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Safety and Efficacy of Proton-Pump Inhibitors are Relevant to their Distinctive Chemical Structures and Physicochemical Properties[1]

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ABSTRACT

Proton pump inhibitors (PPIs) were introduced in 1989 by A.B. hassle, a former Swedish pharmaceutical company. Until 1976, treatments were not sufficient for the diseases associated with gastroesophageal reflux and peptic ulcers. Based on the mechanism of action of trimoprazole, 2-(pyridin-2-ylmethylsulfanyl)-1H-benzimidazole, A.B. hassle formulated and launched the first proton pump inhibitor named omeprazole. Proton pump inhibitors (PPIs) proved to be potent and widely used inhibitors of gastric acid secretion with minimum side effects. The majority of PPIs are derivatives of benzimidazole chemical backbone, whereas the newest member belongs to the imidazopyridine family of compounds. The following study was based on a literature review to evaluate the differences between PPIs' chemical structure and physicochemical properties and their impact on their pharmacology. Studies have shown that PPIs are weak bases with pKa1 values between 3.8 and 4.9. Based on the pKa values, Tenatoprazole has the highest acidic stability of all the PPIs. Furthermore, omeprazole tends to covalently bind with the catalytic α-subunit of the H^+/K^+-ATPase pump and inactivate, considering the mechanism of action. In contrast, the reversible PPIs often act as K+-competitive inhibitors, which tend to compete with the potassium ions to inhibit the gastric activity of the H^+/K^+-ATPase pump eventually. The half-lives of PPIs were observed between the range of 0.5-1 hour, whereas the duration of their acid inhibition for the majority of irreversible PPIs may extend up to 48 hours. The pharmacodynamics response of PPIs is evaluated through the AUC; therefore, the CYP metabolism was categorized into three phenotypes, including poor metabolizers, extensive metabolizers, and mutants. Although PPIs are regarded as relatively safer drugs for acid suppression with minimum side effects, the dosages must be adjusted among patients suffering from some hepatic impairments.

INTRODUCTION

PPIs are the most potent and widely used inhibitors of gastric acid secretion. Around 15 million people in the U.S. are tended to use PPIs for treating gastrointestinal symptoms like frequent heartburn[1]. At the same time, about 40% of adults are suffering from gastrointestinal disorders, furtherly highlighting the necessity of PPIs. The excess production of gastric acid in the stomach through gastric H^+/K^+-ATPase is halted by PPIs[2]. Despite of the PPIs are a group of medications with similar effects, each member's mode of action is different because of the varying substituents found in their chemical structures. Consequently, it is essential to target the alterations in pharmacodynamics and pharmacokinetics of different members of the same group medications to evaluate their efficacy and safety in some instances. The following literature review highlights the detailed structure-activity relationship of PPIs and their mechanism of action regarding the suppression of acid secretion. The main objective

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of the following literature is to provide an overview of how various structural substituents may alter the pharmacokinetics and pharmacodynamics of different member of the same medication phenotype[1].

ORIGIN AND GENERAL CHEMICAL STRUCTURE OF PPIs

According to the study conducted by Marcus and Wright (2020), PPIs were introduced in 1989. This event was considered the era with the most serendipities for drug design development[3]. Until 1976, the employed treatments were not sufficient for diseases associated with gastroesophageal reflux and peptic ulcers. Patients were often subjected to treatments with antacids, surgery and non-selective anticholinergic drugs that only increased the morbidity rates. While working on anti-ulcer drugs, A.B. Hassle, a former Swedish pharmaceutical company, evaluated that pyridinyl-2-ethylamide to inhibit acid secretion among rats. Although the modification of this compound into pyridinyl-2-ethylthioamide succeeded in the inhibition of acid secretion, the mechanism at that time was unknown[4]. After discovering cimetidine (Tagamet)^{R} and its mechanism of action as an antagonist for H_2 receptors, the researchers suspected that the pyridinyl-2-ethylthioamide may have a similar mechanism to that of cimetidine[5]. Despite of its success, the clinical utility of cimetidine was still had limitations while treating gastroesophageal reflux disease. These obstacles forced A.B. hassle to create a novel compound chemically named 2-(pyridinylmethylthio) benzimidazole and commly referred to as trimoprazole. Although the formation of trimoprazole was ultimately by serendipity based on the pyridinyl-2-ethylthioamide structure, trimoprazole still succeeded later on in inhibiting acid secretion. As demonstrated by the study reported by Ahmad (2021), A.B. hassle found through experimentations that trimoprazole and its modified form picoprazole can inhibit the gastric H+/K+-ATPase and subsequent mechanisms involved in the acid secretion[1].

