PPI or H_2RA treatment to infants, children and young people with endoscopy-proven reflux oesophagitis and consider repeat endoscopic examinations as necessary to guide subsequent treatment. 7. Do not offer metoclopramide, domperidone or erythromycin to treat GOR or GORD without seeking specialist advice and taking into account their potential to cause adverse events. ESPGHAN and NASPGHAN Guidelines[2] For healing of erosive esophagitis and relief of GERD symptoms, PPIs are superior to H_2RAs. Both medications are superior to placebo. Administration of long-term acid suppression without a diagnosis is inadvisable. When acid suppression is required, the smallest effective dose should be used. Most patients require only once-daily PPI; routine use of twice-daily dose is not indicated. No PPI has been approved for use in infants < 1 year of age, and there are special concerns pertaining to prescription of PPIs in infants, as described in the Guideline. H_2RAs exhibit tachyphylaxis or tolerance but PPIs do not. Tachyphylaxis is a drawback to chronic use. H_2RAs have a rapid onset of action and, like buffering agents, are useful for on-demand treatment. **Prophylaxis in congenital oesophageal atresia and tracheoesophageal fistula** In a systematic review by Shawyer et al,[3] involving 1,663 patients for analysis, most were single centre studies (92 %) and retrospective (76 %); there were no randomised controlled trials. The quality of literature regarding anti-reflux medication for GER post EA-TEF repair is poor.

Pharmacokinetics

PPIs are metabolised to varying degrees by the hepatic cytochrome P450 (CYP) enzyme system. Despite rapid elimination of omeprazole from plasma (i.e. mean elimination half-life, or t½, ≈ 1 hour), the effect can persist for 24 to 72 hours consequent to strong binding of the active form to its target receptor. Oral bioavailability of omeprazole ranges from 35% to 65% and it is 95% protein bound (Kearnes 2003).

A randomised, double blind, placebo-controlled, crossover design trial of omeprazole therapy was performed by Omari et al in 10 preterm infants (34–40 weeks postmenstrual age). Infants were given omeprazole (0.7 mg/kg daily — prepared as 0.7 mg/kg of IV omeprazole in 2 mL/kg of Mylanta through NG tube) for 7 days and then placebo for 7 days in randomised order. Twenty-four-hour esophageal and gastric pH monitoring was performed on days 7 and 14 of the trial. Compared to placebo, omeprazole therapy significantly reduced gastric acidity (% time pH < 4, 54% vs 14%, P < 0.0005), oesophageal acid exposure (% time pH < 4, 19% vs 5%, P < 0.01) and number of acid GER episodes (119 vs 60 episodes, P < 0.05).

Kaufman et al studied 22 paediatric patients ranging in age from 0.9 to 108 months (23.8 ± 6.5) who underwent isolated liver (n = 10) or intestinal transplantation. Omeprazole was delivered in bicarbonate suspension through a nasogastric tube. Therapy was started after surgery at 0.5 mg/kg every 12 hours. For the entire group, mean gastric pH equalled 6.1 ± 0.3, the same in recipients of isolated liver and intestinal allografts. Twelve of the 22 patients demonstrated a discontinuous omeprazole effect, that is, dissipation of acid reduction before the next dose. Five of the 12 patients with discontinuous omeprazole effect had a mean gastric pH of less than 5 (3.9 ± 0.4). In 4 of these 5, the omeprazole dosing interval was shortened to every 8 or every 6 hours, resulting in an increase in mean pH to 6.6 ± 0.2 (P < 0.01). In the remaining 10 of 22 patients, acid suppression was uninterrupted until the next dose. No patient experienced bleeding attributable to gastric erosion. In conclusion, a dosage of 0.5 mg/kg every 12 hours is sufficient for most patients, but dosing every 6 to 8 hours is required to assure maximal acid suppression in all.

Proper formulation is critical for omeprazole for a good oral bioavailability.

Safety

The FDA reviewed 4 randomised controlled trials evaluating the use of PPIs in infants (ages 1 month to <12 months) for the treatment of symptomatic GERD (Chen LL 2012). These trials used PPIs for a short duration and no serious side effects have been reported. However, it cannot be assumed that PPIs can be used safely for a long time. Among adults, there have been concerns that long-term PPI use may predispose patients to an increased risk of gastric cancer, gastric carcinoid tumors and colorectal cancer. These concerns are based on hypergastrinaemia, alteration of the distribution of gastritis and accelerated development of atrophic gastritis in the presence of *Helicobacter pylori* infection. Suppression of gastric acid secretion may also predispose patients to certain infections (*Clostridium difficile* infections, other enteric infections and respiratory infections, including community-acquired pneumonias). The mechanism for this may be that acid suppression eliminates a defence against pathogens. There have been rare reports of vitamin and electrolyte abnormalities (e.g. vitamin B_{12} deficiency and hypomagnesaemia in adults taking PPIs chronically. There have been cases of hypomagnesaemia that required discontinuation of the PPI in addition to magnesium supplementation. There are reports of calcium deficiency and osteoporosis in adults on chronic PPI therapy and the FDA added these side effects for all PPIs. (Chen LL 2012, Tolia 2008). Additionally, PPIs have been implicated as a cause of acute interstitial nephritis.(Chen LL 2012).

	Tolia and Boyer reported the outcomes of 32–47 months of treatment with PPIs in 133 paediatric patients ranging in age from 0.1 to 17.6 years at the start of treatment. Most patients were dosed twice a day. Parietal cell hyperplasia was observed in 0–16 % of patients during follow-up but, interestingly, the gastric histology was normal significantly more often when treatment continued for longer than 48 months and when patients were treated with higher doses. Gastrin levels were elevated in 73 % of the children, but vitamin B_{12} remained normal. In a recent systematic review (More K et al), a higher incidence of NEC has been reported in preterm VLBW infants in association with the suppression of gastric acidity, induced both by H2-Blockers and PPIs. So far, it is not possible to fit these evidences specifically for PPIs, as data currently available on the occurrence of NEC and infections are jointly concerning both PPIs and H2-blockers.
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