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A Review: On Dexlansoprazole

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Abstract

Although proton pump inhibitors (PPI) have a record of remarkable effectiveness and safety in the management of gastroesophageal reflux disease (GERD), several treatment challenges with PPI have emerged. Dexlansoprazole is the (R)-enantiomer of lansoprazole contained in a formulation that produces two distinct drug releases and significantly increases the duration of active plasma concentrations and percent time pH 4 compared to conventional single-release PPI. In most patients, dexlansoprazole can be taken without regard for meals or meal timing. Dexlansoprazole 60 mg showed comparable efficacy for healing of erosive esophagitis at 8 weeks compared to lansoprazole 30 mg, and dexlansoprazole 30 mg was superior to placebo for maintenance of healed erosive esophagitis at 6 months, with 99 percent of nights and 96 percent of days heartburn-free in patients taking dexlansoprazole 30 mg. The safety profile of dexlansoprazole is similar to that of lansoprazole. The extended pharmacodynamic effects, added convenience, and efficacy and safety of dexlansoprazole offer a novel approach to gastric pH control in patients with acid-related disorders.

Keyword-

Mechanism of Action Dexlansoprazole, Pharmacokinetics & Pharmacodynamic,

pharmacological properties of dexlansoprazole, Indications for proton pump inhibitors therapy, treatment of gastroesophageal reflux disease.

Introduction

Gastroesophageal reflux disease (GERD) is the most common out-patient gastroenterology diagnosis in the United States, with a prevalence of 10% to 20% in the Western world and an annual incidence of 0.38% to 0.45%. In the United States, 20% of the adult population experiences GERD-related symptoms weekly and 7% daily[1]. Erosive esophagitis accounts for up to 30% of the GERD population, while non-erosive reflux disease (NERD) can affect up to 70% of these patients. GERD reduces health-related quality of life and imposes a significant economic burden on the health care system. Acid suppression is the mainstay of therapy

for GERD[2]. The development of proton pump inhibitors (PPIs), which reduce gastric acid secretion through blockade of the active H /K ATPase (proton pump), has revolutionized the treatment of GERD[2,3].

Generally, PPIs are a safe class of drugs that provide symptomatic relief and achieve healing of esophageal mucosa in the majority patients with erosive esophagitis. Moreover, PPIs have been shown to improve the quality of life of GERD patients[3]. Despite the success that PPIs have achieved in treating GERD and GERD-related complications, unmet needs and signifi cant challenges remain. Specifically, approximately 10% – 15% of adult patients with erosive esophagitis fail to achieve complete healing after 8 weeks of treatment. This subset of patients usually demonstrate moderate to severe disease (Los Angeles grades C and D) and comprise approximately 25% – 30% of all erosive esophagitis patients[4]. Moreover, even when continuing the initial healing dose, 15% – 23% of adult patients with Los Angeles grades A and B and 24% – 41% with grades C and D relapse within 6 months. In addition, up to 40% of non-erosive ref ux disease (NERD) adult patients remain symptomatic while on standard dose (once daily) PPI therapy[5]. and a flexible schedule of treatment with a PPI. Dexlansoprazole MR (modified release) with the Dual Delayed Release ™(DDR) formulation was designed to prolong plasma concentration – time profile in the hope of providing improved symptoms control and esophageal mucosal healing with a once-daily dose. The drug was approved by the FDA on 30 January 2009 for once-daily treatment of heartburn associated with symptomatic non-erosive GERD, acute erosive esophagitis healing, and maintenance of healed erosive esophagitis[3,6].