Since trimoprazole was also contributed to toxicity in the experimental subjects, a more defined compound was required. Based on this knowledge, A.B. hassle formulated omeprazole (5-methoxy-2-[(4-methoxy-3,5-dimethyl- pyridin-2-yl)methylsulfinyl]-3H-benzimidazole), the first proton pump inhibitor and launched in 1989, which demonstrated stability in inhibiting the acid secretion without harsh side effects[6].

Currently, five products of PPIs are being commercialized in the market including, esomeprazole, pantoprazole, Rabeprazole, lansoprazole, and pantoprazole. Since, according to the study recorded by Jana et al. (2016), a substituted benzimidazole was primarily observed to inhibit the H+/ K+-ATPase, and accordingly, the majority of PPIs were derivatives benzimidazoles and known as irreversible inhibitors[7]. In contrast, Tenatoprazole is an imidazopyridine derivative and refers as reversible inhibitors. Although the basic structural framework of these compounds is similar, the only differences relies on the nature of substituents located on the benzimidazole or imidazopyridine and pyridine rings. These substituents may play an essential role in the PPI's chemical reactivity and onset of their anti-secretory action. Figure 1 shows the chemical structures of PPIs and their original related precursors.

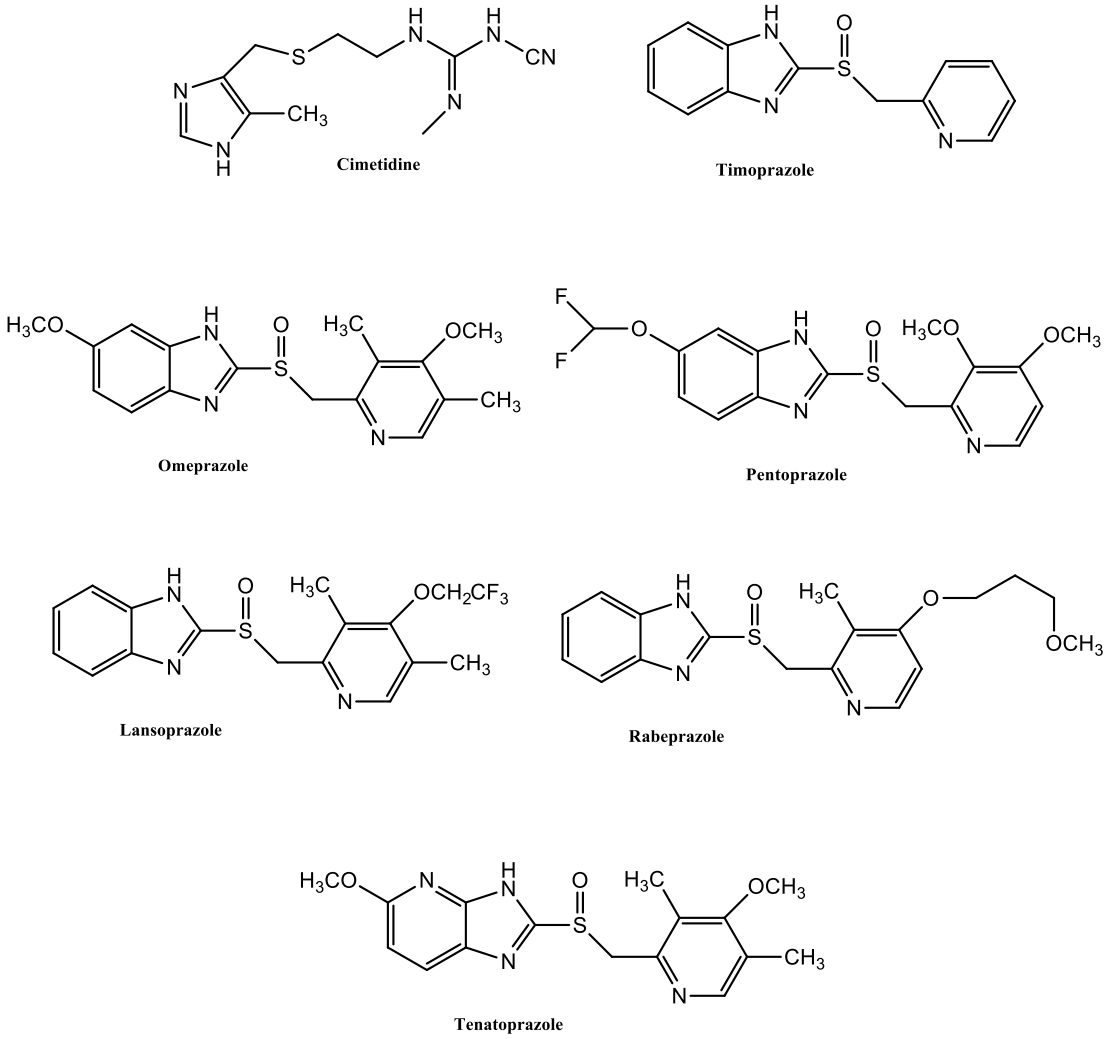


Figure 1. The chemical structures of PPIs relative to H2 blocker (Cimetidine).

PHYSICOCHEMICAL PROPERTIES OF PPIs

Physicochemical properties of a particular drug are the intrinsic physical and chemical properties that could be used to quantify its behaviour and interaction, such as its molecular-size, -weight, -charge, and lipophilicity. However, the physicochemical properties of interest concerning PPIs are majorly associated with the solubility, lipophilicity, photostability, hygroscopicity, dissolution rate, and acid stability in a solution[8]. Ultimately, the acidic stability of the PPIs is assessed in the form of protolytic behaviour, which is estimated by their pKa values, as mentioned by Li et al. (2019)[9]. Since several decades ago, the pKa value of a drug is defined by the pH (hydrogen ion concentration), at which approximately 50% of the drug exist in ionized hydrophilic form Fitch et al. (2015)[10]. As shown in Figure 2, only two nitrogen atoms out of the total three in PPIs can accept a proton, which eventually determines the value of pKa1 and pKa 2. These nitrogen atoms are doubly the benzimidazole nitrogen (N3) and pyridine nitrogen (N1)[11].

