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Comprehensive analysis of nizatidine: Pharmacodynamics and pharmacokinetics in anti-ulcer treatment

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Abstract

Ulcers are characterized histologically as lesions that penetrate through the muscularis mucosae into the submucosal layer, affecting any segment of the gastrointestinal (GI) tract mucosa. They often arise due to excessive acid production from peptic secretions. Nizatidine (NZT) is a potent H2-receptor antagonist used to reduce basal, nocturnal, and stimulated gastric acid secretion. This medication is commonly prescribed for conditions such as gastroesophageal reflux disease, peptic ulcers, and duodenal ulcers.

As a member of the histamine H2 receptor antagonist class introduced before proton pump inhibitors, Nizatidine is noted for its effectiveness comparable to ranitidine. However, Nizatidine is distinguished by its thiazole ring, in contrast to the furan ring found in ranitidine. When administered orally, Nizatidine, especially in combination with antacids, enhances drug delivery to parietal cell receptors, improving the overall bioavailability of the medication and its ability to suppress acid secretion.

Nizatidine is primarily absorbed in the proximal small intestine, exhibiting about 70% absolute bioavailability. Its lower absorption from the colon and a short biological half-life (ranging from 1 to 1.6 hours) suggest the potential benefits of developing sustained-release formulations such as floating gels to prolong its therapeutic effects. Clinical studies indicate that Nizatidine, in doses of 300 mg at bedtime or 150 mg twice daily, shows superior efficacy compared to other H2-receptor antagonists for managing duodenal and gastric ulcers as well as gastroesophageal reflux disease.

Keywords: Nizatidine (NZT); Histamine H2 receptor antagonist; Floating Gel; Bioavailability; Gastro esophageal reflux disease (GERD); Peptic ulcer; and duodenal ulcer

1. Introduction

Inhibition of histamine H2-receptors on the basolateral membrane of gastric parietal cells leads to a decrease in both basal and nocturnal gastric acid secretion. This results in a reduction in the volume, acidity, and overall quantity of gastric acid produced in response to various stimuli, thereby alleviating symptoms associated with ulcers and hyperacidity. Nizatidine (NZT) functions as a competitive and reversible antagonist of the histamine H2-receptors. Classified as a Class III drug, Nizatidine is characterized by its high solubility and relatively low permeability. [1,2]

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Nizatidine is the fourth histamine H2 receptor antagonist to be introduced in the United States and is widely used for treating conditions such as duodenal and gastric ulcers, as well as gastroesophageal reflux disease (GERD). It joins other H2 antagonists like cimetidine, ranitidine, and famotidine in clinical practice. These H2 blockers selectively target the histamine type 2 receptors located on the basolateral membrane of gastric parietal cells. By binding to these receptors, H2 blockers effectively reduce gastric acid production and secretion, thereby alleviating symptoms of acid-related disorders.

Unlike proton pump inhibitors (PPIs), which block the final stage of acid secretion, H2 blockers act earlier in the process and are less potent. However, they can still reduce 24-hour gastric acid output by approximately 70% and are particularly effective at inhibiting basal and nocturnal acid production. Nizatidine was approved by the FDA in 1988 and is available both by prescription and over-the-counter. It is indicated for the management of duodenal and gastric ulcers, GERD, and for the prevention of stress ulcers. Prescription nizatidine is available in 150 mg and 300 mg capsules, as well as in oral and injectable forms under the brand name Axid. Over-the-counter versions are typically 75 mg tablets (Axid-AR). Common side effects are generally mild and may include diarrhea, constipation, fatigue, drowsiness, headache, and muscle pain. [3,4]

2. IUPAC Name of Nizatidine

1-N'-[2-[[2-[(dimethylamine) methyl]-1,3-thiazol- 4-yl]methylsulfanyl]ethyl]-1-N-methyl-2- nitroethene-1,1-diamine [5,6]

2.1. Chemical structure of Nizatidine

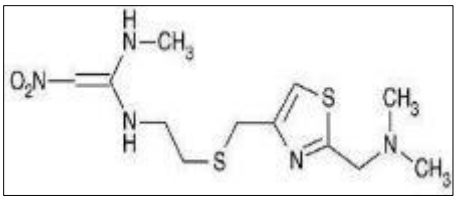

Figure 1 Structure of NizatidineChemical structure of other H2- Receptor Antagonists [5-8]

Table 1 Chemical Profile of Nizatidine

Sr. No	Drug Properties	Values
1	Formula	C12H21N5O2S2
2	Molecular weight	331.46g/mol
3	Melting point	130-132 °C
4	Solubility	Soluble in water
5	Color	Off-white crystalline powder
6	Taste	Bitter
7	Odor	odor like Sulphur

2.2. Pharmacokinetic data of Nizatidine [5,9,10]

Table 2 Pharmacokinetic Profile of Drug

S.no	Pharmacokinetic parameters	value
1	Bioavailability	75%
2	Protein binding	35%
3	Metabolism	Hepatic

