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AN ANALYSIS OF HISTAMINE 2 RECEPTOR ANTAGONISTS AND A PROPOSAL FOR LAFUTIDINE

On April 1st, 2020, the Food and Drug Administration (FDA) made national headlines when it published a press release on a popular gastrointestinal drug used in the United States. FDA requested withdrawal of Zantac (generic drug ranitidine) from all prescription and over-the-counter use immediately, due to concerns of a N-Nitrosodimethylamine (NDMA) contaminant in the formulations.[1] Sustained exposure to NDMA might increase the risk of cancer. FDA has investigated Ranitidine, a histamine-2 receptor antagonist (H2RA), from September of 2019 to April of 2020 for this issue.[1] This press release was the final conclusion of a gradual mass recall of ranitidine across the United States by many different drug companies, and also led to ranitidine's suspension in the European Union and Australia.[1] The withdrawal was met with subsequent investigation by the FDA into other gastrointestinal medications that utilizes similarly chemical synthetic process, such as proton pump inhibitors, antacids, and other histamine receptor antagonists.

Zantac had previously been approved by the FDA for treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and Zollinger-Ellison syndrome.[1] For the millions of patients ingesting ranitidine daily or even twice daily for one or more of these concurring gastrointestinal diseases, this meant an immediate change in their therapy to a different H2RA. This recall resulted in clinicians having a need to find alternate therapy for their patients, and pharmaceutical manufacturers struggled to conduct independent studies on their own drugs to meet this increased raise in demand. The drug companies Amneal Pharmaceuticals and Mylan have recalled and ceased production of another H2RA Axid (generic drug nizatidine) for the exact same reason that their drug had trace amounts of NDMA.[2] The FDA has since started reviewing other H2RA's and proton pump inhibitors for this contaminant.[1] As far as antagonists for the histamine-2 receptor in the gastrointestinal system, there now exists only two drugs that have been approved by the FDA, Tagamet (generic drug cimetidine) and Pepcid (generic drug famotidine).

The popularity of famotidine and cimetidine had ultimately led to backorders for these medications and difficulty for procuring these medications by multiple health systems. Additionally, it has made many health care professionals overly aware of cimetidine's many drug-drug interactions. Cimetidine alters the liver enzymes that break down other drugs to such an extent that prescribers are wary to prescribe this to patients.[2] Health systems and retail pharmacies are thus turning to the alternative best option - famotidine, leading to a serious drug shortage in the United States of this drug. According to the FDA, 20 and 40 mg famotidine tablets from manufacturers Teva Pharmaceuticals, Aurobindo Pharma, and Carlsbad Technology are all on shortage.[2]

Histamine-2 receptor antagonists (H2RA's) were first discovered and synthesized in the late 1960's, after discovering that the classical antihistamines, the histamine-1 (H1) receptor antagonists, could not antagonize every type of

histamine receptor in the body.[3] The idea was for scientists to synthesize specialized compounds to attempt to block the effects of histamine specifically in the stomach. After the discovery of the histamine-2 (H2) receptor and its presence in the gastrointestinal system in addition to the heart, uterus, and smooth muscles, the structure of the receptor was discovered through utilization of lab processes such as PCR.[3] Discovery of the H2 receptor was followed by synthesis of compounds selectively binding to this receptor. In humans, endogenous histamine is produced from enterochromaffin-like (ECL) cells located in the gastric mucosa and aid in production of stomach acid through binding to those H2 receptors on parietal cells of the stomach, leading to heartburn and discomfort.[3] In gastrointestinal diseases such as GERD, the problem arises from the lower esophageal sphincter not closing properly, leading to acid backflow from the stomach into the esophagus and symptoms of heartburn. Preventing acid production by blocking histamine action has been safe and effective treatment strategy for many GI issues.

