

Series: from physiology to the clinic

Gastric secretion and proton pump inhibitors

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Summary

The principal function of the stomach is secretory and digestion thanks to the capacity of store, process and empties of food to the bowel. The acid secretion needs of complex neural functions, endocrines, autocrine y paracrine that act like a hole. The use of proton pump inhibitors is every day more frequent and over the counter, and requires the knowledge of the normal gastric physiology and the mechanism of inhibition for a rational use in clinical practice.

Key words

Physiology, gastric secretion, protons pump inhibitors.

The stomach is the muscular reservoir which food enters after it is swallowed. It allows ingestion of food faster than it can be digested and absorbed. At low rates of secretion, during in the base state of fasting, gastric juice is essentially a solution of NaCl with a small quantity of H⁺ and K⁺ (in other words, a plasma ultrafiltrate). During the ingestion of food the concentration of H⁺ substantially increases while the Na⁺ concentration decreases in equivalent proportions. Up to 2 liters of HCl is produced per day per day. pH can be as low as 1.0, or 2.5 million of times normal blood pH (1).

Components of gastric juice

Gastric secretions are considered to be the first significant phase of digestion since salivary enzymes have limited capacity. By exposing food to a low Ph environment and putting it into contact with the pepsin, gastric secretions allow disassociation of collagen fibers and denaturalization (proteolysis) of proteins which are present in the cellular matrix. This is associated with the mixing action of the stomach. The whole process allows the fractioning of the food into smaller particles.

At the same time gastric juice contributes to sterilizing the food. It is also critical for the absorption of Vitamin B12 (cobalamin) and the absorption of iron (2).

Components of gastric juice

- Hcl
- Parietal Cell
- Hydrolysis of Proteins
- Sterilization

- Intrinsic Factor
- Parietal Cell
- Absorption of Vitamin B12

- Pepsinogen
- Main Cell
- Proteolysis

- HCO₃ (Mucus)
- Epithelial Cell
- Gastroprotection

- Trefoil Factor
 - Epithelial Cell
 - Gastroprotection
-
- Histamine
 - Enterochromaffin cell
 - Acid Secretion Regulation
-
- Gastrin
 - G Cell
 - Acid Secretion Regulation
-
- Somatostatin
-
- D Cell
 - Acid Secretion Regulation

Pepsin is secreted through exocytosis from the main cells as an inactive precursor. Pepsinogen fragments autocatalytically as a result of the low pH resulting in active pepsinogen. Its principal function is to digest ingested proteins, especially amino acids. Increases of pH above 4 inactivate it. This is the minimum pH level which must be reached to cure acid-peptic disorders.

Gastrin is produced by G cells located in the antrum. Gastrin is the greater regulator of the secretion of acid in response to ingestion of food into the stomach, especially ingestion of protein. Gastrin stimulates production of acid by two mechanisms. It directly stimulates the parietal cells through release of histamine and through direct trophic action. Acid is activated by stimulation of cholecystokinin receptors CCK2 present in the parietal cell and in the enterochromaffin cell cells (3).

Histamine is the most important paracrine stimulator of gastric acid. It is located in the gastric mast cells (which do not have physiologic importance for gastric secretion) and most importantly in the enterochromaffin cell cells located in the oxyntic mucosa in direct proximity with the parietal cells. Gastrin is the main stimuli for the release of histamine and in turn it is the main intermediary of the secretion of acid mediated by H₂ receptors.

Somatostatin released from the D cells, which are dispersed throughout the gastric mucosa, is a potent inhibitor of gastric secretions. It exerts its effect by inhibiting the release of histamine. Its secretion increases in the presence of acid and is directly proportional to levels of gastrin.

The intrinsic factor is a 45 kilodalton (kDa) protein which is relatively specialized and resistant to acid. It is produced by exocytosis in the parietal cell and attaches itself to Vitamin B₁₂, allowing the vitamins later absorption in the small intestine.

The gastric mucus is spread into the glandular pits through the superficial epithelial cells of the oxyntic mucosa. Two types of gastric mucus are recognized: visible and soluble.

The visible mucus is composed of mucins (glycoprotein) that form a gelatinous coating with a high concentration of bicarbonate that protects the gastric epithelium from acid and pepsin. The mucin molecules intertwine themselves by means of disulfide bridges and, together with the oligosaccharides of the mucin, confer a highly viscous consistency that expands easily upon hydration.

Soluble mucus also contains mucins but does not have disulfide bonds making it less viscous which allows it to lubricate the alimentary bolus and facilitate its mixture.

The presence of small peptides which are known as the Intestinal Trefoil Factor (ITF) or Trefoil Factor 3 (TFF3), increases the stability of the mucosa. ITF is expressed by goblet cells in the epithelium in intimate association with the production of mucins (5). Its documented functions include: inhibition of apoptosis, promotion of cellular migration and repair in response of daily injuries, inhibition of inflammation, and increased functioning of the mucus barrier through mechanisms which are still not physiologically explained.