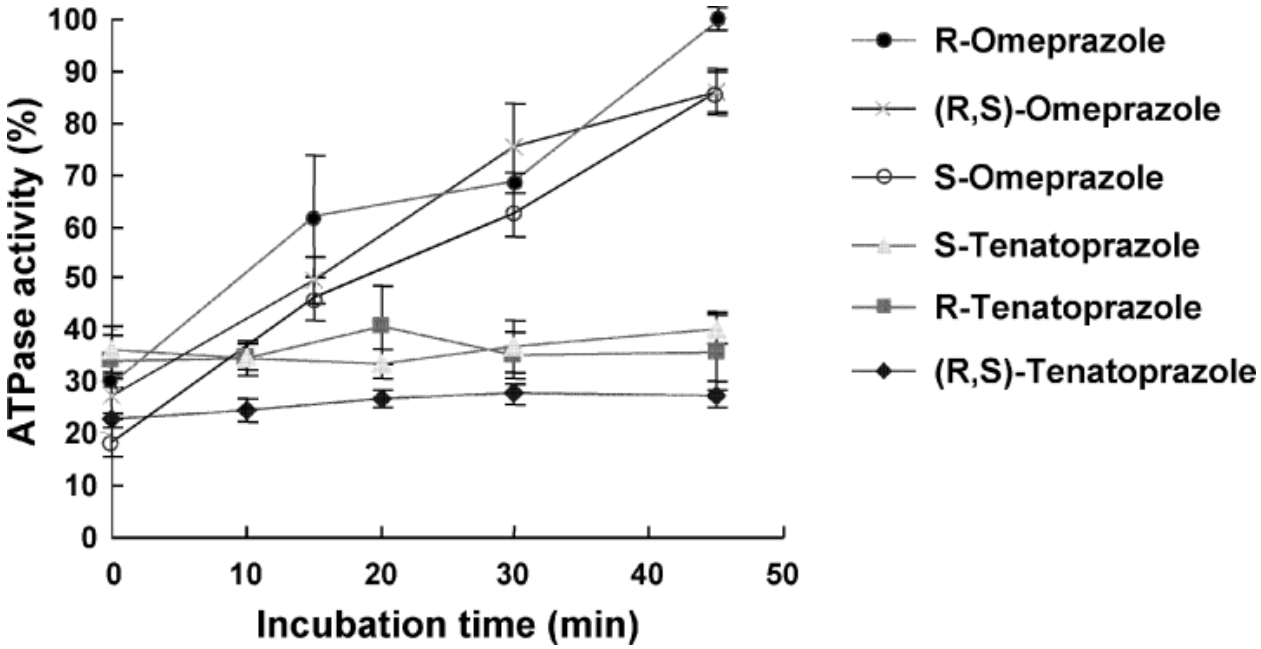


Figure 2. "Stability of proton pump inhibitor inhibition of the gastric H+, K+ -ATPase. Inhibition by tenatoprazole remains stable in the presence of glutathione whereas ATPase activity returns rapidly with omeprazole as a result of reduction of the disulphide bond coupling omeprazole and the pump"[11].

Walsh et al. (2015) [12]highlight that PPIs are weak bases that tend to have pKa1 values between 3.8 and 4.9. The pKa1 values are associated with the pyridine nitrogen and thus ensure that all the drug molecules are completely changed into cations at the parietal cells with a pH of 1.3. This means that after the drug is completely accumulated at the site of action. Contrarily, the pKa2 value of the benzimidazole nitrogen (N3) ensures protonation of the PPIs molecule for further reaction (Bhanumathi Devi et al. 2019)[13]. Considering the most commonly prescribed PPI, omeprazole has a pKa1 value of 4.0, demonstrating high specificity as Shah et al. (2016)[14]. This eventually leads to its preferential concentration in the acidic space of the parietal cells for activation. Moreover, the lower the pKa1 value of a drug at a physiologic pH, its lipophilicity will be greater. Therefore, the lower 4.0 pKa value shows that omeprazole is a lipophilic compound, making it easier to penetrate cell membrane. Contrarily, lansoprazole and pantoprazole tend to have a pKa1 value of 3.83, whereas Rabeprazole tends to have a pKa1 value of 4.53. The lower pKa value of lansoprazole highlights rather poor stability Study by Luong, et al. (2017)[15] .

Chen et al. (2020) evaluated the pKa values of PPIs at environments with pKa1= 8.84, pKa2 = 4.15, and pKa3 = 1.33. Based on the study outcomes, Tenatoprazole has the highest acidic stability of all the PPIs[16]. After Tenatoprazole, pantoprazole has the second-highest, whereas the remaining sequence for acidic stability is such that omeprazole > lansoprazole > rabeprazole.

Although the first three PPIs in this sequence have good acidic stability, they more easily penetrate into their site of action, which is parietal cells, and have greater lipophilicity, whereas lansoprazole and Rabeprazole have lower lipophilicity[17][18].