The discontinuation of Zantac and decreased H2RA's prescriptions is accompanied by surge in new prescriptions for proton pump inhibitors. The proton pump inhibitors (PPI's) mechanism of action differs from that of H2RA's, and are classically used today as a preferred method of treatment for gastrointestinal disease. This is because the H2RA's approved in the United States do not attain a complete healing of gastric lesions and cannot hold back acid secretion near to the extent of PPI's.[4] PPI's inhibit the proton pumps directly that secrete acid in the stomach, unlike the histamine that blocks the H2RA's which only indirectly prevents acid secretion.[4] There is no denying that PPI's are more effective in treatment, the problem lies with the misuse of these medications, and especially the misuse of these medications due to the lack of adequate supply of H2RA's. According to a study at the Hospital de Guadalajara, among patients taking PPI's upon admission to the hospital, 73% had inadequate indication for taking it and 38% were discharged with a PPI without the correct indication.[4] The overuse of PPI's can lead to serious adverse effects; the stronger acid suppression may increase chance of Clostridium difficile infections, bone fracture, or even anemia due to chronic vitamin B12 deficiency.[4] Furthermore, studies have associated PPI's with issues such as lowering serum magnesium, a critical element taking part in over 300 enzymes in the human body.

To prevent the side effects of improperly prescribed PPI's, the United States should explore options for alternative H2RA's, because these medications may be indicated in a patient that does not need PPI therapy. Unfortunately, aside from ranitidine, nizatidine, famotidine, and cimetidine, there is not another H2RA on the market in the United States. However, outside the USA, a different H2RA is gaining traction. The model H2RA drug lafutidine was first marketed in Japan with the brand name Stogar by the multinational biopharmaceutical company Union Chimique Belge (UCB) in April of 2000.[5] It was first approved for oral treatment of gastric ulcers in 2000, which makes it one of the younger H2RA's that have been developed.[5] In India, lafutidine was approved and marketed as the brand name Lafaxid by Zuventus Healthcare Limited. In 2010 lafutidine was approved for GERD, and in 2012 it was approved to help improve symptoms of gastric and duodenal ulcers in peptic ulcer disease in both countries respectively.[5] Like the other H2RA's, lafutidine prevents secretion of gastric acid by blocking histamine binding to its receptor, and therefore can be substituted for the discontinued ranitidine and shortages of famotidine.

Interestingly, lafutidine has additional benefits aside from its acid lowering capacity.

Perhaps the most sought-after benefit of lafutidine and its most exciting is its additional gastroprotective activity leading to complete healing of gastric lesions. During cancer treatment, many of the chemotherapeutic agents used (cisplatin, 5-fluorouracil, etc.) have a possible side effect of mucositis.[6] Mucositis may occur during chemotherapy when treatment inadvertently breaks down the rapidly dividing cells lining the gastro-intestinal tract, leaving the mucosal tissue open to ulcers and infection.[6] Shimatani, T. et al. demonstrated lafutidine can prevent this gastric mucosal injury and accelerate the repair process following damage in various animal models, while Tanaka, M. et al. found that lafutidine does this through capsaicin-sensitive nerves in the enteric nervous system in rat models.[7,8] Despite this promising data, lafutidine has only begun to be tested in human models, but this drug has still found to be safe in humans. Namikawa, T. et al. concluded that lafutidine could be used for supportive care to prevent gastric induced toxicities in patients taking 5-fluorouracil after comparing patients with either stage II or stage III gastric cancer.[6] The grades of diarrhea and nausea in this study were significantly lower in patients taking lafutidine as compared to patients on placebo.[6] From this data, larger scale randomized control trials could be done exploring lafutidine in the millions of patients in the United States who suffer from the adverse effects of chemotherapy ever year.

