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How to Make the Right Choice of Proton Pump Inhibitor for Patients with Gastroesophageal Reflux Disease?

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Aim: to analyze the main pharmacokinetic properties of proton pump inhibitors (PPIs) and their significance in the treatment of gastroesophageal reflux disease (GERD).
Key points. Pantoprazole has a high bioavailability, the absolute bioavailability of pantoprazole at a dose of 40 mg is 77 % from the first dose and does not change with repeated use. Pantoprazole shows a faster onset of action than omeprazole. Simultaneous food intake does not change the bioavailability of pantoprazole. Suppression of hydrochloric acid production while taking pantoprazole accompanies by the achievement of endoscopic remission of GERD by day 28 in 91 % of patients with reflux esophagitis and by day 56 in all patients in the PANSTAR studies. Pantoprazole has little effect on CYP2C19 compared to other PPIs, minimizing the risk of drug-drug interactions. Pantoprazole is the most pH-selective PPI, which determines the specificity of action only in the parietal cells of the stomach and the greatest safety of long-term use in patients with comorbid pathology.
Conclusion. PPIs form the basis of the therapy of acid-dependent diseases, and, in particular, gastroesophageal reflux disease. Pantoprazole is distinguished from other PPIs by its persistent high bioavailability, long-term antisecretory effect, and very low affinity for cytochrome P450.
Keywords: gastroesophageal reflux disease, parietal cell, proton pump inhibitors, pantoprazole, bioavailability, drug-drug interactions
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Как безошибочно выбрать ингибитор протонной помпы у пациента с гастроэзофагеальной рефлюксной болезнью?

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Цель обзора: провести анализ основных фармакокинетических свойств ингибиторов протонной помпы (ИПП) и их значение в лечении гастроэзофагеальной рефлюксной болезни (ГЭРБ).
Основные положения. Пантопразол обладает высокой биодоступностью, абсолютная биодоступность пантопразола в дозе 40 мг составляет 77 % начиная с первого приема и не изменяется при повторном применении. Пантопразол демонстрирует более быстрое начало действия в сравнении с омепразолом. Одновременный прием пищи не изменяет биодоступность пантопразола. Подавление продукции соляной кислоты на фоне приема пантопразола сопровождается достижением эндоскопической ремиссии ГЭРБ к 28-му дню у 91 % пациентов с рефлюкс-эзофагитом и к 56-му дню — у всех пациентов в исследованиях «PANSTAR». Пантопразол в сравнении с другими ИПП оказывает незначительное влияние на CYP2C19, что минимизирует риск межлекарственных взаимодействий. Пантопразол — наиболее pH-селективный ИПП, что обусловливает специфичность действия только в париетальных клетках желудка и наибольшую безопасность длительного приема у пациентов с коморбидной патологией.
Заключение. ИПП составляют основу терапии кислотозависимых заболеваний и, в частности, гастроэзофагеальной рефлюксной болезни. От других ИПП пантопразол отличает стойкая высокая биодоступность, продолжительный антисекреторный эффект, очень низкое сродство с цитохромом Р450.
Ключевые слова: гастроэзофагеальная рефлюксная болезнь, париетальная клетка, ингибиторы протонной помпы, пантопразол, биодоступность, межлекарственные взаимодействия
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The relevance of the problem of GERD

Gastroesophageal reflux disease (GERD) is a chronic relapsing disease caused by impaired motor-evacuation function of gastroesophageal organs, with relapsing gastroesophageal reflux or sometimes duodenogastric reflux, which leads to clinical manifestations (heartburn, eructation, regurgitation, odynophagia, and non-cardiac chest pain) and lesions of distal esophageal segment [1].

