2014

Proton Pump Inhibitors: Omeprazole

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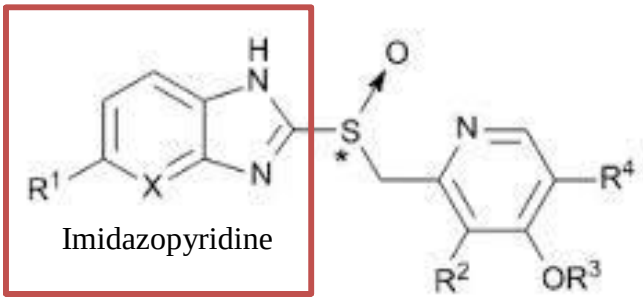
I. Overview

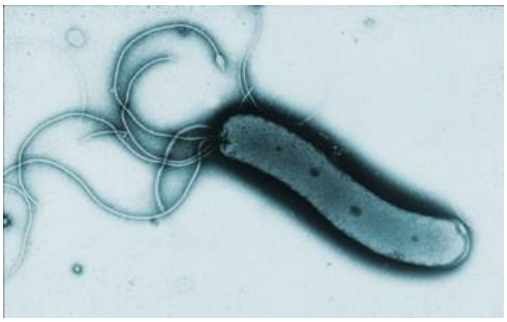
Proton-pump inhibitors (PPIs) are group of drugs having long-lasting reduction of gastric acid production. PPIs are the most effective inhibitors of acid secretion (The Health Strategies Consultancy LLC, 2005). There is similar pharmaceutical group called histamine$_2$ (H_2)-receptor antagonists in increasing intragastric pH. Comparing these two groups, PPIs are proven to be more effective but the effectiveness depends on the individual PPI agents. The individual agents of PPIs are for example esomeprazole, pantoprazole, illaprazole, dexlansoprazole, lansoprazole, rabeprazole, and omeprazole. The majority of PPIs are benzimidazole derivatives but research found that imidazopyridine derivatives may be more effective for treatment purposes (Sachs, Shin, and Howden, 2006).



Proton-pump inhibitors ("Wikipedia: Proton Pump Inhibitors")

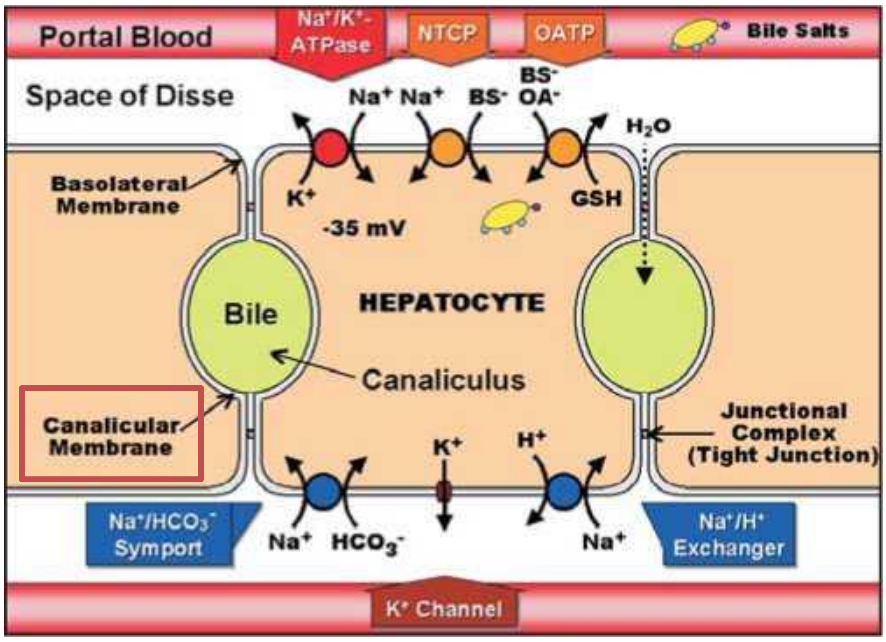
PPIs are used as treatment for acid-related diseases including gastroesophageal reflux diseases (GERD) and peptic ulcer disease. GERD is a symptom of acid reflux whereby gastric acid comes out from stomach to the oesophagus (De Vault and Castell, 1999) whereas peptic ulcer is a disease whereby the lining of the stomach and the duodenum is sore because of the lack of proportion of gastric acid in the stomach (WebMD). They are also used as treatments against Barrett's esophagus and Zollinger-Ellison syndrome (Sachs, 1997). Barrett's esophagus is a disease whereby the lining in the esophagus is replaced with the lining that is similar to that in the intestine. It is known to increase people's vulnerability to cancer (NDDIC, 2013). Zollinger-Ellison is caused by the increase in the production of gastrin. Gastrin is a peptide hormone that stimulates the

secretion of gastric acid in the stomach (Medline Plus, 2012). Besides its effectiveness in treating diseases, PPIs also inhibit the growth of *Helicobacter pylori* which causes peptic ulcer diseases.



