# Chapter 21
# Antacids, Gastrointestinal Prokinetics, and Proton Pump Inhibitors

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## Contents



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A.D. Kaye et al. (eds.), *Essentials of Pharmacology for Anesthesia, Pain Medicine, and Critical Care*, DOI 10.1007/978-1-4614-8948-1_21,

## Antacids

### *Physiology of Acid Secretion*

Gastric acid is secreted by the proton pump (H+, K +-ATPase) located in the luminal membrane of parietal cells (also called oxyntic cells) in the stomach. H+, K +-ATPase stimulation is controlled by three regulatory mechanisms: neurocrine, paracrine, and endocrine. There are three phases of gastric secretion: cephalic, gastric, and intestinal phases [1]. In addition, there is a basal or interdigestive phase where there is constant basal acid secretion in the absence of food and other stimuli [2].

The cephalic phase accounts for 20–30 % of total acid secretion in the stomach, in response to signals arising from sight, smell, and/or thoughts of food that activate the vagal pathway via the cerebral cortex and hypothalamus. In turn, vagal nerves stimulate the enteric nervous system, inducing parietal cells to secrete gastric acid, through release of pituitary adenylate cyclase-activating polypeptide (PACAP) at gastric enteric neurons and consequent stimulation of the PACAP receptor (PAC1) on the surface of gastric ECL (enterochromaffin-like) cells [3].

The gastric phase is activated by antral distension, protein content of food, and pH >4 and accounts for most of the gastric acid secretion (50 %). The intestinal phase is responsible for about 5 % of total gastric acid secretion, activated by intestinal gastrin and absorbed amino acids. All phases lead to increased circulating gastrin.

Gastrin is released by antral G cells, endocrine cells located in the gastric epithelium, pancreas, and duodenum. Although gastrin directly stimulates gastrin receptors in the basal membrane of parietal cells, its major role is indirect gastric acid secretion via gastrin-induced ECL cell histamine release; histamine stimulates parietal cell H2 receptors (see Figs. 21.1 and 21.2) [4].

### *Drug Class and Mechanism of Action: Antacids*

Antacids are inorganic, relatively insoluble weak bases that partially neutralize gastric hydrochloric acid, raising gastric pH [5]. Generally, large doses of antacids are needed to raise gastric pH significantly [6, 7]. Antacid potency is based on molar equivalency required to neutralize a known amount of acid. The acid neutralization capacity among different proprietary formulations of antacids varies with rate of dissolution, water solubility, and rate of gastric emptying [8, 9].

## *Indications for Antacids/Clinical Pearls*

1. Only nonparticulate antacids (e.g., sodium citrate, magnesium trisilicate) should be used when antacids are indicated for selected patients for reducing the risk of pulmonary aspiration [10]. Bicitra® contains 100 g of sodium citrate/1,000 ml, i.e., 0.34 M [11]. Because antacids have a short duration of action, they must be administered every 1–2 h to achieve and maintain pH >3.5–4.0 [12, 13].
2. Antacids bind bile acids, stimulate epithelial regeneration, and increase the production of prostaglandins, which in turn have a protective effect on gastric

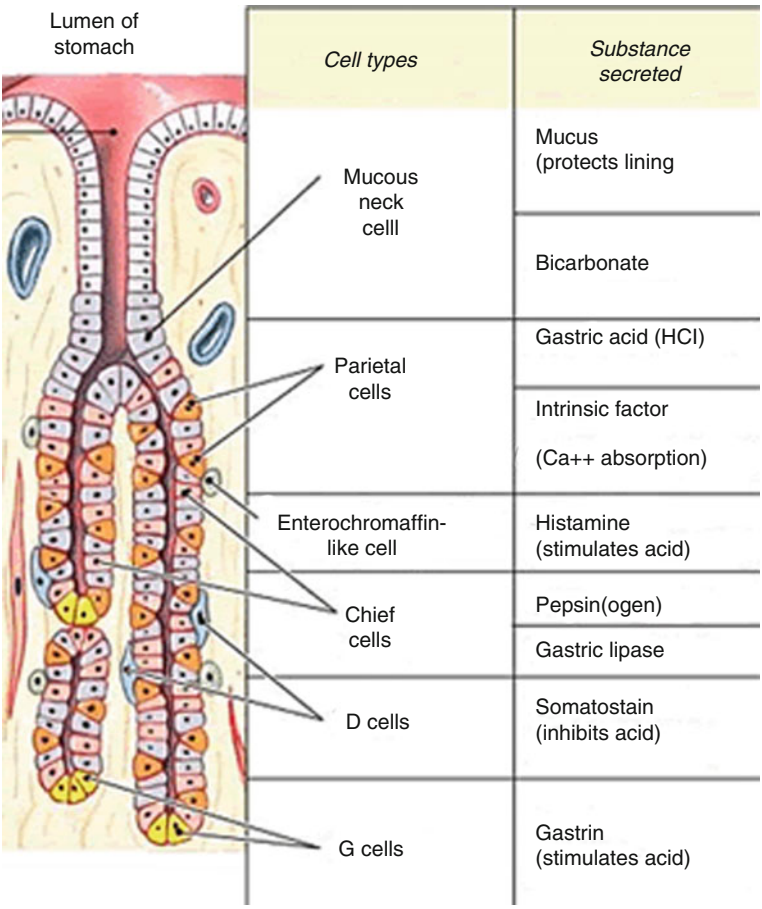



**Fig. 21.1** Normally, acid secretion is mediated by a negative-feedback mechanism that is activated by lowered gastric pH; this negative-feedback system is mediated by somatostatin, secretin, prostaglandins, and a variety of other hormones. Somatostatin is secreted by the D cells which are also endocrine cells of the gastric epithelium. (**a**) Stomach cell types and substance secreted. (**b**) (From Yeo [103], Townsend [104], Copyright © 2012 Saunders, An Imprint of Elsevier)

