EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 4
Issue: 12
340-343
Year: 2017

A REVIEW OF PHARMALOGICAL AND THERAPEUTICAL ACTIVITIES OF AN ANTI-ULCER DRUG NIZATIDINE -REVIEW ARTICLE

Dr. A. Sambasivarao[1] and M. Hareesh Reddy*[2]

[1]Principal, Sri Indu Institute of Pharmacy, Seriguda, Hyderabad.
[2]Associate Professor, Shadan College of Pharmacy, Hyderabad.

***Corresponding Author: M. Hareesh Reddy**
Associate Professor, Shadan College of Pharmacy, Hyderabad.

Article Received on 17/10/2017 **Article Revised on 06/11/2017** **Article Accepted on 27/11/2017**

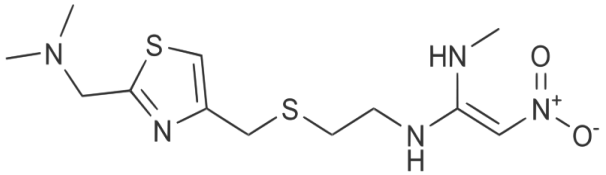
ABSTRACT
Nizatidine is a H2-receptor antagonist that inhibits the production of stomach acid production, and commonly used in the treatment of gastroesophagel reflux disease, peptic ulcers, and duodenal ulcers and induces the stress ulcers. Nizatidine proved to be the latest new histamine H2 receptor antagonist introduced prior to the advent of proton pump inhibitors. It is considered to be equi-potent with ranitidine and differs by the substitution of a thiazole ring in place of the furan ring in ranitidine. Oral treatment of gastric disorders with an H2-receptor antagonist like Nizatidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of drugs to reduce acid secretion..This principle may be applied for improving systemic as well as local delivery of Nizatidine which would efficiently reduce gastric acid secretion. Nizatidine is absorbed only in the initial part of the small intestine and has 70% absolute bioavailability. Moreover, colonic metabolism of Nizatidine is partly responsible for the poor bioavailability of Nizatidine from the colon and short biological half-life of drug (1-2 hours) which favors development of a controlled release formulation.

KEYWORDS: Nizatidine, Histamine H2 receptor antagonist, Proton pump inhibitor, Bioavailability, Gastroesophagel reflux disease, Peptic ulcer and duodenal ulcer.

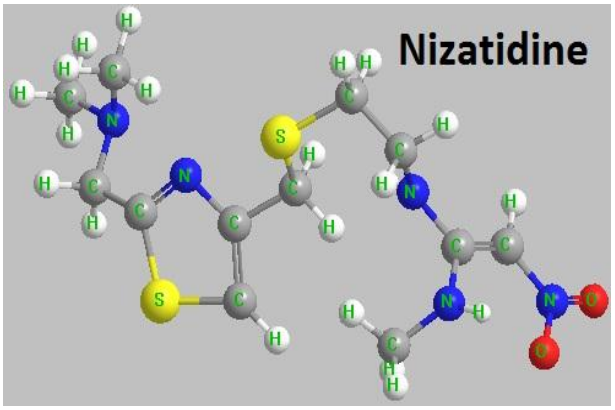
INTRODUCTION

- **Systematic (**IUPAC**) name**

N-(2-[(2-[(dimethylamino) methyl] thiazol-4- yl) methylthioc] ethyl)-N-methyl-2- nitroethene-1,1-dimine.



Chemical structure of Nizatidine



Pharmacokinetic data of Nizatidine

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

Chemical data

1	Formula	C12H21N5O2S2
2	Molecular weight	331.46g/mol
3	Melting point	130-132 °C
4	Solubility	Soluble in water
5	Colour	Off-white crystalline powder
6	Taste	Bitter
7	Odor	Sulphur like odor

Mechanism of action

Nizatidine is a H2-receptor antagonist that inhibits the production of stomach acid production.H2-receptor antagonist like nizatidine used in combination with antacid promotes delivery of local drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases

the efficacy of drugs to reduce acid secretion. This principle may be applied for improving systemic as well as delivery of nizatidine which would efficiently reduce secretion of gastric acid.[1-3]

Adverse effects

Get emergency medical help, if you have signs of an allergic reactions: swelling of your face, lips, tongue, or throat, difficulty breathing.[4-6] Stop using nizatidine and call your doctor at once if you have: worsening heartburn;; pale skin, chest pain, jaundice, feeling light-headed or short of breath. Common side effects may include:

Headache,
Dizziness
Diarrhea
Runny or stuffy nose.

