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Anti-Ulcer Tablet of Pantoprazole: A Brief Review Of Its Pharmacological Properties and Therapeutic Uses with Respect To Effervescent Tablets

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ABSTRACT

Peptic ulcer is a common gastrointestinal disease seen among many peoples. It may be caused by irregular food habits, spicy foods, either an infection or long-time use of medications, drugs and stress. An ulcer depends upon the presence of acid and peptic activity in gastric juice plus a breakdown in mucosal defences. A number of anti-ulcer drug are available for curing ulcer disease. Standard treatment is including antibiotics and proton pump inhibitors. But the same time these drugs are expensive and there are many side effects caused by these drugs comparing to other herbal medicines. Pantoprazole is an irreversible proton pump inhibitor (PPI) that reduces gastric acid secretion. It is used to treat stomach ulcers, gastro-oesophageal reflux disease (GORD), acid reflux, and heartburn. Zollinger-Ellison syndrome is a rare disorder brought on by a pancreatic or intestinal tumour that is treated with pantoprazole. Both a generic and a brand-name version of the oral tablet medication pantoprazole are offered. A stomach H+/K+-ATPase (hydrogen-potassium adenosine triphosphatase) inhibitor is pantoprazole. Although oral dose forms are the most common drug, they nevertheless have significant drawbacks compared to other delivery systems, such as the possibility of medication absorption that is too sluggish and complicated by gastric residence time. It can be treated by using a lesser dosage of the medication instead of taking it in liquid form. Another technique is the effervescent technique, which can be used to create a dosage form that can speed up the time the drug dissolves and combines with the body. This technique is typically employed with preparations for rapid release. Effervescent tablets are being used more frequently and widely to modify the behaviour of drug release, such as in sustained and controlled release preparations, pulsatilla drug delivery systems, and so forth, along with the development of novel pharmaceutical techniques. The present review illustrated about the etiology of peptic ulcer, its complications, pharmacological property of pantoprazole antiulcer drug and the new effervescent tablet methodology.

Keywords: Peptic ulcer; Pantoprazole; Proton pump inhibitor; Floating Delivery System; Effervescent Tablet.

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INTRODUCTION

Typically, the stomach lining or mucus would contain peptic ulcer disease (Gastric body). Moreover, the proximal duodenum of the small intestine is where it develops. A person may simultaneously have duodenal and stomach ulcers. Moreover, a number of disorders, such as renal failure, chronic lung disease, acute stress, and ischemia (insufficient blood flow to an organ) can result in stomach ulcers. In the last 20 years, the focus of research on the pathophysiology of ulcers has mainly switched away from psychosocial variables and towards Helicobacter pylori infection and nonsteroidal anti-inflammatory medicines (NSAIDs). Support for H. pylori infection as the main contributor of peptic ulcer disease [1]. The most frequent negative side effects of nonsteroidal anti-inflammatory medications (NSAIDs) are upper gastrointestinal (GI) side symptoms (NSAIDs). It results from an imbalance between the defensive (bicarbonate ion, mucus secretion, and prostaglandins) and aggressive (acid, pepsin, *H. pylori* infection, and non-steroidal anti-inflammatory medicines, or NSAIDs) components, as well as from the mucosal cell's unique resilience. It is also influenced by a person's lifestyle, including everyday stress, alcohol, smoking, and drinks with a lot of caffeine. Clinical practise is increasingly recognising other Gastrointestinal side effects. NSAIDs can harm the small bowel and colon, and the extent of the harm may be greater than that of NSAID-associated gastropathy, as has been increasingly obvious in recent years. Although it can happen at any age, it affects people most frequently between the ages of 30 and 60 in the global population. The estimated annual death toll from peptic ulcers is 15,000. Peptic ulcer bleeding and perforation incidence estimates for each year were 19.4-57 and 3.8-14 per 100,000 people, respectively [2].