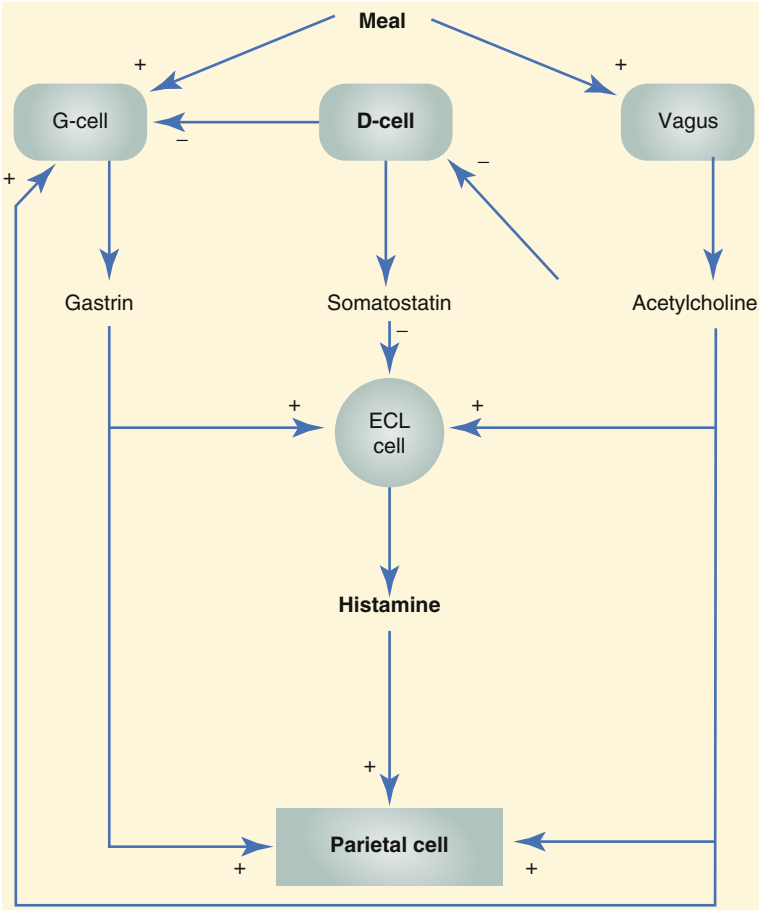



**Fig. 21.1** (continued)

mucosa [12]. Antacids can be used for temporary relief of symptoms of duodenal ulcers, gastric ulcers, stress gastritis, and GERD.

3. Sodium hydroxide and aluminum hydroxide have been used to decrease steatorrhea in patients with pancreatic insufficiency [14]. Calcium and magnesium salts worsen steatorrhea [14, 15].
4. Aluminum (which binds bile acids more tightly than magnesium) and magnesium salts bind to bile acids and are effective in reducing cholerrheic diarrhea [16].
5. Among the antacids, calcium and aluminum salts are thought to cause constipation. However, studies have shown no evidence for this [17, 18]. Magnesium salts tend to cause diarrhea [19]. The absorbable antacid sodium bicarbonate does not affect stool frequency. The side effects of antacids may be used to advantage in particular patients. If the patient has a tendency to constipate, then

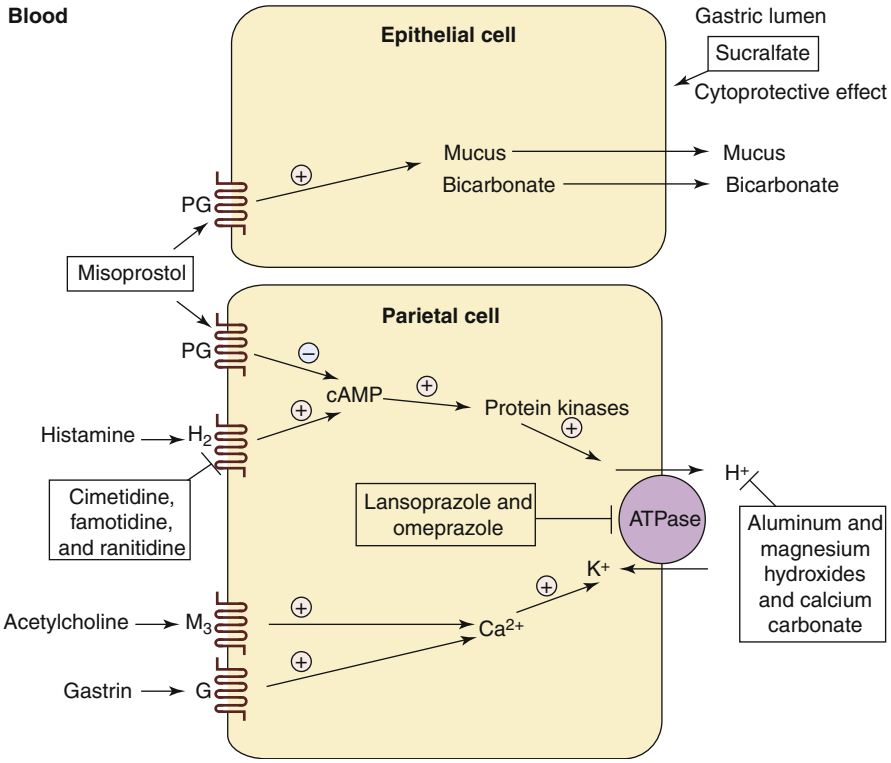



**Fig. 21.2** H+, K+-ATPase is irreversibly blocked by the proton pump inhibitors (PPIs). The effect of histamine is blocked by H2 receptor antagonists (cimetidine, famotidine, and ranitidine). Prostaglandins (e.g., misoprostol) inhibit gastric acid secretion and stimulate secretion of mucus and bicarbonate by epithelial cells. Sucralfate binds to proteins of the ulcer crater and exerts a cytoprotective effect, whereas antacids (salts of aluminum, calcium, or magnesium) neutralize acid in the gastric lumen (From Brenner [105], Copyright © 2012 Saunders, An Imprint of Elsevier)

a magnesium antacid may be the best choice. In a patient with a tendency to loose stools, calcium or aluminum antacids may be preferable [20].

## *Dosing Options for Antacids*

The dose for magnesium hydroxide and aluminum hydroxide is 600–1,200 mg three to four times daily. The dosage for calcium carbonate is 1–2 g daily, administered in 3–4 divided doses; the duration of action of antacids is very short and requires redosing. Sodium citrate 0.3 M has a pH of 8.4 and has a very unpleasant metallic taste. The nonparticulate antacid Bicitra® contains citric acid and sodium citrate with a pH of 5.2, lower than sodium citrate and so more palatable.

It is available in a 30 ml [3], 0.3 M solution and should be administered 15–30 min prior to induction of general anesthesia to prevent aspiration of gastric contents.

## *Drug Interactions of Antacids*

Generally, it is advisable to space other drugs from antacids by 1–2 h. Drug interactions involving antacids occur through three mechanisms: (1) antacid binding of another drug in the gastrointestinal tract, (2) antacid-induced changes in gastrointestinal pH, and (3) changes in the urinary pH [21–27].