In 2018, a meta-analysis was performed, which combined data from 108 studies with over 460,000 participants. According to the meta-analysis, GERD global prevalence is 13.3 %. Prevalence is highest in Greece (51.2 %) and lowest in China (2.5 %) [2]. The lowest prevalence of GERD is observed in Asia (10 %), while the highest prevalence of the disease is recorded in European countries (17.1 %) and on the American continent (North America — 15.4 %, South America — 17.6 %, and Central America — 19.6 %) [2].

It should be noted that GERD prevalence is higher in patients over 50 years of age (by 32 %), in obese patients (by 73 %), in smokers (by 26 %), and in patients taking non-steroidal anti-inflammatory drugs (NSAIDs) / acetylsalicylic acid (by 44 %); all the conditions listed above are risk factors for GERD [3]. Studies show GERD prevalence in Russia of 11.3 to 23.6 % [3, 4]. We observe a global trend of continuous increase in GERD incidence, as confirmed by a systematic analysis published in 2020 and based on Global Burden of Disease Study 2017. The systematic analysis shows that the disease prevalence increased by 18.1 % from 1990 to 2017: from 7,859 to 9,283 cases per 100,000 people [5].

GERD is associated with quality of life impairment comparable to that observed in diabetes mellitus, arthritis or heart failure, which results from its chronicity and devastating symptoms [6]. Impaired quality of life is directly associated with disturbed sleep, anxiety and depression, reduced productivity, impaired sexual life, etc. [6, 7]. Nocturnal symptoms reported in 70–75 % of patients with clinical manifestations of GERD have the greatest impact on quality of life [8, 9]. It should be noted that the reduction of productivity is comparable to that caused by headache or back pain [6]. Clinical studies demonstrate that effective treatment of GERD can have a positive impact on quality of life as soon as after 8 weeks of therapy [10].

Basis of GERD pharmacological therapy

Several drug classes are used to treat GERD, with the main of which being proton pump inhibitors (PPIs), H2-blockers, prokinetic agents, and antacids/alginates. Only PPIs can achieve the three main goals of treatment: relieve symptoms, heal erosions, and prevent relapses. Additionally, in patients with Barrett esophagus PPIs can prevent progression and development of esophageal dysplasia and adenocarcinoma [1]. PPIs maintain intragastric pH > 4.0 for more than 18 hours a day, which is required to heal esophageal mucosa erosions, and pH > 6.0 for 18–24 hours a day, which is necessary to provide effective eradication therapy, suppress gastrointestinal bleeding, and prevent ulcerative disease relapses [11, 12].

Individual studies, as well as large-scale systematic reviews and meta-analyses have demonstrated that PPIs are the most effective agents used in GERD. Cases of one or several esophageal erosions (esophagitis grade A according to the Los Angeles classification) should be treated with PPIs for 4 weeks, while patients with multiple erosions (esophagitis grades B–D according to the Los Angeles classification) or complicated GERD should receive 8 weeks of PPIs. PPIs are prescribed at the standard therapeutic dose, i.e., 40 mg pantoprazole daily, 40 mg esomeprazole daily, 20 mg rabeprazole daily, 30 mg lansoprazole daily, 60 mg dexlansoprazole daily, and 20 mg omeprazole twice daily [1, 13].

All PPIs share the same mechanism of action: they inhibit the activity of H^+/K^+-adenosine triphosphatase (H^+/K^+-ATPase) located on the apical membrane of parietal cells and responsible for the final stage of hydrochloric acid synthesis (Figure). H^+/K^+-ATPase transports protons (H^+) from the cytosol of the parietal cell into the secretory duct lumen in exchange for K^+. For the transport, ATP energy is used against concentration gradient, as pH inside the parietal cell is 7.4, while in the secretory duct lumen it is as low as 0.8. Cl^- ions are released from parietal cells via specific chloride channels, coupling with the proton in the secretory duct lumen, which results in hydrochloric acid secretion [14–16]. Histamine, gastrin and acetylcholine are the primary agents stimulating hydrochloric acid secretion. They act via specific cell receptors located in the basolateral membrane of parietal cells, i.e., acetylcholine (M_3), histamine (H_2), and cholecystokinin (CCK_2) [14–16].

