Role of Proton Pump Inhibitor in the Management of Acid-Related Disorders

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ABSTRACT

Proton pump inhibitor (PPI) is the strongest inhibitor to gastric acid secretion. PPI is effective in all gastric acid disorders, such as: peptic ulcer, gastroesofageal reflux disease, non steroid anti inflammatory drugs (NSAIDs) gastropathy, and Zollinger-Ellison syndrome. Several studies comparing one PPI to another. Although some differences have been reported, there are small differences with unclear clinical importance.

PPI has side effects that may be related to diarrhea due to Clostridium difficile, pneumonia, hip fracture, vitamin B12 deficiency, and IgE mediated allergic reaction. Several studies revealed strong association but have limitation in design and sampel size. PPI therapy should be according to indication, dose, and appropriate period.

***Keywords**: proton pump inhibitor, gastric acid disorder, indication, dose, period*

ABSTRAK

Penghambat pompa proton (PPP) adalah inhibitor paling kuat terhadap sekresi asam lambung. PPP efektif untuk terapi semua gangguan asam lambung termasuk ulkus peptikum, penyakit gastroesofageal reflux, gastropati karena obat anti inflamasi non steroid (OAINS), dan sindrom Zollinger-Ellison. Beberapa penelitian membandingkan beragam PPP satu dengan yang lainnya. Walaupun dilaporkan ada beberapa perbedaan, namun besaran perbedaannya kecil dan tidak jelas kepentingan klinisnya.

PPP kemungkinan berkaitan dengan efek samping diare karena Clostridium difficile, pneumonia, fraktur panggul, defisiensi vitamin B12, dan reaksi alergi yang dimediasi IgE. Beberapa penelitian menunjukkan hubungan yang kuat namun memiliki keterbatasan desain dan besaran sampel. Terapi PPP harus sesuai dengan indikasi, dosis, dan jangka waktu yang tepat.

***Kata kunci**: penghambat pompa proton, gangguan asam lambung, indikasi, dosis, jangka waktu*

INTRODUCTION

The invention of proton pump inhibitor (PPI) in the end of 1980 optimalize treatment of gastric acid disorder. Clinicians should evaluate the role of gastric acid in extraesofageal manifestation from gastroesofageal reflux disease (GERD), including non-cardiac chest pain and tracheopulmonar disease.[1]

Chronic treatment using PPI is indicated to several conditions, such as long duration therapy of GERD and supporting therapy in preventing peptic ulcer which is induced by nonsteroidal anti inflammatory drug (NSAID).[2,3] In year 2008, there was 113,4 billion prescription of PPI with sales of 13.9 trillion US dollars.[4] PPI is considered safe, with rare serious side effects. However, recently it has been observed that PPI treatment is associated with increased fracture risk although results of clinical studies are still controversial.[5] PPI strongly inhibits gastric acid secretion, increases intra gaster pH, and decrease the concentration of hidrogen ion several hundreds or

thousands fold. As a consequence, PPI has the potency to influence essential micronutrients, including vitamin C, vitamin B12, and iron when it passes the gaster, disturbs their activity in the gastric lumen and also the bioavailability.[6]

This review article provides the pharmacologic appearance and clinical efficacy of PPI in various acid-related disorders and issues about the comparison of these drugs, long term effects, side effects, and drug interaction.

PHYSIOLOGY OF GASTRIC ACID SECRETION

Gaster in normal individual consist of one million parietal cells which secrete 0.16 million of gastric acid (hydrochloric acid or HCl) in gastric lumen in response to 3 important physiologic stimuli, such as acetylcholine, histamine, and gastrin.[7]

Histamine release by gastrin from enterochrommafin-like cells (ECL) seem to be the main physiologic mechanism in which gastrin stimulate gastric secretion, although parietal cells also has gastrin receptors. ECL cells integrate stimuli message from cholinergic nervous and inhibition from local somatostatin.[7]

Acetylcholine is a main neurocrine transmiter released by postganglionic vagal nerve and stimulate generation of hydrogen ion directly through M3 muscarinic parietal cell receptors. Histamine is primary paracrine transmiter which is bound to H2 specific receptor in basolateral membrane parietal cells, while gastrin which is secreted in antral G cell combines primary endocrine pathway. Gastrin stimulate generation of hydrogen ion directly and indirectly by stimulating histamine secretion from ECL cells in proximal area parietal cells.[7]