Proton-pump inhibitors are a class of drugs that includes pantoprazole. It functions by reducing the production of stomach acid. In 1989, the first PPI was introduced to the American market, and during the next ten years, both the variety of PPIs and their listed indications have steadily increased. Efficacy, tolerability, and cost are the three main considerations to address when choosing which agent to list on a formulary. After six years of usage abroad, pantoprazole was given the go-ahead for marketing in the United States in March 2000. In 2001, the short-term treatment of GERD patients with pantoprazole IV was approved. A stomach hydrogen-potassium adenosine triphosphatase (H+/K+ - ATPator) is pantoprazole sodium (Protonix). It is the fourth PPI that may be taken orally and is approved for clinical use in the United States. It and other PPIs have the same basic chemical makeup and workings. A further new drug application from Wyeth for a pantoprazole intravenous formulation has been approved by the Food and Drug Administration (FDA). The first PPI to be made available both orally and intravenously is

pantoprazole. The FDA-labeled indication is for the short-term management of gastroesophageal reflux disease-related erosive esophagitis (GERD) [3].

Although the oral route is the most recommended way to provide medication, there are still certain disadvantages, such as sluggish absorption. It is possible to credit some of the oral route's success to its simplicity in administration. [4] Limited gastric residence times hinder oral continuous medication delivery systems (GRTs). The efficacy of the supplied dose can be decreased by rapid GI transit, which can limit total drug release in the absorption zone [4, 5].

Due to how simple they are to take, effervescent pills are becoming more and more common in a range of industries, including supplements and pharmaceutical use. Effervescent pills are made to burst when they come into touch with liquids like juice or water, frequently dissolving into a solution [6]. The matrices used in these buoyant delivery systems are made of swellable polymers like Methocel or polysaccharides, such as chitosan, and effervescent substances, such as sodium bicarbonate and citric or tartaric acid6, or matrix materials with liquid chambers that gasify at body temperature [7, 8], are examples of these materials. A floating chamber that is filled with vacuum, air, or an inert gas can be used to make a medication delivery system float in the stomach [9]. By evaporating an organic solvent, such as ether or cyclopentane, or by the CO2 generated by the effervescent reaction of organic acids with carbonate-bicarbonate salts, gas can be introduced into the floating chamber [10]. The matrices are made in such a way that when they enter the stomach, the acidity of the gastric content's releases carbon dioxide, which is then trapped in the jellified hydrocolloid. The dose form moves upward as a result, maintaining its buoyancy. decreased specific gravity

The system was made up of double-layered seeds that were sustained-release tablets. An effervescent layer with both tartaric acid and sodium bicarbonate made up the inner layer. A swellable membrane layer made primarily of polyvinyl acetate and pure shellac made up the outer layer. Moreover, two sublayers of the effervescent layer were created to prevent direct contact between tartaric acid and sodium bicarbonate. The outer layer contained tartaric acid, whereas the inner sublayer contained sodium bicarbonate. The system immediately sunk to the bottom of a buffer solution when submerged in it at 37°C, forming bloated pills that resembled balloons and had densities significantly lower than 1 g/ml. The carbon dioxide produced was what caused the reaction.In this study, we will briefly discuss unusual causes of gastric ulceration as well as anti-ulcer remedies with pantoprazole effervescent tablets [11].

ORGANIC ETIOLOGIES OF PEPTIC ULCER

Helicobacter Pylori

Infection with *H. pylori* is causally related to peptic ulcer disease. In individuals with both stomach and duodenal ulcers, *H. pylori* eradication significantly lowers the risk of recurrent ulcers [12]. Particularly in Western societies, the prevalence of *H. pylori* infection in peptic ulcer disease appears to be decreasing. Although early research claimed that up to 90% of duodenal ulcers and 70% of stomach ulcers had *H. pylori* infection, more recent investigations have shown that the prevalence is only 50% [13].

Causes

When *H. pylori* bacteria invade your stomach, *H. pylori* infection results. The most common way for *H. pylori* bacteria to spread from one individual to another is through direct touch with saliva, vomit, or stool. It's also possible for contaminated food or water to disseminate *H. pylori*. It is still unclear how the *H. pylori* bacteria in some individuals causes gastritis or a peptic ulcer [14].

