Long-term Effects of Histamine Receptor Blockade on Nocturnal Gastric Acid Breakthrough

Proton pump inhibitors (PPIs) are extremely effective in suppressing gastric acid secretion and are emerging as the therapy of choice in many patients with peptic ulcer disease, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome. However, it has been shown that gastric acid secretion often continues at therapeutic PPI doses especially at night, a phenomenon termed nocturnal acid breakthrough (NAB). The clinical consequence of NAB is that some patients may continue to experience symptoms at night and develop medically “refractory GERD.” For these patients, histamine type 2 receptor antagonists (H2RAs) have often been added to their therapeutic regimen in an attempt to abolish NAB. However, there is controversy over the efficacy of this approach in light of the development of H2RA tolerance. Fackler et al. examined prospectively the efficacy of combined therapy in blocking NAB in 23 healthy volunteers and 20 GERD patients. All subjects underwent baseline esophageal pH testing, which was followed by a 28-day treatment period with PPI only or PPI plus H2RA. Repeat pH testing was performed 1, 7, and 28 days thereafter. Fackler et al. conclude that the beneficial effects of combined H2RA and PPI therapy are only temporary, where significant differences in acid suppression between PPI twice daily, and PPI twice daily with H2RA are lost after 1 week of therapy as a result of the development of H2RA tolerance.

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The H63D Mutation of Hereditary Hemochromatosis Is Not Clinically Significant

Hereditary hemochromatosis, the most common inborn error of metabolism in individuals of northern European descent, is characterized by the progressive iron overload and multi-organ damage, including the development of cirrhosis, cardiomyopathy, and diabetes mellitus. The genetic basis of this disease has been attributed to 2 mutations of an MHC class I-like gene called HFE. The first and predominant mutation involves a cysteine to tyrosine substitution at amino acid 282, termed C282Y. The C282Y mutation is observed in up to 10% of alleles in the general population. More than 50% of patients homozygous for C282Y have clinical evidence of hemochromatosis, and an additional 25% show biochemical evidence of iron overload. The second mutation, which involves a histidine to aspartic acid substitution at amino acid 63 (called H63D) is less common, although its clinical significance, in contrast to C282Y, is less well understood. The study by Gochee et al. accessed a well-defined population in Bussleton, Australia, to determine the frequency and influence on total body iron of the H63D mutation. Of the 2531 patients studied, 2.1% were homozygous for the H63D, 23.6% heterozygous, and the remainder was wild-type. Serum transferrin saturation was significantly increased in male and female H63D homozygotes and heterozygotes compared with wild-type. However, homozygosity for H63D was not associated with the development of clinically significant iron overload. The authors conclude that, in the absence of the C282Y mutation, the H63D mutation is not clinically significant.

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Predictive Factors of Cirrhosis Development in Ursodeoxycholic Acid–Treated Patients With Primary Biliary Cirrhosis

Ursodeoxycholic acid (UDCA) has been effective in improving liver function as well as delaying the progression of liver fibrosis in patients with early-stage primary biliary cirrhosis (PBC). Although most patients have prolonged benefit, some still exhibit active disease that progresses to cirrhosis and eventual death. The study by Corpechot et al. attempts to determine the incidence and predictive factors for the development of cirrhosis in UDCA-treated patients with PBC. A Markov model was used to describe the progression toward cirrhosis in 183 UDCA-treated patients with PBC. Although the incidence of cirrhosis after 5 and 10 years of UDCA treatment was related to the stage of PBC at onset of therapy, progression to cirrhosis was most dramatic and rapid in patients with initial stage III disease (defined by lobular fibrosis and/or bridging necrosis; see Figure). Independent predictive factors of cirrhosis included serum bilirubin >17 mmol/L, serum albumen <38 g/L, and moderate to severe lymphocytic piecemeal necrosis. These data therefore are useful in identifying patient subsets of more aggressive disease that may benefit from adjuvant therapeutic trials.

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Figure 1. Incidence of cirrhosis in UDCA-treated patients with PBC. The probability of cirrhosis is shown as a function of time and histological stage. (A) Stage I, (B) stage II, and (C) stage III. Gray areas are 95% confidence intervals.
Insights Into Intestinal Bicarbonate Secretion

Intestinal bicarbonate secretion is an important, but not well understood, physiological process that is essential for delivery of water and electrolytes into the intestinal lumen, and, in the duodenum, for neutralization of acidic gastric chyme. Several studies have also shown that defective or inhibited duodenal bicarbonate secretion may contribute to the pathogenesis of duodenal ulcer disease caused by the loss of the bicarbonate protective effect of the mucosa. The mechanism of duodenal bicarbonate secretion has been partially elucidated and appears to involve the coupling of the cystic fibrosis transmembrane regulator (CFTR) anion channel and a Cl⁻/HCO₃⁻ exchanger, albeit the latter has not been adequately characterized. Although several studies have reported potential candidate molecules for luminal membrane Cl⁻/HCO₃⁻ exchange, none have provided convincing evidence of its identity. In 1993, DRA was identified as an anion transporter that was interestingly down-regulated in intestinal adenomas (hence the abbreviations forming its name). Mutations of the DRA gene were found to be the apparent cause of congenital chloride diarrheas where abnormalities of luminal membrane Cl⁻/HCO₃⁻ exchange in distal intestine could be found. Subsequent studies have confirmed that DRA is an anion exchanger, although controversy existed regarding the specific anions that it transports. Jacob et al. examined the possibility that DRA was the luminal membrane transporter of the gut, particularly in the duodenum where it might be involved in CFTR-associated active bicarbonate secretion. They find DRA expression high in the duodenum and colon of the rat, rabbit, and human GI tract and located in the luminal membrane of enterocytes (see Figure). In contrast, the expression and function of Na-absorbing transporters such as luminal membrane Na-H exchange were relatively low in the duodenum compared with those of DRA, suggesting DRA is more likely involved in mediating duodenal HCO₃⁻ secretion. Although the data are not conclusive, they implicate DRA as the anion exchanger that is involved in CFTR-associated bicarbonate secretion in the duodenum.

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The Importance of Chemokines in the Development of C. difficile Toxin–Induced Intestinal Inflammation

Chemokines are a multigene family of chemoattractant cytokines that have a role in the recruitment and activation of inflammatory cells at sites of injury or infection. They are made by a variety of cell types, including the intestinal epithelium, and bind to specific 7 transmembrane domain G-protein-coupled receptors that share functional and structural homology to the rhodopsin receptor. The beta chemokines, or CC chemokines, are one of the largest subfamilies of chemokines for which there are many distinct CC receptor (CCR) subtypes. The CCR1 receptor, for instance, is expressed by many types of inflammatory cells, as well as neural cells and astrocytes. Its ligands include RANTES, macrophage inflammatory protein (MIP)-1α, and monocyte chemoattractant protein (MCP-2 and -3), which mediate chemotaxis and activation of many inflammatory cells. To examine the role of CCR1 in certain types of intestinal mucosal inflammation, these authors studied the effects of the Clostridium difficile toxin A in CCR1-gene targeted (deficient) mice. Toxin A, a mediator that contributes to the development of antibiotic-associated colitis, was injected into ileal loops of wild-type, MIP-1α, and CCR1-knockout mice. Although luminal fluid accumulation was evident in all mice, the effects were far less in CCR1- and MIP-1α-deficient mice (see lower panel). In addition, the administration of an inhibitor of RANTES attenuated the ileal fluid secretion in wild-type mice stimulated by toxin A. The study by Morteau et al. demonstrates the important role of the CCR1 receptor and its ligands in mediating enterotoxin-induced mucosal inflammation and secretion.

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