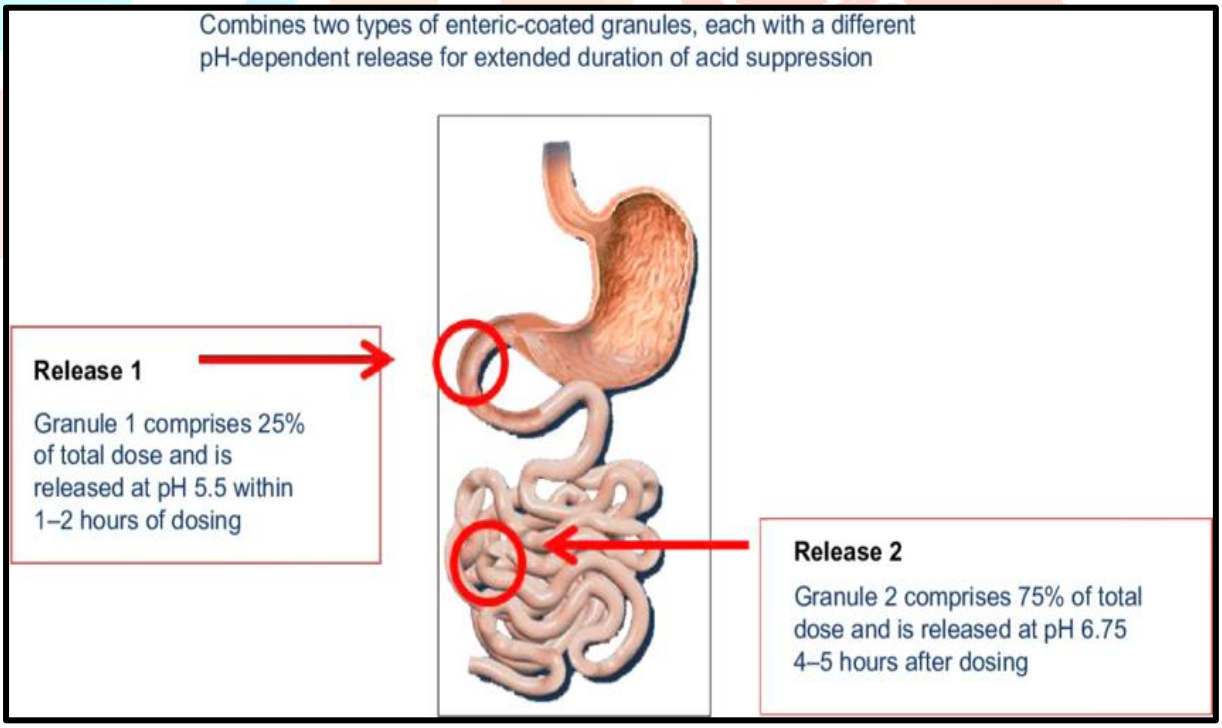

Fig No- 1 : extraesophageal manifestations

In general, treatment of extraesophageal manifestations of GERD with a PPI has been a very disappointing clinical experience[6]. Other unmet needs include faster and more effective control of postprandial heartburn, improved heartburn relief during sleep for both erosive esophagitis and NERD patients, improved acid control in Barretts esophagus patients, and a flexible schedule of treatment with a PPI. Dexlansoprazole (modified release) with the Dual Delayed Release ™(DDR) formulation was designed to prolong plasma concentration

– time profile in the hope of providing improved symptoms control and esophageal mucosal healing with a once-daily dose[7]. The drug was approved by the FDA on 30 January 2009 for once-daily treatment of heartburn associated with symptomatic non-erosive GERD, acute erosive esophagitis healing, and maintenance of healed erosive esophagitis[8].

Mechanism of Action Dexlansoprazole

is a novel modified-release formulation of dexlansoprazole, the R-enantiomer of lansoprazole. Lansoprazole and its enantiomers are equipotent in inhibiting H+ , K+ -ATPase proton pump in their activated form, in the gastric parietal cells. This enzyme inhibition blocks the final steep in acid production.7 However, dexlansoprazole constitutes[9] . 80% of circulating drug following oral administration of lansoprazole. Moreover, its clearance is lower than that of lansoprazole.17 Therefore, dexlansoprazole was selected for further clinical development.

