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A Critical Appraisal of Enantiomer Concept of Proton Pump Inhibitors

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ABSTRACT

Proton pump inhibitors (PPIs) one of the most prescribed drugs worldwide, inhibit acid secretion in the stomach by irreversible hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase) blocking. Currently conventional PPIs in markets are mainly in racemic forms (containing both R- and S- forms). It has been suggested that the beneficial effects of racemic PPIs mostly depend on one of the enantiomers, and a drug containing pure enantiomers might be superior to racemic PPIs. Enantiomers are mirror image stereoisomers of a molecule. In this article, we aim to analyze the comparative studies of the enantiomers of PPIs with non-racemic counter-parts and to assess whether enantiomers, as suggested by certain studies and primarily promoted by some pharmaceutical companies, demonstrate superior efficacy.

Key words: proton pump inhibitor – PPI – enantiomer.

Abbreviations: DDR: dual delayed release; DR: dual released; GERD: gastroesophageal reflux disease; EC: enteric coated; HC: hydrochloric acid; H^+/K^+ ATPase: hydrogen/potassium adenosine triphosphatase; MR: modified release; PPI: proton pump inhivitor.

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INTRODUCTION

Proton pump inhibitors (PPIs) are the drugs, which are some of the most prescribed in worldwide, inhibiting acid secretion in the stomach by irreversible hydrogen/potassium adenosine triphosphatase blocking. They are the most efficient drugs for the management of peptic ulcer disease, gastroesophageal reflux disease (GERD), gastrinoma, gastroprotection for nonsteroidal antiinflammatory drugs, acetylsalicyclic acid and *Helicobacter pylori* (*H. pylori)* eradication treatment. 93 million boxes for a whole population of 83 millions were prescribed in Turkey in 2023, causing an increasing financial burden on the economy over the years. In a recent study, it has been shown that approximately one-quarter of adults use PPIs worldwide, and unfortunately, PPIs are often used longer than necessary [1]. Because long term consumption of these drugs might be associated with possible different side effects, a decision for long term usage should be made carefully, related to the underlying disease as well as with cost efficiency assessment.

Although PPIs are effective in relieving symptoms and treatment of GERD, approximately 30% (27-42%) of patients remain symptomatic on PPI use [2]. Their majority still continue to use them.

Currently available conventional PPIs are mainly in racemic forms (containing both -r and -s forms). Racemic means that, the drugs are containing equal amounts of -s form and -r form of the same compounds. Healing of esophagitis with racemic PPIs may be difficult and relapses may be evidenced specifically in patients with severe erosive esophagitis [3]. It has been suggested that the beneficial effects of racemic PPIs mostly depend on one of the enantiomers, and a drug containing pure enantiomers might be superior to racemic PPIs [4]. Therefore, enantiomer forms of these drugs have been developed. Enantiomers are mirror image stereoisomers of a molecule and have been developed as possess of asymmetric sulfur in conventional PPIs, and clinically marketed for use (R- or S- enantiomers) (Fig 1). These enantiomers might have several clinical advantages when compared to their racemates. While some PPI enantiomers are on the market (esomeprazole,

