A COMPARISON BETWEEN PROTON PUMP INHIBITORS AND H2 RECEPTOR ANTAGONIST

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Abstract: *Proton pump inhibitors (PPIs) suppress the production of stomach acid and work by inhibiting the proton pump (H+/K+ ATP-ase) and this include esomeprazole ,omeprazole, lansoprazole, rabeprazole, pantoprazole. H2 blockers interfere with acid production by blocking or antagonizing the actions of histamine. Famotidine,Cimetidine, Ranitidine are a few of them.Long term use of PPI can lead to increased risk of fractures, vitamin deficiency,.community acquired pneumonia. Though complications are less, long term use of H2RA can lead to rebound acid hypersecretion and tachyphylaxis that make their use for shorter duration.*

Key Words: *Long term ADR, rebound acid hypersecretion, tachyphylaxis, PPI vs H2RA.*

1. INTRODUCTION:

Proton Pump Inhibitors: Proton pump inhibitors (PPIs) suppress the production of stomach acid and work by inhibiting the proton pump (H+/K+ ATP-ase). Recent guidelines indicate that PPIs should be the first drug treatment, because they are more effective than H2 blockers. Once symptoms are controlled, patients should receive the lowest effective dose of PPIs.Oral PPIs include esomeprazole ,omeprazole, lansoprazole, rabeprazole, pantoprazole, and dexlansoprazole.

Studies report significant heartburn relief in most patients taking PPIs. PPIs are effective for healing erosive esophagitis and may also be helpful in patients with chronic laryngitis that is suspected to be caused by GERD. In addition they are also effective in relieving chest pain and laryngitis caused by GERD and also reduce the acid reflux that typically occurs during strenuous exercise.

Patients with impaired esophageal muscle action are still likely to have acid breakthrough and reflux, especially at night. PPIs also may have little or no effect on regurgitation or asthma symptoms. These medications have no effect on non-acid reflux, such as bile backup.

Adverse Effects. Proton-pump inhibitors may pose the following risks:

- Side effects are uncommon but may include headache, diarrhea, constipation, nausea, and itching.
- Long-term use of these drugs has been linked to an increased risk of hip fractures, possibly because stomach acid may be needed to absorb calcium from the diet. Patients who are on long-term PPI therapy may need to take a calcium supplement or the osteoporosis drugs, bisphosphonates to reduce their fracture risks.
- There is some evidence that PPIs increase the risk for community-acquired pneumonia, especially within the first 2 weeks of starting the medication. Researchers do not know the reason for this possible association. Newer research indicates that PPIs may also increase the risk for hospital-acquired pneumonia.
- Pregnant women and nursing mothers should avoid proton pump inhibitors, although recent studies suggest that PPIs do not pose an increased risk of birth defects.
- PPIs may interact with certain drugs, including anti-seizure medications (such as phenytoin), anti-anxiety drugs (such as diazepam), and blood thinners (such as warfarin).
- Long-term use of high-dose PPIs may produce vitamin B12 deficiencies, especially in diabetics than in non diabetics
- PPI use can inhibit active magnesium transport in the intestine, though it is not clear if this is an idiosyncratic effect. Long-term PPI users who are highly adherent to treatment can eventually deplete total body magnesium stores and present with severe complications of hypomagnesaemia.
- A preliminary study suggests that long-term administration of PPI may cause weight loss and changes to the microbiota in the terminal ileum.
- Some evidence suggests that acid reflux may contribute to the higher risk of cancer in Barrett's esophagus, but it is not yet confirmed whether acid blockers have any protective effects against cancer in these patients. Moreover, long-term use of proton pump inhibitors by people with *H. pylori* may reduce acid secretion

enough to cause atrophic gastritis (chronic inflammation of the stomach). This condition is a risk factor for stomach cancer. To compound concerns, long-term use of PPIs may mask symptoms of stomach cancer and thus delay diagnosis. To date, however, there have been no reports of an increased risk of stomach cancer with the long-term use of these drugs.