Helicobacter pylori (Bioweb)

H.pylori damages the coating lining of stomach and duodenum causing the gastric acid to reach the inner lining and irritate them (NDDIC, 2013).When PPIs are combined with antibiotics, it has been shown medically that this eradicates the growth of bacterium. Some PPI agents like lansoprazole, rabeprazole, and omeprazole have similar characteristics. These agents are used mainly to inhibit gastric acid secretion. They are mainly targeting the gastric acid pump, H^+, K^+—adenosine triphosphatase (ATPase) in the canalicular membrane of the parietal cell (Horn J, 2000).



Canalicular membrane (Richard, 2012)

The rates of absorption of omeprazole and lansoprazole decrease when they are taken together with food (Astrazeneca pty ltd, 2005).

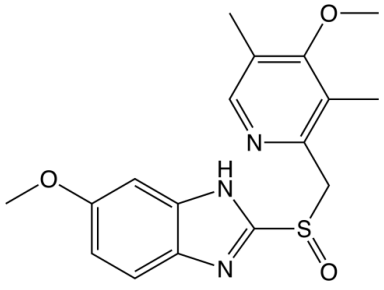
In general, PPIs may lead to increased risk of development of food allergies by suppressing acid-mediated breakdown of proteins. Proteins that are not digested then travel into the digestive system, leading to sensitization to a range of food or drugs (Diesner and Knittelflder, 2008). Risk of developing drug hypersensitivity may occur. Consumption of acid-suppressive drugs during pregnancy may also cause childhood asthma ("Wikipedia: Proton Pump Inhibitor"). The effects of PPIs may be categorized into two types, namely short-term effects and long-term effects. Short-term effects may include headache, nausea, diarrhea, abdominal pain, fatigue, and dizziness (Rossi, 2006). Infrequent harmful effects include rash, itch, flatulence, constipation, anxiety, and depression. PPIs may also cause erythema multiforme, pancreatitis, Stevens-Johnson syndrome, thrombocytopenia, hyperprolactinaemia and acute interstitial nephritis in some rare cases (Simpson et al., 2006). Other effects that may be caused by the PPIs are community-acquired pneumonia (Eom et al., 2010), skin ageing (Namazi and Jowkar, 2010), transmucosal gastric leak (Murray and Gabello, 2009), myopathies, and rhabdomyolysis (Clark and Strandell, 2006).

Long-term consumption of PPIs may lead to several side effects. The common one is the increased risk of fractures of the hip, wrist, and spine (Sharara et al., 2012). This is because gastric acid is used by food particles to dissociate iron salts into complexes that will be absorbed by the body as a source of iron (Annibale, Capurso, and Delle Fave, 2003). Gastric acid is also needed to release vitamin B_{12} from food particles (Rossi, 2006). Since gastric acid is reduced, iron and vitamin B_{12} absorption are also reduced. The bones can then become more fragile as homocysteine (non-protein α amino acid) increases (Abrahamsen and Vestergaard, 2013). Other side-effects are occurrence of anemia, heart arrhythmias, and Fundic gland polyps ("Wikipedia: Proton Pump Inhibitor"). Zinc absorption interference and gastric symptoms built up can also be caused by long-term use of PPIs (Farrell, 2011). Rare harmful effects include acute interstitial nephritis leading to chronic kidney disease and renal disease (Sierra and Suarez, 2007).

One common and harmful effect of proton pump inhibitor is diarrhea. PPIs can cause a diarrhea since PPIs inhibit gastric acid secretion. Bacteria such as Salmonella can then colonize the gut causing enterocolitis accompanied by diarrhea or loose bowels (Garcia et al., 2007). Shimura et al investigated the occurrence of diarrhea caused by three different PPIs namely lansoprazole, rabeprazole, and omeprazole. The investigation was conducted since there is an increase in the usage of PPIs for treating patients with GERD. Targets for this investigation were outpatients older than 20 years old who were taking a PPI for more than a month. They were then told to record the occurrences of diarrhea and loose bowel for a month daily. The result would then be categorized through diarrhea-related QOL impairment and Bristol Stool Scale Form. The former was categorized into 5 grades from embarrassment to the inability to perform daily activities, while the latter was an aid to categorize human faeces into seven categories. χ^2-test will then be used to determine whether there is correlation among the three different PPI agents. Results found that there was no significant difference for the incidence of diarrhea among the 3 types of PPIs and there was no link between diarrhea and the length and dosage of PPI administration. The rate of occurrence of diarrhea in all patients was as low as 3.5% (Shimura et al., 2012).