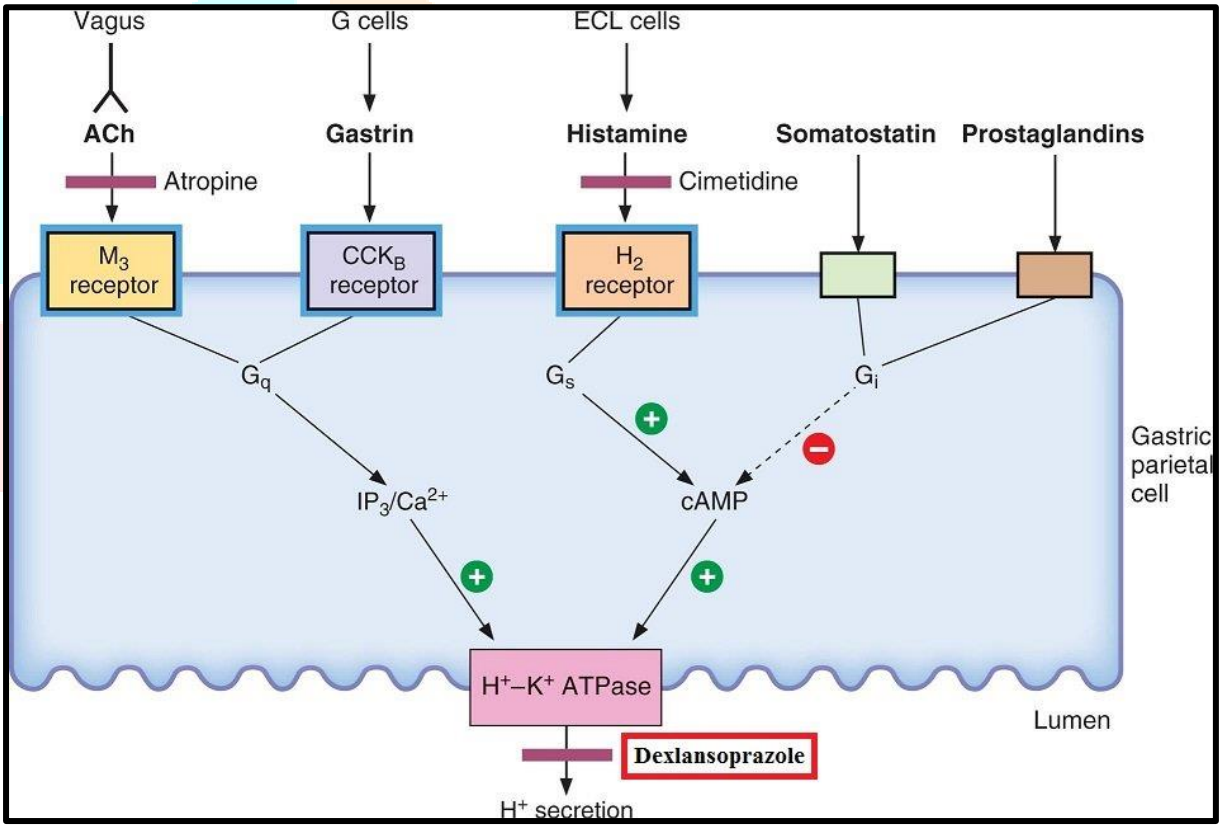

Fig No: 2 Mechanism of Action Dexlansoprazole

Indications for proton pump inhibitors therapy

Proton pump inhibitors are widely used in the therapeutic management of hydrochloric acid-related diseases, including the treatment of symptoms and healing of erosive oesophagitis, treatment of complications and prevention of gastroesophageal reflux disease (GERD) recurrence, therapy of peptic ulcer disease, eradication of Helicobacter pylori bacteria, functional dyspepsia, prevention and healing of gastroduodenal mucosal injury induced by nonsteroidal anti-inflammatory drugs (NSAIDs) and in Zollinger-Ellison syndrome and

systemic mastocytosis[11,19]. In addition to the indications listed above, PPIs are also used in other clinical conditions, e.g. in the pharmacotherapy of non-variceal upper gastrointestinal bleeding, prevention of aspiration in intensive care units (ICU) to prevent stress-related mucosal damage (SRMD) in severely ill patients. The first proton pump inhibitor and the prototype drug for other PPIs is omeprazole, which has been on the pharmaceutical market since 1989. Since that time, other proton pump inhibitors have also been successively incorporated into clinical practice, including lansoprazole, rabeprazole and pantoprazole. The PPIs enumerated here are racemic mixtures of enantiomers, i.e. optical right- and left-handed isomers[7.8.9].

The year 2001 saw the market launch of esomeprazole, the first inhibitor produced in the form of an optical isomer and being a left-handed (S)-isomer of omeprazole. The newest drug in this class, which has been available for hyposecretory treatment since 2009 in the USA and since 2015 in Poland (the second country in Europe after Switzerland) is dexlansoprazole, a right-handed (R)-isomer of lansoprazole marketed under the brand name Dexilant[30,31].