STRUCTURE-ACTIVITY RELATIONSHIP OF PPIs

Lipnick (2020) defined the structure-activity relationship as the association between the chemical structure and biological activity[19]. In the case of PPIs, the structure-activity relationship is determined by the substituted molecule of 2-pyridylmethylsulfinylbenzimidazole (Figure 3). According to Matsui et al. (2015), this active chemical entity is also referred to as the pharmacophore of the PPIs that is responsible for the pharmacological and biological interaction[20].

To perform the required function, the sulfonyl moiety in the PPI pharmacophore needs to form a disulfide bond with the proton pump CYS residues for activation [21]. However, the sulfonyl moiety is not reactive enough to perform this function; therefore, it remains in an inactivated form known as a prodrug. As these molecules do not require enzymatic activation, they are rather referred to as "misnomers". The mechanism of action requires two reactions of protonation, followed by a subsequent rearrangement of the structural units to convert the prodrug into active sulfenamide or sulfenic acid derivatives[1]. According to the study by Dey and Ghosh (2020)[22], the first protonation, which is associated with the pyridine ring, is responsible for accumulating the inactivated PPI drug around the luminal surface of parietal cells, which provides an acidic space for the prodrug. Because of the weak base pKa values (0.4-0.5), the PPIs are selectively accumulated in the term of concentration in the acidic space of the canaliculus (pH=0.8) of stimulated secretory cells where the secretion takes place, and the pH drops to 1.0[9]. This property of the PPIs is referred to as the acidic space-dependant concentration that helps to determine the PPIs' therapeutic response and intensity. Because of this property, the PPIs concentration at the site of action (surface of proton pump) is increased up to 1000 times more than in blood. The second protonation is associated with the benzimidazole nitrogen atom, which activates the C-2 carbon, as demonstrated by Manna et al. (2019). This activation allows the formation of tetracyclic cation between the unprotonated fraction of pyridine and the benzimidazole nitrogen atom, which eventually transforms into sulfenic acid[23].

Further dehydration of this tetracyclic cation tends to change the sulfenic acid into sulfonamide, which is a highly reactive thiophilic reagent. This mechanism is referred to as the acid-dependent conversion of the PPIs. Although the pharmacophore (2-pyridylmethylsulfinylbenzimidazole) is similar in the majority of PPIs, the different substituents on the pyridine and benzimidazole can determine which cysteine unit to bind with. A study by Sun et al. (2017) highlighted that while omeprazole binds at cysteine 892 and cysteine 813, Tenatoprazole and pantoprazole at cysteine 813 and cysteine 822, and finally lansoprazole binds at cysteine 813 and cysteine 321. This highlights the structure-activity relationship of different PPIs[16].