4	Biological half–life	1 – 2 hrs.'
5	Excretion	Renal

2.3. Mechanism of action

Nizatidine functions as a competitive antagonist by vying with histamine for binding to H2 receptors located on the basolateral membrane of gastric parietal cells. This competitive inhibition leads to a decrease in both basal and nocturnal gastric acid production. Additionally, Nizatidine reduces the gastric acid response to various stimuli, including food, caffeine, insulin, betazole, and pent gastrin. Enhanced local delivery of Nizatidine improves the bioavailability at the receptor sites on the gastric wall, thereby increasing the drug's efficacy in lowering acid secretion. Optimizing systemic delivery of Nizatidine could further enhance its effectiveness in reducing gastric acid output. [5]

3. Pharmacodynamics Studies

Structurally, Nizatidine bears close resemblance to other H2-receptor antagonists such as cimetidine, famotidine, and ranitidine. However, Nizatidine stands out as the most effective inhibitor among these H2-receptor antagonists when it comes to reducing gastric acid secretion.[11]

3.1. Histamine Receptor Selectivity

In studies involving isolated rat uterine strips, Nizatidine demonstrated an interaction with histamine H2 receptors present in the tissue. Additionally, in comparative studies, Nizatidine showed greater potency on a weight-to-weight basis compared to cimetidine. In vivo experiments using dogs with innervated gastric fistulas and Heidenheimer pouches revealed that Nizatidine shifted the dose-response curve for gastric acid output stimulated by histamine to the right in a dose-dependent manner. [12, 13]

4. NZT Effect on Secretion of Gastric Acid

4.1. Animal Studies

When Nizatidine (NZT) was administered intravenously at a dose of 0.075 µmol/kg, intramuscularly at 0.7 µmol/kg, orally in the range of 0.05 to 1.0 µmol/kg, and subcutaneously at 0.7 µmol/kg, it was shown to inhibit gastric acid secretion in both in vivo and in vitro studies using isolated bullfrog mucosa. Nizatidine proved to be 18 times more effective than cimetidine in these investigations. [14]

4.2. Human Studies

The impact of Nizatidine (NZT) on gastric acid secretion was evaluated in healthy volunteers through both oral and intravenous (IV) administration. The study assessed its effects on basal acid secretion as well as its response to stimulation by pent gastrin, caffeine, peptone, and standard test meals. [15]

5. NZT Effect on Pepsin

Research indicates that H2 receptor antagonists such as famotidine, ranitidine, and cimetidine generally reduce pepsin secretion. However, a study involving a single dose of Nizatidine (NZT) administered to healthy volunteers found no impact on pepsin activity. Contrastingly, another study by Hammond and Offen in 1988 reported that a single dose of Nizatidine, ranging from 75 mg to 300 mg, effectively inhibited pepsin secretion stimulated by betazole.[16]

5.1. Effect on Serum Gastrin

There was no significant variation in serumgaster in levels who received oral NZT (30,100 or hyper gastronome and prolonged suppression ofgastric secretion. [11]

5.2. Pharmacokinetic Properties

300mg) and those receiving a placebo. [17]

6. Effect on Endocrine Function

6.1. Anti-androgenic and other effects

Cimetidine is known to interact competitively with androgen receptors, leading to the displacement of dihydrotestosterone. In contrast, Nizatidine does not compete with androgen binding sites in the cytosol of prostatic tissue in male rats. Additionally, Nizatidine is not associated with alterations in the hypothalamic-pituitary-adrenal (HPA) axis or the thyroid gland. [11,18,19]

7. Effect on the Hepatic Metabolism of Drugs

Nizatidine does not influence the metabolism of drugs that are processed by the liver's mixed-function oxidase system. In contrast, cimetidine can impact the elimination of various medications, including warfarin, phenindione, phenytoin, diazepam, and chlordiazepoxide. [11,19]

8. Effect on Gastric Mucosa

A prolonged study involving rats administered with high doses of Nizatidine (NZT) examined its pharmacokinetic properties following both oral and intravenous (IV) administration in healthy subjects and patients with renal impairment. The findings indicated that Nizatidine's pharmacokinetics are dose-proportional and linear. No significant differences were observed in the drug's behavior whether administered orally or IV, and subsequent samples were analyzed using high-performance liquid chromatography (HPLC).[21]

8.1. Absorption

Nizatidine (NZT) is rapidly absorbed, reaching peak plasma concentrations within 1 to 3 hours. Its absorption is not influenced by the intake of food, but the concurrent use of antacids, such as aluminum hydroxide gel, can reduce its absorption by 10 to 30%. [11]

8.2. Distribution

Apart volume of distribution was found 1.2 - 1-6L/kg after analysis of data received from oral and I.V. doses. [11]