CONTROL OF GASTRIC SECRETIONS

Regulation of gastric secretion is a real paradigm of gastrointestinal functioning as a whole. It depends of an intricate equilibrium of chemical transmitters which simultaneously stimulate and inhibit different actions. Those functions are carried out through neural, endocrine, autocrine and paracrine pathways (4).

Classically, gastric secretion is divided into three phases: cephalic, gastric and intestinal.

Cephalic Phase: Even before food is ingested the stomach is prepared to receive an alimentary bolus by way of cerebral centers that respond to visual stimuli, smells, tastes and even thoughts about food. Enteric neurons, activated by way of the vagus nerve, release acetylcholine, which acts directly on the parietal cells and the enterochromaffin cell cells, and gastrin GRP which is a peptide which, when it is released in the proximity of G cells, causes them to release gastrin. Gastrin in turn activates parietal and main cells through the blood.

Gastric Phase: This phase is quantitatively more important. The presence of food in the gastric lumen stimulates chemical and mechanical receptors. This is how the presence of amino acids and short chain peptides can stimulate the release of gastrin from the G cells. Gastric distension causes a reflexive neural pathway to trigger receptors begin to release acetylcholine or GRP.

Intestinal Phase: This phase contributes only a small portion the secretion of gastric acid due to the presence of food in the intestine. Its mediators are still controversial, among them are the neuropeptide related to the calcitonin gene related peptide (CGRP). It acts on the D cells to induce the release of somatostatin. This phase is not completely understood, but it is thought that it could serve to sterilize any gastric leftovers and prepare them for the next meal.

ACID SECRETION

The human stomach possesses approximately 1 trillion parietal cells that secrete 0.16 M HCl. The parietal cells' functions are highly specialized. They have perhaps the most "expensive" energy process of any type of cell, plus they have the best ionic transport system in the entire human organism. Moreover, they possess receptors for histamine, gastrin and acetylcholine in its basolateral membrane.

In their base state they contain specialized membrane structures known as tubulovesicles. They also have pits in their apical membranes which are like microscopic blind alleys which are known as secretory canaliculi.

When the cell is stimulated, the canaliculus fuses with the apical membrane. In turn the tubulovesicle fuses with the canaliculus, which results in an increase of as much as 10 times the base state area of glandular apical membrane in contact with the gastric lumen. When they are in repose, the tubulovesicles store most of the molecules of H⁺ K⁺ ATPase (proton-pumps). When the cell activates, those pumps move themselves to the gastric lumen where they exchange H⁺ for K⁺.

Concomitant with the activation of the Cl⁻ proton-pump, channels that are attached to the eliminated H⁺ are activated and discharge HCO₃⁻ ions through the basolateral membrane of the parietal cell. This maintains intracellular pH at equilibrium.

PROTON-PUMP INHIBITORS (PPIs)

Since their introduction at the end of the 1980s, PPIs have dramatically improved handling of acid peptic disorders (5). They are weak bases (protonable pyridines) that are partially absorbable since passage through the acid medium of the stomach fragments their molecules. The basic structures of available PPIs are similar basic with substitutions of chemical radicals accounting for their differences. The average half life of these PPIs is 90 minutes (14). Omeprazole and esomeprazole have acid dissociation constants (pK_as) of 4.0 while lansoprazole and pantoprazole have a pK_a of 3.9 and rabeprazole's pK_a is 5.0. This characteristic allows them to accumulate selectively in the secretory canaliculi of the parietal cells.

It is precisely this canalicular acid medium that allows the conversion of PPIs to their cationic active forms which are thiophilic sulfonamides. These form covalent bonds with cysteine 813 residues from the alpha subunit of H⁺ K⁺ ATPase (which are also responsible for transporting H⁺) (14). In this way PPIs irreversibly inhibit acid production. Pantoprazole has the additional capacity of forming covalent bonds with cysteine 822 residues. Whether or not this represents any significant clinical difference has not been verified.

Not all pumps are active at any given moment. Consequently a single PPI dose inhibits only 70% of active pumps (14). The ability to secrete acid again is restored with the generation of new proton pumps in tubulovesicles when these are converted to active pumps on the surface of the canaliculi. Due to their slowness to achieve optimal acid inhibition, clinical use of two daily PPI doses during the first three days is useful for achieving quicker inhibition (16). Similarly, occasional PPI doses do not provide adequate acid inhibition nor do they produce a satisfactory clinical response (unlike H₂ antagonists which have quicker action) (15).

On the other hand, acid secretion in healthy subjects does not totally recover until between 48 and 96 hours after administration of PPIs has been suspended. PPIs are the most powerful inhibitors of acid production that exist. They are more effective when the parietal cell is stimulated to produce postprandial acid since the amount of H⁺ K⁺ ATPase present in the parietal cell is greater after prolonged fasting. For this reason they should be administered before the first meal of the day.