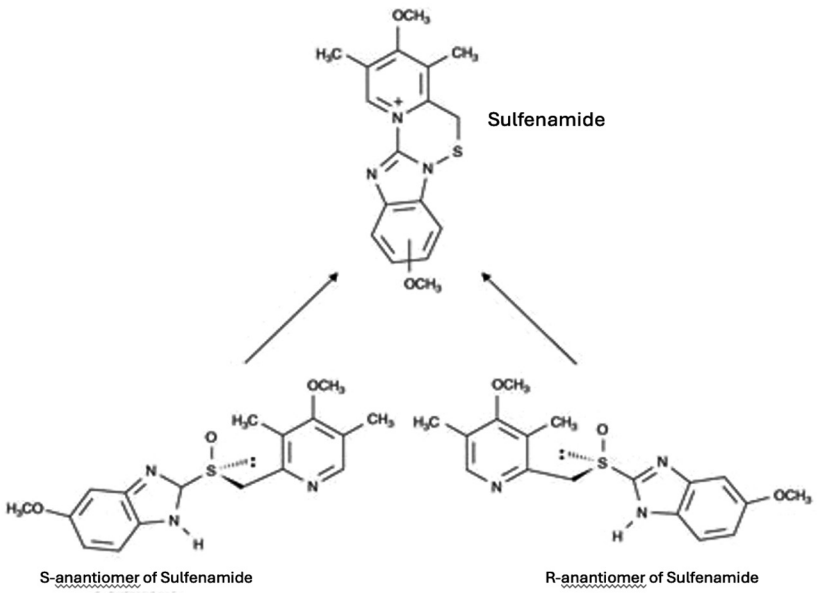

Fig. 1. The enantiomer form of the molecule. This is the schematic R- and S- enantiomer form of omeprazole.

dexlansoprazole) others have restricted availability and limited clinical evidence (dexrabeprazole, S-pantoprazole, S-tenatoprazole).

However, the actual clinical significance and purported superiority of enantiomers relative to non-racemic mixtures have yet to be conclusively demonstrated and are commonly underappreciated. One important issue is the dosage of some enantiomer PPIs such as esomeprazol and lansoprazol that are marketed at twice the dose of their non-racemic counterparts, whereas the racemic forms of rabeprazole and pantoprazole are administered at half the dose of the original molecules. Pivotal clinical comparative between racemic forms vs enantiomers studies have been performed and mainly supported by the pharma industry. The majority of the comparison studies have been performed with omeprazole 20 mg vs. esomeprazol 40 mg or lansoprazole 30 mg vs. dexlansoprazole 60 mg. Dexrabeprazole 10 and S-pantoprazole 20 mg studies are very limited compared to their non-racemic counterparts (rabeprazole 20 mg and pantoprazole 40 mg) .

We aim to analyze the comparative studies between the enantiomers of PPIs and their comparative studies with non-racemic mixtures counter-parts and to evaluate whether enantiomers are superior.

PHARMACOLOGY

The gastric acid pump, which is an H^+/K^+ ATPase, takes the major role in the secretion of hydrochloric acid (HCl). HCl is present in cytoplasmic membranes of the resting parietal cell in stomach. HCl activation takes place when H^+ ion pumps out into canalicular place in exchange for K^+ ion and stimulates the secretion of acidic fluid into the lumen. This activation of parietal cell is controlled by food intake and some neuroendocrine pathways activation by histamine, gastrin and acetylcholine. Modification of these pathways offers an opportunity for the modulation of acid secretion. Acetylcholine pathway modulation in muscarinic receptors with muscarinic antagonists (e.g. atropine) decreases gastric acid secretion, but this pathway is not specific to the gastrointestinal system. Additionally, muscarinic antagonists have adverse effects such as blurred vision and a dry mouth. The other modulation pathway is histaminic antagonism, with competitive H2 receptor competitive antagonists such as famotidine and ranitidine and the parietal cells can still respond to other activators such as acetylcholine [5].Furthermore, ranitidine was removed from the market following evidence indicating potential health risks [6].

PPIs are pharmaceutical agents that act by irreversibly inhibiting the H^+/K^+ ATPase enzyme system located on the secretory surface of gastric parietal cells that play a pivotal role in the production of HCl in the stomach. PPIs are administered orally in the form of prodrugs, which are inactive compounds that require activation in the acidic environment of the stomach. The absorption of PPIs into the circulation occurs mainly in the proximal small bowel. Following the absorption, PPIs reach the stomach via the systemic circulation and suppress gastric acid secretion by irreversibly inhibiting the H^+/K^+-ATPase enzyme in parietal cells. When reaching the acidic environment, PPIs undergo chemical conversion to their active forms, which then binds to the H^+/K^+ ATPase. It may take a few days to achieve the full effect. PPIs are most effective when the concentration of H^+/K^+ ATPase enzyme in the parietal cells is highest, which is following a prolonged fast, especially before breakfast. PPIs inhibit only the activated form of the H^+/K^+-ATPase, particularly following stimulation of acid secretion by food intake. Therefore, PPI should be taken at least 30 minutes before the breakfast, to ensure there is an adequate accumulation of the drug in the parietal cells before the H^+/K^+ ATPase is activated. If required, a second dose may be taken before the evening meal.