Even though they have an identical mechanism of action, pharmacological characteristics of PPIs are different. These differences can explain varying onset times and duration of antisecretory effect and differences in the safety profile which should be given special attention.

Bioavailability, maximum plasma concentration of a medicinal product (C_{max}), area under

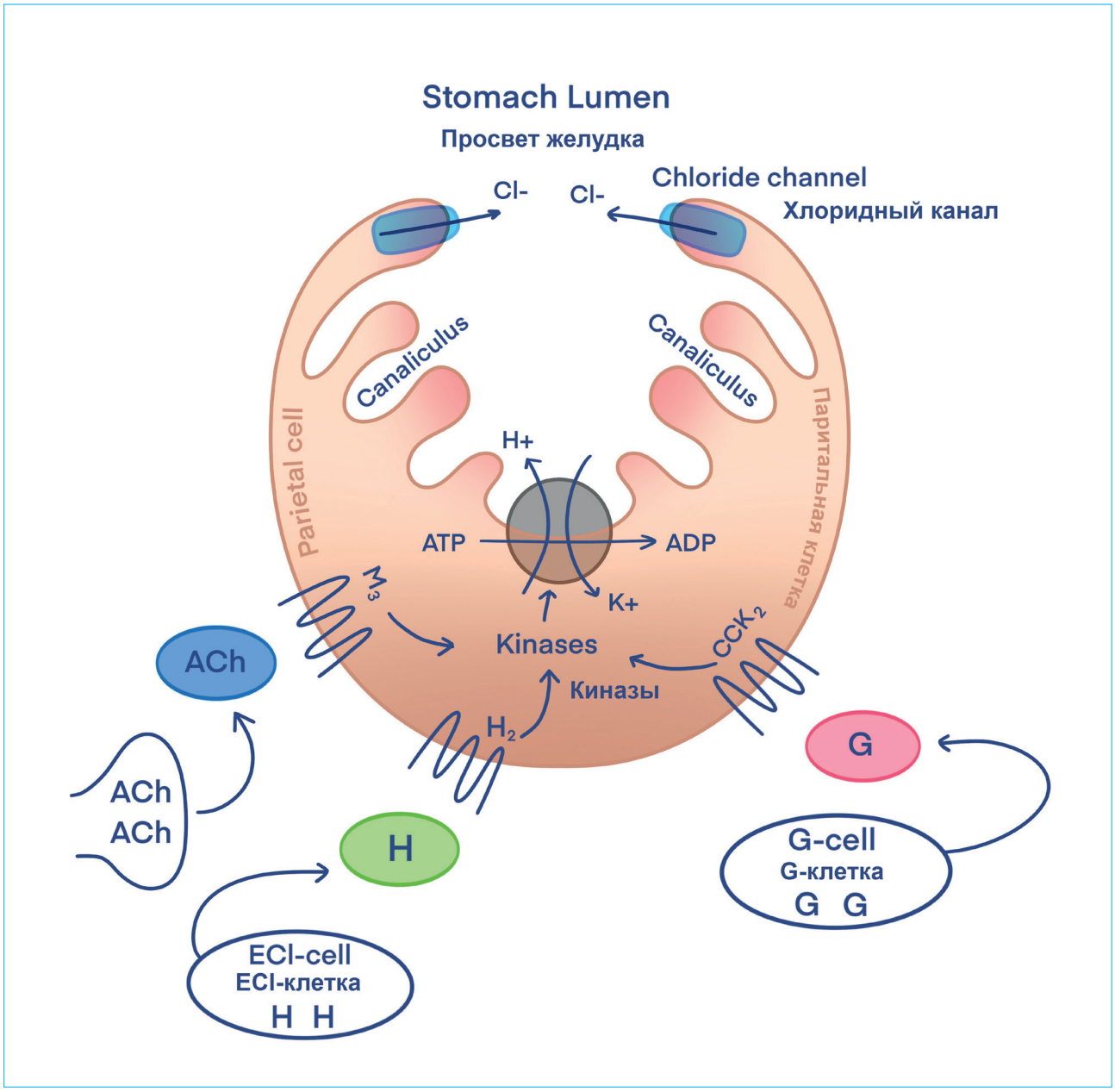

Fig. Anatomy of a parietal cell and PPI mode of action. Canaliculus — secretory duct; Ach — acetylcholine; G — gastrin; H — histamine; M_3, M_3 — muscarinic ACh receptors; H_2 — histamine H_2 receptors; CCK_2 — cholecystokinin receptor; ECL cell — enterochromaffin-like cells

Рис. Строение париетальной клетки и механизм действия ИПП. Canaliculus — секреторный каналец; ACh — ацетилхолин; G — гастрин; H — гистамин; M_3 — M_3 мускариновые рецепторы ацетилхолина; H_2 — гистаминовые H_2 рецепторы; CCK_2 — рецептор холецистокинина; ECL cell — энтерохромаффиноподобные клетки

concentration-time curve (AUC) and half-life (T1/2) are the main pharmacokinetic parameters of PPIs (Table) [17–19].

Bioavailability of PPIs

Bioavailability is one of the most important characteristics of medicinal products. Bioavailability reflects the extent and rate to which the active ingredient (the initial medicinal product or its metabolite) is absorbed to the system circulation, thus becoming available at the site of drug action. The table shows bioavailability of various PPIs. Pantoprazole 40 mg has absolute bioavailability of 77 %, starting from the first dose, without any changes for repeated doses [20]. Among other PPIs, omeprazole has the lowest bioavailability, it is about 30–40 % after the Dose 1 and increases to 60–65 % by Dose