Dexlansoprazole in the treatment of gastroesophageal reflux disease

At present, the basic indication for using dexlansoprazole is gastroesophageal reflux disease in all its forms, i.e. non-erosive reflux disease (NERD) with symptoms present during the day or at night causing sleep disorders, and erosive oesophagitis of all severity grades. A particularly intensive treatment suppressing the secretion of gastric acid is necessary in patients with severe erosive oesophagitis (grades C and D according to the Los Angeles classification, in which coalescing epithelial erosions involve a considerable part or the entire oesophageal circumference). Healing such severe lesions requires a powerful suppressive effect on the secretion of acidic gastric juice using fixed therapeutic doses in maintenance treatment, because the incidence of recurrence of erosive oesophagitis in this form of GERD exceeds 90% during 6 months [2, 12, 16, 17]. It is known that some GERD patients (17–35%) treated with omeprazole or other proton pump inhibitors continue experiencing symptoms of the disease [17–20]. Studies show that up to 35.4% of patients and 34.8% of physicians are not fully satisfied with the outcome of treatment based on traditional PPIs [21]. The resistance to hyposecretory treatment can arise from a variety of factors. Some of them are physician-related (incorrect diagnosis, inappropriate drug dose, insufficiently long treatment), others – patient-related (lack of compliance, genotypic differences determining drug metabolism), and yet others – drug-related (duration of maintaining gastric pH above 4). One of the causes underlying the inefficacy of PPIs in the treatment of GERD can also be non-acidic reflux or nocturnal acid breakthrough in the stomach accompanied by sleep disorders [22, 23]. Another problem relates to inappropriate diagnosis, with GERD diagnosed instead of functional heartburn, eosinophilic oesophagitis, early achalasia of the cardia, autoimmune diseases or coexisting mental disorders [18, 19, 21, 23, 24].

As a result, in addition to confirming the diagnosis, further options for improving therapeutic outcomes should be investigated, such as extending therapy, increasing the dose, or changing the inhibitor. Dexlansoprazole is the newest of the bunch. A comparison of the effects of a single dose of dexlansoprazole 60 mg and

esomeprazole 40 mg on the mean gastric pH value over 24 hours and the percentage of time with pH > 4 in healthy volunteers revealed the following statistically significant differences: 4.3 vs. 3.7 (p = 0.003) and 58 percent vs. 48 percent (p 0.001), respectively [25]. In contrast to studies comparing the effect of different PPIs on the production of hydrochloric acid in the stomach in physiological conditions in healthy volunteers, there have been no significant differences in terms of clinical efficacy in the treatment of GERD patients. However, very favourable results for dexlansoprazole have been published in recent years, obtained in well-designed clinical trials. Dexlansoprazole's efficacy in GERD has been evaluated in clinical trials for the relief of daytime and nocturnal symptoms, as well as the healing of mucosal injury in erosive oesophagitis and the preservation of the healing impact on erosive lesions. Heartburn was eliminated within 4 weeks in 50 percent of patients receiving dexlansoprazole MR at a dose of 60 mg, in 55 percent of patients treated with the 30 mg dose, and in 50 percent of patients treated with the 20 mg dose in one of the trials involving patients with the non-erosive form of the disease.

An indirect comparison of randomized studies assessing the activity of two proton pump inhibitors in the isomeric form – dexlansoprazole 60 and esomeprazole 40 – in the elimination of symptoms and healing of erosions in GERD patients has shown the two PPIs to have a similar efficacy in healing, and dexlansoprazole to be much more effective in alleviating symptoms in NERD patients [26].

Dexlansoprazole, as expected, provides significant relief to individuals suffering from nighttime heartburn and sleep disturbances induced by GERD due to its unique pharmacodynamic features. According to patients' assessments, dexlansoprazole 30 mg provided a statistically significant higher percentage of days without heartburn for 24 hours and heartburn-free nights (54.9 percent and 80.8 percent, respectively) than placebo in a 4-week study of 947 patients diagnosed with the non-erosive form of GERD divided into groups receiving the study drug at doses of 30 or 60 mg or placebo (18.5 percent and 51.7 percent , respectively). Importantly, the other trial dose (60 mg) was found to have no further advantage over the 30 mg doseplacebo group [9]. Another randomized multicentre trial has involved 305 patients with night-time heartburn and GERD-related sleep disorders. The patients took 30 mg of dexlansoprazole or placebo once daily for a total of 4 weeks. The study drug ensured a statistically significant higher percentage of heartburn-free nights (73.1%) than placebo (35.7%), and the proportions of patients without sleep disorders after the therapy were, respectively, 69.7% vs. 47.9% (p < 0.001).