Metabolization of PPIs are done by hepatic P450 enzymes, by the action of CYP2C19. Because the expression of this

enzyme varies among populations, the metabolic degradation of PPIs may be reduced in certain ethnic groups [7–10]. In patients with poor CYP2C19 metabolizers, another enzyme named the CYP3A4 metabolism takes a role in degradation. PPIs metabolism with CYP3A4 is lower than CYP2C19, and individuals whose don't express CYP2C19 and individuals who do not express CYP2C19 are classified as poor metabolizers (PM). Other patients with CYP2C19 expression are accepted as extensive metabolizers (EM). In addition, the bioavailability of PPIs increases in the elderly, therefore the dosage in these groups should be monitored closely. Enantiomers have been shown have a higher metabolic stability and [11, 12], especially in these patients. Therefore, enantiomers have been developed especially in extensive metabolizer patients.

There are many brands of PPIs in the market: omeprazole, lansoprazole, rabeprazole, pantoprazole, tenatoprazole, ilaprazole and their enantiomers esomeprazole, dexlansoprazole, dexrabeprazole, S-pantoprazole and S-tenatoprazole. All the PPIs marketed as an original form omeprazole, lansoprazole, pantoprazole and rabeprazole are racemic mixtures (50/50 mixture of its R- and S- enantiomers). Tenatoprazole is one of the racemic PPIs and has a 5 to7-fold longer elimination half-life than other racemic PPIs [13, 14]. It is not currently offered in the market. The latest PPI, ilaprazole which is especially recommended for peptic ulcer treatment, currently exists on Asia markets [15]. These drugs are described in this article as racemic drugs. Esomeprazole, dexlansoprazole, S-pantoprazole, S-tenatoprazole, and dexrabeprazole consist of a single enantiomeric form and are therefore classified as enantiomer-based agents.

Dexlansoprazole

Dexlansoprazole is the R-enantiomer of lansoprazole. It accounts for more than 80% of the circulating drug after administration of oral lansoprazole [16]. In addition, dexlansoprazole has been shown to have a lower clearance time and a 5-fold greater systemic exposure than its racemate lansoprazole [16]. Modified release (MR) form has been defined, and available for use in certain markets. This form has has a delayed release formulation and has dual delayed release (DDR) technology which was designed to lengthen the concentration in plasma to improve mucosal healing of esophagus and symptom control by using a once daily dose [17].

Dexlansoprazole MR is a modified release formulation of dexlansoprazole, which contains two types of granules that dissolve at a different pH level; one type dissolves in pH 5.5 in proximal duodenum, the other type of granules is sensitive to pH 6.8 is released in the distal ileum. As a result, dexlansoprazole MR administration results in a dual peaked time concentration profile. Furthermore, dexlansoprazole medication taken before, after or during a meal has been shown to have a similar effect on intragastric pH and does not appear to be meal dependent. Both dexlansoprazol MR 60 mg and 90 mg has been documented to be more efficient than lansoprazole 30 mg in esophagitis healing rates in gastroesophageal reflux disease [18].

Today, while lansoprazole is available in the marketsas a 30 mg dose, dexlansoprazole MR form is available in the market at a dose of 60 mg, which is used in higher doses than its racemic form. In addition, dexlansoprazole at 60 mg was evidenced to be superior to lansoprazole 30 mg in a study [19]. However, the lansoprazole at dose of 30 mg was shown noninferior to dexlansoprazole MR 30 mg [20]. The therapeutic level and safety range of dexlansoprazole MR shown between 30 and 90 mg, and the therapeutic and safety range of dexlansoprazole MR has been established at 30–90 mg, and the maintenance of treatment response - defined as the healed rate of erosive esophagitis over six months - has been reported to be highest with the 60 mg dose, which is also associated with a low incidence of adverse effects [19]. Additionally, studies have shown that doses below 30 mg produce a less therapeutic effect [21]. Therefore, the manufacturer has placed the drug at a 60 mg dose on the market. Again, although enantiomers claimed to be more efficient than racemates in the literature, the dose of enantiomers used today in market is higher than the original molecular dose (Fig. 2). Although the racemic form of 60 mg might have superiorities *in vivo* or *in vitro* studies, the clinical difference is not clear and convincing. Additionly to this, it is possible that lansoprazole 60 mg might be superior to lansoprazole 30 mg with a similar fashion.