## *Side Effects of Antacids/Black Box Warnings*

1. Side effects of aluminum antacids include constipation, belching, and flatulence; diarrhea is most common with magnesium-containing antacids [17–19].
2. Aluminum toxicity can occur in patients with impaired renal function with ingestion of aluminum-containing antacids [28]. Aluminum may accumulate in the brain producing acute aluminum neurotoxicity, manifested as rapidly progressive encephalopathy with confusion, seizures, myoclonus, and coma.

   Hypercalcemia can occur with prolonged ingestion of antacids, especially in patients with impaired renal function. Sodium-containing antacids used in excess may cause sodium overload in susceptible patients with congestive heart failure, ascites, and renal impairment. The milk–alkali syndrome, rarely observed currently, was originally reported as the triad of metabolic alkalosis, hypercalcemia, and renal insufficiency in patients with peptic ulcer disease who ingested large amounts of calcium and absorbable alkali [29].
3. Allergic reactions, including asthma and eosinophilic esophagitis, have been reported with the use of antacids [30].
4. Excessive use of gastric acid inhibitors including antacids increases the risk of intestinal infections [31].

## *Summary of Antacids*

Antacids are inorganic salts available over the counter, which increase gastric pH and help improve some gastrointestinal disorders over the short term, but should not be used on a long-term basis as they are not completely benign medications. Their use or misuse is associated with serious side effects relating to mineral metabolism and allergic reactions, and patients and clinicians should use them judiciously.

**Table 21.1** Prokinetic agents

| | |
|---|---|
| Cholinergic agonists | Bethanechol, neostigmine, acotiamide |
| Dopamine antagonists | Metoclopramide, domperidone, itopride |
| Macrolides, motilin receptor agonists/motilides, ghrelin receptor agonists | Erythromycin, mitemcinal |
| Substituted benzamides | Cisapride, mosapride, renzapride, prucalopride |
| 5-Hydroxytryptamine agonists/antagonists | Ondansetron, granisetron, tegaserod |
| Cholecystokinin receptor antagonists | Loxiglumide, dexloxiglumide |
| Gonadotropin-releasing hormone analogs | Leuprolide |
| Somatostatin analogs | Octreotide |
| Prostaglandins | Misoprostol, lubiprostone |
| Opioid receptor antagonists | Alvimopan, methylnaltrexone |

Not all drugs in this table are currently available clinically

# GI Prokinetics

## *Introduction*

Gastrointestinal prokinetic drugs augment gastrointestinal motility by increasing peristaltic contractile force and frequency in the small bowel, thus accelerating transit in the gastrointestinal tract. Prokinetic drugs provide symptomatic relief of abdominal bloating due to delayed gastric emptying, as seen with gastroparesis. These agents are also of value in promoting gastric emptying in patients undergoing anesthesia and surgery.

## *Drug Class and Mechanism of Action*

Gastrointestinal prokinetic drugs act on diverse receptors to stimulate motility in the gastrointestinal tract (Table 21.1).

### Cholinergic Agonists: Bethanechol, Neostigmine, and Acotiamide

Bethanechol, an ester derivative of choline, stimulates muscarinic M2-type receptors on the gastrointestinal smooth muscle cell. Owing to their nonspecific action and inconsistent evidence for effectiveness in motility disorders, their use has nearly disappeared with the availability of newer agents.

Neostigmine, a reversible acetylcholine esterase inhibitor, facilitates parasympathetic and enteric stimulation of colonic motility. Neostigmine may be effective in producing rapid colonic decompression in those who failed conservative therapy in acute colonic pseudo-obstruction or Ogilvie's syndrome [32–34].

Evidence for improvement of postoperative ileus is less clear [35]. The dose of neostigmine in one randomized controlled trial was 0.5 mg administered subcutaneously twice daily [36]. Common adverse events include bradycardia, increased bronchotracheal secretions, and abdominal cramps; cardiac arrest has been reported [37]. Cardiovascular monitoring is indicated when using neostigmine, and atropine or glycopyrrolate must be available. Contraindications include recent myocardial infarction, acidosis, systolic blood pressure <90 mmHg, pulse <60 beats/min, bronchospasm requiring medical treatment, and creatinine >3 mg/dL.

## Dopamine Antagonists: Metoclopramide, Domperidone, and Itopride

### Metoclopramide

Metoclopramide, a para-aminobenzoic acid derivative, is an antiemetic and a gastrointestinal prokinetic agent that stimulates gastrointestinal smooth muscle by multiple mechanisms. It is an antagonist at central and peripheral dopamine DA2 receptors, has direct and indirect effects on cholinergic receptors, and is a mixed 5-HT3 antagonist and 5-HT4 agonist [38–40]. Indications for metoclopramide include gastroesophageal reflux, although the drug does not promote endoscopic healing of esophagitis [38]. Metoclopramide accelerates gastric emptying and is approved for short-term treatment (≤12 weeks) of gastroesophageal reflux and diabetic gastroparesis (≤8 weeks) [38, 40–42]. Metoclopramide may shorten the duration of ileus, but there is little evidence of its efficacy in pseudo-obstruction [35].

Metoclopramide with or without H2 receptor blockers and antacids has been used to decrease the risk of pulmonary aspiration in patients with a full stomach, prior to the induction of general anesthesia. It has also shown to be useful as a prophylactic and a therapeutic antiemetic drug. The recommended dose of metoclopramide for most conditions is 10–15 mg orally before meals and at bedtime; the parenteral dose is 10 mg. Drug clearance is impaired in patients with cirrhosis and renal failure [43].

Metoclopramide may decrease the therapeutic effects of dopaminergic antiparkinsonian agents and increase the toxicity of antipsychotics, serotonergic agents, and tricyclic agents. Metoclopramide causes side effects in 10–20 % of patients, especially at higher doses and at the extremes of age. Mild side effects include mild anxiety, nervousness, and insomnia. More severe reactions include confusion, hallucinations, extrapyramidal symptoms and acute dystonic reactions [44], gynecomastia secondary to enhanced release of prolactin in adults [45], oculogyric crisis in children [46], neuroleptic malignant syndrome [47], and tardive dyskinesia [48]. Tardive dyskinesia (TD) is rarely reversible, and the FDA has required a black box warning associated with chronic use (>3 months) of metoclopramide. Advanced age, female gender, diabetes, renal failure, chronic alcohol intake, cirrhosis, tobacco use, schizophrenia, known organic CNS pathology, and concomitant

use of dopaminergic neuroleptics are risk factors [48]. The annual incidence of metoclopramide-induced TD dramatically increased after the withdrawal of cisapride from the US market in 2000 [49]. Metoclopramide should be stopped immediately if TD is suspected, and alternative treatments of the gastrointestinal symptoms should be used. As a preventive measure, it is better to avoid continuous metoclopramide use for longer than 12 weeks. Dopamine antagonists may facilitate release of norepinephrine. Because monoamine oxidase (MAO) inhibitors impair metabolism of endogenous norepinephrine, dopamine antagonists should not be given in conjunction with MAOs [50].