Although the interaction of these three pathways is coordinated to stimulate or inhibit generation of hydrogen ion, histamine tends to represent dominant route as gastrin stimulate acid secretion by inhibiting histamine release from ECL cells. Because the dominancy of this pathway, blockage of H-2 receptors becomes the main way of inhibiting acid secretion in mid 1970s.[7]

As long as not stimulated (base phase), percentage of parietal cells volume comprises of tubulovesicle which is a long tube with smooth membrane surface and from secretory canaliculi an invagination area in apical membrane. During food stimulation, the amount of this tubulovesicles decreases and transforms into microvili around secretory canaliculi which cause expansion of the parietal cells' surface area in preparation to actively transport hydrogen ion in large amount against an ion gradient 3,000,000:1. Hydrogen ion is actively secreted in the exchange of potassium ion with the help of H-K-ATPase which is also known as proton pump located in the apical surface of parietal cells. H-K-ATPase plays role in the last pathway in which HCl is secreted to the gastric lumen, where HCl acts to hydrolize food protein and maintains sterile environment.[7]

PHARMACOLOGICAL ASPECTS OF PROTON PUMP INHIBITOR

Introduction of H-K-ATP-ase as the end phase of acid secretion, influence the development of PPI which is targeted to decrease this enzyme. All PPI has usual structural motive but with variable substitution. PPI in piridin has weak proton with pKa 4.0 for omeprazole/esomeprazole and lansoprazole/dexlansoprazole, about 3.9 for pantoprazole and about 5.0 for rabeprazole. As a result, they accumulate specifically and selectively in secretory canaliculi, a very acidic space in parietal cell. In that space, PPI convert acid catalyst into reactive species, thiophillic sulphonamode, a permanent cation.[7]

The conversion rate varies in its composition and proportional contract to pKa benzimidazole rabeprazole > omeprazole/esomeprazol = lansoprazole/dexlansoprazole > pantoprazole.[7] Reactive species interact with outer membrane of H-K-ATPase which face secretory lumen of parietal cells, producing formation of disulphide bond and cystein 813 which is located in alpha subunit enzyme. Inhibition of this covalent enzyme by thiophillic sulphonamide produce specific disruption which is long-lasting in gastric acid secretion.[7]

PPI is the strongest inhibitor of gastric acid secretion.[1] PPI acts most effective when parietal cell is stimulated to secrete acid after meal, which give clinical implication on administration time. Due to the number of H-K-ATPase present in parietal cells is higher after long fasting, PPI has to be given before the first meal in a day. In most people, once daily PPI is enough to produce acid inhibition, and second dose sometimes need to be given before dinner.[1] PPI may not be given in combination with H2-antagonist, prostaglandin, and other antisecretory because the decrease effect of acid inhibition if given simultaneously.[1] H2 antagonist can be used with PPI, but with enough interval timing (the exact interval time cannot be defined yet). As an example, H2 antagonist can be given before sleep or all night long in patients

with nocturnal recurrence, including burning sensation in the chest after consuming PPI in the morning.[1]

During meal, all parietal cells and proton pumps are active. Considering that PPI only inhibit enzymes which are activated in canaliculi membrane, the decrease of gastric acid after initial dose is not yet optimal. After second and third dose, inhibition of gastric acid secretion then occur.[1]

The dose of once daily PPI inhibit acid secretion upto maximum around 66% after five days. Several use of PPI are not adequate to inhibit acid, therefore do not produce consistent and satisfyinv clinical response (different with H2 antagonist which has faster onset of action).[1] Due to the delay in optimal acid inhibition, initial use with twice daily dose (for the first 2-3 days) may be helpful to obtain faster gastric acid inhibition. Additionally in the later onset, because sulphonamide from PPI binds covalently to H-K-ATPase, the recovery of acid secretion is delayed, depending on the enzyme turnover and biological reversibility of disulphide bond. Maximum capacity of gastric secretion may not come back after 24-48 hours of PPI cessation. Rebound of acid hypersecretion may occur after discontinuation of PPI.[1]

