Focus on....

Omeprazole

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The recognition that the enzyme hydrogen-potassium-ATPase (H-K-ATPase) was involved in the final step of acid secretion culminated in the development of a class of drugs called the proton pump inhibitors (PPIs), which are targeted at inhibiting this enzyme.[1] The PPIs are the most potent inhibitors of gastric secretion available.[1] They are most effective when the parietal cell is stimulated to secrete acid postprandially, a relationship that has important clinical implications for timing of administration.[1] Since the amount of H-K-ATPase present in the parietal cell is greatest after a prolonged fast, PPIs should be administered before the first meal of the day.[1]

Omeprazole was the first PPI to become available clinically.[1] It is currently available as 10 mg, 20 mg and 40 mg MUPS tablets, as 10 mg, 20 mg and 40 mg capsules and as a 40 mg/vial intravenous infusion.

Indications

Omeprazole is indicated in[2]:

Adults

- Treatment of duodenal ulcers, including prevention of relapse of duodenal ulcers
- Treatment of gastric ulcers, including prevention of relapse of gastric ulcers
- Treatment of symptomatic gastro-oesophageal reflux disease and the short-term relief of functional dyspepsia
- Treatment of reflux oesophagitis
- Long-term management of patients with healed reflux oesophagitis
- Treatment of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric and duodenal ulcers
- Prevention of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric and duodenal ulcers in patients at risk (age > 60 years; previous history of gastric and duodenal ulcers; previous history of upper gastrointestinal (GI) bleeding)
- In combination with appropriate antibiotics for *Helicobacter pylori (H. pylori)* eradication in peptic ulcer disease
- Treatment of Zollinger-Ellison Syndrome

Children

- Short-term (up to three months) treatment of severe ulcerative reflux oesophagitis resistant to previous medical treatment

Pharmacokinetics

Omeprazole is acid labile and is therefore administered orally as enteric-coated granules in capsules or tablets.[2] Absorption of omeprazole is rapid, with peak plasma levels occurring approximately 1–2 hours after dosing.[2] Absorption of omeprazole takes place in the small intestine and is usually completed within 3–6 hours.[2] Bioavailability depends on dose and gastric pH and may reach 70% with repeated administration.[2] Concomitant intake of food has no influence on the bioavailability.[2]

Omeprazole is more than 95% bound to plasma proteins.[2] Clearance from the circulation is by hepatic metabolism with a plasma elimination half-life of 30 to 90 minutes.[2] Hepatic metabolism occurs primarily by the cytochrome P450 system (CYP2C19).[2] The inactive metabolites are excreted mainly in the urine (80%) while the remaining 20% are excreted via the faeces.[2] As a consequence of the high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions with other substrates for CYP2C19.[2] However, due to low affinity to CYP3A4, omeprazole has no potential to inhibit the metabolism of other CYP3A4 substrates.[2]

Dosing

Omeprazole should be given in the morning and swallowed with half a glass of liquid.[2] The tablets or capsules should not be crushed or chewed.[2]

Efficacy

Suppressing gastric acid secretion enhances healing of acid-related diseases.[3] Good healing of reflux oesophagitis is achieved when the intragastric pH is greater than 4 for 16 hours of the day, and peptic ulcer is optimally healed when the intragastric pH is greater than 3 for 16 hours per day.[3] Generally, all PPIs provide good gastric acid suppression.[3] Acid suppression studies comparing omeprazole, lansoprazole, rabeprazole and pantoprazole show equivalent efficacy.[3] Most studies using standard doses have