Not only does lafutidine have gastroprotective function, but it also has been found to activate calcitonin gene-related peptide (CGRP). CGRP is a very potent vasodilator. The binding of this molecule to its receptor inhibits pain transmission, decreases artery dilation without the unwanted effect of active vasoconstriction in smooth muscles of the stomach, and inhibits inflammation due to mast cell activation.[7] Chiefly for the purposes of stomach acid, CGRP can facilitate the release of somatostatin from antral D cells.[7] Somatostatin then inhibits gastric acid secretion, directly acting on somatostatin receptors in the parietal cells. This function makes lafutidine unique from the other H2RA's, which do not activate CGRP through this mechanism. In Shimatani, T. et al. it was also studied through comparisons of 10 mg lafutidine to 20 mg famotidine that plasma concentrations of CGRP exceeded 60 pg/ml with lafutidine, while concentrations of CGRP did not increase above 30 pg/ml in those treated with famotidine.[7] Suppression of the transmission of pain to the brain of stomach acid secretion or backflow into the esophagus may improve the efficacy of lafutidine to treat underlying gastrointestinal conditions.[7] Lafutidine therefore may have therapeutic potential in NSAID-associated gastric mucosal injury in humans. Essentially, if treatment with lafutidine means the patient does not have as much stomach pain as treatment with famotidine, lafutidine may be a better option.

Additionally, lafutidine compares favorably to lansoprazole triple therapy for the treatment of helicobacter pylori. Helicobacter pylori is a gram-negative bacterium that colonizes the small intestine and GI tract and plays a critical role in ulcer recurrence.[9] The treatment of this infection in patients with no prior risk factors or clarithromycin resistance includes triple therapy with a PPI, clarithromycin, and amoxicillin. Several studies have now shown that this therapy may not be the best possible therapy. Isomoto, H. et al. found lafutidine-clarithromycin-amoxicillin triple therapy efficacy in eradicating H. pylori was comparable to that of lansoprazole-based triple therapy regimen.[9] Seeing lafutidine therapy succeed in this area only gives it more traction

as a good treatment option for patients who are struggling with ulcer recurrence due to H. pylori infection. The specific study done in Isomoto, H. et al. also concluded that CYP2C19 genetic predisposition is not necessarily a factor in the treatment success.[9] CYP2C19 metabolizes drugs such as lansoprazole, the PPI used in this study, while it does not metabolize lafutidine.[9] Therefore, seeing lafutidine therapy succeed in this area will make it a good treatment option for patients who are struggling with ulcer recurrence due to H. pylori infection as a low risk-high reward therapy for those with CYP2C19 genetic predispositions.

Lafutidine also has a longer duration of action in the human body. In the recently published human studies on lafutidine, when used for the treatment of gastric mucosal lesions, lafutidine may be prescribed once daily and has a longer half-life in the body than its counterpart famotidine.[10] Ohara, S. et al. demonstrated along with this that lafutidine was superior to placebo and non-inferior to famotidine in a patient population of Asian descent in Japan.[10] In many patients, existing therapy with famotidine may have to be taken twice daily dosing to relieve heartburn symptoms during the night. Being able to inhibit acid secretion during the day and throughout the night with once daily dosing is very favorable. M. Tanaka et al. established in their study that lafutidine accelerated the healing of indomethacin-induced antral ulcers in animal models to the same degree as other H2RA's, while clinically showing longer lasting H2 antagonism and prolonged anti-secretion in a Japanese population.[8] For those patients that had been taking ranitidine twice daily to treat stomach acid, this could mean lower pill burden. This would improve adherence to the medication, and lead to more favorable outcomes. It is worth noting that in India the lafutidine 10 mg orally is administered twice daily for the treatment of gastric and duodenal ulcers,[10] so more studies would have to be done in the United States in different populations.

Despite the advantages of approving lafutidine in the United States, there is still a lack of data and clinical trials to support its immediate approval by the FDA. The trials that do exist in lafutidine exist mostly through patient populations of Japan, who represent only one subset of the population of the USA. Those of strictly Asian descent have different capacities to digest medicines depending on their pharmacogenomics, and may present with different CYP enzyme capabilities. Because of the struggle of the United States in obtaining and prescribing proper H2RA therapy, it becomes necessary to conduct clinical research with lafutidine on this side of the Pacific Ocean. Also, as many more Americans get prescribed PPI's the potential risks of undergoing PPI therapy are going unconsidered. In conclusion, the availability of H2RA's does not have to be such a strife if we merely look outside of our borders and explore the options for acid lowering therapy originating from other countries.

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