### Domperidone

Domperidone is an antiemetic and prokinetic agent that has peripheral dopamine DA2 receptor antagonist properties and unlike metoclopramide does not readily cross the blood–brain barrier. Thus, it is free from the troublesome central nervous system side effects associated with metoclopramide. Domperidone increases esophageal peristalsis and lower esophageal sphincter tone, increases gastric motility and peristalsis, facilitates gastric emptying, and decreases small bowel transit time. Domperidone is different from other prokinetic agents in that it has no cholinergic activity and its action is not inhibited by atropine [50, 51]. Currently, in the USA, domperidone requires an investigational new drug program request through the FDA.

### Erythromycin

Erythromycin, a macrolide antibiotic, was the first nonpeptide compound for which agonism at the motilin receptors and gastroprokinetic properties were demonstrated [52–54]. Motilin, a hormone released from endocrine cells in the duodenal mucosal layer, stimulates gastric and duodenal motility via action on G-protein-coupled receptors called motilin receptors, which are localized in smooth muscle cells and nerve endings [55, 56].

Erythromycin is available in oral and intravenous forms. Oral erythromycin may improve gastric emptying and symptoms for several weeks, but its chronic use has been associated with tachyphylaxis due to downregulation of the motilin receptors [57]. The current off-label prokinetic indications for intravenous erythromycin are acute exacerbation of diabetic gastroparesis, optimizing small bowel feeding tube placement and optimizing endoscopy visualization for acute UGI bleeding [56]. It is recommended that the prescribed intravenous infusion be slow, over at least 60 min per dose. Erythromycin must be prescribed with caution in patients with renal and/or hepatic impairment. Side effects/warnings for erythromycin include abdominal pain, nausea, vomiting at high doses by inducing spastic gut contractions, and the risk of sudden cardiac death by prolongation of the QT interval and torsade de pointes [58–61].

### Substituted Benzamides

Cisapride is a serotonin 5-HT4 agonist and 5-HT3 antagonist that stimulates the release of acetylcholine from postsynaptic neurons in the enteric nervous system. It was initially introduced as a prokinetic in the 1990s and later withdrawn from the market in 2000 following reports of serious cardiac events (QTc prolongation, torsade de pointes, and cardiac arrest). Its current use is through a limited access protocol requiring special authorization from the FDA.

### 5-HT Agonists/Antagonists

Ondansetron, granisetron, and other similar 5-HT agonists/antagonists have both prokinetic and antiemetic effects; their primary use is as an antiemetic and is discussed in detail in the antiemetic section of this book. Prokinetic effects of these agents are moderate.

### Somatostatin Analog: Octreotide

Octreotide is a synthetic analog of somatostatin with a longer duration of action. In low doses, it stimulates motility, primarily through the induction of migrating motor complexes (MMC) [62–64]. However, higher doses often are employed for its antisecretory effects, which may inhibit motility. Octreotide infusion increases LES pressure and esophageal body contraction [65, 66]. However, the net effect of octreotide on gastric emptying and intestinal transit remains controversial and may be dose related. Several studies have indicated that despite its MMC-stimulating effect, octreotide delays gastric emptying and intestinal transit. Octreotide has been shown to reduce the sensation of rectal distention through inhibition of visceral afferent pathways.

Indications for octreotide include severe dysmotility syndromes such as malignant intestinal pseudo-obstruction [63], bacterial overgrowth in scleroderma [65], and postoperative ileus [67].

The most common side effects include abdominal discomfort, diarrhea, biliary tract symptoms, impaired glucose tolerance, hypoglycemia (shortly after starting treatment), persistent hyperglycemia (during long-term treatment), gallstones (10–20 % of patients on long-term treatment), and pancreatitis (associated with gallstones).

### Prostaglandins

The role of prostaglandins in gastrointestinal motility is complex and difficult to interpret, and the effect depends on the type of prostaglandin, dose, and the muscle layer studied [68]. Misoprostol, a PGE1 analog, hastens postprandial intestinal motility and accelerates orocecal transit time [69]. The NSAIDs diclofenac

sodium and indomethacin do not appear to stimulate gastric motility in humans [70]. Lubiprostone, a bicyclic fatty acid derived from prostaglandin E1, activates the apical membrane of the chloride channel in the intestinal epithelium that stimulates intestinal fluid secretion, enhances and stimulates contraction in colonic as well as gastric muscles, and may act as a prokinetic agent [71, 72].

Lubiprostone is approved for the treatment of chronic idiopathic constipation and constipation predominant irritable bowel syndrome (IBS-C). Common side effects of lubiprostone include abdominal pain, nausea, vomiting, diarrhea, bloating, and, rarely, dyspnea [73].

#### Opioid Antagonists Used as Prokinetic Agents

Opiates regulate gastrointestinal motility through effects on the enteric nervous system by promoting an inhibitory effect on gastrointestinal motility [74]. Methylnaltrexone and alvimopan are two recently marketed peripherally acting mu-opioid receptor antagonists that do not readily cross the blood–brain barrier and used to treat opioid-induced bowel dysfunction and functional constipation [75]. Alvimopan is approved for short-term in-hospital treatment of postoperative ileus. The dose is 12 mg orally, taken up to 5 h preoperatively and twice daily postoperatively for up to 7 days (15 doses total). The efficacy and safety of these drugs for long-term use are not well understood [76]. These agents are contraindicated in patients with mechanical bowel obstruction. Methylnaltrexone is available as a subcutaneous formulation. The dose for an average adult patient is 12 mg (0.6 ml; 0.15 mg/kg) every other day. Side effects are similar to alvimopan.

## Proton Pump Inhibitors: PPIs

### *Introduction of PPIs*

Proton pump inhibitors (PPIs) are commonly prescribed medications for the treatment of several acid-related gastrointestinal disorders. As a class, PPIs are generally considered remarkably safe; however, there are increasing concerns about the consequences of long-term use, since numerous adverse effects have been associated with chronic therapy.