Pharmacokinetics

In two phase I randomized, open-label, cross-over studies , the authors evaluated the pharmacokinetics and pharmacodynamics of four different doses of dexlansoprazole MR (30 mg, 60 mg, 90 mg, and 120 mg) as compared with lansoprazole 15 mg and 30 mg (20). Forty patients received each dose daily for five consecutive days in a random sequence[10]. The first peak in the plasma concentration – time profile of dexlansoprazole occurred approximately 1 – 2 hours after oral administration, as was observed after oral administration of the conventional delayed release capsules of lansoprazole. However, a second peak occurred

approximately 4 – 5 hours after oral administration, prolonging the plasma concentration – time profile. The results of the C max, AUC t , and AUC 24 of the aforementioned regimens [11]. All dexlansoprazole MR doses achieved greater area under the curve (AUC) without an equivalent increase in C max as compared with lansoprazole. Dexlansoprazole (30 – 120 mg qd for 5 days) has demonstrated a longer mean residence time (MRT) than lansoprazole following oral administration (5.5 – 6.4 hours versus 2.8 –3 hours, respectively). This is primarily attributable to the prolongation of the mean absorption time (MAT), the result of the dual delayed release formulation[12]. However, there was no evidence of significant systemic drug accumulation after once-daily administration[13]. The pharmacokinetic profile of dexlansoprazole, as was determined in healthy persons, was subsequently confirmed in GERD patients[14].