THE ROLE OF PPI IN MANAGEMENT OF ACID-RELATED DISORDERS

Peptic Ulcer Disease

PPI heals gastroduodenal ulcers faster than H2 receptor antagonist. A meta-analysis comparing the recovery of duodenal ulcer revealed that omeprazole 20 mg daily in the morning for 4 weeks was more superior than ranitidine 300 mg and cimetidine 800 mg given at night before bed. Other similar meta-analysis showed that lansoprazole 30 mg every morning cured more ulcers significantly than ranitidine 300 mg and famotidine 40 mg before bed.[8] The peak cure rate was 60-85% for 2 and 4 weeks regimen of lansoprazole, while it was only 40-75% for H2 antagonist. Pantoprazole and rabeprazole was also more superior in accelerating ulcer healimg than H2 antagonist. Optimal duration of use for PPI should be 4-8 weeks in duodenal ulcers and acute gastritis.[8]

Eradication of *Helicobacter pylori*

PPI plays its role in *H. pylori* eradication with antibiotics regimen. Antibiotics combination in eradication of *H. pylori* has 2-3 possible options. Triple therapy consists of Clarithromycin 500 mg twice daily, Amoxicillin 1 g twice daily, and PPI one capsule twice daily for 10-14 days. Fourth daily therapy consists of metronidazole, tetracycline, bismuth, and PPI in case of *H. pylori* resistance against clarithromycin or patients allergic to amoxicillin. Twice daily therapy including PPI and antibiotics for 5 days followed by PPI and two different antibiotics for 5 days showed 90% rate of eradication.[8]

Treatment and Prevention of Gastroduodenal Ulcers Associated with Non-Steroid Anti Inflammatory Drug

Some studies showed that PPI was more effective than H2 antagonist to treat gastroduodenal ulcers related to non-steroidal antiinflammatory drug (NSAID) when NSAID should not be terminated. PPI was also more effective than misoprostol in primary prevention against NSAID-related ulcers.[3]

Risk factors of having gastrointestinal complications related to NSAID include previous gastrointestinal events (particularly those with complications), age, and concomittant use of anticoagulants, corticosteroids, other NSAIDs including low dose aspirin, high dose NSAID, and other chronic conditions such as cardiovascular disease. Low dose aspirin is associated with the risk of gastrointestinal complication. *H. pylori* infection increases the risk of NSAID-related gastrointestinal complications. There is benefit of using *H. pylori* infection test and initiating eradication when it is positive in patients who need long term NSAID treatment. It depends on the underlying risk in each patients whether they need concomittant use of gastroprotective drugs after eradication or not.[3]

PPI may significantly reduce gastric and duodenal ulcers and their complications in patients treated with NSAID or COX-2 inhibitors.[3] COX-2 inhibitors are associated with the significantly lower incidence of gastric and duodenal ulcers as compared to traditional NSAIDs. This benefit vanishes as the patients also use low dose aspirin. The application of this drug is also reduced due to its association with myocardial infarction and other thrombotic cardiovascular events. The lowest dose of celecoxib is used to minimize the risk of cardiovascular events.[3]

Patients who need NSAID therapy with high risk (such as bleeding of previous ulcers or multiple gastrointestinal risk) should receive alternative treatments or, if anti inflammatory treatment is absolutely necessary, COX-2 inhibitors and concomittant use of misoprostol or PPI.[3] Patients with moderate risk can be treated with either COX-2 or tradisional nonselective NSAID and misoprostol or PPI.[3] Patients with low

risk, such as those who have no risk factor, can be treated with non-selective NSAID.[3] Patients who are recommended with anti inflammatory analgetics and need low dose aspirin for cardiovascular disease should receive naproxen and misoprostol or PPI.

Moderate risk gastrointestinal patients with high cardiovascular risk should be treated with naproxen and misoprostol or PPI. Patients with high gastrointestinal and cardiovascular risk should avoid the use of NSAID or coxibs. Alternative treatments should be preacribed. All patients, regardless of their risks, who initiate long term NSAID traditional therapy should be considered for *H. pylori* test and be treated if it is positive.[3]

Gastroesophageal Reflux Therapy

Many studies have documented the significant effication of PPI in controlling GERD and treating esophagitis. A comparative study revealed the benefits of PPI over H2 antagonist. The recommended dose of PPI given before breakfast reduced the symptoms of and treated esophagitis in 85-90% patients.[9]

Empirical PPI therapy test is performed using double dose PPI for 1-2 weeks in patients presumably having GERD without further investigations using endoscopic examination. Test will be considered positive if more than 75% symptoms receeded after one week of therapy.[9]

At least 10-15% of GERD patients had suboptimal response against PPI especially those with advanced stage esophagitis. The reason for these failures remain unclear, however, they are associated with suboptimal treatments. Polymorphisms in Cytochrome P450 2C19 genes (CYP2C19) which coded cytochrome P450 isoenzymes that metabolized different PPI preparations are common in Asia and other populations.[10] Genetic mutation may cause someone become slow metabolizer and prolong the antisecretory effects of PPI. Acid inhibitory duration will decrease in fast metabolizers, and difference of PPI metabolism will result in incomplete acid secretion inhibition and high prevalence of GERD symptoms relapse at night.

