and without a history of PUD was greater in patients prescribed LDASA in combination with clopidogrel (66.3% vs. 37.6%; p<0.001) than in those prescribed either LDASA without clopidogrel (47.5% vs. 25.0%; p<0.001) or clopidogrel without LDASA (63.4% vs. 41.9%; p<0.001). For patients prescribed LDASA without clopidogrel, there was no difference in LDASA dosing between those with a history of PUD and those without; 81.8% of patients in both groups were prescribed 75 mg/day. Patients with a history of PUD were more likely than those without to be prescribed an enteric-coated or modified-release formulation of LDASA (22.0% versus 15.0%; p<0.001). **Conclusions.** Concern about the gastrointestinal safety of antiplatelet agents is reflected in the increased prescription of clopidogrel without LDASA and co-prescription of PPIs in patients with a history of PUD. This is in line with the recommendations of current guidelines. However, contrary to guidelines, nearly half of patients with a history of PUD are not prescribed a PPI.

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Histamine Receptor Antagonists Added to PPIs Improve Gastric Acid Control When Taken Chronically

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Background: Addition of histamine-2 receptor antagonists (H2RAs) to proton pump inhibitor therapy is a controversial subject. Studies agree that addition of H2RAs at night to a PPI decreases nocturnal gastric acid breakthrough. Some small studies have suggested that there is tachyphylaxis to H2RAs, but other studies have shown that after a month of therapy, nocturnal acid breakthrough remains better-controlled in patients on a combination of PPI and H2RAs. Methods: This study is a retrospective analysis of patients who underwent combined 24 hour impedance pH testing at the Medical University of South Carolina Esophageal Disorders Lab. All patients were on long-term daily therapy with either twice daily PPI only (n=174) or a twice daily PPI with bedtime H2RA (n=51). Data on gastric acid control were analyzed using the Sandhill ® Scientific High Definition G.I. Diagnostics software and reported as median pH of gastric acid contents for each individual subject. Meal times were excluded from pH analysis. The results were tabulated and analyzed with Graphpad statistical analysis software using a one-tailed Mann-Whitney test. Results: The median recumbent gastric pH of patients on twice daily PPI was 5.37, with the 25th and 75th percentile 3.05 and 6.31, respectively. The median recumbent gastric pH of patients on a twice daily PPI with a bedtime H2RA was 6.31, with the 25th and 75th percentile 4.81 and 7.36. The difference in the groups was significant (p<0.01). The median gastric pH of the PPI only group was 5.37 and for subjects on both PPI and H2RA was 5.43. The difference was not significant (p=0.28). The median upright pH of the PPI only group was 5.33, and was 5.1 for patients on PPI and H2RA. This difference was not significant (p= 0.1). Conclusion: The results of this study further validate the chronic use of nocturnal histamine 2 receptor antagonists for control of night-time acid breakthrough, and downplay the concern of tachyphylaxis proposed by other studies. As expected, the effect was seen during the recumbent period of the tests. Given the short half life of H2RAs, it is reasonable to see the effect only during this period.

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Inhibition of Lysosomal Enzyme Activities by Proton Pump Inhibitors