### *Drug Class and Mechanism of Action of PPIs*

PPIs cause pronounced and long-lasting gastric acid suppression by irreversible inhibition of the proton pump (gastric H+/K + adenosine triphosphatase) via covalent binding to cysteine residues. The amount of H+/K + adenosine triphosphatase

present in the parietal cell is maximum after a prolonged fast, and so PPIs are most effective when administered before the first meal of the day.

## *Indications of PPIs/Clinical Pearls*

Indications for the use of PPIs are peptic ulcer disease (PUD), *Helicobacter pylori*, chronic nonsteroidal anti-inflammatory drug (NSAID) use, Barrett esophagitis, erosive esophagitis, and Zollinger–Ellison syndrome.

1. *Peptic ulcer disease* (*PUD*): Clinical trials have consistently demonstrated that proton pump inhibitors are superior to standard doses of histamine2 receptor antagonists for GERD and PUD management [76]. Patients with bleeding peptic ulcers treated with PPIs have demonstrated decreases in the risk of rebleeding, the need for transfusions or surgery, and a reduction in length of hospital stay, although no evidence has been noted for an effect on mortality [77].
2. *H. pylori* is associated with gastric and duodenal ulcers. *H. pylori* must be eradicated to facilitate healing and to decrease the risk of ulcer recurrence; PPIs are used for this purpose as part of triple therapy (PPI + two antibiotics) or quadruple therapy (PPI + bismuth + two antibiotics).
3. *NSAID long-term use*: According to the American College of Gastroenterology 2009 guidelines, patients taking long-term daily NSAIDs should be considered for preventive therapy with daily PPIs [78].
4. *Barrett esophagitis*: PPIs are more effective than H2 antagonists in Barrett esophagitis in providing symptomatic relief, preventing stricture formation, and promoting effective and faster healing of esophagitis and esophageal ulcers. It is unknown whether high-dose PPI therapy helps reduce the risk of esophageal malignancy, and further studies are warranted to address this issue [79].
5. *Erosive esophagitis*: PPIs provide healing of erosive esophagitis and relief of symptoms in patients with GERD.
6. *Zollinger–Ellison syndrome*: PPI therapy is remarkably effective in controlling gastric acid hypersecretion, thereby reducing morbidity and potential mortality of this syndrome [80].

## *PPIs' Dosing Options, Pharmacodynamics, and Pharmacokinetics*

PPIs differ in bioavailability, half-lives, metabolism, pKa, routes of excretion, peak plasma levels, and drug interactions (Table 21.2). Lansoprazole and pantoprazole have the greatest bioavailability and achieve the highest plasma levels. All PPIs have short half-lives, typically 1–2 h. All PPIs are metabolized via hepatic P450 enzymes, with CYP2C19 and CYP3A4 playing dominant and minor roles, respectively. Rabeprazole is the most potent PPI, metabolized mostly by CYP3A4,

**Table 21.2** Comparison of proton pump inhibitors

| Agent | Bioavailability % | T1/2; hours | Metabolism | pKa | Elimination | Dose; mg |
|---|---|---|---|---|---|---|
| Omeprazole | 45 | 0.5–1 | Hepatic | 4 | Renal | 20–40 |
| Lansoprazole | 85 | 1.5 | Hepatic | 4 | Renal/fecal | 15–30 |
| Rabeprazole | 52 | 1–2 | Hepatic | 5 | Renal | 20 |
| Pantoprazole | 77 | 1 | Hepatic | 3.9 | Renal | 20–40 |
| Esomeprazole | 89 | 1–1.4 | Hepatic | 4.0 | Renal | 20–40 |

and has less drug interactions, whereas omeprazole is less potent, preferentially metabolized by CYP2C19, and has more drug interactions. Pantoprazole and esomeprazole are available as intravenous formulation in the USA. None of the PPIs require dose adjustment for hepatic or renal insufficiency. Several studies have shown that no PPI is superior to another. All patients should be maintained on the lowest possible dose that provides symptomatic relief.

## *Side Effects of PPIs/Black Box Warnings*

PPIs are associated with primary adverse events, typically in the order of 1–5 %, and include nausea, diarrhea, headache, constipation, and rash. Secondary adverse effects associated with long-term use of PPIs include osteoporosis, increased risk of infections, formation of gastric polyps or carcinoid, interstitial nephritis, and altered metabolism of other medications. Other concerns associated with long-term PPI use are hypomagnesemia and reduced vitamin B12 and iron absorption.

1. *Osteoporosis*: Long-term PPI use causing profound acid suppression impairs calcium, folate, riboflavin, and vitamin B12 absorption, which in turn influences homocysteine levels, collagen cross-linking, with decreased bone mineral density and bone strength. Hypergastrinemia resulting from profound acid suppression also causes release of parathyroid hormone from hyperplastic parathyroid glands and contributes to increased bone resorption and decreased metabolic bone density [81]. PPIs may also act on the vacuolar proton pump located on osteoclasts [82], causing an acidic environment, protease activation, dissolution of bone matrix, decreased bone mineral density, osteoporosis, and increased risk of fractures. According to a recent review, the levels of risk reported have generally been low [83].
2. *Increased risk of infections*: Gastric acidity acts as a major defense mechanism of the body by sterilizing the contents entering the digestive tract, preventing bacterial colonization of the upper gastrointestinal tract, and influencing the normal intestinal flora composition. PPIs increase gastric pH, resulting in more bacterial overgrowth in the stomach and deconjugation of bile acids [84]. Chronic PPI use may also impair leukocyte function by increasing basal cytosolic calcium

concentrations in neutrophils and decreasing intracellular and extracellular reactive oxygen species impairing bactericidal activity [85]. PPIs may be associated with an increased risk of community-acquired pneumonia, an effect not demonstrated with long-term therapy [86, 87]. There is evidence that PPI therapy may increase the risk of enteric infection, especially with *Clostridium difficile*, *Salmonella*, and *Campylobacter* species [88].