8.3. Metabolism and Elimination

In studies where Nizatidine (NZT) was administered at doses up to 485 mg/kg over two years, it was observed that the primary route of excretion for NZT is through the kidneys. The drug is metabolized in the stomach's mucosa, where it influences enterochromaffin-like cells, leading to an increase in their density. Nizatidine is eventually metabolized into several compounds, including N-2-mono-desmethyl nizatidine, Nizatidine-N-2-oxide, and Nizatidine sulphoxide. [11]

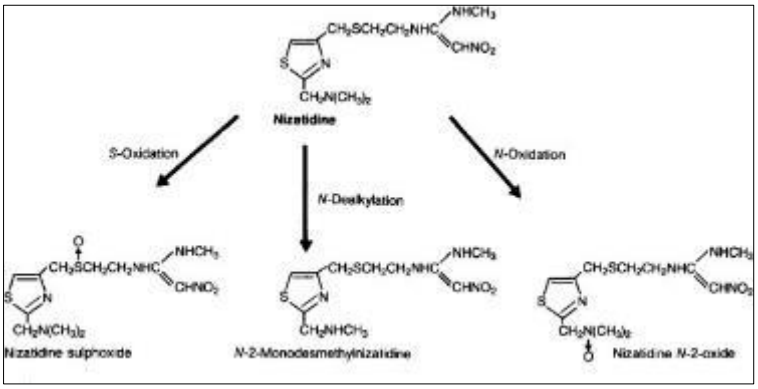

Figure 2 Metabolism of Nizatidine

8.4. Elimination Half-life

The elimination half-life for NZT after oral or I.Vadministration is 1 to 1.6 hrs. [11]

Influence of disease on Pharmacokinetics ofNZT

8.5. Renal dysfunction

The major route of NZT elimination is the kidney and it would seem that any renal dysfunction results alteration of drug pharmacokinetics. Impaired renal function slow rate of elimination. [11]

8.6. Hepatic Dysfunction

Pharmacokinetics of NZT not affected by hepaticdysfunction. [18]

8.7. Influence of Age on Pharmacokinetics of NZT

When examining the pharmacokinetics of a single oral dose of Nizatidine (NZT) ranging from 100 to 300 mg in both elderly (75 years) and younger (40 years) healthy volunteers, it was observed that the area under the curve (AUC) was directly proportional to the dose for both age groups. However, the elimination half-life of NZT was extended in elderly participants, resulting in a higher AUC and reduced plasma clearance compared to the younger group. [11,22]

8.8. Side effects

In a study evaluating the safety of Nizatidine (NZT) for the treatment of duodenal and gastric ulcers, involving 3,500 patients across the USA and Europe over one year, it was found that adverse effects post-therapy were minimal. Common side effects included headache, asthma, chest pain, rhinitis, cough, pruritus, and diarrhea. According to recent data from the manufacturer, Eli Lilly and Co., a study involving 5,000 patients revealed that adverse effects occurring more frequently than with a placebo included urticaria, drowsiness, and sweating. [11]

9. Effect on Biochemical Values

As per trials that were conducted in the USA and Europe reviews no significant clinical changes in mean laboratory values occurred byNZT. [23]

9.1. Drug interaction

At typical therapeutic doses, Nizatidine (NZT) generally does not affect the metabolism of drugs processed by the hepatic mixed oxidase system. Multiple studies have demonstrated that NZT does not significantly alter the pharmacokinetics of various medications, including diazepam, lorazepam, metoprolol, warfarin, and chlordiazepoxide. [24]

9.2. Nizatidine Dosing Information Adult dosing information Duodenal Ulcer Initial:

300mg orally once / day at bedtime, or 150 mg orally twice /day.

Maintenance:150mgorallyoncea day at bedtime. Duodenal Ulcer Prophylaxis150mgorallyonce/day at bedtime.

Gastric Ulcer 300 mg orally once / day at bedtime, or may use 150mgorally twice/day.

9.3. Erosive Esophagitis 150 mg twice daily

9.3.1. Gastroesophageal Reflux Disease (GERD)

150 mg twice daily.

9.3.2. Dyspepsia

75 mg orally once or twice/day, taken right beforeor up to 60 minutes before eating. [25, 26]

9.4. Contraindications

Nizatidine is contraindicated in individuals with a known hypersensitivity to the drug. Due to the potential for cross-sensitivity within this class of medications, H2-receptor antagonists, including Nizatidine and other drugs in this category, should be avoided in patients with a history of allergic reactions to any other H2-receptor antagonists. [28,29,30]

10. Conclusion

In conclusion, Nizatidine is an effective H2-receptor antagonist that plays a significant role in managing conditions like peptic ulcers and gastroesophageal reflux disease by reducing gastric acid secretion. Its distinct thiazole ring structure sets it apart from ranitidine, and its favorable absorption profile (approximately 70% bioavailability) enhances its therapeutic effectiveness, particularly when combined with antacids. However, its short half-life indicates a potential benefit in developing sustained-release formulations to extend its action. Clinical studies support Nizatidine's superior efficacy at standard doses compared to other H2-receptor antagonists, highlighting its valuable role in gastrointestinal health management.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

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