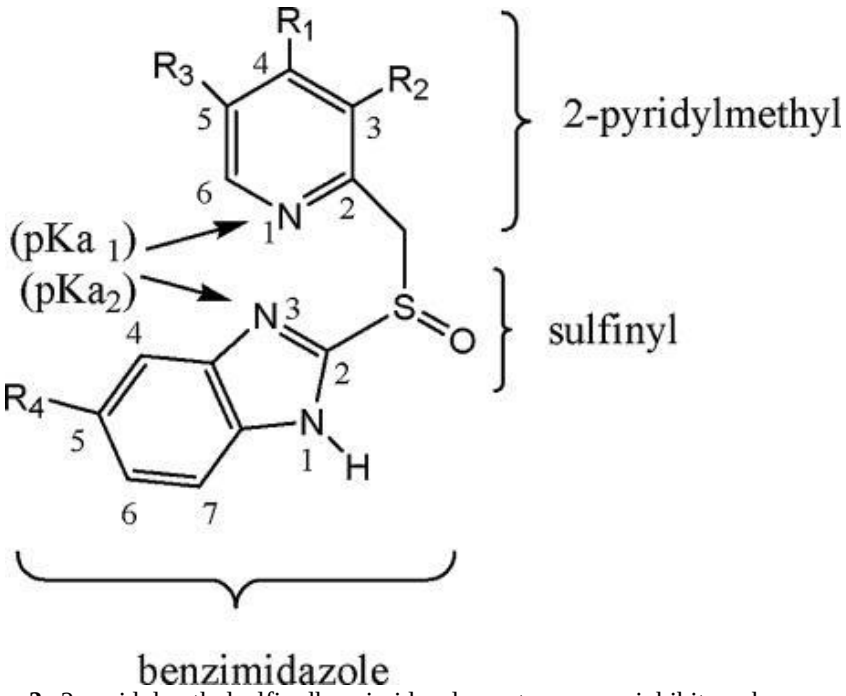
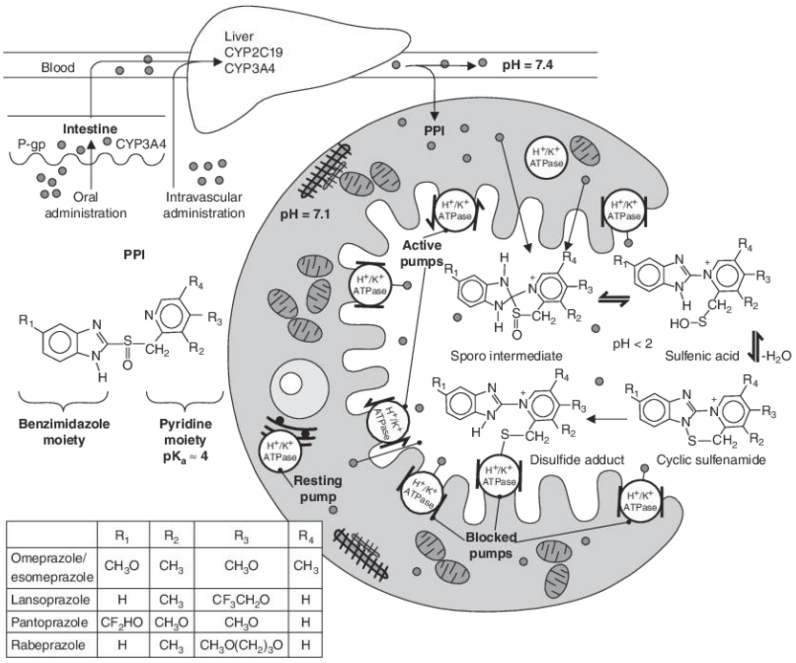


Figure 3. 2-pyridylmethylsulfinylbenzimidazole proton pump inhibitor pharmacophore with pKa1 and pKa2 sites[24].

MECHANISM OF ACTION OF PPIs

PPIs work by inhibiting gastric acid production (Figure 4). A study by Shin et al. (2006) [25]indicated that the primary regulator of gastric secretion in gastric parietal cells is the H^+/K^+-ATPase pump, also known as the proton pump. The first step of gastric acid secretion involves phosphorylation of the catalytic subunit of the Mg-ATP while the protons are exported. Following this step, the potassium-dependant dephosphorylation in the luminal surface of parietal cells, whereas the potassium is reabsorbed. As a result, the gastric Hydrogen-potassium ATPase exchange the cytoplasmic protons for the exoplasmic potassium. Therefore, H^+/K^+-ATPase is the main acidifying factor of gastric fluids as it creates an acidic environment in the lumen of the parietal cells[26].

The PPIs are categorized into two classes: irreversible and reversible inhibitors based on their mechanism of action. A study by Yang et al. (2016) mentioned that the irreversible PPIs are referred to as covalent inhibitors, which contain the substituted 2-(pyridinemethylsulfinyl) benzimidazole moiety[27]. For instance, omeprazole, an irreversible inhibitor, tend to covalently bind with the catalytic α-subunit of the H^+/K^+-ATPase pump and inactivates it subsequently, as mentioned by Granja et al. (2017)[28]. After diffusing from the bloodstream into the parietal cells, the acidic space eventually accumulates omeprazole, whereas the charged forms generated are unable to diffuse back. Therefore, two molecules of omeprazole tightly bond with one ATPase enzyme to deactivate it. Contrarily, Inatomi et al. (2016) study showed that the reversible PPIs often act as K+-competitive inhibitors, which compete with the potassium ions to inhibit gastric activity H^+/K^+-ATPase pump eventually[29].