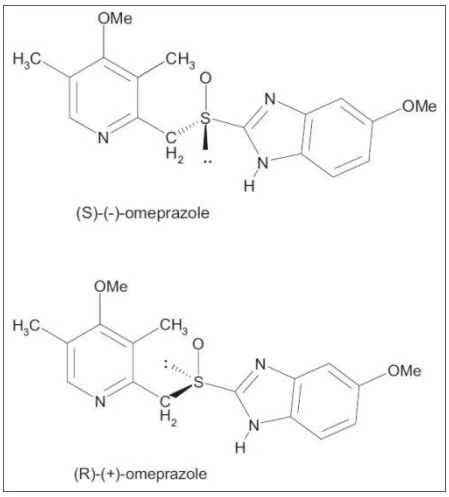
II. Specific agent of PPIs (Omeprazole)

Omeprazole is one of the proton-pump inhibitors used to treat diseases like dyspepsia, peptic ulcer, gastroesophageal reflux disease, laryngopharyngeal reflux, and Zollinger-Ellison syndrome. The chemical name of omeprazole is 6-methoxyl-2-((4-methoxy-3,5-dimethylpyridin-2-yl) methylsulfinyl)-1 *H*-benzo[*d*]imidazole.



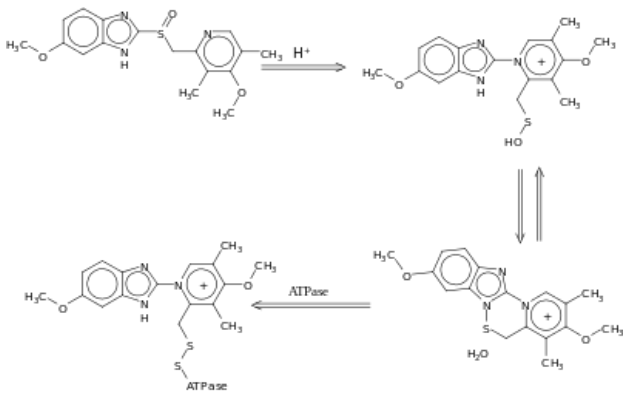
Omeprazole (“wikipedia: Omeprazole”)

Omeprazole contains a tricoordinated sulfinyl sulfur in a pyramidal structure and thus it is able to exist as either the (*S*)-(-) or (*R*)-(+) enantiomers. The major difference is that S-enantiomers metabolize more slowly than the R-enantiomers (Vyas et al., 2011). Omeprazole is a racemate meaning that it exists as equal mixture of the two ("Wikipedia: Omeprazole").



Enantiomers (Vyas et al., 2011)

Both of the enantiomers will then be converted to achiral products like sulfenic acid and sulfonamide configurations in the acidic conditions of the canaliculi of parietal cells. These achiral products will then react with a cysteine group in H^+/K^+ ATPase which leads to the ability of the parietal cells to produce gastric acid ("Wikipedia: Omeprazole").



Conversion of enantiomers (Wikipedia)

Omeprazole works by inhibiting parietal cell H^+/K^+ ATPase, the gastric "proton pump". After omeprazole is released from coating, it is converted into active sulfonamide form in the acidic environment (MedicineNet, 2009). This active sulfonamide form is then form covalent bond to cysteine residues to release proton pumps. These bonds result in a complete inhibition of gastric acid production and this inhibition will last until new proton pump molecules are synthesized (Madanick, 2011). In acidic environment, omeprazole breaks down and this can cause omeprazole to be broken down in the stomach before reaching the target. Thus, omeprazole is produced as capsule containing enteric-coated granules (Bandolier, 2003). Interaction between omeprazole and other kinds of drugs can result in the inhibition of metabolism of drugs for example omeprazole will inhibit the metabolism of clarithromycin, benzodiazepines, phenytoin, and warfarin (MediciNet, 2009). Since omeprazole and clarithromycin inhibit the metabolism of the other, it can be used as a short-term therapy for *H. pylori* eradication (Bandolier, 2003).

III. Specific effects of Omeprazole

A. Effect of Omeprazole on human arteries.

Examination on the effect of using H^+/K^+ -ATPase inhibitors on human internal mammary and radial arteries was conducted and it was found that Omeprazole causes concentration-dependent, reversible, and reproducible relaxations of arteries which were contracted with phenyilephrine, histamine, ouabain, amd K^+ free solution before the experiment was conducted. Potassium ions play essential roles in regulating cell volume, vascular reactivity and acid-base balance. The proton pump actively takes up K^+ in exchange of H^+ that flows out, (Naseri and Yenisehirli, 2005) regulating the intracellular pH and K^+. Through this regulation, the proton pump is responsible for the acid secretion. (Sachs et al., 1976).