Complications Associated withH. PyloriInfection Include*:*

- The lining of the stomach becoming inflamed. An infection with *H. pylori* can irritate and inflame the stomach (gastritis).
- Ulcers. The protective lining of the stomach and small intestine can be harmed by *H. pylori*. This might enable stomach acid to cause an open wound (ulcer). In about 10% of *H. pylori* carriers, an ulcer will form [15].
- A significant risk factor for some kinds of stomach cancer is *H. pylori* infection [16].

Prevention

Healthcare professionals occasionally do *H. pylori* tests on healthy individuals in regions of the world where the virus and its consequences are prevalent. It is debatable among doctors if there is a benefit to testing for *H. pylori* infection when you do not exhibit any symptoms or signs of infection. Speak with your healthcare professional if you have questions regarding *H. pylori* infection or believe you may be at a high risk for stomach cancer. You and your partner can determine if *H. pylori* testing might be beneficial for you [17].

NSAIDs (Nonsteroidal anti-inflammatory drugs)

The 1938 endoscopic investigation by Douthwaite and Lintott was the first to show that non-steroidal anti-inflammatory medicines (NSAIDs) can result in ulcers and bleeding in the upper gastrointestinal tract [18].

Causes-

NSAIDs interfere with the stomach's capacity to defend itself against gastric acids, which can result in ulcers. Although these acids are essential to the digestion process, if the stomach's protective barriers are breached, they may cause harm.

- Blood circulation that aids in the repair and renewal of cells in the stomach's mucosal layer.
- Bicarbonate produced by foveolar cells, which helps neutralize stomach acid.
- Mucus produced by foveolar cells that line the stomach [19].

Symptoms

- The digestive tract may experience symptoms from a peptic ulcer, but not everyone does.
- The most typical symptom is upper abdominal discomfort, which can be either dull or searing and is felt above the stomach. Some people may just feel a little discomfort, while others may feel intense pain. The pain will typically start right after eating, but for some people, it could also start at night. It might continue for a short while or several hours.
- Other, less frequent symptoms include feeling sick to your stomach, feeling full after even a small meal, bloating, burping, gas, nausea, vomiting, lack of appetite, and weight loss.
- Rarely, individuals with peptic ulcers may notice blood in their faeces or have stools that are dark in colour due to blood in them. Vomit could also contain blood from one or more peptic sores [20].

Risk Factors

All NSAIDs have the potential to result in stomach bleeding, ulcers, and dyspepsia. However, some individuals are more prone than others to having peptic ulcer disease [21].

Peptic ulcers caused by NSAIDs are more likely to occur in people who:

- Have a history of ulcers
- 70 or older
- Take high-dose NSAIDs
- Also take blood thinners
- Also take corticosteroids
- Are taking NSAIDs regularly for a long time
- Are taking more than two types of NSAIDs
- Have an infection with H. pylori
- Smoke
- Drink alcohol
- Use aspirin daily (including low-dose aspirin for cardioprotective purposes).

According to studies, up to 25% of people who take NSAIDs for a prolonged period of time will develop an ulcer, but only a small proportion of those will experience severe side effects.

Treatment

NSAID-induced ulcers usually heal once the NSAID is stopped. Treatment may be recommended to speed up the healing process. In other cases, surgery may be needed [22].

Medications- A healthcare provider may recommend taking one or more medications.

Over-The-Counter Options Include:

- An antacid, because it helps neutralize stomach acid
- Bismuth subsalicylate (such as Pepto-Bismol or Kaopectate)

Prescription Medications That Might Be Recommended Include:

- An H2-blocker, which prevents the production of stomach acid by blocking histamine
- A proton pump inhibitor (PPI), such as Aciphex (rabeprazole) or Konvomep (omeprazole and sodium bicarbonate), which lowers the amount of acid in the stomach
- Mucosal protective agents (MPAs), which work to keep the body producing the beneficial mucosal layer in the stomach. The bigger issue for those who have developed peptic ulcer disease as a consequence of NSAID therapy is how to manage pain after those drugs are stopped. When it comes to chronic pain, a team of experts may be needed, including a pain management healthcare provider [23].