Unlike in the case of H₂ antagonists, tolerance to PPIs has not been observed. Possibly this is because they block the common final route of acid secretion: the H⁺ K⁺ ATPase pump. Upon suspension of medication, rebound acid hypersecretion occurs just as frequently with H₂ antagonists as it does with PPIs. It seems to occur more frequently in patients who are negative for H. Pylori. The mechanisms of rebound hypersecretion could be hypertrophy and hypersecretion from the parietal cells and/or hypergastrinemia of the enterochromaffin cells. This may be the reason the rate of gastric fundic gland polyps has increased in the last 20 years (17). Hypergastrinemia has also been associated with a possible increase in the probability of dysplasia and adenocarcinoma in patients who have Barrett's Esophagus. Prospective studies are still needed to confirm whether or not hypergastrinemia increases the risk of neoplasias in these patients (18).

PPIs are metabolized by isoenzymes of cytochrome P450, most importantly CYP2C19 (10, 14). Homozygotic mutations in the CYP2C19 gene can be found in 5% of Caucasians and in 15% of Asians. They allow for higher

plasmatic levels of PPI (slow metabolizers). This translates into longer periods of time during which acid is inhibited, and into higher rates of *H. pylori* eradication. However, when other medications that are also metabolized by cytochrome P 450 (e.g. Warfarin or clopidrogel) are being concomitantly administered, problems maintaining therapeutic levels of both medications may arise when saturations of isoenzymes are at the same or higher levels. Pantoprazole has the lowest potential for being metabolized by P450 cytochrome, making it the PPI with the smallest theoretical risk of medicinal interaction (Although in practical terms, the aforementioned interaction is considered to be clinically irrelevant).

PPIs all have similar chemical structures and mechanisms of action, but with differences in their pKas, bioavailability and plasmatic levels. Differences in clinical efficacy among PPIs are small. At the same time treatment cost differences are not yet clear, and pharmacologically equivalent doses for different PPIs have not yet been established. Both of these factors make comparisons even harder. There have been reports of healing higher for esophagitis with esomeprazole in some studies, but these studies were small and related specifically to esophagitis grades C and D (14).

Follow-up studies of intragastric pH show that daily doses divided between administration before breakfast and before dinner is the most effective way to optimize control of gastric pH (8). Even so, 45% of healthy people taking esomeprazole in two daily doses present escape phenomenon or nocturnal acid rebound (defined as a Ph drop below 4.0 for at least one continuous hour) (6-9). During episodes of dropping pH, reflux can develop in 15% of patients with gastroesophageal reflux disorder, in 50% of patients with Barrett's esophagus and in up to 70% of patients with scleroderma (8, 10, 14). Nocturnal use of H2 antagonists for handling nocturnal escapes were initially considered to be a solution to this phenomenon (11). However, because their regular use generates tachyphylaxis, only 21% to 30% of these patients obtain sustained control of acid suppression (12). In spite of these discouraging numbers some authors consider that they can be useful parts of current clinical practice. If tolerance to H2 antagonists is suspected, then their intermittent use, or use on demand, may have clinical utility (13).

PPIs have generally been considered as very safe medications. Nevertheless, in recent years there have been reports of possible associations with high numbers of enteric infections, higher impact of *Clostridium difficile* infections, increases in hip fractures, greater risk of pneumonia acquired in the community, and absorption deficits for Ca+, vitamin B12, and iron.

It has been suggested that suitable absorption of ingested calcium requires an acidic gastric environment and a

slightly acidic environment in the proximal duodenum. Altered calcium absorption could lead to a state of secondary hyperparathyroidism in response to diminished ionic calcium levels. High levels of parathormone would activate compensatory mechanisms, one of which is osteoclastic bone resorption. In time this can lead to diminution of bone mass and increased risk of fractures. If production of gastric acid is necessary for ionization of Ca and its subsequent absorption, theoretically we should expect that the chronic use of PPIs will increase the risk of fractures. Nevertheless, there are no well designed studies that measure PPIs impact on the absorption of Ca+. Similarly, existing studies of increased risk of fractures do not allow us to recommend suspension of prolonged treatment in terms of dosage and suitable indications. Well-designed prospective studies are required in order to measure the effect of PPIs on the metabolism and absorption of Ca+ (19, 22).

Chronic ingestion of PPIs has also been associated with an increase in the incidence of pneumonia acquired in the community, although to date causality has not been verified. In clinical practice, risk-benefits should be evaluated for chronic use in patients with high risk of pneumonia (Older patients with chronic obstructive pulmonary disease (COPD) who chronically take immunosuppressants or corticoids and who require frequent antibiotic use) (20, 21). Generally PPI overuse is worrisome because of its possible adverse events. The consensus for their use indicates that they should be used in the appropriate doses during the required time while we await prospective studies that will allow us to explain whether or not PPIs play a role in these events (13).

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