History of PPI consumption is necessary in individuals who responded poorly against PPI. The optimum time to consume it is soon before breakfast. With proper time of consumption, the second dose taken before dinner would be helpful.[10]

New PPI product with longer biological half-time is now being developed. This prodrug is changed into an active sulphonamide by acids in the secretory canaliculi.[11] Substitution of benzimidazole with imidazopyridine reduces the rate of metabolism, increases plasma and biological half-time from 60-90 minutes to 9.3 hours.[11] The benefits of this preparation need careful examination.

Maintenance Therapy

Most GERD patients, especially those who have grade III and IV esophagitis, will suffer a relapse when the treatment is stopped. A study of maintenance therapy compared ranitidine, cisapride, ranitidine and cisapride, omeprazole, and omeprazole with cisapride. All patients suffered from esophagitis upon preliminary endoscopy and were treated with omeprazole 40 mg daily for 8 weeks prior to taking any of maintenance regimens. After 12 months of therapy, remission state was maintained in 80-90% of the omeprazole group, compared to 49-60% in other groups. This study showed the superiority of PPI in maintaining remission and similar effective prophylactic dose as compared to that of early recovery.[11]

Complication of GERD

PPI is effective in treating complications of GERD. In esophageal stricture, PPI decreases esophageal dilatation which is needed to overcome dysphagia more effective compared to H2 antagonist. In Barrett's esophagus, PPI is commonly used in Barrett's metaplasia patient, although there has been no study which show the regression of Barrett's esophagus or decrease risk of esophageal malignancy with pharmacological or surgical therapy. The dose of PPI is the same with the dose to cure esophagitis without metaplasia. Barrett's metaplasia patients need continuous surveillance for the development of dysplasia or adenocarcinoma.[11]

SIDE EFFECTS AND LONG TERM SAFETY

Three things need to be noted regarding safety of long term PPI, including prolonged hypergastrinemia, possible association of PPI and gaster atrophy, and chronic hypochlorhydria effect.[12-17]

PPI and Hip Fracture

Possibility of increased risk of fracture provoked US Food and Drugs Administrations (FDA) to recommend health services which prescribe PPI need to the consider lower dose which can overcome patients' condition adequately. Results of clinical studies on PPI treatment associated to increased risk of fracture are still controversial.[5]

A systematic review and meta-analysis on observational study revealed association between the use of PPI and increased risk of hip fracture (95% CI = 1.14-1.37; OR = 1,25) and vertebra (95% CI = 1.32-1.72; OR = 1,50), but there is no evidence in the duration effect in the subgroup analysis. Nevertheless, observational study cannot clarify if this is causal relationship or results from confounding factors. Randomized control trials are needed to prove or deny this result.[5]

PPI and *Clostridium difficile* Infection

There has been no conclusive evident showing that PPI can increase disease risk associated to *Clostridium difficile (C. difficile)*. *C. difficile* is an anaerobic organism with spores. Acid fast spore is assumed to be the main vector in disease transmission. Although spore may survive in alkali environment, there is scarce epidemiology evident connecting the use of PPI with *C. difficile* infection. Although the role of gastric acidity maintain sterile environment in upper gastrointestinal tract, other significant effects in other intestinal infection which has not been detected.[18]

PPI and Vitamin also Iron

PPI very strongly inhibits gastric acid secretion, increases intragastric pH, and decreases hydrogen ion concentration several hundreds or thousands fold. As a consequence, PPI has the potency to influence essential micronutrient, such as: vitamin C, vitamin B12, and iron when it passes gaster, disrupts its activity in the gastric lumen and also its bioavailability.[6] Nonetheless, concerns regarding long term effects of PPI in iron and vitamin B_{12} absorption each effect is usually mild, not clinically significant, and is overcomed by supplementation therapy.[6]