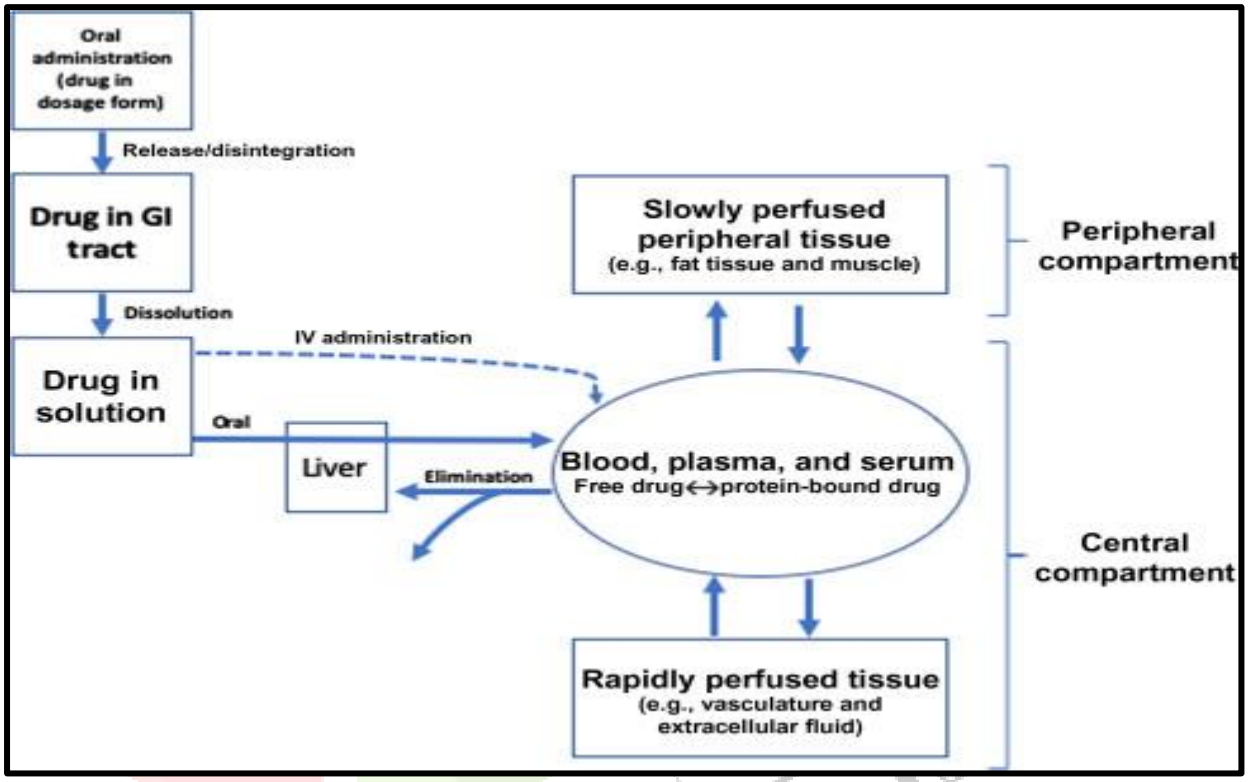

Fig No: 2: Pharmacokinetics

Pharmacodynamics

Dexlansoprazole (60 mg, 90 mg, and 120 mg) achieved significantly higher mean 24-hour intragastric pH values and percentage of time intragastric pH 4 as compared with lansoprazole 30 mg[15]. Mean intragastric pH values increased by more than 0.5, and percent of time intragastric pH 4 by more than 10% during the 16 – 24-hour interval for all the studied regimens as compared with standard dose of lansoprazole[16].

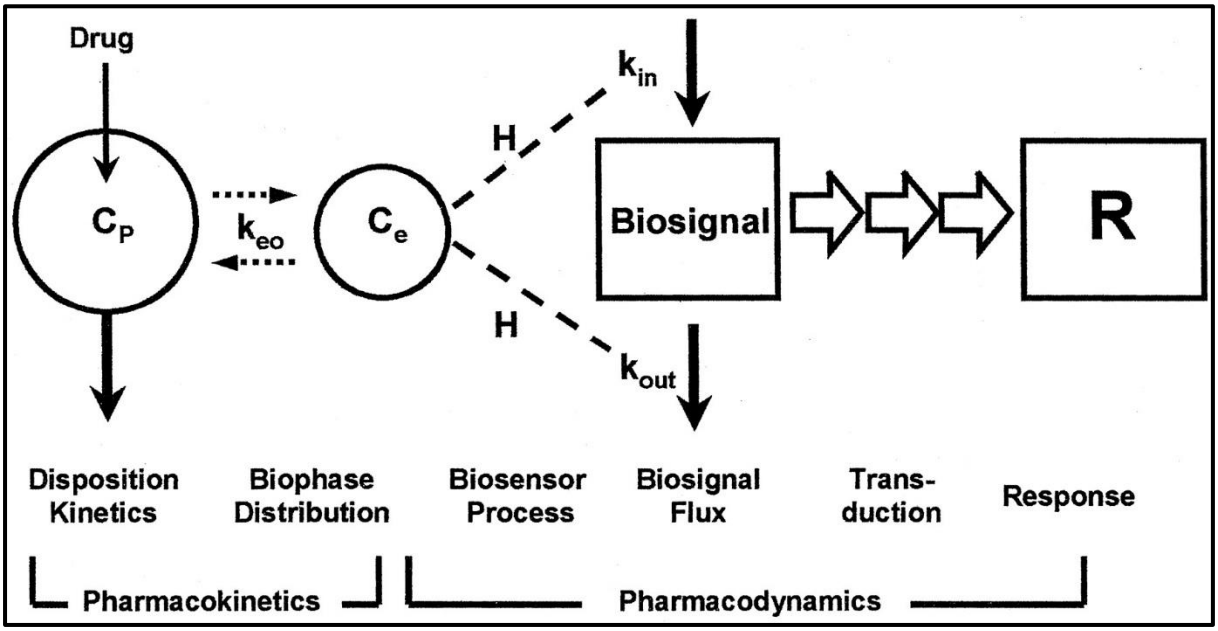

Fig No: 3. Pharmacodynamics

In a retrospective post-hoc analysis and modeling, which was performed using data from three open-label, multiple-dose, phase I studies, the authors determined that a plasma dexlansoprazole concentration of 125 ng/mL corresponds to the longest time intragastric pH is greater than 4 over a 24-hour period[17]. After daily administration of dexlansoprazole (60 to 120 mg/day) for 5 days, the drug concentration in the plasma was maintained above the aforementioned threshold level for a period that was 2 – 3 times longer than after administration of lansoprazole 30 mg[18]. Thus, dexlansoprazole at the dose range used in these studies improved the concentration – time profi le and provided extended acid suppression as compared with lansoprazole 30 mg/day[19].

