Review Article

Ranitidine Ban – A Review

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ABSTRACT

Peptic ulcer are chronic lesions which occur in any parts of gastro intestinal tract and is caused due to excess acid secretion in the stomach. Ranitidine is a H2 (histamine-2) blocker drug, which decreases the amount of acid secretion in the stomach. It is available in different formulation like tablet (150-300mg), capsule(150-300mg) and as parentrals (50-400mg).It is given twice daily and is used to treat intestinal and stomach ulcers and prevent them from coming back after they have healed .The U.S Food And Drug administration has observed that, in some Ranitidine medicines, commonly sold under the brand-name Zantac, found traces of a nitrosoamine impurity called N-Nitrosodimethylamine (NDMA) at lower level and that impurity linked to the development of causing certain Cancers. Due to this defect, Ranitidine was Banned in many Countries including India.

Keywords: Ranitidine, peptic ulcer, N-Nitrosodimethylamine (NDMA), cancer causing, banning.

INTRODUCTION

Peptic ulcer has unquestionably been a disease of the twentieth century. Peptic ulcer is a chronic disease affecting up to 10% of the world's population. Peptic ulcers are sores within the inner lining of the stomach, duodenum section of the small intestine, and sometimes the esophagus. In 1958 John Lykoudis, general practitioner in Greece, treated people for peptic ulcer disease with antibiotics, long before it was commonly recognized that bacteria were a dominant cause for the disease. In 1982 two Australian scientists, Robin Warren and Barry J. Marshall identified Helicobacter pylori as a causative factor for ulcers, Warren and Marshall concluded that most gastric ulcers and gastritis were caused by colonization of this bacterium. Amongst them, the most common causes of peptic ulcers are infection with the bacterium *Helicobacter pylori* (*H. pylori*) and long-term use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) (Advil, Aleve, others). Stress and spicy foods do not cause peptic ulcers. However, they can make your symptoms worse [1]

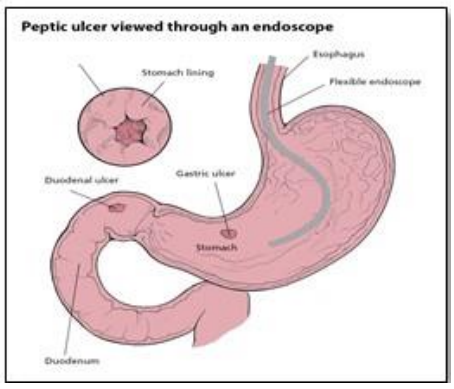

Figure 1: Peptic ulcer

An ulcer present in the stomach is called a gastric ulcer, while that in the duodenal part of small intestine is duodenal ulcer. The most common symptoms of a duodenal ulcer are waking at night with upper abdominal pain or upper abdominal pain that increase after ingestion of food. With a gastric ulcer the pain may worsen with eating. The pain is commonly described as a burning or dull ache. Other symptoms include belching, vomiting, weight loss, or loss of appetite. About a third of older people have no symptoms. Complications include bleeding, perforation and stomach blockage .Bleeding occurs in as many as 15% of people around the world .[2]

Duodenal ulcers are generally seen in people between ages 30 -50 and are more commonly seen in men than women. Stomach ulcers tend to occur in later life i.e., after age of 60, and affect women more often than men. An estimated one in every ten people living in Western countries will have an ulcer in the stomach or small intestine at some point in their lives. Certain Ayurvedic, Unani, allopathic drugs were used for the treatment of Ulcers. Medications include Antibiotics, Antacids and medicines which protect the inner mucosal lining of stomach. etc. One of the commonly used drug for peptic ulcer is Ranitidine.[3]

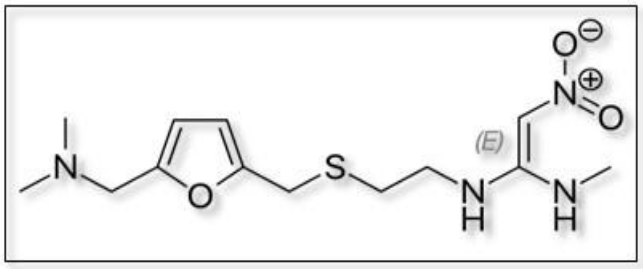

Figure 2: Chemical structure of Ranitidine

RANITIDINE

Ranitidine is a member of class of histamine H_2-receptor antagonists which possess antacid activity. Ranitidine, which is sold under the brand name Zantac among others. Ranitidine was discovered in 1976 and in 1981 it came into commercial use. It is on the World Health Organization's List of Essential Medicines and one of the safest and most effective medicines needed in a health system. It is available as a generic medication:[4]

molecular formula: $C_{13}H_{22}N_4O_3S$

Molecular Weight: 314.41 g/mol

Physical description: solid

Colour: yellow

Odour: charecteristic

Taste: Bitter

Bioavailability: 50% (by mouth)

Protein binding: 15%

Metabolism: Liver: FMOs, including FMO3; other enzymes

Onset of action: 55–65 minutes (150 mg dose)

55–115 minutes (75 mg dose)

