Gastric disorders: modifications of gastric content, antacids and drugs influencing gastric secretions and motility

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Abstract

Gastric disorders have clinical implications in both anaesthesia and critical care medicine. Aspiration of acidic gastric contents in the perioperative setting is linked to pneumonitis and later development of pneumonia. Pharmacological strategies to minimize this risk include histamine-2 receptor antagonists, sucralfate, proton pump inhibitors and sodium citrate. Use of gastric acid-suppressing therapy is widespread in critical care. The aim is to reduce the incidence of stress-related mucosal bleeding. Intestinal failure is common in critical illness. Medications that decrease gastric motility and contribute to ileus, include opioid analgesics, catecholamines and α_2-adrenoceptor antagonists. Current pharmacological strategies for increasing gastric motility include the use of metoclopramide and erythromycin either alone or in combination. Limited efficacy has been demonstrated with these medications. A range of further medications, with different drug targets, are being investigated as alternatives. These include motilin agonists, peripherally acting opioid receptor antagonists, cholecystokinin antagonists, 5-HT_4 antagonists and cholinesterase inhibitors.

Keywords Antihistamines; prokinetics; proton pump inhibitors

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Learning objectives

After reading this article you, should be able to:

- discuss the role of drugs used to control acid secretion in intensive care and anaesthesia
- discuss the role of prokinetics in managing ileus
- name two examples of each kind of drug

Introduction

Gastric disorders are of major importance in both anaesthesia and intensive care medicine. One of the primary responsibilities of the anaesthetist is to protect the airway. Many factors increase the risk of gastric reflux. These include emergency surgery, difficult intubations, inadequate depth of anaesthesia, lithotomy position, gastrointestinal disorders, depressed conscious level, increased severity of illness and obesity. Functional dyspepsia is defined as the presence of symptoms originating in the gastroduodenal region (early satiation, postprandial fullness, epigastric pain or burning), in the absence of any organic, systemic or metabolic disease that could explain the symptoms. Gastroparesis is diagnosed in case of severely delayed gastric emptying in the absence of mechanical obstruction. It can be caused by a variety of gastrointestinal and systemic causes including diabetic, idiopathic and postsurgical. Both conditions are highly prevalent and increase the risk of gastric reflux and pulmonary aspiration during anaesthesia. Factors that predispose to pneumonia following aspiration are a gastric content with pH less than 2.5, reduced lower or upper oesophageal sphincter tone, poor swallow coordination and a depression of protective airway reflexes. Drug administration is amongst the methods used to reduce this risk. An understanding of the pharmacology of these drugs is therefore important for the anaesthetist.

Acute intestinal failure (including ileus) is a common problem in the postoperative period and in critically ill patients. Management includes pharmacological methods, with newer targeted agents being developed and evaluated. Constipation and diarrhoea are common in the intensive care unit (ICU) and may be iatrogenic. Stress-related mucosal bleeding is also a recognized complication of treatment for critical illness. An understanding of the drugs used to treat these conditions is essential for the intensivist.

Basic physiology

An understanding of the basic physiology involved aids in the understanding of the pharmacological action of the drugs described in this review. By convention, the stomach is separated into proximal and distal sections. The proximal region functions as a reservoir. It accommodates to the ingesta and delivers it to the distal stomach. The distal stomach controls peristaltic and non-peristaltic trans-pyloric flow. The pylorus opens to allow flow into the duodenum, which has nutrient receptors that release peptides that alter motility patterns and control gastric emptying. The control of human gastroduodenal sensorimotor function is only partially understood. Serotonin (5-HT) is particularly difficult to study due to the large number of receptors expressed in the gastrointestinal (GI) tract and the lack of specific antagonists. Motilin receptors are found predominantly in the gastric antrum and proximal duodenum. When stimulated they induce isolated contractions of smooth muscle. Other drug targets include dopamine, opiate, ghrelin, cholecystokinin (CCK) and cholinergic receptors.

Gastric parietal cells are the acid-producing cells of the stomach. Gastric acid secretion occurs in response to a variety of hormonal, paracrine and neurocrine inputs. Gastrin is the primary hormonal stimulant; histamine and acetylcholine are paracrine stimulants. Inhibitors of secretion include somatastatin (from gastric D cells) and the hormones CCK, secretin,

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Neutralization reaction of hydrochloric acid by sodium citrate

$Na_3C_6H_5O_7 + 3HCl \rightarrow 3NaCl + H_3C_6H_5O_7$

Figure 1

neurotensin and glucagon-like peptide. Histamine-2 receptors are thought to be the primary stimulus for acid secretion and act via cyclic adenosine monophosphate (cAMP) to activate the H^+K^+-ATPase. Gastrin binds to CCK-2 receptors leading to an increase in intracellular calcium and activation of the H^+K^+-ATPase.