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Background: Proton pump inhibitors (PPIs) have been the most commonly prescribed drugs for acid-related disorders. In general, under acidic conditions, PPIs are protonated to their active forms. In the canaliculi of gastric parietal cells, activated PPIs irreversibly bind to a sulfhydryl group on the proton pump and thereby inhibit acid secretion by parietal cells. Lysosomes contain a large variety of hydrolases which are involved in the degradation of cytoplasmic materials. The pH in lysosomes is normally about 5. Objectives: This study is to investigate if PPIs can be activated at pH5 and if PPIs have any effects on lysosomal enzyme activities. Methods: The activation of PPIs (Lansoprazole, Omeprazole, and Pantoprazole) at pH5 was assayed by mass spectrometry using a synthesized peptide (laminin 925-933) as substrate. Four cell lines (A549, Caco2, HEK293, and HepG2) were treated with PPIs at concentrations of 0, 10, or 30 μM. After treatments, acid phosphatase (AP) and β-N-acetylglucosaminidase (NAG) activities were measured using kits from Sigma. Results: For all PPIs tested, PPI-peptide adducts were detected by mass spectrometry in the reaction mix of PPI and substrate peptide at pH5, indicating PPIs were activated at pH5. Mixed at a molar ratio of PPI:peptide = 10:1, most of the laminin peptides was detected as PPI-peptide adducts after incubation for 10 minutes at room temperature. Lansoprazole showed dose dependent inhibitory effects on AP activities in all cell lines tested. For example, compared to control (0 μM), 10 and 30 μM lansoprazole resulted in 71% and 99% inhibition on AP activities in HEK293 cells, respectively. Omeprazole showed less inhibitory effects on AP activities than lansoprazole did. 10 and 30 μM omeprazole resulted in 14% and 36% inhibition on AP activities in HEK293 cells, respectively. Similar to lansoprazole and omeprazole, pantoprazole inhibited AP activities in Caco2 and HEK293 cells. A549 and HepG2 cells were not sensitive to pantoprazole treatments. The sensitivities to lansoprazole and omeprazole are also cell line dependent. Caco2 cells were more sensitive than other cell lines. 10 μM lansoprazole inhibited AP activities by 94%, 71%, 58%, and 10% in Caco2, HEK293, A549, and HepG2 cells, respectively. The effects of PPIs on NAG activities were similar to that on AP activities in all cell lines tested. Conclusions: Our studies showed that PPIs could be activated in lysosomes at pH5 and inhibited the lysosomal enzyme activities. These findings have very important clinical implications. The inhibitory effects of PPIs on lysosomes could contribute to the adverse effects observed in the long term use of PPIs.

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The Role of Calcium-Activated Chloride Channels (CaCCS) in the Process of Gastric Acid Secretion

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To accomplish gastric acid secretion the parietal cell uses a proton pump (H,K-ATPase) that traffics to the surface of the cell, a K channel to recycle K, and a Cl channel to secrete Cl into the lumen of the gland. The molecular identity of the H,K-ATPase, and K channel(s) is fairly well characterized, however the Cl channel has remained elusive. INTRODUCTION: In the present study we chose to investigate the presence of a calcium activated chloride channel (CaCC) that could fit the criteria of secreting sufficient quantities of Cl to combine with H. Tannic acid has been shown to be a potent inhibitor of CaCCs. In this study we examined the effects of tannic acid on isolated rat and human gastric glands. METHODS: Hand-dissected rat and human gastric glands were loaded with the fluorescent pH indicator dye BCECF-AM, single gastric glands were exposed to a NH4Cl prepulse to acidify the parietal cells. To monitor intracellular pH BCECF was excited at 490 ± 10 nm and 440 ± 10 nm, respectively, and the emission intensity recorded at 530 ± 10 nm. Raw ratio fluorescence data was converted to absolute pH units, using the High K+/nigericin calibration technique. To induce acid secretion all glands were exposed to 100 micrololar carbachol, a potent secretagogue that is known to elevate intracellular calcium. Tannic Acid was added over a concentration range of 10-40 micromolar. RESULTS: Tannic acid was shown to have a dose dependent effect on carbachol induced acid secretion over a range from 10-40 micromolar . In isolated human glands we could show that 20uM tannic acid could prevent carbachol induced acid secretion. DISCUSSION: The Cl efflux pathway on the apical surface of the parietal cell is critical for regulated acid secretion. Previous studies have attempted to identify this pathway but failed to find a suitable candidate. When parietal cells secrete acid there is normally a rise in intracellular calcium that triggers insertion of the H,K-ATPase into the apical membrane and secretion of acid. We thought that a CaCC could be an appropriate target for the Cl efflux pathway. By using the selective CaCC blocker tannic acid we now present proof that inhibition of this CaCC protein prevents acid secretion. These results provide a new molecular target for drug development to prevent the hypersecretion of acid in both the rat and human.