2. H2 BLOCKERS:

H2 blockers interfere with acid production by blocking or antagonizing the actions of histamine. It takes 30 - 90 minutes for them to work, but the benefits last for hours. People usually take the drugs at bedtime. Some people may need to take them twice a day.
H2 blockers inhibit acid secretion for 6 - 24 hours and are very useful for people who need persistent acid suppression. They may also prevent heartburn episodes. In some studies, H2 blockers improved asthma symptoms in people with both asthma and GERD. However, one study suggested that they rarely provide complete symptom relief for chronic heartburn and dyspepsia, and they have done little to reduce physician office visits for GERD.

H2 blockers include.:

- Famotidine. Famotidine is the most potent H2 blocker. The most common side effect of famotidine is headache, which occurs in 4.7% of people who take it. Famotidine is virtually free of drug interactions, but the Food and Drug Administration (FDA) has issued a warning on its use in patients with kidney problems.
- Cimetidine. Cimetidine is the oldest H2 blocker. It has few side effects, although about 1% of people taking it will have mild temporary diarrhea, dizziness, rash, or headache. Cimetidine interacts with a number of commonly used medications, such as phenytoin, theophylline, and warfarin. Long-term use of excessive doses (more than 3 grams a day) may cause impotence or breast enlargement in men. These problems get better after the drug is stopped.
- Ranitidine. Ranitidine may provide better pain relief and heal ulcers more quickly than cimetidine in people younger than age 60, but there appears to be no difference in older patients. A common side effect associated with ranitidine is headache, occurring in about 3% of people who take it. Ranitidine interacts with very few drugs.
- Nizatidine Capsules. Nizatidine is nearly free from side effects and drug interactions. A controlled-release form can help alleviate night time GERD symptoms.

Drug Combinations.

- Over-the-counter antacids and H2 blockers: This combination may be the best approach for many people who get heartburn after eating. Both classes of drugs are effective in relieving GERD, but they have different timing. Antacids work within a few minutes but are short-acting, while H2 blockers take longer but have long-lasting benefits
- Proton pump inhibitors and H2 blockers: Doctors sometimes recommend a night time dose of an H2 blocker for people who are taking PPIs twice a day. This is based on the belief that adding the H2 blocker will prevent a rise in acid reflux at night. However, one study reported no additional benefits from the night time H2 blocker. Some experts recommended that patients who are on PPIs take an H2 blocker only to prevent breakthrough symptoms, such as before a heavy meal.

Long-Term Complications. In most cases, these medications have good safety profiles and few side effects. H2 blockers can interact with other drugs, although some less so than others. In all cases, the physician should be made aware of any other drugs a patient is taking. Anyone with kidney problems should use famotidine only under a doctor's direction

3. FDA WARNING FOR FAMOTIDINE:

Famotidine is removed primarily by the kidney. This can pose a danger to people with kidney problems. The FDA and Health Canada are advising physicians to reduce the dose and increase the time between doses in patients with kidney failure. Use of the drug in those with impaired kidney function can affect the central nervous system and may result in anxiety, depression, insomnia or drowsiness, and mental disturbances.

4. PPI VS H2RA:

- Gastric acid-suppressing therapies arguably reduce stress-related mucosal bleeding (SRMB). However, they may contribute to pneumonia and Clostridium difficile infection (CDI). The risks of these infectious complications depend on the extent of acid suppression and may vary by patient population. PPIs are associated with the greatest hazard for these infections, likely because they provide stronger acid suppression. Intermittent administration of H2RAs has theoretical advantages over continuous H2RA or PPI therapies as this dosing strategy does not fully suppress gastric acid and may limit infection risk.
- A high-dose pantoprazole infusion is more effective than a ranitidine infusion for prevention of re-bleeding after endoscopic epinephrine injection in patients with peptic ulcers and active bleeding or non-bleeding visible vessels. In all bleeding peptic ulcer patients is needed to make the eradication of H. pylori infection with the aim to prevent re-bleeding in long term.
- Studies showed that patients given high-dose ranitidine therapy (300 mg b.d.) had rapid relapse of oesophagitis, while lansoprazole 30 or 15 mg daily had a prophylactic effect. Similar results were reported from other studies where a rapid relapse of erosive oesophagitis occurred in patients given rantidine 150 mg b.d., while prophylaxis was seen in those given low-dose lansoprazole 15 mg daily.This allows the convenience of step-down therapy from lansoprozole 30 mg to 15 mg as needed.