Indication	Recommended dose (adults)[2]	
Duodenal ulcer (treatment)	20 mg once daily for 2–4 weeks In patients with poorly responsive duodenal ulcer, a dose of 40 mg once daily may be recommended and healing is usually achieved within 4 weeks	
Prevention of relapse of duodenal ulcer	10–20 mg once daily If necessary, the dose may be increased to 40 mg once daily	
Gastric ulcer (treatment)	20 mg once daily for 4–8 weeks In patients with poorly responsive gastric ulcer, a dose of 40 mg once daily may be recommended and healing is usually achieved within 8 weeks	
Prevention of relapse of gastric ulcer	20 mg once daily If necessary, the dose may be increased to 40 mg once daily	
Symptomatic gastro-oesophageal reflux disease	20 mg once daily Some patients may respond to 10 mg once daily, and therefore individual dose reduction should be considered. If symptom control has not been achieved after 2–4 weeks of treatment with omeprazole 20 mg once daily, further investigation is recommended.	
Reflux oesophagitis	20 mg once daily for 4–8 weeks In patients with poorly responsive reflux oesophagitis, a dose of 40 mg once daily may be recommended and healing is usually achieved within 8 weeks	
Long-term management of patients with healed reflux oesophagitis	10 mg once daily If necessary, the dose may be increased to 20–40 mg once daily	
Treatment of NSAID-associated gastric and duodenal ulcers	20 mg once daily for 4–8 weeks	
Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk	20 mg once daily	
In combination with appropriate antibiotics for *H. pylori* eradication in peptic ulcer disease	20 mg once daily in combination with appropriate antibiotics If necessary, the dose of omeprazole may be increased to 40 mg once daily	
Treatment of Zollinger-Ellison Syndrome	60 mg once daily Dosage should be adjusted individually and continued for as long as clinically indicated. With doses > 80 mg daily, the dose should be divided and given twice daily	
Severe ulcerative reflux oesophagitis in children from one year	**Recommended dose (children)**	
	Weight	**Dose**
	10–20 kg	10 mg once daily If needed, increase to 20 mg once daily
	> 20 kg	20 mg once daily If needed, increase to 40 mg once daily
For patients with swallowing difficulties and for children who can drink or swallow semi-solid fluid[2]: • Patients can open the capsule and swallow the enteric coated pellets with half a glass of water. • Patients should be advised that the dispersion should be taken immediately and always be stirred just before drinking and rinsed down with half a glass of water.		

not shown a significant difference between the four PPIs for the healing of reflux oesophagitis or duodenal ulcer.[3]

Safety of omeprazole

The PPIs are an extremely safe class of drugs.[1] However, differences in their metabolism may lead to specific drug interactions.[1] The long-term safety of the PPIs has been best established with omeprazole, since it was the first PPI to become available clinically.[1] Data support the safety of omeprazole over more than 15 years of use.[1]

Special warnings and precautions for use

In the presence of any alarm symptoms (e.g. significant unintentional weight loss, recurrent vomiting, dysphagia, haematemesis or melaena) and when gastric ulcer is suspected or present, malignancy should be excluded, as treatment with omeprazole may alleviate symptoms and delay diagnosis.[2]

Omeprazole, like all acid-blocking medicines, may reduce the absorption of vitamin B_{12} (cyanocobalamin).[2]

Severe hypomagnesaemia has been reported in patients treated with PPIs for at least three months, and in most cases for a year.[2] Patients expected to be on long-term treatment should have magnesium levels measured before and periodically during treatment.[2]

PPIs, especially if used in high doses and over long durations (> 1 year) may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in the presence of other recognised risk factors.[2]

Drug interactions

Omeprazole is a CYP2C19 inhibitor. When starting or ending treatment with omeprazole, the potential for interactions with other drugs metabolised through CYP2C19 should be considered.[2]

The elimination of diazepam, warfarin and phenytoin may be prolonged when omeprazole is given concomitantly.[2] Monitoring of INR and phenytoin serum levels is recommended and dosage reductions may be necessary when omeprazole is given comcomitantly.[2]

An interaction is observed between clopidogrel and omeprazole.[2] Concomitant use of omeprazole and clopidogrel should be discouraged.[2]

The decreased intragastric acidity during treatment with omeprazole may affect the absorption of substances with a gastric pH-dependent absorption.[2] The plasma levels of nelfinavir and atazanavir are decreased in case of co-administration with omeprazole and concomitant administration is not recommended.[2]

There is a possible interaction of omeprazole with digoxin and a 10% increase in the digoxin bioavailability may be expected.[2]

Adverse effects

The most common side-effects (1–10% of patients) are headache, abdominal pain, constipation, diarrhoea, flatulence, nausea and vomiting.[2]

Important prescribing points

- PPIs should only be used for the appropriate indications and not for a longer duration than essential.[4]
- Patients at risk of osteoporosis should ensure an adequate intake of calcium and vitamin D.[4]
- Patients taking PPIs long term may need monitoring of magnesium levels.[4]
- PPIs may be associated with an increased risk of *Clostridium difficile*-associated diarrhoea (CDAD). A diagnosis of CDAD should be considered in patients taking PPIs who develop diarrhoea that does not improve.[4]

References:

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