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Aggravation by Clopidogrel, an Antiplatelet Drug, of HCL/Aspirin- Induced Gastric Hemorrhagic Lesions in Rats: Prophylactic Effect of Irsogladine

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Backgrounds & Aims: Antithrombotic therapy plays a central role in the treatment of apoplexy, cardiac disorders and peripheral arterial diseases. However, recent studies suggest that the risk of upper gastrointestinal bleeding is increased by concomitant use of antiplatelet drugs with a low-dose aspirin. In the present study, we examined the effect of an antiplatelet drug clopidogrel, a P2Y12 receptor antagonist, on the gastric bleeding induced by luminal perfusion with aspirin in rats and investigated the prophylactic effects of irsogladine on the gastric bleeding under such conditions. Methods: Male SD rats were used after 24 h fasting. Under urethane anesthesia, two catheters were inserted into the stomach, one from an incision in the esophagus and another through the pylorus via an incision in the duodenum. The stomach was then superfused with saline at a rate of 0.4 ml/min using an infusion pump, and the perfusate was collected every 5 min. After an equilibration period with saline perfusion for 60 min, the stomach was perfused with aspirin (5~25 mM) dissolved in HCl (30~100 mM) for another 60 min. Clopidogrel (10~100 mg/kg) was given p.o. 24 h before the perfusion. Various antiulcer drugs, including irsogladine (1~10 mg/kg), cimetidine (100 mg/kg), omeprazole (30 mg/kg), teprenone (300 mg/kg), rebamipide (30 mg/kg) was given i.d., immediately ate the operation, while PGE2 (1 mg/kg) was given i.v. as a single injection. Results: Gastric ulcerogenic responses to aspirin were most reproducible when the stomach was perfused with 25 mM aspirin acidified with 50 mM HCl (acidified aspirin). The ulcerogenic and bleeding responses to acidified aspirin were dose-dependently aggravated by pretreatment of clopidogrel, despite provoking by itself neither bleeding nor damage, and these responses were significant at 30 mg/kg or greater. Irsogladine dose-dependently reduced the severity of gastric damage and bleeding caused by clopidogrel plus acidified aspirin. The increased ulcerogenic and bleeding responses induced by clopidogrel plus acidified aspirin were also reduced by pretreatment of PGE2, teprenone and rebamipide, while cimetidine or omeprazole had no effect. Conclusion: These results suggest that clopidogrel, the antiplatelet drug, increases the gastric bleeding induced by acidified aspirin. Irsogladine, a mucosal protective drug, is useful for preventing gastric bleeding caused by co-administration of clopidogrel and acidified aspirin.

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Prior Endoscopy in Patients With Newly Diagnosed Celiac Disease; a Missed Opportunity

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Background: Celiac disease (CD) is under-diagnosed in the United States, and patients with CD report a duration of symptoms of a median of 11 years prior to diagnosis. Factors related to the performance of gastrointestinal endoscopy may contribute to the delay in diagnosis. We aimed to identify newly diagnosed patients who had undergone a prior esophagogastroduodenoscopy (EGD) and examine factors contributing to the missed diagnosis. Methods: Patients with biopsy-proven CD provided consent to be included in a prospectively maintained database. We identified all patients age ≥18 years whose diagnosis of CD was made by endoscopy with biopsy at our institution (n=316), and searched the electronic medical record for a prior EGD at the same institution. We compared those patients with a prior EGD to those with without a prior EGD with regard to age at diagnosis and gender, and enumerated the indications for EGD among those with missed/incident CD. Results: Of the 316 patients diagnosed by EGD with biopsy at the Celiac Disease Center, 17 (5%) had previously undergone EGD at the same institution. A majority of these patients (13/17;