Characteristics and pharmacological properties of dexlansoprazole

Due to its unique formula, dexlansoprazole can be referred to as a new-generation proton pump inhibitor[20]. A modification of the chemical structure and pharmaceutical form of the drug has improved its bioavailability and metabolism, and the efficiency of inhibiting the proton pump function in the parietal cells of the gastric mucosa[21]. The pharmaceutical form of dexlansoprazole is based on the unique technology of modified dual release. The active ingredient is released in two phases at different pH values and with a time interval. Consequently, the drug achieves two peak concentrations in the blood, and the total serum concentration of dexlansoprazole is three times higher than that of the left-handed enantiomer. Also, dexlansoprazole has a lower elimination rate than S-lansoprazole and persists longer in the serum. It inhibits acid secretion for a longer period, and its AUC (area under the curve) values are 3–5 times higher than those determined for the racemic mixture or the left-handed isomer. The active ingredient in the form of two types of granules is released from a Dexilant capsule twice, at different pH values[22]. One part, representing 25% of the drug dose, is released at the pH level of 5.5 in the proximal duodenum. The remaining part (75%) are released in the distal small intestine, where the pH is 6.75. This dual release mechanism makes it possible to achieve two peak serum concentrations of the drug: one within 1–2 h and the other within 4–5 h after administration[23].

Consequently, dexlansoprazole modified release ensures the longest period of drug retention in the circulation and the most powerful inhibitory effect on the proton pump of all available proton pump inhibitors[24].