Table. Pharmacokinetics of PPIs
Таблица. Фармакокинетические свойства ИПП

Parameter Показатель	Omeprazole 20 mg Омепразол 20 мг	Pantoprazole 40 mg Пантопразол 40 мг	Lansoprazole 30 mg Лансопразол 30 мг	Rabeprazole 20 mg Рабепразол 20 мг	Esomeprazole 40 mg Эзомепразол 40 мг	Dexlansoprazole 60 mg Декслансопразол 60 мг
Bioavailability, % Биодоступность, %	30–65	77	80–85	52	64–89	76
C_{max}, h C_{max}, ч	0.5–1	2.5	1.5–2.2	3.5	1–2	First peak: 1–2 Second peak 4–5* Первый пик: 1–2 Второй пик 4–5*
AUC (umol/L×h) AUC (мкмоль/Л×Ч)	1.11	9.93	5.01	0.86	4.32	6.52
$T_{1/2}$, h $T_{1/2}$, ч	0.5–1.5	1	1.3–1.7	0.7–1.5	1.3	1–2
Relationship between the dose and AUC Зависимость дозы и AUC	Non-linear Нелинейная	Linear Линейная	Linear Линейная	Linear Линейная	Non-linear Нелинейная	Linear Линейная
Dissociation constant (pKA) Константа диссоциации (pKa)	4	3.8	4	5	4	3.9
Renal excretion, % Выведение с почками, %	77	80	14–23	90	80	51

Note.* Product with two-phase active ingredient release.
Примечание.* Препарат с двумя фазами высвобождения активного вещества.

7 [21]. A double-blind, placebo-controlled clinical study demonstrated that after 3 days of pantoprazole 40 mg, meal-stimulated hydrochloric acid secretion decreased by 88 %, while omeprazole 20 mg decreased the parameter by 70 % only. Additionally, pantoprazole demonstrated a more rapid onset of action vs. omeprazole [22].