	R_1	R_2	R_3	R_4
Omeprazole/ esomeprazole	CH_3O	CH_3	CH_3O	CH_3
Lansoprazole	H	CH_3	CF_3CH_2O	H
Pantoprazole	CF_2HO	CH_3O	CH_3O	H
Rabeprazole	H	CH_3	$CH_3O(CH_2)_3O$	H

Figure 4. Mechanism of action of proton pump inhibitors (PPIs)[30].

DIVERSITY IN THE PHARMACOKINETICS OF PPIs

Pharmacokinetics is the study associated with evaluating the time course required by a drug for drug absorption, distribution, metabolism, and excretion [1][16]. One of the significant parameters to be measured in the pharmacokinetics of a drug is its half-life, which is the time taken by a drug during which its active components reduce to half. Among healthy human beings, PPIs tend to have a half-life of about 1 hour, as demonstrated by Weersink et al. (2018)[31]. However, Tenatoprazole, which has slow absorption, rather shows a half-life of 9 hours. Tenatoprazole is a significant example of this efficacy improvement as it has the advantage of suppressing acid secretion during night-time. However, the slow activation demonstrated by Tenatoprazole tends to blunt the advantage for acid suppression in the daytime. Contrarily, a study by Rostas and McPherson (2018) highlighted that the duration of acid inhibition for most irreversible PPIs is approximately 48 hours because the drugs bind covalently or tightly to the H^+/K^+-ATPase[32].

The degree of acid inhibition by the PPIs is poorly correlated with their C_{max} (maximal plasma drug concentration). However, the area under the plasma concentration-time curve (AUC) highly collaborates with the suppression of acid according to Qi et al. (2017)[33]. Considering the oral bioavailability of the PPI, they readily become available for absorption after administration. A study by Brinkworth et al. (2016) highlighted different bioavailabilities of PPIs. These researchers found that lansoprazole tends to have 80% to 90%; pantoprazole has 77%, whereas esomeprazole has 89% bioavailability. Based on these values, the bioavailabilities of PPIs is suspected as high.

Moving toward the absorption of the PPIs, they are rapidly absorbed and metabolized in the liver by the CYP enzymes. The most commonly interacting CYP enzymes include CYP2C19 and 3A4. However, Tenatoprazole still demonstrates slow absorption and metabolism rates. Considering the excretion, omeprazole is completely metabolized in the liver. Approximately 80% of the drug components are excreted through urine within few hours, while the rest are excreted through bile. On the other hand, around 71% of pantoprazole is excreted through urine, while the rest, 18%, is through Faeces[1][31][33].

DIVERSITY IN PHARMACODYNAMICS OF PPIs

Pharmacodynamics is the study associated with the interaction of drugs within the body. The pharmacodynamics response of PPIs is evaluated through the AUC, which is the area under the curve that highlights the changing concentration of drugs within blood plasma as a function of time. Moreover, the metabolism is an another essential factor for understanding pharmacodynamics. The PPIs have a higher sensitivity towards CYP enzymes, and CYP enzymes differ based on the metabolizer's strength. Therefore, the metabolism profile for any PPI may differ from metabolizer to metabolizer, which is categorized into three phenotypes, including hetEM, PM and homEM. While the first phenotype, hetEM, is associated with metabolizers that contain wild-type with one mutant allele. The second poor CYP2C19-metabolizing phenotype (PM) associates with poor metabolizers, and the third 2C19 phenotype homEM is related to extensive metabolizer’s. A research study by Harris et al. (2021)[34] highlighted that the systematic drug exposure AUC of omeprazole among poor metabolizers increases up to 7.5 folds in PM than in hetEM and homEM. As Poor metabolizers lacking sufficient CYP enzymes, lower plasma PPI concentration is metabolised while a significant amount is left in the bloodstream.