For some individuals, a class of drugs known as COX-inhibitors may be used to manage pain. COX-inhibitors have been demonstrated to be effective for treating pain and have fewer adverse effects on the intestinal system than other classes of NSAIDs. However, it is typically advised to use these medications at the lowest effective dosage because they have also been shown to have cardiovascular side effects [24].

Surgery

In some cases, surgery for a peptic ulcer may be needed. This is more often the case when there are complications as a result of the ulcer, such as:

- Serious bleeding
- Perforation (hole in the small intestine and stomach)
- Obstruction

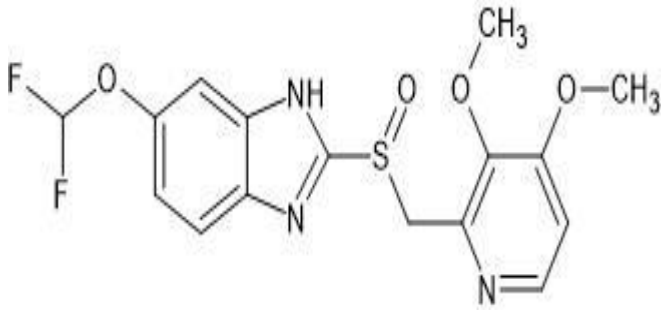
Prevention

- It goes without saying that abstaining from NSAID use altogether or using them just occasionally can help prevent peptic ulcers.
- Your healthcare provider may prescribe you one of the drugs used to treat peptic ulcers in order to stop one from happening in the first place if you must take an NSAID due to a condition you are attempting to manage.

- It has been proved that eating spicy food and experiencing daily stress do not induce ulcers. However, making the aforementioned lifestyle adjustments can lower your risk [25].

PANTOPRAZOLE[26]

Structure of Pantoprazole:



Chemical Formula: C16H15F2N3O4S

Weight Average: 383.37

Generic Name: Pantoprazole

Brand Name: Protonix

Drug class: Proton pump inhibitors

Pharmacology

PPIs work by inhibiting the H+/K+ - ATPase enzyme in the secretory canaliculus of a stimulated parietal cell. The enzyme's function within this cell is to secrete acid by forcing an exchange of H3O+ for K+ when a K+ -Cl- pathway is parallel to the pump [27]. The secretion of HCl into the stomach is the result of pump turnover. This is the final common acid secretion pathway. Pump inhibition prevents acid secretion regardless of whether it is triggered by muscarinic, gastrin, or histamine receptor stimulation. Pantoprazole, like the other PPIs, inhibits ATPase only when acid secretion is occurring. PPIs accumulate in the secretory canaliculus of the parietal cell when the cell secretes acid due to a low pK a value. Pantoprazole is an acid-activated prodrug, as protonation is required to form the active compound, which is capable of reacting with free SH groups on the ATPase enzyme. The covalent binding of PPIs to H+/K+ - ATPase irreversibly inhibits hydrogen ion transport [28].

Mechanism Of Action

PPIs are classified into two groups: benzimidazole and imidazopyridine. Pantoprazole belongs to the benzimidazole class of PPIs. The distinction between these two groups is that benzimidazoles have a slower rate of metabolism, resulting in a shorter plasma presence. Pantoprazole, like other PPIs, works pharmacologically by blocking H+,K+-adenosine triphosphatase (H+,K+- ATPase), the proton pump that is the final step in acid secretion by the parieta1 cells of the stomach mucosa. The secretion of hydrochloric acid (HCl) into the gastric lumen is primarily regulated by the proton pump's H(+)/K(+)-ATPase, which is abundant in the stomach's parietal cells. ATPase is an enzyme found on the parietal cell membrane that enables hydrogen and potassium exchange within the cell, resulting in potassium extrusion and the creation of HCl (gastric acid) [29, 32]. Proton pump inhibitors, such as pantoprazole, are weak bases that accumulate in the acidic area of the parietal cell before being converted to active sulphonamide derivatives in the canaliculi (small canal) of the

gastric parietal cell, also in an acidic environment. This active form then forms disulfide connections with critical cysteines on the gastric acid pump, preventing it from functioning. Pantoprazole specifically binds to the sulfhydryl group of H+, K+-ATPase, an enzyme involved in speeding the final step in the acid secretion route. The enzyme is inactivated, inhibiting gastric acid secretion. The inhibition of gastric acid secretion is stronger with proton pump inhibitors such as pantoprazole and lasts longer than with the H (2) antagonists [33, 34].