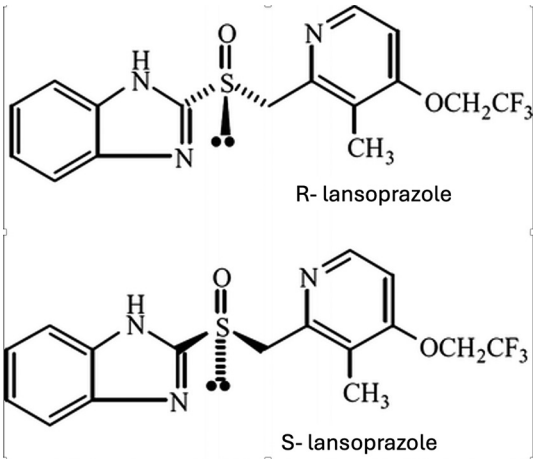

Fig. 2. The schematic form of enantiomers of lansoprazole.

Esomeprazole

Esomeprazole is the single form of S-enantiomer of omeprazole. It has been shown to have more stability, more bioavailability and a lower variability than its racemate omeprazole [22, 23]. Plasma protein binding for the enantiomer of esomeprazole as well as the racemic omeprazole has been shown as high as 97% [23]. After administration of omeprazole or esomeprazole, both drugs converted to an active inhibitor form in parietal cells, achiral sulfenamide form. Thus, the acid-inhibitory effect is directly correlated with the extent of drug exposure, regardless of whether the agent is omeprazole or esomeprazole [24, 25]. It is claimed that esomeprazole has a lower first pass hepatic metabolism and slower plasma clearance than its racemic form, which enables attainment of elevated plasma concentrations [26]. Esomeprazole 40 mg inhibits more effectively gastric acid secretion than its racemic form omeprazole 20 mg [26, 27]. AIn addition, evidence from meta-analyses indicates that esomeprazole 40 mg achieves a higher endoscopic healing rate than omeprazole 20 mg, with both agents demonstrating similar safety profiles

[28, 29]. But, no significant difference has been observed between esomeprazole 20 mg and omeprazole 20 mg [29]. A comparison of esomeprazole 40 mg and omeprazole 40 mg has been evaluated only in one open-label, crossover, 5 days study. Results indicated that a once daily administration of esomeprazole 40 mg resulted in greater acid control when compared with 40 mg once daily omeprazole. Authors also emphasized that the clinical relevance of this difference in acid control had to be proven in larger clinical studies [30]. To the best of our knowledge, these have not taken place yet which means that it is difficult to conclude that esomeprazol 40 mg is superior to omeprazole 40 mg.

Esomeprazol also has been compared with different forms of PPIs in current literature and conflicting results were observed. Esomeprazole was found to be more effective than lansoprazole in maintaining remission in patients with healed reflux esophagitis [31-33]. When compared to pantoprazole, oral esomeprazole 40 mg has been shown to be more faster and effective in intragastric acid suppression than intravenous pantoprazole 40 mg in healthy subjects [34, 35], but has an equivalent effect on esophageal pH [36]. There are conflicting results in treating and maintaining esophagitis in the current literature. Esomeprazole 40 mg has been found to have similar effects in symptom reducing when compared to pantoprazole 40 mg [37, 38] but healing rates in patients with erosive esophagitis was lower than pantoprazole 40 mg [37]. In contrar, esomeprazole 20 mg was found more effective than pantoprazole 20 mg in maintenance therapy in patients with reflux esophagitis in another study [39, 40]. But, esomeprazole, especially at 40 mg dose, has been recommended in GERD patients as first line therapy in a recent network meta-analyses [41, 42]. Indeed, in a meta-analysis regarding the eradication of *H. pylori*, treatment with esomeprazole was found to have higher *H. pylori* eradication rates in comparison with first generation PPIs (omeprazole, pantoprazole and lansoprazole) [43]. Thus, enantiomer esomeprazole at a dose of 40 mg seems to be more effective than first generation PPIs in terms of the eradication rates.