Experiment was conducted using internal mammary and radial artery segment from 19 patients undergoing coronary artery by-pass grafting. Solution was then bubbled with 95% O_2 and 5% CO_2 to prevent tissue ischemia. Before the experiment, Omeprazole was dissolved in methanol. The concentrations producing 50% of maximum contraction and 50% of maximum relaxation were then calculated using non-linear regression analysis. Findings showed that Omeprazole had no effect on the basal tone of isolated human

arterial rings. However, they are able to relax all arteries that were contracted with phenylephrine, histamine, high K^+, ouabain, and K^+ free solution before the experiment was conducted. Omeprazole produced concentration-dependent relaxation of the rings that were contracted with either phenylephrine or histamine. It also produced concentration-dependent relaxations in arteries that were contracted with K^+-free solution. The ability of Omeprazole as a relaxant was also found to be independent from anatomical location or structure of the arteries (Naseri and Yenisehirli, 2005).

B. Effect of Omeprazole in children.

Proton pump inhibitors (PPIs) are used to treat gastric hypersecretory diseases in children although currently there is no established dosage for children. Besides, they can also be used to treat ulcers, gastro-esophageal reflux disorders (GERD) (Marchetti, Gerarduzzi, and Ventura, 2003), Barrett's esophagus, pseudo-Zollinger-Ellison syndrome (De Giacomo et al., 1990). These drugs are also useful in increasing gastric pH before and after surgery (Kaufmann et al., 2002) and improving fat absorption in children with cystic fibrosis (Francisco et al., 2002). Cystic fibrosis is a disorder that is passed genetically which affects lungs, pancreas, liver, and intestine. It causes sodium and chloride to be transported abnormally and thus results in the thickening of secretions. Study was done to investigate the effectiveness of omeprazole in treating GERD in children age 12-19. 32 children were suffering from severe esophagitis and were given omeprazole and ranitidine at advisable dosage. Result showed that health of children treated with omeprazole improved tremendously although for severe GERD, high-dose ranitidine was as effective as omeprazole (Marchetti, Gerarduzzi, and Ventura, 2003).

Gastric ulcer in children can be caused by *H. Pylori* infection and PPIs like omeprazole can be used to eliminate *H. pylori* ("Wikipedia: Omeprazole"). Investigation was done by Kato et al. to see the effectiveness of omeprazole in treating ulcers. 22 children age 8-16 was given omeprazole to eliminate *H. pylori.* Some children were given omeprazole and amoxicillin and some were given omeprazole, amoxicillin, and clarithromycin. Results showed that ulcers were treated completely. The percentage of elimination of *H. pylori* is higher in those treated with triple drugs therapy than that treated with dual drugs therapy (Kato et al., 1997).

Treatment with omeprazole may result in temporary increase in liver function studies without reports of hepatitis (Romero-Gomez et al,. 1999). Patients suffering from Zollinger-Ellison syndrome who are undergoing long-term treatment with omeprazole can experience a reduction in serum vitamin B_{12} levels (Termanini et al., 1998).

IV. Conclusion

The proton-pump inhibitors (PPIs) are drugs used mainly to inhibit gastric acid production by targeting the gastric acid pump, H^+, K^+, adenosine triphosphatase (ATPase) in the canalicular membrane of the parietal cell (Horn J, 2000). Many PPIs agent like omeprazole, lansoprazole, rabeprazole, esomeprazole are available to public due to its effectiveness in suppressing gastric acid secretion (Sachs, Shin, and Howden, 2006). These PPI agents are also able to treat harmful diseases, with the common ones being GERD and stomach ulcers. It inhibits the growth of *Helicobacter pylori* in the latter (NDDIC, 2013). In general, PPIs are able to cause several side-effects ranging from the less harmful to more adverse despite their effectiveness for treatment of acid-related diseases. In Japan, an investigation is conducted to analyze the occurrence of diarrhea in patients undergoing treatment for GERD. Diarrhea is mentioned to be one of the harmful side-effects of using PPIs. Few different PPI agents are given to patients and results show that the rate of occurrence of diarrhea remains low, showing that it is well-tolerated (Shimura et al., 2012).

Omeprazole, an agent of PPI, exists as S- and R- enantiomers with equal probability (Vyas et al., 2011). In order to reach the intended location without being digested, omeprazole is produced as capsule containing enteric-coated granules (Bandolier, 2003). Not only that it is effective in treating patients with GERD, its interaction with another drug can eradicate *H. pylori* which poses danger to human's health (Wikipedia article). Omeprazole also has other uses. It is able to relax human arteries (Naseri and Yenisehirli, 2005) and treat children with GERD, while improving fat absorption in children with cystic fibrosis (Francisco et al., 2002). It can also increase intragastric pH before and after surgery (Kaufmann et al., 2002) and eliminate *H. pylori* in children suffering from stomach ulcers ("Wikipedia: Omeprazole").

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