ADVANCES IN UPPER GI DISORDERS

Current Developments in the Management of Upper GI Disorders

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Potassium-Competitive Acid Blockers and Hypergastrinemia

Carmelo Scarpignato, MD, DSc, PharmD, MPH
Professor of Medicine & Clinical Pharmacology
United Campus of Malta, Msida, Malta
Honorary Clinical Professor, Faculty of Medicine
Chinese University of Hong Kong
Adjunct Professor of Clinical Pharmacology
University of Parma, Parma, Italy

G&H What is known about the effects of potassium-competitive acid blockers on gastrin levels?

CS Potassium-competitive acid blockers (P-CABs), like other antisecretory drugs (ie, proton pump inhibitors [PPIs] and histamine-2 receptor antagonists), inhibit gastric acid secretion and raise intragastric pH. The rise in plasma gastrin—often considered as a side effect—is, in fact, a direct and proportional consequence of effective acid inhibition: the greater the intragastric pH elevation, the greater the increase in basal and postprandial plasma gastrin concentrations.

G&H Which mechanisms are responsible for the rise in gastrin levels in patients taking a PPI or a P-CAB?

CS Hypergastrinemia represents a predictable physiologic feedback response to acid suppression. In the stomach, acid stimulates antral D cells to release somatostatin, which inhibits gastrin release from G cells. Any drug that reduces intragastric acidity disrupts this inhibitory loop, leading to increased gastrin (as well as pepsinogen I) secretion (Figure). Gastrin then attempts to restore acidity by stimulating enterochromaffin-like (ECL) cells and, indirectly (via ECL cells and histamine), parietal cell secretion. When the proton pump is pharmacologically blocked by whatever mechanism, this compensatory loop remains active, sustaining elevated gastrin levels. With long-term therapy, this can lead to functional upregulation of gastrin production and hyperplasia of G cells, ECL cells, and parietal cells—changes that are fully reversible upon drug discontinuation.

G&H Is there a difference among particular P-CABs regarding their tendency to promote hypergastrinemia?

CS As a class, P-CABs induce faster and more pronounced hypergastrinemia than PPIs, owing to their rapid onset and more complete and longer-lasting acid suppression. Pharmacokinetic and pharmacodynamic distinctions among individual agents are beginning to emerge. At clinically approved doses, vonoprazan (Voquezna, Phathom Pharmaceuticals) produces the greatest gastrin elevation (fasting levels typically increase 5- to 6-fold). Tegoprazan (BLI5100, Sebela Pharmaceuticals), which is less potent, with slightly shorter duration and lower pH-holding capacity, induces moderate to high (2- to 3-fold) increases in gastrin levels, a pattern also observed with fexuprazan (Fexuclue, Daewoong Pharmaceutical). Data for other P-CABs remain limited.

G&H Are there any potential complications of hypergastrinemia?

CS Chronic hypergastrinemia can produce several physiologic and morphologic changes. In humans, these are usually mild, benign, and reversible. Prolonged acid suppression commonly leads to ECL cell hyperplasia—initially simple, potentially progressing to linear or micronodular forms when gastrin levels are very high—and to elevations in chromogranin A (CgA). Gastrin's trophic effects may also induce parietal cell hypertrophy/hyperplasia and oxyntic gland elongation. These changes regress after stopping therapy. Gastric neuroendocrine tumors (NETs), although theoretically possible after very long-term, high-dose acid suppression, are exceedingly