Elimination half-life: 2–3 hours

Excretion: 30–70% Kidney

Boiling Point: 437.1±45.0

Melting Point: 134

pKa: 8.2 and 2.7

Solubility: soluble in water

Uses

Ranitidine is used to treat stomach and intestinal ulcers and prevent them from coming back in the future after they have healed. It is also used to treat certain stomach and throat (esophagus) problems (such as erosive esophagitis, gastroesophageal reflux disease-GERD, Zollinger-Ellison syndrome). It acts by decreasing the amount of acid your stomach makes. It relieves symptoms such as cough that doesn't go away, stomach pain, heartburn, and difficulty in swallowing.[5]

Mechanism of action

After a meal, the hormone gastrin, produced by cells in the lining of the stomach, stimulates the release of histamine, which then binds to histamine H_2 receptors and activate it, leading to the excess secretion of gastric acid. When Ranitidine is administered, it reduces the secretion of gastric acid by reversible binding to histamine (H_2) receptors, which are seen on gastric parietal cells. This process leads to the inhibit binding of histamine to this receptor, leading to the reduction of gastric acid secretion. The relief of gastric-acid related symptoms can occur as soon as after 60 minutes of administration of a single dose, and the effects last about 4-10 hours, providing fast and effective symptomatic relief to the disease.[6]

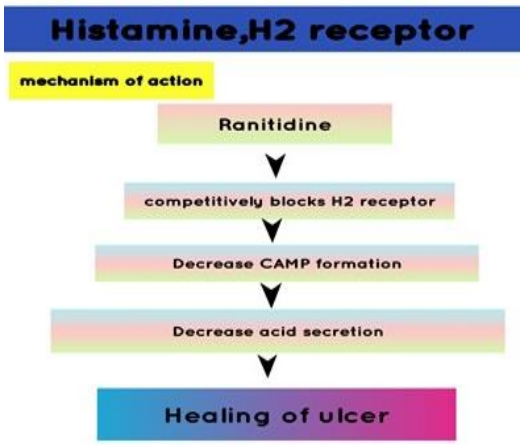

Figure 3: Mechanism of action of Ranitidine

Side effects

Common side effects include Constipation, diarrhea, nausea, dizziness, vomiting, or stomach pain, Headache, Insomnia, decreased sex drive or difficulty having an orgasm, Swollen or tender breasts. Serious side effects include; Coughing up green or yellow mucus, Easy bruising or bleeding, Unusual weakness, Fast or slow heartbeat, Visual problems, Headache with a severe blistering, peeling, and red skin rash, Yellowing of the eyes or skin, Dark urine, Clay-colored stools, Loss of appetite.[7]

Interactions:

- Anticoagulants (blood thinners) such as warfarin (Coumadin)
- Triazolam (Halcion)
- Alcohol

Zantac Dosage:

Zantac comes as a tablet, syrup, effervescent tablet, and effervescent granules to take by mouth. It's usually taken once daily at bedtime or two to four times daily.

This medicine may be taken with or without food. Follow the directions on your prescription or package labeling carefully. You should dissolve the effervescent tablets and granules in a full glass of water before drinking.[8]

Drug forms and strengths:

Oral

-Treatment dose: 150 mg orally 2 times a day or 300 mg orally once a day after the evening meal or at bedtime.

Maintenance dose: 150 mg orally once a day at bedtime

-Duration of therapy: 8 weeks (treatment); up to 1 year (maintenance

Parenteral

IM or IV (bolus or intermittent infusion) Injection:

-Usual dose: 50 mg IM or IV every 6 to 8 hours

-Maximum dose: 400 mg/day

Continuous IV Infusion:

-Usual rate: 6.25 mg/hour

Figure 4: Ranitidine tablet

-Patients may use antacids for the treatment of pain. Both once or twice a day oral dosing regimens were shown to be effective in inhibiting gastric acid secretion. Injectable formulations do not require dilution when given as an IM injection.

-Intermittent IV bolus injections should be diluted up to 2.5 mg/mL and injected at a rate of up to 4 mL/min. Intermittent IV infusions should be diluted up to a concentration of 0.5 mg/mL and infused at a rate of up to 5 to 7 mL/min (approximately 15 to 20 minutes).Most patients receiving oral formulations heal within 4 weeks after administration; there are no safety data for the treatment of uncomplicated duodenal ulcer beyond 8 weeks. Studies have not been conducted to assess safety in oral maintenance therapy longer than 1 year.

Figure 5: Ranitidine injection

Ranitidine ingredients

Ranitidine HCl is a white to pale yellow granular substance that is soluble in water. It has a bitter taste and sulfur-like odor.

Each Zantac 150 Tablet which is used for oral administration contains 168 mg of ranitidine HCl which is equivalent to 150 mg of ranitidine. Each tablet also contains the inactive ingredients FD&C Yellow No. 6 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin, and yellow iron oxide.

