Acid Inhibition and Gastroesophageal Reflux Disease

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THE PROBLEM

Malfunction of the lower esophageal sphincter results in acid reflux into the esophagus. Reflux is mostly episodic so that the esophagus is not often presented with a continuous acid load. Prediction of esophageal disease related to reflux takes into account the pH of the refluxate and the duration of reflux. Expulsion of the refluxate back into the stomach shortens the time of exposure. The volume of reflux is also an important parameter for estimation of the acid load to the esophageal epithelium. It is the magnitude of this acid load that determines the presence or absence of pathology or symptoms. Intravesophageal pH monitoring provides an approximate measure of the acid load to the lower esophagus [2, 3].

The human esophageal epithelium is a multi-layered, stratified squamous epithelium. Afferent nerves are present, reaching into the superficial layers of the mucosa. With incompetence of the lower esophageal sphincter (LES)b, acid reflux results with pain and damage to the epithelium depending on the pH of the refluxate. Rather than being protected by a continuous tight junction, this epithelium has largely regional cell-to-cell contact via desmosomes but, being multi-layered, provides a winding path for proton diffusion into the epithelium. It is nevertheless significantly more acid sensitive than the gastric epithelium that is provided with "tight" tight junctions.

The threshold of acidity for damage and pain may be different. A higher acidity is likely needed for damage to the epithelial cells compared to the acidity required for stimulation of the pain fibers. This is probably because the epithelial cells have acid recovery mechanisms (such as Na/H or anion exchange) mostly absent in the pain fibers. Dependent on the location of the pain fibers and the access thereof to H+, different individuals will have different sensitivities to luminal acidity. These thoughts raise the question as to the therapeutic aims of acid control, elevation of mean diurnal pH for healing of erosions or prevention of acidic excursions for symptom relief or both.

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bAbbreviations: LES, lower esophageal sphincter; PPI, proton pump inhibitor.
ESOPHAGEAL HANDLING OF ACID

Given the absence of continuous tight junctions, the lower esophageal epithelium is an inviting target for acid back diffusion. Mucus is an aqueous gel and is unlikely to provide a significant barrier to acid back diffusion.

Resistance to acid may, therefore, depend more on the ability of the esophageal epithelium to neutralize an acid load than on restriction of entry of acid. Neutralization of acid will occur at the surface due to net HCO₃⁻ secretion and in the paracellular pathway since the epithelial cells can produce the buffer or absorb H⁺. However, once damage has occurred, the paracellular pathway is shorter or more open and the lesion consequently more sensitive to acid than the normal epithelium.

The measured average net flux of bicarbonate is about 78 µmol/30 min/10 cm in the human esophagus [1]. It appears to be subject to regulation by muscarinic receptors, responding to the vagal stimulation of acid secretion by the stomach. It is possible to approximate the pH of unbuffered refluxate that can be neutralized by esophageal surface secretion. If buffering is present, such as that due to amino acids or weak acids such as citrate, the acid load will be greater in the buffering range of gastric contents and not reflect only pH.

With reflux or unbuffered gastric contents at a pH of 4.0, there is a load of acid equivalent to 100 nmol/ml. If 10 ml of gastric contents at that pH is refluxed each min for 30 min and spreads over a length of 10 cm, 30 µmol of acid is presented to the esophagus. This is within the average neutralizing ability of the secreted HCO₃⁻. Reflux at pH 4.0 should, therefore, be largely neutralized at or close to the esophageal surface.

At pH of 3.0, there is 10-fold more acid, and 300 µmol of acid is presented to the lower esophagus, with 10 ml refluxing each min. This is beyond the capacity of net HCO₃⁻ secretion to neutralize the HCl. Acidification of intercellular spaces is likely, which may result in pain in some individuals. Epithelial cell pH may remain within viable limits give adequate Na/H or Cl/HCO₃⁻ exchange.

ESOPHAGEAL HANDLING OF PEPSIN

Gastric contents contain pepsin in addition to acid. Proteolytic activity of pepsin requires a pH below 3.0, and probably there is adequate neutralization of intercellular pH if the refluxate does not fall much below 3.0. At a refluxate of pH 2.0, since the esophageal surface cannot neutralize this acid load, peptic activity may begin to contribute to esophageal damage. Peptic activity is less likely to contribute directly to pain.

RATIONALE FOR TREATMENT

Treatment of reflux esophagitis can be accomplished by improving the response or structure of the LES or by effective inhibition of acid secretion. Currently available compounds targeted to the LES are relatively nonselective compounds and have lower efficacy than acid inhibition. Ideally, control of GERD, in terms of both healing and symptom relief, would not allow gastric pH to fall much below 4.0 at any time.

The most effective means of control of intragastric pH is the use of PPIs. PPIs only inhibit active gastric acid pumps, and only about 80 percent of the pumps are active during the plasma dwell time (60 to 90 min) of the drugs that are given 30 min after breakfast. The half-life of recovery of the pumps is about 24 hr, due primarily to de novo biosynthesis of the pump (t½ = 50 hr [4]) and perhaps also to reversal of the disulfide bond linking PPI to the pump. On once-a-day treatment, the inhibition of maximal acid output is about 70 percent [5]. Steady-state inhibition is found on about the third day on once-a-day treat-
ment dosing since previously resting pumps have to be recruited to respond to the drug. Improvement in effect of PPIs is achieved by divided doses, not by increasing the single dose. On twice-a-day treatment, inhibition of maximal acid output rises to 80 percent and steady-state is achieved on day two.

Meta-analysis of the degree of acid inhibition required for optimization of healing rates for erosive esophagitis that has shown that elevation of mean diurnal intra-gastric pH to at least 4.0 is required for about 18 hr per day [6]. This result may reflect the calculated ability of the epithelium and its cells to handle acid reflux. This seems to be achieved in most patients on once-a-day PPI therapy. If eradication of Helicobacter pylori blunts the effect of PPIs on intra-gastric acidity, as has recently been suggested [7], twice-a-day PPI therapy may be required to reach optimal healing pH.

Thus, inhibition to pH below 4.0 is sufficient to optimize healing but is often inadequate for complete symptom control, since intra-gastric acidity may increase to pH below 2.0, especially towards the end of digestion of a meal. Short periods of high acidity, which may not result in epithelial damage, may be sufficient to stimulate esophageal nerves, and the meta-analysis only addresses diurnal pH, not periods of high acidity.

Rapid symptom control may require more frequent dosing for the first three days until steady-state inhibition is reached or reformulation of the PPIs.

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