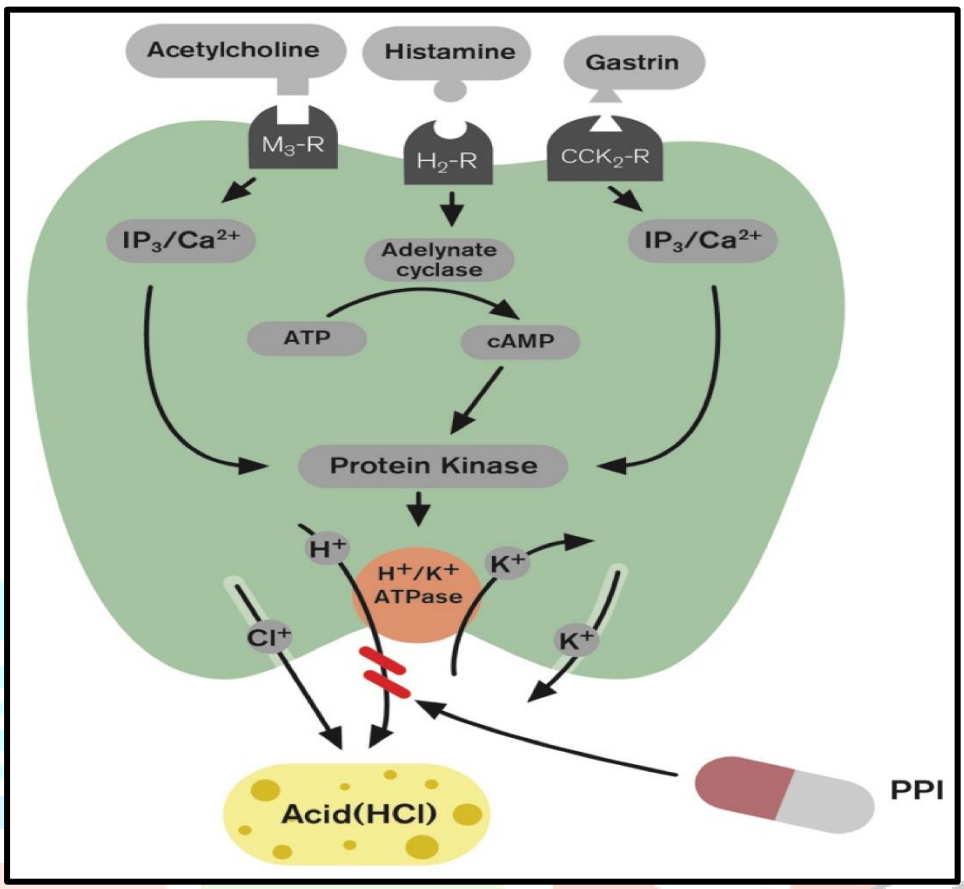

Fig No: 3 .pharmacological properties of dexlansoprazole

As is commonly known, all PPIs used to date required compliance with a defined time interval. The drug had to be taken 30–60 min before a meal, so that after being absorbed from the gastrointestinal tract and passing through the hepatic enzymatic system it can reach active (meal-activated) proton pumps in order to inhibit their function in the most effective manner possible[25]. In this respect, dexlansoprazole is an exceptional drug because it relieves patients of the need to maintain a strict regime with regard to meal times and drug intake at specific times in relation to meals, and drug efficacy is independent of these factors[26]. It is a widely recognized fact that patients fail to adhere to therapy and insufficiently comply with recommendations which make drug-taking times conditional on meal times and require an appropriate interval between them. Only about 40% take PPIs in line with recommendations, which results in weaker inhibition of acid secretion and represents one of the causes of therapeutic failure[27]. It is also associated with the observed difference in PPIs efficacy between clinical trials and daily practice. The participants of clinical trials are a selected group of patients whose therapy method can not be transposed to everyday practice. The significant factor influencing the efficacy of classic proton pump inhibitors is closely monitoring the time the administration and usage of drugs in clinical trials. As a result, the efficacy of treatment in clinical trials is much higher than in daily

practice[28]. Therefore, an essential advantage of improving cooperation (compliance) of the patients and the effectiveness of the therapy is the fact that the administration of Dexialnt after or before breakfast, lunch, dinner or evening snack has no clinically significant effect on intragastric pH control during the day[28].

The mean percentages of time during which the pH level in the stomach was > 4 over a 24-hour period after drug intake were 71%, 74%, 70% and 64%, respectively, for the regimens of taking the drug before the meals listed above[29]. As a result, dexlansoprazole maintains appropriate plasma concentrations and a therapeutic effect for a longer period than PPIs with a single release mechanism, and the efficacy of Dexilant is independent of meal times[230,31.32]. The effectiveness of the suppressing effect produced by a proton pump inhibitor upon hydrochloric acid secretion is expressed by the time during a 24-hour period when the intragastric pH level can be maintained above 4 because then the activity of pepsin – previously activated from pepsinogen in the acidic environment – radically drops and remains at a minimum level. The elimination of the destructive effect of pepsin in the increasing pH environment supports the healing of morphological features of mucosal damage in the upper[33,34].

Side-effects

The safety and tolerability of dexlansoprazole were evaluated in more than 4,500 patients in seven trials of the phase III clinical development program[32,33]. Overall, dexlansoprazole in all studied doses was well tolerated and demonstrated a side-effect profile comparable to lansoprazole[35,36,37,38]. The most commonly reported treatment-emergent adverse events (with a frequency of 2%) were diarrhea, abdominal pain, nausea, vomiting, flatulence, and upper respiratory tract infections[39,40]. Diarrhea was the most common adverse event leading to discontinuation of dexlansoprazole therapy in 0.7% of the patients. No changes in the cardiacrhythm or in QT interval were detected in healthy volunteers who received a single dose of dexlansoprazole MR 90 mg or 300 mg[41,42].

Conclusions

Dexlansoprazole is the R-enantiomer of lansoprazole with a unique dual delayed release delivery system that results in a plasma concentration – time profile that is characterized by two distinct peaks 3 – 4 hours apart. The DDR formulation provides longer duration of therapeutic level of plasma drug concentration as compared with the conventional delayed release lansoprazole. Dexlansoprazole is currently approved for three clinical indications: healing of erosive esophagitis at a dose of 60 mg orally once daily for up to 8 weeks, maintenance of erosive esophagitis healing at a dose of 30 mg orally once daily for up to 6 months, and relief of symptoms in NERD patients at a dose of 30 mg once daily for 4 weeks. The safety profile of dexlansoprazole MR is similar to that of lansoprazole. The pharmacokinetic profile of dexlansoprazole is not influenced by food.

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