- **Rebound acid hypersecretion**

Rebound acid hypersecretion after proton pump inhibitors has been shown for both basal and maximal acid output by 14 days after treatmentand thereby enhances the need for continued therapy to prevent recurrent disease.Acid rebound is caused by expansion of the ECL and parietal cell mass through the trophic effects of gastrin, the levels of which are increased due to the suppression of the negative antral feedback.. It is found in *Helicobacter pylori* -negative, but not positive.It is a prolonged phenomenon, lasting for at least 2 months after a 2-month treatment course. This duration is likely to reflect its development as a result of trophic effects on the oxyntic mucosa. This trophism is caused by the marked hypergastrinaemia that occurs secondary to the profound acid suppression during proton pump inhibitor treatment

Rebound acid hypersecretion after taking histamine H_2-receptor antagonists :It has been demonstrated both basally and in response to meal and gastrin-releasing peptide stimulation, but not in response to peak pentagastrin stimulation. It is present by 3 days after treatment but has resolved by 10 days

- **Tachyphylaxis/tolerance**

Tachyphylaxis/tolerance has not yet been shown in several short-term studies after taking proton pump inhibitors.

Tachyphylaxis/tolerance after the use of H_2-receptor antagonists is well established. It manifests as a loss of acid inhibitory efficacy and is also a class effect. It is present within a few doses but is not progressive after 29 days.While the mechanism for H_2RA tachyphylaxis remains speculative, it may involve the up-regulation of parietal cell receptors for other mediators of acid secretion (*i.e.*, acetylcholine, gastrin), the sensitization of H_2 receptors, the impairment of inhibitory neurohormonal control of acid secretion, and/or an alteration in receptor turnover after chronic competitive inhibition.

Although a single (first) dose of an H_2RA can be effective for controlling gastric acid and preventing or relieving food-related heartburn, tolerance, is consistently detected at the first time point assessed after the first dose, including the second day and/or second dose. Even if symptom relief is achieved with an H_2RA, it may be due to desensitization of the esophagus to acid exposure, potentially providing symptom relief without significantly decreasing esophageal acid exposure. When recommending OTC drugs for treatment of frequent heartburn, clinicians should be aware of the potential for rapid development of tachyphylaxis in patients who use H_2RAs for 2 or more consecutive days.

Tachyphylaxis to H_2RAs does not appear to be progressive, as studies have typically demonstrated no further reduction in antisecretory effect after the initial loss of potency is detected. However, once tachyphylaxis to an H_2RA has developed, increasing the dose does not appear to be effective in overcoming the loss of anti-secretory effect.

The physiologic effect of tachyphylaxis has been found to persist for 3 d after H_2RA dosing is discontinued. In one study, ranitidine was dosed twice daily for 7 d, dosing was stopped for 3 d, and then dosing was resumed for 3 d. Tachyphylaxis was evident by day 2 of dosing in the first period, and the physiological effects of tachyphylaxis were still evident (decreased response to the H_2RA) when dosing was re-initiated after the 3-d hiatus. This study showed that it took longer than 3 d to recover the beneficial effects of an H_2RA once tachyphylaxis had occurred, supporting that only occasional, isolated doses of an H_2RA provide the maximum benefit of the drug.

5. CONCLUSION:

Patients with frequent heartburn may be better managed by daily use of an OTC PPI, rather than repeated doses of H_2RAs.Though PPI has increased long term ADR they are suited for long term use.

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