Along with metabolism, the intragastric pH is also elevated. Such as approximately six pH among PM, 4-5 among hetEM, and 3-4 among homEM, as demonstrated by Çelebi et al. (2016)[35]. Similarly, AUC for PPIs increases sevenfold among patients with hepatic impairment, whereas the half-life is also prolonged. Moreover, Rabeprazole tends to have a lower response towards CYP metabolism, therefore, has a lower risk of the drug to drug interactions. CYP has a relatively minor role in rabeprazole metabolism.

EFFICACY OF PPIs

Acid associated diseases could be cured with inhibition of acid secretion. Such as maintaining an intragastric pH higher than 4 for almost 16 hours could be required for healing the reflux esophagitis, as demonstrated by Graham and Tansel (2018)[36]. Contrarily, an intragastric pH higher than three maintained for almost 16 hours could be used to treat peptic ulcers. Therefore, acid output and intragastric pH are the main in vivo parameters to compare different PPIs. Although the purpose served by all PPIs is the same, each one is used at different doses, which highlights their difference in efficacy. Such as the doses prescribed are omeprazole 20 mg, esomeprazole 40 mg, pantoprazole 40 mg, lansoprazole 30 mg, and tenatoprazole 40 mg. A study by Aubert et al. (2015) compared the effectiveness of these PPIs with similar dosages and observed that Rabeprazole had the highest first-day median 24-hour pH[11]. The improvement in the efficacy of the PPIs is associated with increasing the half-life of the PPI, which eventually improved the acid inhibition. Therefore, the effectiveness of the PPIs could be improved by several means such as slowing the metabolism, replacing the benzimidazole with imidazopyridine, and increasing the half-life of the drug. Aside from metabolism and half-life enhancement, another approach was adopted, which included slow absorption of the PPI. Such as synthesizing a derivative of omeprazole showed slow absorption, whereas the plasma half-life was increased up to threefold.

SAFETY OF PPIs

Although studies such as (Roy et al., 2016) highlight PPIs as relatively safe drugs for acid suppression with minimum side effects, the dosages must be adjusted among patients suffering from hepatic impairment[37]. Such as elderly patients must be prescribed with care. On the other hand, drug-drug interaction must also be taken into account while prescribing PPIs. As the administration of PPIs tends to induce achlorhydria, which lacks gastric acid, it can eventually affect the pharmacokinetics of co-administered medications[38]. Studies have evaluated certain drugs that are suspected of having drug-drug interaction with the PPIs. Such as the absorption of cephalosporin antibiotics, indinavir, vitamin B12 and ketoconazole is decreased if coadministered with PPIs.

On the other hand, the absorption of digoxin, clarithromycin and theophylline increases if co-administered with PPIs. In addition, both ketoconazole and indinavir have decreased tablet dissolution because of achlorhydria (lack of gastric acid). Moreover, certain studies have also highlighted that PPIs must be avoided for long-term use among elders. At the same time, other studies such as Fossmark et al. (2019) have highlighted that PPI may induce specific side effects such as kidney disease, dementia, liver disease, gastric neoplasia, and fractures[39].

CONCLUSION

PPIs, also known as PPIs, are the most widely used suppressants of acid secretion in the gastric cavity. The different classes of PPI include omeprazole, pantoprazole, Tenatoprazole, and Rabeprazole, which tend to have a similar pharmacophore molecule 2-pyridylmethylsulfinylbenzimidazole, whereas the only difference relies on the substituents on both rings. Based on the structure-activity relationship, the different classes demonstrate variations in the mode of action, efficacy, pharmacokinetics, pharmacodynamics and safety. The above literature highlights several studies supporting the facts. Upon evaluating these terms, the dosages of PPIs could be eventually adjusted to fetch optimum response with minimum side effects.

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