Nizatidine dosing information

Adult dosing information

A) Duodenal Ulcer

Initial: 300mg orally once/ day at bedtime, or alternatively may use 150 mg orally twice/day. Maintenance: 150 mg orally once a day at bedtime.

B) Duodenal Ulcer Prophylaxis

150 mg orally once/day at bedtime.

C) Gastric Ulcer

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

D) Erosive Esophagitis

150 mg twice daily.

E) Gastro esophageal Reflux Disease

150 mg twice daily.

F) Dyspepsia

75 mg orally once or twice/day, taken right before or up to 60 minutes before eating.

Pediatric dosing information

1) More than 1 year: In mild to moderate reflux esophagi is: 10 mg/kg/day divided in two doses for 8 weeks **Gastro esophageal Reflux Disease:** Investigational:
2) Greater than or equal to 4 to 11 years: 6 mg/kg/day divided in two doses, one dose given at 9 PM the night before surgery, and the other given at 6:30 AM the day of surgery.

What should I avoid while taking nizatidine?

To help manage your heartburn symptoms, avoid certain things that can make heartburn worse, such as:

- Being overweight
- Smoking
- Drinking alcohol; or
- Eating spicy foods, fried foods, chocolate, caffeine, or acidic fruits or vegetables.
- lying down or bending over shortly after eating;
- Eating at late night;
- Overeating or eating quickly
- Wearing clothing that is tight around your wrist.

What other drugs will be affect nizatidine?

Other drugs may be interacting with nizatidine, including prescription and over-the-counter (OTC) medicines, vitamins (A, D, E, K, B-complex and C) and herbal products. Tell each of your health care providers about all medicines you use now and any medicine you start or stop using.

How should I take nizatidine?

Use exactly as directed on the label, or as prescribed by your doctor. Do not use in smaller or larger amounts or for longer than recommended.

Take this medicine with a plenty glass of water.

Nizatidine works best if you take it within 1 hour before you drink or eat anything that may cause you to have heartburn.

Do not take more than 2 tablets in a 24-hour (one day) period.

Measure liquid medicine with the sterile dosing syringe provided, or with a special dose-measuring spoon or medicine cup. If you do not have a dose-measuring device, ask your pharmacist or chemist for one.

Call your doctor if your heartburn symptoms do not improve after two weeks (14 days) of treatment, or if you have worsening heartburn.

Nizatidine may be only part of a complete program of treatment that also includes changes in lifestyle habits or diet. Follow your doctor's instructions very perfectly.

Although most ulcers heal within 28 days (4 weeks) of nizatidine treatment, it may take up to 8 to 12 weeks of using this medicine before your ulcer heals. For best results, keep using the medication as per direction.

Nizatidine can cause unusual or complicated results with certain medical tests. Tell any doctor who treats you that you are using nizatidine.

Store at room temperature (22°C to 26°C) away from moisture, heat, and light. Keep the bottle tightly closed when not in use.

Treatment by Condition Related to Nizatidine.

- Medications of duodenal ulcers.
- Medications of treatment for healing ulcer of the duodenum.
- Medications of Benin tumors of the hormone producing glands.

- Medications of inflammation of esophagus from backflow of stomach acid.
- Medications of zollinger-Ellison syndrome.

CONTRAINDICATIONS[7-10]

Nizatidine is contraindicated in patients with known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including nizatidine and other drugs of this class should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Pharmacokinetics