Bioavailability may be influenced by age, sex, physical activity, concomitant therapy, meals and other factors. However, it's important to note that co-administration with meals does not change pantoprazole bioavailability [23].

Continuously high bioavailability of pantoprazole from Day 1 onwards ensures rapid and marked inhibition of acid secretion and, as a result, symptom relief [17].

Adherence is known to largely depend on the rate of symptom relief [24]. PAN-STAR, a meta-analysis based on three multicenter, prospective trials conducted in Slovenia, Poland, and the Russian Federation (252 subjects), demonstrated complete relief of symptoms in the majority of patients with erosive reflux disease and non-erosive reflux disease treated with pantoprazole (Nolpaza) 40 mg once daily [10]. Powerful inhibition of acid secretion associated with pantoprazole lead to endoscopic cure of GERD in 91 % of reflux-esophagitis patients by Day 28 and in all patients by Day 56. A very favourable tolerability profile of pantoprazole (95 % of patients reported no adverse events) combined with rapid symptom relief and complete healing of erosions was associated with significantly improved quality of life after pantoprazole treatment completion. It should be mentioned that treatment discontinuation after 4 weeks (in patients with very few erosive lesions) is not associated with any significant increase in the severity of symptoms or any significant decrease in the quality of life [10].

Choice of PPIs considering the risks of drug-to-drug interactions

Comorbidities are frequent in patients with GERD. The most common GERD comorbidities include arterial hypertension, hypercholesterolemia, obesity, type II diabetes mellitus, asthma, depression, and anxiety disorders [25–30]. Two or more comorbidities are present in over 60 % of patients [25]. It should be noted that the occurrence of comorbidities increases with age and is higher in patients with non-erosive reflux disease (NERD) [25]. Thus, patients with comorbidities

take several products concomitantly; and as a consequence, the resulting drug-to-drug interactions may lead to changes in effect of one of the products and to undesirable effects. So, the concomitant use of two products causes adverse effects in 6 % of patients, while 5 products increase the rate to 50 % [29, 30].

PPIs are metabolized in the liver by the following P450 cytochrome isoforms: CYP3A4, CYP2B6, CYP2C19, CYP2D6, CYP2C8, CYP1A2, and CYP2C19 [31-33]. Activity of CYP2C19 is considered the most relevant, as this isoenzyme takes part in metabolism of many medicinal products: antidepressants (citalopram, escitalopram, sertraline, amitriptyline), antithrombotic agents (clopidogrel, Rwarfarin), antifungal agents (voriconazole), antitumor agents (cyclophosphamide), antiepileptic agents (carbamazepine, diazepam, phenytoin), propranolol, and nifedipine [33–35].

Lansoprazole and esomeprazole have been demonstrated to be the most potent CYP2C19 inhibitors, followed by dexlansoprazole and omeprazole. Rabeprazole and pantoprazole have the lowest inhibitory potency [31–35]. However, a nonenzymatically formed product of rabeprazole, rabeprazole thioether, has a potent inhibitory effect on CYP2C19. In vitro study using human liver microsomal preparations and recombinant CYP2C19 demonstrated that the inhibitory potency of pantoprazole on CYP2C19 was almost 3 times as low as that of rabeprazole and 10 times as low as that of omeprazole [32]. Therefore, the inhibitory effect of pantoprazole on CYP2C19 was lower than that of the other PPIs, which minimizes the risk of drug-to-drug interactions.

As to the system of cytochrome P450, pantoprazole has the lowest affinity to it. This can be explained by the fact that after initial metabolism by CYP2C19 and CYP3A4, further biotransformation is mediated by cytosolic sulfotransferase [35, 36]. Numerous studies have not demonstrated any significant interactions of pantoprazole with such commonly used products and substances as antacids, warfarin, caffeine, carbamazepine, clarithromycin, clopidogrel, diclofenac, ethanol, levothyroxine sodium, metoprolol, naproxen, and oral contraceptives [36–47].