Each Zantac 300 Tablet which is used for oral administration contains 336 mg of ranitidine HCl equivalent to 300 mg of ranitidine. Each tablet also contains the inactive ingredients croscarmellose sodium, D&C Yellow No. 10 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

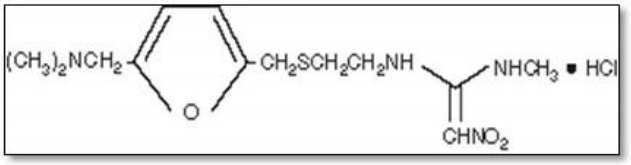

Figure 6: Structure of Ranitidine

Ranitidine hydrochloride (HCl) is the active ingredient present in Zantac 150 Tablets and Zantac 300 Tablets, USP, it is a histamine H_2-receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl] thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, HCl. [9]

N-Nitrosodimethylamine

N-Nitrosodimethylamine (NDMA), also known as dimethylnitrosamine (DMN), is a semi-volatile organic chemical, it is produced as by-product of several industrial methods such as manufacturing of unsymmetrical dimethylhydrazine (UDMH), which is a component of rocket fuel that requires NDMA for its synthesis. It's also used as a byproduct of many manufacturing processes at industrial sites, including tanneries, pesticide manufacturing plants, and rubber and tire manufacturers and also seen at very low levels in certain foodstuffs, especially those which are cooked, smoked, or cured in therapeutic purposes. It causes toxicity to the liver and other organs and is a probable human carcinogen. It is also used to create cancer in rats for laboratory studies and cancer research. The chlorination of drinking and wastewater, which treatment plants do to purify our water, can unintentionally create NDMA as well [10]

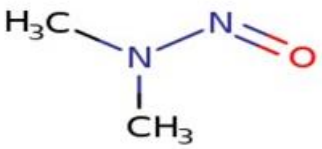

Figure 7: Structure of N-Nitrosodimethylamine (NDMA)

Properties:

NDMA is a yellow, oily liquid with a faint, characteristic odour with sweet taste. It is an industrial by-product or waste product of several industrial processes, [11]

Chemical formula:C2H6N2O

Molar mass: 74.083 g·mol−1

Appearance: Yellow, oily liquid

Odor: faint, characteristic

Density: 1.005 g/ml

Boiling point: 153.1 °C; 307.5 °F; 426.2 K

Solubility: in water290 mg/ml (at 20 °C)

log P: −0.496

Vapor pressure:700 Pa (at 20 °C)

Refractive index (nD):1.437

Uses: Used as an antioxidant, as an additive for lubricants and as a softener of copolymers.

Adverse effects:

Acute Effects: Acute exposure to N-nitrosodimethylamine leads to liver damage in humans, with symptoms that include nausea, vomiting, headaches, dizziness and malaise.

Hematological and severe liver effects (hemorrhagic necrosis) were also reported in animals which when acutely exposure through inhalation and ingestion. Tests regarding acute exposure of rats, mice, and hamsters have found that N-nitrosodimethylamine has relatively high to extreme acute level toxicity chances from inhalation or oral exposure.

Chronic Effects (Noncancer): Chronic exposure of N-nitrosodimethylamine in humans may cause liver damage (swelling) and low platelet counts and also risk of jaundice. Chronic oral exposure resulted in severe liver damage in many animals. [12]

Cancer Risk:

Data from human studies are of limited use because exposure of nitrosamines on humans generally results from contact with the mixtures of these compounds. N-Nitrosodimethylamine has been found to be carcinogenic in many animal species, and also several defects inducing tumors in various organs and by various routes of exposure. When N-nitrosodimethylamine was inhaled it increased the incidences of liver, kidney, and lung tumors have been observed in rats and mice. Liver tumors have also been observed in orally exposed rats, mice, and hamsters.

As the risk of cancer increased FDA and other agencies around the world continue to investigate ranitidine and its effects. On September 13, 2019, the FDA announced that preliminary tests found low levels of N-nitrosodimethylamine (NDMA) in ranitidine, a heartburn medication used by millions of Americans. The drug companies Novartis (through its generic division, Sandoz) and Apotex announced that they were recalling all of their generic ranitidine products sold in the US. These announcements came after a Connecticut-based online pharmacy informed the FDA that it had detected NDMA in multiple ranitidine products under certain test conditions. effects. As of September 27, 2019, two manufacturers had issued recalls 0f Ranitidine in the United States, better known under brand name Zantac, was recalled due to cancer concern, due to presence of NDMA in it, as NDMA is considered a probable carcinogen for humans and is known to cause tumors and deaths in animals based on laboratory results. The FDA says, NDMA is reasonably safe to consume in small doses and said in September 13th statement that early test in ranitidine "barely exceeds amounts you might expect to find in common foods". It's not clear how ranitidine formulations have become contaminated with NDMA. A similar chemical, dimethylamine, is used in the synthesis of ranitidine, and it may be possible some NDMA is created when the drug is made. Alternatively, ranitidine may be broken-down, producing NDMA during storage. It will be important to determine the source of the contamination if new formulations are to be made free from NDMA. [13]

CONCLUSION

Ranitidine being a heartburn drug also used in the treatment of peptic ulcer was banned in many countries including India due to the presence of a carcinogenic impurity, Nitrosodimethylamine (NDMA). All Ranitidine products with expiration dated September 2019 to June 2021 are being recalled many pharmaceutical companies.

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