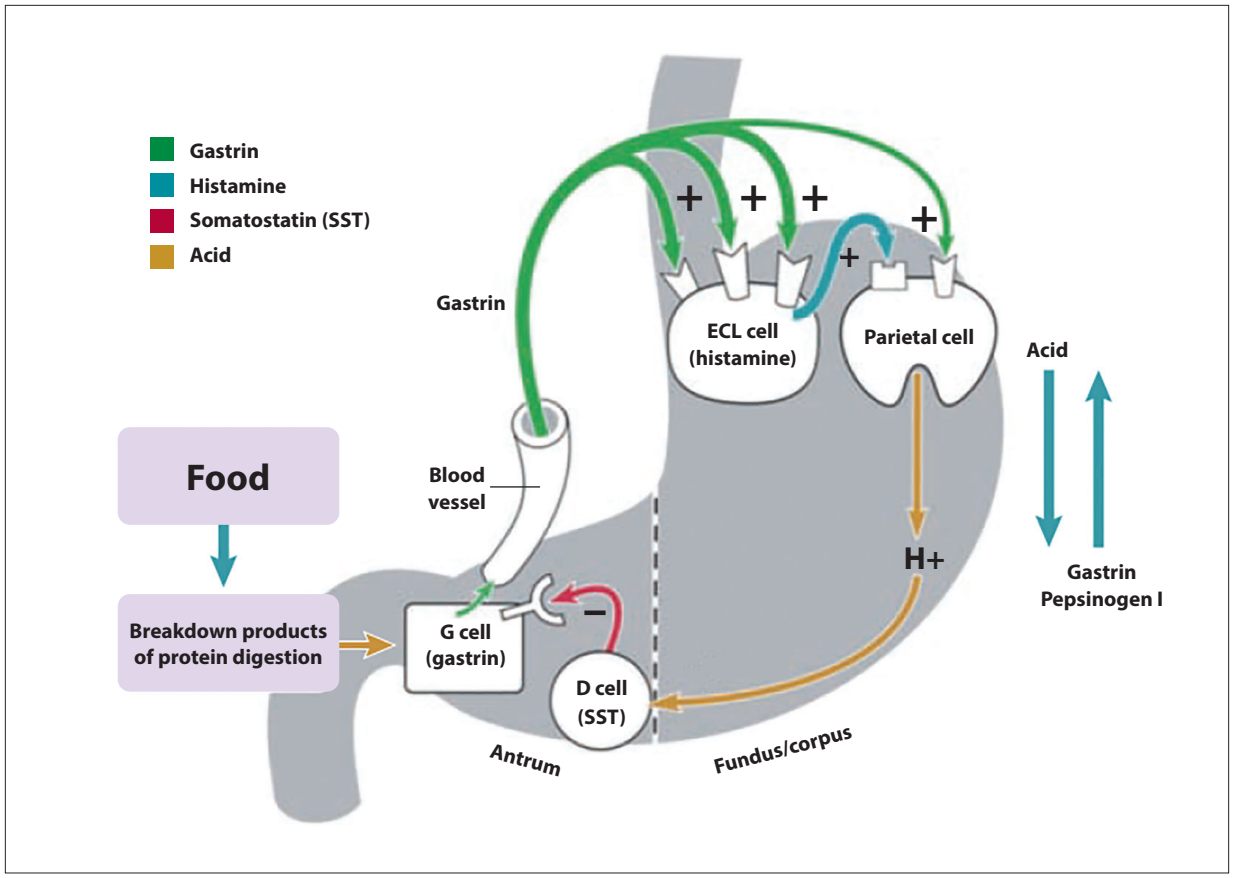

Figure. Endogenous mediators involved in the physiologic control of gastric acid secretion. Gastrin, released in response to products of protein digestion, reaches parietal cells and ECL cells via the bloodstream, stimulating acid secretion—thus lowering intragastric pH—both through histamine release and through binding to cholecystokinin-2 (gastrin) receptors on parietal cells. As a consequence of the acid–gastrin feedback mechanism, reduction in acid secretion induced by antisecretory drugs triggers an increase in circulating gastrin levels. Pepsinogen I, secreted by chief cells, normally diffuses into the gastric lumen. However, when acid secretion is inhibited, its concentrations become sufficiently elevated to allow back-diffusion into the systemic circulation, thereby serving as an additional marker of the functional state of the stomach.

ECL, enterochromaffin-like.

rare. In contrast, fundic gland polyps are relatively common but benign and typically regress after discontinuation of therapy.

G&H Are there any predictors of the development of extreme hypergastrinemia in patients taking a P-CAB?

CS Yes. Higher daily doses and long treatment duration predict proportionally greater gastrin elevations. *Helicobacter pylori* infection enhances gastrin responses to acid suppression and, over long periods, gastritis will extend to the corpus (promoting atrophy) as a consequence of the proximal migration of the microorganism; *H pylori* eradication has therefore been recommended prior to long-term therapy. Very high gastrin levels occur more readily in patients with baseline mucosal inflammation or impaired acid secretion. The proposed association between chronic antisecretory therapy post–*H pylori* eradication and gastric cancer remains unproven.

G&H Would monitoring of gastrin levels in patients taking P-CABs be appropriate? If so, how often?

CS Routine fasting gastrin measurement is not recommended because hypergastrinemia is an expected, reversible physiologic effect of acid suppression. No guideline currently suggests routine gastrin testing during P-CAB therapy. Most patients stabilize at moderate elevations (typically 200-500 pg/mL) without clinical implications. Targeted monitoring of gastrin (preferably gastrin-17 ±

CgA) is reasonable in selected high-risk scenarios—such as autoimmune gastritis, known ECL cell hyperplasia, familial predisposition to gastric NETs, or suspected gastrin-mediated pathology.

G&H Is there a specific gastrin level that you would consider concerning enough to discontinue a P-CAB?

CS No universally accepted cutoff exists. However, fasting gastrin values higher than 1000 pg/mL (or >5- to 10-fold baseline) generally warrant closer evaluation. In such cases, clinicians may consider dose reduction, discontinuation, or diagnostic reassessment (eg, endoscopy with biopsies or imaging). Ultimately, management decisions should integrate the patient's symptoms, underlying conditions, and risk profile rather than rely solely on an isolated gastrin threshold.

More than 3 decades of experience with potent acid suppression (and associated hypergastrinemia) show an excellent safety profile for the vast majority of patients.

G&H Is P-CAB–related hypergastrinemia pharmacologically inevitable? Are there any potential interventions to mitigate it?

CS Yes, P-CAB–associated hypergastrinemia is pharmacologically inevitable because it reflects the extent of the antisecretory effect. It can be attenuated by using the lowest effective dose for the shortest necessary duration, eradicating *H pylori* before long-term treatment, and avoiding drug-drug interactions that elevate P-CAB exposure and deepen acid suppression, with consequent gastrin rise.

G&H How would you address concerns about P-CAB–related hypergastrinemia?

CS I would emphasize that hypergastrinemia is a predictable physiologic response, mirroring the antisecretory activity, rather than an adverse effect. More than 3 decades of experience with potent acid suppression (and associated hypergastrinemia) show an excellent safety profile for the vast majority of patients. Clinicians should apply appropriate prescribing principles: confirm clinical indications, use the minimal effective dose, and periodically reassess the need for long-term therapy. Awareness of rare but theoretical risks is important, but these should not deter appropriate use.

G&H What other research is needed in this area?

CS Standardization of gastrin assay protocols and clear definition of clinically meaningful cutoffs of concern are needed. As P-CABs are relatively new in Western practice, long-term real-world safety data are essential. Randomized trials comparing continuous vs step-down P-CAB therapy—particularly in gastroesophageal reflux disease—should evaluate symptom control, mucosal healing, and gastrin response to assess whether similar efficacy could be achieved with lower P-CAB exposure.

Disclosures

Professor Scarpignato is an advisory board member of Alfasigma, Cosmo Pharmaceuticals, Dicofarm Group, and Phathom Pharmaceuticals.

Suggested Reading

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