1) The absolute oral bioavailability of nizatidine exceeds 70%.
2) Peak plasma concentrations (700 to 1,800 g/L for a 150-mg dose and 1,400 to 3,600 g/L for a 300-mg dose) occur from 0.5 to 3 hours following the dose. A concentration of 1,000 g/L is equivalent to 3 mol/L; a dose of 300 mg is equivalent to 905 moles.
3) Plasma concentrations 12 hours after administration are less than 10 g/L.
4) The elimination half-life is 1 to 2 hours, plasma clearance is 40 to 60 L/h, and the volume of distribution is 0.8 to 1.5 L/kg. Because of the short half-life and rapid clearance of nizatidine, accumulation of the drug would not be expected in individuals with normal renal function who take either 300 mg once daily at bedtime or 150 mg twice daily. Nizatidine) exhibits dose proportionality over the recommended dose range.
5) The oral bioavailability of nizatidine is unaffected by concomitant ingestion of Propentheline. Antacids consisting of aluminum and magnesium hydroxides with simethicone decrease the absorption of nizatidine by about 10%. With food, the AUC and C_{max} increase by approximately 10%.
6) In humans, less than 7% of an oral dose is metabolized as N2-mono-desmethylnizatidine (H2-receptor antagonist) which is the principal metabolite excreted in the urine. Other metabolites are the N2-oxide (less than 5% of the dose) and the S-oxide (less than 6% of the dose).
7) More than 90% of an oral dose of nizatidine is excreted in the urine within 12 hour periods. About 60% of an Intial oral dose is excreted as unchanged drug. Renal clearance is about 500 mL/min, which indicates excretion by active tubular secretion. Less than 6% of an administered dose is eliminated by the feces.
8) Moderate to severe renal impairment significantly increases the half-life and decreases the clearance of nizatidine. In individuals who are functionally a nephric, the half-life is 3.5 to 11 hours, and the plasma clearance is 7 to 14 L/h. To avoid accumulation of the drug in individuals with clinically significant renal impairment, the amount or frequency of doses of nizatidine should be reduced in proportion to the severity of dysfunction
9) Approximately 35 percent of nizatidine is bound to plasma protein, mainly to 1-acid glycoprotein. Phenobarbital, propranolol, acetaminophen, warfarin Propentheline and diazepam did not affect plasma protein binding of nizatidine in vitro.

Nizatidine - Clinical Pharmacology

Nizatidine is a competitive, reversible inhibitor of histamine at the histamine H2-receptors, particularly those in the gastric parietal cells.

Antisecretory Activity.

Effects on Acid Secretion

Nizatidine significantly inhibited nocturnal gastric acid secretion for up to 12 hours. Nizatidine also significantly inhibited gastric acid secretion stimulated by betazole, food, caffeine and pentagastrin.

Table 1: Effect of Oral Nizatidine on Gastric Acid Secretion.

	Time After Dose (h)	% Inhibition of Gastric Acid Output by Dose (mg)				
		20 to 50	75	100	150	300
Betazole	Up to 3	---	93	---	100	99
Caffeine	Up to 3	---	73	---	85	96
Meal	Up to 4	41	64	---	98	97
Pentagastrin	Up to 6	---	25	---	64	67
Nocturnal	Up to 10	57	---	73	---	90

Effects on Other Gastrointestinal Secretions

Pepsin

Oral administration of 75 mg to 300 mg of Nizatidine did not affect pepsin activity in gastric secretions. Total pepsin output was reduced in proportion to the reduced volume of gastric secretions.

Serum Gastrin

Nizatidine had no effect on basal serum gastrin concentration. No rebound of gastrin secretion was observed when food was ingested 12 hrs after administration of nizatidine.

Intrinsic Factor

Oral administration of 75 mg to 300 mg of nizatidine increased betazole-stimulated secretion of intrinsic factor.

REFERENCE

1. PR Ne ws wire, "Eli Lilly and company and Reliant pharmaceuticals Announce Agreement for U.S Sales and Marketing Rights to Axid ®," Indianapolis, September 7, 2000.
2. The United States pharmacopoeia 32 National Formulary, 28. (USP).
3. European pharmacopoeia 4.3, Council of Europe, 2002.
4. F.Parente and G.B. Porro, "Acid inhibitory Characteristics of Nizatidine in Man: An Overview," Scandinavian Journal of Gastrioenterology, 1994; 29(s205): 3-7.
5. International Conference on Harmonization (ICH), "Stability Testing of New Drug Substance and and Products," ICH Topic Q1A (R2), ICH Secretariat, Geneva, 2005.
6. International Conference on Harmonization (ICH), "Photo stability Testing of New Drug Substances and Products," ICH Q1B Guidline, ICH Secretariat, Geneva, 2005.
7. S.W. Baertschi, K.Alsante and A.R. Reed, "Pharmaceutical Stress Testing: Predicting Drug Degradation," Drugs and Pharmaceutical Sciences, 2005; 153: 1-482. d.o.i 10.1201/9788453567.
8. The United states Pharmacopoeial Convention, "Validation of Compendia Methods <1225>," The United States Pharmacopeia, Rockville, 2009.
9. US FDA guidance, "Analytical procedures and methods Validation," Food and Drug Administration, Rockville, 2002.
10. M.Atmaca, M.Kuloglu. B.Ustundag and Kilic.N. "Nizatidine for the treatment of patients with quetiapine-induced weight gain," Hum Psychopharmacology, 2004; 19(1): 37-40.doi10.1002.