Rules of PPIs use based on proton pump structural characteristics

Half-life of the proton pump protein is 30 to 48 hours [48]. It means that at least 20 % of proton pumps are newly synthesized within 24 hours, with more active pump synthesis at night vs. daytime. Administration of PPIs before bedtime does not inhibit nocturnal gastric acid breakthrough, due to active proton pumps synthesis and their position in deeper regions of the parietal cell, which changes in the morning when proton pumps are released and become more available for PPIs [48]. Considering the short half-life of most PPIs, the product is cleared by the start of active nocturnal acid secretion. As 70 % of proton pumps are activated by breakfast, for the maximum effect of acid secretion, PPIs should be taken 30 to 60 minutes before breakfast at a standard dose [19].

Is it possible to completely inhibit hydrochloric acid secretion? Studies have demonstrated that a single therapeutic dose of a PPI provides stable inhibition of gastric acid secretion, down to 66 % of the maximum levels. Increased dose, i.e., a dose exceeding the therapeutic one, has almost no effect on the parameter.

S. Müssig et al. looked at 24-h median intragastric pH values in subjects taking a morning or evening dose of pantoprazole 40 mg once daily [50]. There was a greater increase from baseline in pH values following morning administration of pantoprazole as compared with evening administration ($P < 0.05$).

Taking this into account, once-daily therapeutic dose of PPI is more effective and safe when administered in the morning.

Stability of hydrochloric acid secretion inhibition

Hydrochloric acid secretion can be restored after inhibition by PPIs either via *de novo* synthesis of new pump enzyme, or by breakage of the disulphide bond between the PPI and the pump protein [17].

Depending on PPI structure, they can bind to different proton pump cysteines. Omeprazole binds to cysteine 813 and cysteine 892, lansoprazole binds to cysteine 813 and cysteine 321, rabeprazole binds to cysteine 813, cysteine 892, and cysteine 321. Pantoprazole is the only PPI that binds both to cysteine 813 and cysteine 822 [50, 51]. When acid is transported by H^+/K^+-ATPase, the second proton is added, turning the compound into sulfenic acid. If this metabolic process is fast, as with omeprazole and lansoprazole, PPI reacts with cysteine 813 and/or cysteine 321 and cannot reach cysteine 822 located deeper within the membrane domain of TM6. However, if activation is postponed, the product can bind to cysteine 822 before turning into sulfenic acid. Due to additional binding of pantoprazole with cysteine 822, restoration of acid secretion is possible only after the new proton pump protein is synthesized, which results in longer effect of the product [50, 51]. Of all PPIs, pantoprazole has the longest effect, which lasts for 46 hours vs. 28 hours for rabeprazole and 24 hours for omeprazole [52].

pH selectivity

PPIs are lipophilic weak bases that are ionised and activated at low pH levels. The rate of PPIs accumulation in parietal cell canaliculi depends on the value of ionisation (dissociation) constant. The value of dissociation constant (pKa), which can be within the range of 3.8 to 5 for different PPIs, allows for selective accumulation of the product in secretory ducts of parietal cells, where pH is 0.8. pKa determines the pH value at which half of the product is protonated, turning into the active form — sulfenamide. Higher pKa values lead to a less stable product and faster protonation. Pantoprazole has pKa of 3.8, omeprazole, esomeprazole, lansoprazole, and dexlansoprazole — 4, and rabeprazole — 5 (Table). Thus, pantoprazole is the most pH-selective PPI, while rabeprazole is the least pH-selective PPI.

High pH-selectivity is associated with low probability of proton pumps inhibition in tissues with higher pH values, i.e. it ensures specificity of activity in gastric parietal cells only and greater safety of long-term administration in comorbid patients. These results were supported by a study with up to 15 years of follow-up, where 142 subjects with severe acid-dependent diseases (peptic ulcer or reflux esophagitis) received maintenance therapy with 40–160 mg pantoprazole daily [53]. 15 years of follow-up did not reveal any serious undesirable effects with confirmed or suspected relation to pantoprazole. Moderate increases in gastrine levels (resulting from inhibition of acid secretion) were not associated with any clinically relevant changes of gastric mucosa throughout the entire follow-up period. Thus, long-term pantoprazole therapy is not associated with any safety concerns.