Table 1: FDA approved indications for pantoprazole in the treatment of gastroesophageal reflux disease (GERD) in US [35]

Year	Indication	Route	Duration
2000	Healing of erosive esophagitis	Po capsule	8-16 weeks
2000	Maintenance of erosive esophagitis	Po capsule	Continuous
2001	Erosive esophagitis with GERD unable to tolerate po	iv	7-10 days
2007	Erosive esophagitis with GERD unable to tolerate po capsule	Po suspension	Continuous

Adverse Effects

- The primary adverse effects of pantoprazole include diarrhoea, headache, upper respiratory tract infection, and abdominal pain.
- Long-term complications of pantoprazole use include diarrhoea attributed to Clostridium difficile or microscopic colitis, small-intestinal bacterial overgrowth, iron deficiency, calcium deficiency, interstitial nephritis, and diminished absorption of medications such as clopidogrel.
- Those taking higher, multiple daily doses for more than a year have an increased risk of bone fracture.
- Vitamin B12 deficiency can cause severe nerve damage and deterioration of brain functions. This has been observed in some persons who have been taking pantoprazole for more than three years.
- Chronic inflammation of the stomach's lining (atrophic gastritis) when taking pantoprazole long term. People with H. pylori are particularly at risk.
- Low blood magnesium (hypomagnesemia), which has been seen in some people taking pantoprazole for as few as 3 months. More often, it occurs after a year or more of treatment[36].

Pharmacokinetics

Pantoprazole has dose-dependent pharmacokinetics. Pantoprazole has a bioavailability of 77% when taken orally, and its absorption is unaffected by meals or antacids. The pharmacodynamics of PPIs are more important than their pharmacokinetic parameters because the duration of effect is

determined by the pace of de novo proton-pump regeneration rather than the duration of medication circulating in the body. Although the mean plasma half-life (t 1/2) of pantoprazole following a single 40-mg intravenous dosage was 1 hour. However, in people who have a mutation in the gene that codes for the CYP2C19 enzyme, the half-life can be as long as 3 hours [37].

ORAL DOSAGE

Adults:

For up to 8 weeks, use 40 mg PO once day. After 8 weeks of treatment, patients who have not healed. Throughout clinical studies, therapy was limited to 12 months or fewer. 20 mg PO once daily was also effective in reducing daytime or evening episodes of heartburn in a maintenance therapy trial. In reported therapeutic trials, patients with esophagitis were given higher oral doses of 80 mg/day (up to 120 mg/day). Continue 40 mg PO once daily for healing maintenance; occasional PPI therapy is required [38].

Children and Adolescents 5 years and older weighing 40 kg or more:

40 mg PO once daily for up to 8 weeks. Safety beyond 8 weeks has not been established.

Children and Adolescents 5 years and older weighing 15 to 39 kg:

20 mg PO once daily for up to 8 weeks. Safety beyond 8 weeks has not been established.

Children younger than 5 years or weighing less than 15 kg:

Pharmacokinetic data and paediatric evaluations suggest a dose of 0.6 to 1.2 mg/kg/day PO as an oral suspension; the greater dose is frequently prescribed for erosive illness. For GERD symptom relief, doses as low as 0.3 mg/kg/day PO have been examined. Several trials for high dosing in erosive esophagitis have allowed for doses of 15 mg/day PO for patients aged one year and 20 mg/day PO for children aged two to five years [39].

Infants:

1 month and up the recommended dose is 1.2 mg/kg/day PO (as an oral suspension). After 2 weeks of conservative treatment, infants aged 1 to 11 months (mean age 5.1 months, n = 128) with GERD symptoms were given 1.2 mg/kg/day PO. Treatment was well tolerated, with no difference in withdrawal rates or mild-to-moderate adverse events between the pantoprazole and placebo groups (p 0.001). PPIs should not be used as first-line therapy for symptomatic GERD in otherwise healthy infants (ages 1 to 11 months); instead, they should be used in infants with acid reflux illness confirmed by endoscopy (e.g., erosive esophagitis) and nonpharmacologic measures such as diet modification and positioning strategies are recommended [40].