Modification of gastric acid

Although there is a lack of evidence to support the use of pharmacological agents to reduce the risk of aspiration during anaesthesia, practice in some centres stills includes the administration of sodium citrate prior to caesarean section. This should be administered intragastrically at 1–2 hourly intervals and the effect varies with the gastric pH. Potential adverse effects include aluminium toxicity (if the antacid contains aluminium), electrolyte disturbance, diarrhoea and feeding-tube blockage. Figure 1 shows the chemical reaction between sodium citrate and stomach acid.

Gastric antisecretory therapies for the prevention of stress-related mucosal bleeding or damage (SRMB/SRMD) are routinely administered in the intensive care. Evidence supports their prescription to substantially reduce the incidence of clinically important bleeding events secondary to stress ulceration. The incidence of clinically important bleeding events (defined as macroscopic bleeding resulting in haemodynamic instability or the need for red blood cell transfusion) is approximately 3.5% of ICU patients ventilated for 48 hours or more. Other risk factors for mucosal bleeding in ICU patients include coagulopathy, neurosurgery, shock, respiratory failure, sepsis, polytrauma, tetraplegia, severe burns and multi-organ failure. These conditions combined with use of vasoconstrictors lead to splanchnic hypoperfusion, which contributes to acid back-diffusion and reduction in bicarbonate secretion, mucosal blood flow and gastrointestinal motility.

The most commonly used group of agents is the histamine-2 receptor antagonists (H_2RA). Other commonly used agents include proton pump inhibitors (PPI) and sucralfate. Their sites of action are summarized in Figure 2.

Sucralfate must be administered intragastrically and therefore requires the presence of a nasogastric tube in an intubated patient. Because it is a basic aluminium salt of sucrose octasulphate there are concerns over its effectiveness after administration of feed or acid-suppressing agents. It exerts its topical effect by binding to the surface proteins of the ulcer site. Reported adverse events include constipation, feeding-tube occlusion, bezoars, aluminium accumulation (particularly in renal impairment) and hypophosphataemia. Drug binding with sucralfate can reduce the effects of warfarin, phenytoin, digoxin, quinidine and the fluoroquinolones. A significant amount of nursing time is involved in the administration of sucralfate. A 2010 meta-analysis comparing sucralfate and H_2RA showed a non-significant trend towards decreased SRMB with H_2RAs, but increased gastric colonization and ventilator-associated pneumonia. H_2RAs have replaced sucralfate as the agent of choice to reduce SRMB in most UK centres.

H_2RAs significantly reduce the risk of SRMB compared with placebo. However they demonstrate tachyphylaxis during prolonged intravenous (IV) dosing, meaning pH is not reliably maintained above 4. Tolerance can develop in 48 hours. This is thought to be due to increasing competitive inhibition from endogenous histamine. H_2RAs do not inhibit vagally induced acid secretion. This lessens their efficacy in neurosurgical or head trauma patients. Side effects include headaches, dizziness, diarrhoea, nausea, constipation and rarely thrombocytopenia,

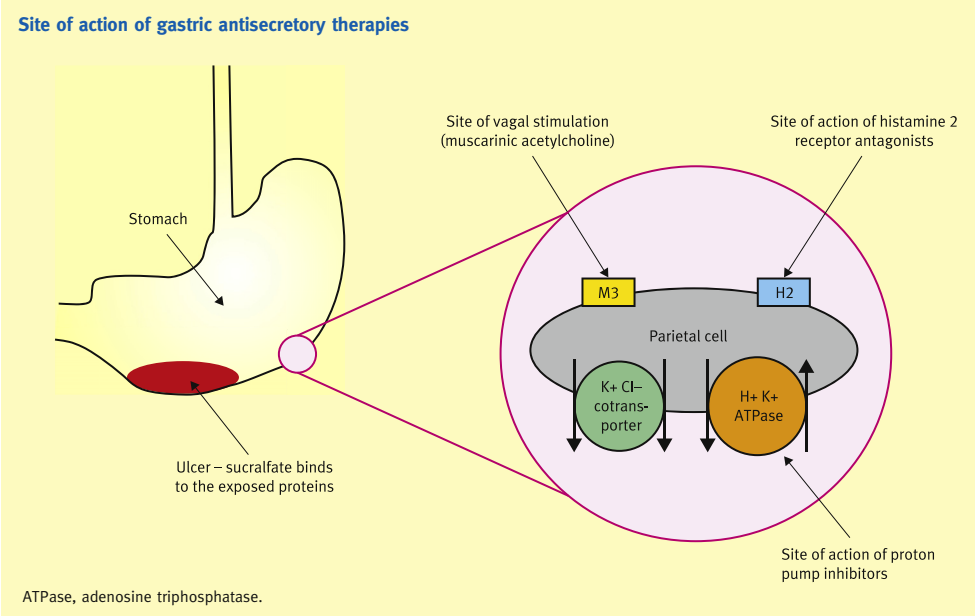

Figure 2

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