3. *Formation of gastric polyps or carcinoid*: PPI use leads to diminished acid secretion, diminished somatostatin release, enterochromaffin-like cell hyperplasia, and increased G-cell release of gastrin. Gastric cells may become hyperplastic and form fundic gland polyps in 7–10 % of patients taking PPIs for more than 12 months. Such polyps are benign and typically regress with the discontinuation of PPI. Hypergastrinemia has raised the concern of long-term PPI use possibly predisposing some patients to the development of neuroendocrine tumors. Gastric carcinoids have been observed in rodents given PPIs, but the relationship of PPIs to carcinoid in humans is unclear.
4. *Intersitial nephritis*: PPI-related acute interstitial nephritis is a rare, idiosyncratic inflammatory reaction of the renal interstitium and tubules that may lead to renal failure. There is insufficient evidence to establish a causal relationship between the two, but there may be an association [89].
5. *Hypomagnesemia*: Several case series report severe hypomagnesemia, refractory to supplementation associated with long-term PPI use [90–96]. The cause of hypomagnesemia remains poorly understood but does not involve increased urinary excretion of magnesium [95, 97]. PPI use can inhibit active magnesium transport in the intestine. The FDA issued a warning in March 2011 that prescription PPIs may cause low serum magnesium levels if taken for prolonged periods of time and suggested that prescribers consider checking a baseline serum magnesium level in patients about to start PPI therapy, as well as periodic monitoring during therapy [100].

## *PPI Drug Interactions*

### PPIs and Clopidogrel

Concerns have been raised about a possible interaction between PPIs, especially omeprazole and clopidogrel that could decrease the antiplatelet efficacy of clopidogrel and increase the risk of cardiovascular (CV) events [99–101]. The FDA and the European Medicines Agency (EMA) have issued warnings regarding the concomitant use of these medications. PPIs can attenuate metabolism of clopidogrel to its active metabolite by inhibiting various hepatic CYP450 enzymes, especially CYP2C19. Concomitant use of a PPI with clopidogrel reduces clopidogrel active metabolite generation and subsequent platelet inhibition. Observational studies provide a mixed clinical picture of this drug interaction. The only randomized trial [102] studying the PPI–clopidogrel interaction did not demonstrate any difference

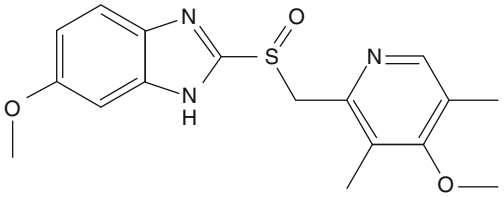
in cardiovascular outcomes, but did show a reduction in gastrointestinal bleeding with the use of PPIs.

Several other drugs interact with PPIs and may increase or decrease the therapeutic effects of each other, and so the product information should be thoroughly read before PPI administration.

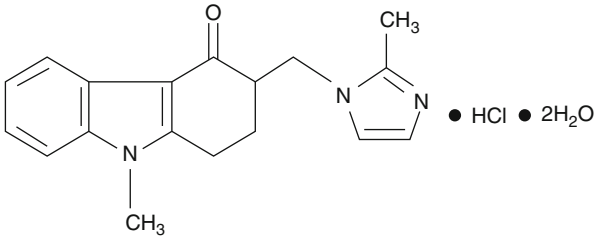
### *Summary of PPIs*

The indications for PPI use include peptic ulcer disease, erosive and Barrett esophagitis, gastritis, and chronic NSAID use. Risks associated with PPI use include increased risk of fractures, infections, drug interactions, and low magnesium. PPIs should be used judiciously, and their long-term use reevaluated periodically.

## Chemical Structures




**Chemical Structure 21.1** Omeprazole




**Chemical Structure 21.2** Ondansetron

## References

1. Wolfe MM, Soll AH. The physiology of gastric acid secretion. N Engl J Med. 1988;319:1707–15.
2. Feldman M. Gastric secretion: normal and abnormal. In: Feldman M, Scharschmidt BF, Sleisenger MH, editors. Gastrointestinal and liver disease. Philadelphia: Saunders; 1998. p. 587–603.
3. Zeng N, Athmann C, Kang T, et al. PACAP type I receptor activation regulates ECL cells and gastric acid secretion. J Clin Invest. 1999;104:1383–91.
4. Dubois A. Control of gastric acid secretion. In: Brandt LJ, editor. Clinical practice of gastroenterology. Philadelphia: Current Medicine; 1999. p. 180–8.

5. Fordtran JS, Collyns JAH. Antacid pharmacology in duodenal ulcer. Effect of antacids on postcibal gastric acidity and peptic activity. N Engl J Med. 1966;274:92–7.
6. AHFS drug information. In: Mc Evoy GK, editor. Bethesda: American Society of Health-System Pharmacists; 1998. p. 2374–9.
7. Littman A, Pine BH. Antacid and anticholinergic drugs. Ann Intern Med. 1975;82:544–15.
8. Mirrissey JF, Barreras RF. Antacid therapy. N Engl J Med. 1974;290:550–4.
9. Harvey SC. Gastric antacids and digestants. In: Goodman LS, Gillian A, Gillian AG, editors. The pharmacological basis of therapeutics. 6th ed. New York: Macmillan; 1980. p. 988–1001.
10. American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Anesthesiology. 2011;114(3):495–511.
11. James CF, Gibbs CP. Nonparticulate antacids. Anesth Analg. 1982;61(9):801.
12. Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. Chest. 2001;119:1222–41.
13. Tryba M, Cook D. Current guidelines on stress ulcer prophylaxis. Drugs. 1997;54:581–96.
14. Graham DY, Patterson DJ. Double-blind comparison of liquid antacid and placebo in the treatment of symptomatic reflux esophagitic. Dig Dis Sci. 1983;28:559–63.
15. Regan PT, Malagelada JR, DiMagno EP, et al. Comparative effects of antacids, cimetidine and enteric coating on the therapeutic response to oral enzymes in severe pancreatic insufficiency. N Engl J Med. 1977;297:854–8.
16. Cousar GD, Gadacz TR. Comparison of antacids on the binding of bile salts. Arch Surg. 1984;119:1018–20.
17. Clemens JD, Feinstein AR. Calcium carbonate and constipation: a historical review of medical mythopoeia. Gastroenterology. 1977;72:957–61.
18. Saunders D, Sillery J, Chapman R. Effect of calcium carbonate and aluminum hydroxide on human intestinal function. Dig Dis Sci. 1988;33:409–13.
19. Strom M. Antacid side-effects on bowel habits. Scand J Gastroenterol. 1982;75(Suppl):54–5.
20. Maton PN, Burton ME. Antacids revisited, a review of their clinical pharmacology and recommended therapeutic use. Drugs. 1999;57(6):855–70.
21. Tatro DS. Drug interaction facts. Facts and comparisons. 3rd ed. St Louis; 1992.
22. Welling PG. Interactions affecting drug absorption. Clin Pharmacokinet. 1984;9:404–34.
23. Hurwitz A. Antacid therapy and drug kinetics. Clin Pharmacokinet. 1977;2:269–80.
24. Hansten PD, Horn JR, Koda-Kimble MA, et al., editors. Principles of antacid interaction. In: Drug interaction & updates quarterly. Vancouver: Applied Therapeutics, Inc.; 1993. p 69–72.
25. Hansten PD, Horn JR, Koda-Kimble MA, et al., editors. Antacid drug interactions. In: Drug interaction & updates quarterly. Vancouver: Applied Therapeutics, Inc.; 1993. p 137–51.
26. Gugler AH. Effects of antacids on the clinical pharmacokinetics of drugs: an update. Clin Pharmacokinet. 1990;18:210–9.
27. Lomaestro BM, Bailie GR. Absorption interactions with fluoroquinolones. Drug Saf. 1995;12:314–33.
28. Herzog P, Holtermüller KH. Antacid therapy—changes in mineral metabolism. Scand J Gastroenterol Suppl. 1982;75:56–62. [0085-5928] Herzog.
29. McMillan DE, Freeman RB. The milk alkali syndrome: a study of the acute disorder with comments on the development of the chronic condition. Medicine. 1965;44:485–501.
30. Merwat SN, Spechler SJ. Might the use of acid-suppressive medications predispose to the development of eosinophilic esophagitis? Am J Gastroenterol. 2009;104:1897–902.
31. Canani RB, Terrin G. Gastric acidity inhibitors and the risk of intestinal infections. Curr Opin Gastroenterol. 2010;26:31–5.
32. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med. 1999;341:137.
33. Trevisani GT, Hyman NH, Church JM. Neostigmine: safe and effective treatment for acute colonic pseudo-obstruction. Dis Colon Rectum. 2000;43:599.