Neonates:

There is no evidence of safety or efficacy. There is a scarcity of data. Pharmacokinetic data and paediatric reviews suggest a dosage range of 0.6 to 1.2 mg/kg/day PO (as oral suspension). The average doses were 1.25 mg/day PO (equivalent to 0.6 mg/kg/day) and 2.5 mg/day PO (equivalent to 1.2 mg/kg/day) [41].

Advantages

Pantoprazole is a medication used to treat certain stomach and oesophageal issues (such as acid reflux). It works by reducing the quantity of acid produced by your stomach. This drug relieves symptoms such as heartburn, swallowing difficulties, and coughing. It aids in the healing of acid damage to the stomach and oesophagus, the prevention of ulcers, and the prevention of oesophageal cancer [42].

Effervescent Tablet

Effervescence is made up of an alkali metal carbonate salt and a soluble organic acid, one of which is frequently the API. If this combination comes into touch with water, carbon dioxide is produced. Examples of commonly used acids and alkalis include:

- Acidic citrus
- Acid tartrate
- acetic acid
- Benzoic acid
- Acid adipic
- Bicarbonate of sodium
- Sodium carbonate
- Sesquicarbonate sodium
- bicarbonate of potassium
- Carbonate of potassium

ADVANTAGES AND DISADVANTAGES

Advantages

- Swift start of action
- Do not consume the pill.
- Good intestinal and stomach tolerance.
- Greater portability
- Enhanced palatability
- More stability

- A more constant reaction
- Inclusion of a lot of the active substances
- Precise dosing
- Better Therapeutic Impact
- Effervescent pills may be used as an alternative in remote places, particularly if parenteral versions are not available because of high costs or a lack of trained medical personnel.

Disadvantages

- Several of the active components have a bad flavour.
- Extraordinary packaging materials are needed for larger tablets.
- Because to the high quantity of more or less expensive excipients and specialised production equipment, it is relatively expensive to make
- The administration of a clear solution is recommended, while it is now commonly accepted that a fine dispersion.

FORMULATION METHODOLOGIES

WET GRANULATION:

Wet granulation is the agglomeration method that is most frequently employed in the pharmaceutical sector. The three steps of the wet granulation process are wet massing, wet sizing, and wet drying of the powder mixture. 24-36 Key wet granulation process phases

- Combining excipients and the drug(s).
- Making the binder solution.
- 3 Combining the powder combination with the binder solution to create a wet mass
- Moist particles are dried.
- Blending screened granules with a lubricant, glidant, and disintegrant.

Advantages

- Enables powder handling mechanically without compromising the mix quality.
- Improves the flow of powders by enlarging and puerility the particles.
- Improves and enhances the powder density's homogeneity.

Limitations

- The expense of wet granulation is its biggest drawback. Due to personnel, time, equipment, energy, and space requirements, the process is costly.
- Material loss throughout different processing phases.

DRY GRANULATION:

The powder combination is compacted during the dry granulation process without the use of heat or solvent. It is the least preferable granulation technique. The two fundamental steps are to compress the material into a compact, and then to mill the compact to produce granules. There are two approaches to dry granulation. Slugging, in which the powder is crushed again and the resultant tablet or slug is ground to produce the granules, is the more popular technique. The second approach involves using pressure rollers and a device like a chilosonator to recompress the powder [42-45].

CONCLUSION

In high-income countries, peptic ulcer disease is now less common than it was in the past. It is typically linked to prolonged NSAID use or H. pylori infection. Usual triple or quadruple therapy for H. pylori infection includes PPI, two antibiotics, and bismuth sulphate with or without bismuth oxychloride. When using NSAIDs, PPI can be added to them or used in place of them. Peptic ulcer disease complications are extremely serious and frequent, necessitating an immediate surgical or medical response to save the patient's life.

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