PPI and Food Allergy

PPI plays role in increasing allergy reactivation in patients with acid suppression treatment. PPI plays role in food allergy which is mediated by immunoglobulin E. Acid suppression treatment increases gastric pH into around 5. The optimum pH for pepsin in the gaster is 1.8-3.2. Therefore, acid suppression disturbed pepsin enzymatic activity in digesting protein. When food protein is not degraded in gaster, the protein structures are maintained, therefore IgE antibody to food appears.[19]

PPI and Pneumonia

PPI creates hypochlorhydria or achlorhydria in gastrointestinal tract, thus ingested pathogen survives while actually should be killed by the actual gastric pH. Regurgitation of ingested bacteria to the oropharyng may induce respiratory tract infection.

Studies showed the increased risk of pneumonia associated with PPI administration. Several studies stated that this association is due to the underlying confounding condition, which is GERD, and not the PPI administration itself. Patients with severe reflux may have more risk of aspiration and experience pneumonia not only because they use acid suppression treatment. Further study is needed to evaluate the relationship of pneumonia and PPI treatment.[20]

PPI and Acute Interstitial Nephritis

Several case reports and literature reviews showed that PPI was associated with acute interstitial nephritis (AIN). AIN cases are considered to be related with PPI if medical records revealed that PPI is the only change in the treatment before the diagnosis of AIN. From 28 identified cases of AIN, 18 (64%) is associated with the use of PPI (omeprazole, pantoprazole, esomeprazole, or rabeprazole). The median age of patients was 74, median of PPI use was 11 weeks. The presenting signs were unspecific, including 39% patients complained of fatigue, 39% nausea, 22% weight loss. The most common abnormal findings in urinalysis include pyuria (72%), proteinuria (67%), and eosinophiluria (61%). Normocytic normochrome anemia is found in 89% cases and C-reactive protein is increased in 78% cases. Kidney biopsy showed interstitial eosinophillia in 83% cases.[21]

During 3 months of AIN diagnosis and PPI cesation, mostly patients' kidney function recovers. Calculation of glomerulus filtration rate is lower compared to the start in 3 months and 6 months. No AIN predictor data linked to PPI.[21]

AIN associated PPI is an idosyncratic reaction without predictable risk factor. The pathogenesis is unclear, but may appear due to hypersensitivity reaction towards drugs or their metabolites. This metabolite may function as a hapten and resemble kidney antigen, or they gather into immune complex which circulates. Drug induced AIN is treated with corticosteroid, for example in this study all patients received prednisone 50-70 mg per day for 8-12 weeks, but this approach has not been evaluated with randomized controlled trial (RCT). Most patients with drug induced AIN will experience kidney function recovery, some will remain to experience kidney function disturbance, and some develop into terminal stage of chronic kidney disease. Considering that drug induced AIN has reversible

potency, the important key to prevent its development is by recognition and diagnosis. If PPI treatment is given, patients need to be followed and sought for nonspecific complains which has potency to be related with the various manifestation of PPI related AIN.[2]

Proton Pump Inhibitor and Clopidogrel

Food and drug administration (FDA) stated that the combined use of omeprazole and clopidogrel should be avoided because effect in the level of clopidogrel active metabolite and anti coagulation activity. Considering the inhibitory level between various PPI, it is still unknown other PPI which disrupts clopidogrel. Esomeprazole is an omeprazole containing PPI which inhibit CYP2C19 and also need to be avoided combination with clopidogrel.[25]

However, large scale randomized trial on omeprazole vs. placebo in the use of clopidogrel revealed no significant difference in cardiovascular events (95% CI = 0.68-1.44; HR = 0.99) along with the significant decrease of gastrointestinal event (95% CI = 0.18-0.63; HR = 0.34).[26]

CONCLUSION

PPI is the strongest available gastric acid secretion inhibitor. PPI is effective to manage all acid related disorders, including peptic ulcer, gastroesofageal reflux disease, NSAIDs gastropathy, and Zollinger-Ellison syndrome. Several studies compared various PPI. Although some differences have been reported, there is only small difference and the clinical significance is unclear.

PPI is probably associated with diarrhea due to *Clostridium difficile*, pneumonia, hip fracture, vitamin B12 deficiency, and IgE mediated allergic reaction. Several studies showed strong relationship, but had limitations in study design and size. Further research is needed to know the real association between PPI and its various side effects.

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