34. Loftus CG, Harewood GC, Baron TH. Assessment of predictors of response to neostigmine for acute colonic pseudo-obstruction. Am J Gastroenterol. 2002;97:3118–22.
35. Holte K, Kehlet H. Postoperative ileus: progress towards effective management. Drugs. 2002;62(18):2603–15.
36. Hallerbäck B, Ander S, Glise H. Effect of combined blockade of beta-adrenoceptors and acetylcholinesterase in the treatment of postoperative ileus after cholecystectomy. Scand J Gastroenterol. 1987;22(4):420–4.
37. Maher L, Young PJ. Cardiac arrest complicating neostigmine use for bowel opening in a critically ill patient. Crit Care Resusc. 2011;13(3):192–3.
38. Ramirez B, Richter JE. Review article: promotility drugs in the treatment of gastroesophageal reflux disease. Aliment Pharmacol Ther. 1993;7:5–20.
39. Albibi R, McCallum RW. Metoclopramide: pharmacology and clinical application. Ann Intern Med. 1983;98:86–95.
40. McCallum RW. Clinical pharmacology forum: motility agents and the gastrointestinal tract. Am J Med Sci. 1996;312:19–26.
41. Shaffer D, Butterfield M, Pamer C, Mackey AC. Tardive dyskinesia risks and metoclopramide use before and after U.S. market withdrawal of cisapride. J Am Pharm Assoc. 2004;44:661–5.
42. McCallum RW, Ricci DA, Rakatansky H, et al. A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. Diabetes Care. 1983;6:463–7.
43. Bateman DN. Clinical pharmacokinetics of metoclopramide. Clin Pharmacokinet. 1983;8(6):523–9.
44. Walker M, Samii A. Chronic severe dystonia after single exposure to antiemetics. Am J Emerg Med. 2006;24:125–7.
45. McCallum RW, Sowers JR, Hershman JM, Sturdevant RAL. Metoclopramide stimulates prolactin secretion in man. J Clin Endocrinol Metab. 1976;42:1148–52.
46. Edwards M, Koo MW, Tse RK. Oculogyric crisis after metoclopramide therapy. Optom Vis Sci. 1989;66:179–80.
47. Nonino F, Campomori A. Neuroleptic malignant syndrome associated with metoclopramide. Ann Pharmacother. 1999;33(5):644–5.
48. Rao AS, Camilleri M. Review article: metoclopramide and tardive dyskinesia. Aliment Pharmacol Ther. 2010;31:11–9.
49. Kenney C, Hunter C, Davidson A, Jankovic J. Metoclopramide, an increasingly recognized cause of tardive dyskinesia. J Clin Pharmacol. 2008;48:379–84.
50. Reddymasu SC M.D., Soykan I M.D., McCallum RW M.D. Domperidone: review of pharmacology and clinical applications in gastroenterology. Am J Gastroenterol. 2007;102:2036–45.
51. Reynolds JC. Prokinetic agents: a key in the future of gastroenterology. Gastroenterol Clin N Am. 1989;18:437–57.
52. Weber Jr FH, Richards RD, McCallum RW. Erythromycin: a motilin agonist and gastro intestinal prokinetic agent. Am J Gastroenterol. 1993;88(4):485–90.
53. Moayyedi P, Soo S, Deeks J, Delaney B, Innes M, Forman D. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database Syst Rev. 2006;18:CD001960.
54. Karamanolis G, Tack J. Promotility medications—now and in the future. Dig Dis. 2006;24:297–307.
55. Itoh Z. Motilin and clinical application. Peptides. 1997;18:593–608.
56. Galligan JJ, Vanner S. Basic and clinical pharmacology of new motility promoting agents. Neurogastroenterol Motil. 2005;17:643–53.
57. Camilleri M, et al. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2013;108:18–37.
58. De Ponti F, Poluzzi E, Montanaro N. QT-interval prolongation by non-cardiac drugs: lessons to be learned from recent experience. Eur J Clin Pharmacol. 2000;56:1–18.
59. Drici MD, Knollmann BC, Wang WX, Woosley RL. Cardiac actions of erythromycin: influence of female sex. JAMA. 1998;280:1774–6.
60. Shaffer D, Singer S, Korvick J, Honig P. Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. Clin Infect Dis. 2002;35:197–200.