Currently, the standard therapeutic dose of esomeprazole for treatment ranges from 20 to 40 mg once daily, administered as an enteric-coated (EC) formulation. It is currently on the market at a 40 mg dose in western countries, but at a 10 to 20 mg dose in East Asian countries [44].

To prolong the antisecretory effect of esomeprazole, dual released (DR) form has been developed recently to extend the duration of gastric acid suppression, especially during nighttime [45]. Sustained exposure of esomeprazole in the DR formulation (Esomezol DR) has evidenced well maintained and higher acid inhibition when compared to the EC formulation, especially during the night. It has been suggested to be used alternatively to EC formulation, especially in relieving nocturnal acid related symptoms [45].

S-pantoprazole

S-pantoprazole is S-enantiomer of pantoprazole. It is more effective than a placebo in symptom control in patients with nonerosive reflux disease [46]. Also, S-pantoprazole 20 mg has been shown to be faster and with a stronger acid suppression than its racemic form at a 40 mg dose in healthy volunteers, but did not have any superiority on symptom resolution [47]. In addition, S-pantoprazole 20 mg has demonstrated similar efficacy in treatment of reflux esophagitis [48, 49], but more effective in improving GERD symptoms [49] when compared to pantoprazole 40 mg. S-pantoprazole is not currently on the market.

S-tenatoprazole

S-tenatoprazole is S-enantiomer of tenatoprazole. It has been shown that S- tenatoprazole metabolizes 7 times more slowly than its racemic form, and it has a safe general pharmacological profile [50]. S-tenatoprazole has significantly greater and more potent acid suppression than esomeprazole [51]. Consequently, S-tenatoprazole is a promising PPI with a safe clinical pharmacological profile. But, it is not currently on the markets and more studies are required to prove the clinical efficacy of S-tenatoprazole.

Dexrabeprazole

Dexrabeprazole is the novel single form of R- enantiomer of rabeprazole. There are few studies that have evaluate the efficacy of dexrabeprazole. Pai et al. [52] demonstrated that dexrabeprazole 10 mg was more efficient than rabeprazole 20 mg in the healing of endoscopic lesions such as esophagitis and strictures in reflux patients [52]. Furthermore, more than a 50% improvement in regurgitation symptoms was found to be faster and higher with 10 mg dexrabeprazole than with 20 mg rabeprazole in this study. Recently, Bor et al. [53] analyzed the efficiency of dexrabeprazole at the dose of 10 mg compared with 20 mg rabeprazole and found that dexrabeprazole has a similar efficiency with 20 mg rabeprazole. Different from other enantiomers, dexrabeprazole had similar efficacy with a lower dose than its racemates. Despite its apparent advantages, clinical evidence remains limited, and the drug is commercially available in only a small number of countries.

CONCLUSIONS

Enantiomers have a huge impact and marketing share within all acid inhibitory medications such as prostaglandins, H2 antagonists, potassium-competitive acid blockers. The advantages of these agents over the racemic form are generally acknowledged, even though supporting clinical evidence remains sparse. The efficacy of enantiomers over their racemic forms has been shown basically only at higher doses (double dose) except dexrabeprazole, S-pantoprazole and tenatoprazole. In contrast to other marketed enantiomers, dexrabeprazole has been shown to achieve similar therapeutic efficacy as its racemic counterpart at half the dosage, based on evidence from a limited number of studies. The results of equal doses between enantiomers and their racemic forms are conflicting and more studies are required.

Robust comparative studies are urgently needed to determine whether enantiomers offer genuine advantages over their racemic counterparts, as current evidence does not support superior efficacy at equivalent doses. Enantiomers are associated with higher costs, which are not justified by demonstrable clinical benefits. Interestingly, dexrabeprazole and S-pantoprazole appear to maintain comparable efficacy at half

the racemic dose; however, these findings are based on limited data. Validation in larger trials could not only confirm their efficacy but also suggest a potentially improved safety profile.

Conflicts of interest: None to declare.

Authors' contribution: Y.S.S. and S.B, conceived and designed the study. Y.S.S. collected the data and drafted the manuscript. S.B. revised the manuscript. Both authors read and approved the final version of the manuscript.

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