Area under concentration-time curve

Importantly, there is a poor correlation between C_{max} and the degree of acid suppression; however, the area under the plasma concentration–time curve (AUC) does correlate well with acid suppression [19]. As shown in the Table, pantoprazole has the highest AUC concentration-time value. Due to its potent acid-inhibitory effect and long-term anti-secretory effect, pantoprazole can relieve symptoms of acid-dependent diseases.

As has been stated above, the efficacy of healing esophageal erosions is directly related to intragastric pH levels. This was confirmed by a placebo-controlled clinical trial which compared an increase in gastric pH levels in patients receiving 40 mg pantoprazole and 20 mg omeprazole [35]. The study demonstrated that the first dose of pantoprazole was associated with significantly greater increase in intragastric pH, both 24-hour (1.45 vs. 1.3, $p < 0.05$), and daytime (1.6 vs. 1.3; $p < 0.01$). Repeated pantoprazole dosing was associated with a greater increase in pH vs. omeprazole (3.15 vs. 2.05, $p < 0.01$, when average 24-hour pH is calculated; 3.8 vs. 2.65; $p < 0.05$, when average daytime pH is calculated) [35].

PPI use during the COVID-19 pandemic

The coronavirus infection pandemic makes us reconsider our approaches to management of many diseases, as now we have to choose medicinal products that are not associated with COVID-19 and have minimum risks of drug-to-drug interactions.

A recent meta-analysis that included over 83,000 cases of SARS-CoV-2 didn't find any increased risk of SARS-CoV-2 infection or mortality associated with PPIs [54]. Therapy with PPIs was associated with lower rates of coronavirus infection, as demonstrated in a systematic review and meta-analysis that included 12 studies with over 290,000 subjects [55].

Management of patients with comorbidity during coronavirus pandemic is characterized in National Consensus Statement 2020 [56]. To relieve hyperacidity-related symptoms, PPIs with the minimum risk of drug-to-drug interactions should be used, specifically, pantoprazole 40 mg/day or rabeprazole 20 mg/day. To control reflux esophagitis symptoms, manage chronic gastritis, and relieve gastric symptoms associated with COVID-19, pantoprazole or rabeprazole are also therapies of choice [56].

Conclusion

Proton pump inhibitors are the basic agents for acid-dependent diseases and, specifically, for gastroesophageal reflux disease. Even though PPIs share a mechanism of action, i.e., they inhibit the activity of H^+/K^+-ATPase responsible for the final stage of hydrochloric acid synthesis, they differ in pharmacokinetic properties. These differences are reflected in time to onset and duration of the anti-secretory effect, and in the safety profile.

Unlike other PPIs, pantoprazole is characterised by continuously high bioavailability observed as early as on Day 1, which ensures fast and significant acid suppression leading to symptom relief. Pantoprazole has the longest-lasting anti-secretory effect of all PPIs, which can be explained by molecule binding with cysteine 822 that is buried deep within the membrane domain, leading to recovery of hydrochloric acid secretion only after *de novo* synthesis of pump protein. Pantoprazole

safety is based on high pH-selectivity of the product, which ensures specificity of its action only in gastric parietal cells, as well as on its low affinity to cytochrome P450. Very low affinity of pantoprazole to cytochrome P450 minimizes the risk of drug-to-drug interactions, which makes it the product of choice in comorbid patients, including during COVID-19 pandemic.

Therefore, pantoprazole is the first-choice proton pump inhibitor that ensures a rapid and lasting effect in relieving acid-dependent disease symptoms.

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