61. Berthet S, Charpiat B, Mabrut JY. Erythromycin as a prokinetic agent: risk factors. J Visceral Surg. 2010;147:e13–8.
62. Thompson JS M.D., Quigley EMM M.D. Prokinetic agents in the surgical patient. Am J Surg (Omaha, NE). 1999;177:508–14.
63. Mercadante S, Porzio G. Octreotide for malignant bowel obstruction: twenty years after. Crit Rev Oncol Hematol. 2012;83(3):388–92.
64. Owyang C. Octreotide in gastrointestinal motility disorders. Gut. 1994;35 Suppl 3:S11–4.
65. Soudah HC, Hasler WL, Owyang C. Effect of octreotide on intestinal motility and bacterial overgrowth in scleroderma. NEJM. 1991;325:1461–7.
66. Gunshefski LA, Rifley WJ, Slattery DW, et al. Somatostatin stimulation of the normal esophagus. Am J Surg. 1992;163:59–62.
67. Cullen JJ, Eagon C, Dozois EJ, Kelly KA. Treatment of acute postoperative ileus with octreotide. Am J Surg. 1993;165:113–20.
68. Waller SL. Prostaglandins and the gastrointestinal tract. Gut. 1973;14(5):402–17.
69. Soffer EE, Launspack J. Effect of misoprostol on postprandial intestinal motility and orocecal transit time in humans. Dig Dis Sci. 1993;18:851–5.
70. Bassotti G, Bucaneve G, Furno P, et al. Double blind, placebo controlled study on the effects of diclofenac sodium and indomethacin on postprandial gastric motility in man. Dig Dis Sci. 1998;42:1172–6.
71. Kapoor S. Lubiprostone: clinical applications beyond constipation. World J Gastroenterol. 2009;15(9):1147–7.
72. Bassil AK, Borman RA, Jarvie EM, McArthur-Wilson RJ, Thangiah R, Sung EZ, Lee K, Sanger GJ. Activation of prostaglandin EP receptors by lubiprostone in rat and human stomach and colon. Br J Pharmacol. 2008;154:126–35.
73. Chamberlain SM, Rao SS. Safety evaluation of lubiprostone in the treatment of constipation and irritable bowel syndrome. Expert Opin Drug Saf. 2012;11(5):841–50.
74. Wood JD, Galligan JJ. Function of opioids in the enteric nervous system. Neurogastroenterol Motil. 2004;16 Suppl 2:17–28.
75. Neyens R, Jackson KC. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. J Pain Palliat Care Pharmacother. 2007;21:27–33.
76. Lambert R. Review article: current practice and future perspectives in the management of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 1997;11:651–62.
77. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor therapy for peptic ulcer bleeding: cochrane collaboration meta-analysis of randomized controlled trials. Mayo Clin Proc. 2007;82:286–96.
78. Lanza FL, Chan FK, Quigley EM, Practice parameters committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009;104:728–38.
79. Chubineh S M.D., Birk J M.D. Proton pump inhibitors: the good, the bad, and the unwanted. South Med J. 2012;105(11):613–8.
80. Wilcox CM, Hirschowitz BI. Treatment strategies for Zollinger–Ellison syndrome. Expert Opin Pharmacother. 2009;10(7):1145–57.
81. Neena S. Abraham, proton pump inhibitors: potential adverse effects. Curr Opin Gastroenterol. 2012;28:615–20.
82. Jefferies KC, Cipriano DJ, Forgac M. Function, structure and regulation of the vacuolar (H+)-ATPases. Arch Biochem Biophys. 2008;476:33–42.
83. Chen J, Yuan YC, Leontiadis GI, Howden CW. Recent safety concerns with proton pump inhibitors. J Clin Gastroenterol. 2012;46:93–114.
84. Theisen J, Nehra D, Citron D, et al. Suppression of gastric acid secretion in patients with gastro esophageal reflux disease results in gastric bacterial overgrowth and deconjugation of bile acids. J Gastrointest Surg. 2000;4:50–4.
85. Zedtwitz-Liebenstein K, Wenisch C, Patruta S, et al. Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. Crit Care Med. 2002;30:1118–22.

86. Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Ann Intern Med. 2008;149(6):391–8.
87. Giuliano C, Wilhelm SM, Kale-Pradhan PB. Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. Expert Rev Clin Pharmacol. 2012;5(3):337–44.
88. Moayyedi P, Leontiadis GI. The risks of PPI therapy. Nat Rev Gastroenterol Hepatol. 2012;9:132–9.
89. Sierra F, Suarez M, Rey M, Vela MF. Systematic review: proton pump inhibitor associated acute interstitial nephritis. Aliment Pharmacol Ther. 2007;26:545–53.
90. Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. N Eng J Med. 2006;355:1834–6.
91. Broeren MA, Geerdink EA, Vader HL, van den Wall Bake AW. Hypomagnesemia induced by several proton-pump inhibitors. Ann Intern Med. 2009;151:755–6.
92. Dornebal J, Bijlsma R, Brouer RML. An unrecognized potential side effect of proton pump inhibitors: hypomagnesaemia. Ned Tidjschr Geenesk. 2009;153:A711.
93. Kuipers MT, Thang HD, Arntzenius AB. Hypomagnesaemia due to use of proton pump inhibitors – a review. Neth J Med. 2009;67:169–72.
94. Hoorn EJ, van der Hoek J, de Man RA, et al. A case series of proton pump inhibitor-induced hypomagnesemia. Am J Kidney Dis. 2010;56:112–6.
95. Regolisti G, Cabassi A, Parenti E, et al. Severe hypomagnesemia during long-term treatment with a proton pump inhibitor. Am J Kidney Dis. 2010;56:168–74.
96. Mackay JD, Bladon PT. Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series. QJM. 2010;103:387–95.
97. Shabajee N, Lamb EJ, Sturgess I, et al. Omeprazole and refractory hypomagnesaemia. BMJ. 2008;337:a42.
98. Administration US FDA. FDA Drug Safety Communication: low magnesium levels can be associated with long-term use of Proton Pump Inhibitor drugs (PPIs). 2011. http://www.fda.gov/Drugs/DrugSafety/ucm245011.htm.
99. Gilard M, Arnaud B, Cornily JC, et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. J Am Coll Cardiol. 2008;51:256–60.
100. Pezalla E, Day D, Pulliadath I. Initial assessment of clinical impact of a drug interaction between clopidogrel and proton pump inhibitors. J Am Coll Cardiol. 2008;52:1038–9.
101. Juurlink DN, Gomes T, Ko DT, et al. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ. 2009;180:713–8.
102. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, Shook TL, Lapuerta P, Goldsmith MA, Laine L, Scirica BM, Murphy SA, Cannon CP, COGENT Investigators. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med. 2010;363(20):1909–17.
103. Yeo C. Shackelford's surgery of the alimentary tract. 6th ed. Philadelphia: WB Saunders; 2007.
104. Townsend CM. Sabiston textbook of surgery. 19th ed. Philadelphia: Saunders Elsevier; 2012.
105. Brenner GM. Pharmacology. 4th ed. Philadelphia: Saunders Elsevier; 2012.