IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Short Communication
May 2020 Vol.:18, Issue:2

Truths, Myths, Conceptions for Ban and Recall of Ranitidine

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ISSN 2349-7203
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Submission: 21 April 2020
Accepted: 29 April 2020
Published: 30 May 2020

www.ijppr.humanjournals.com

Keywords: Ranitidine, NDMA (N-nitrosodimethyl amine), Valisure online pharmacy company, FDA (Food and drug administration)

ABSTRACT

To describe the significance of the cause of the ban and recall of ranitidine around the world. It includes the misconceptions, the cause of the ban, the regulatory orders, recalling the ban of this drug. Drug ranitidine is sold under the trade name Zantac more commonly which decreases stomach acid production. Commonly used in the treatment of peptic ulcer disease, gastroesophageal reflux disease, and Zollinger Ellison Syndrome. In India, various drug makers such as Dr.Reddy's, Sun Pharma, GlaxoSmithKline, JB chemicals, and Zydus Cadila sell over 180 products based on Ranitidine. The issue of ban surfaced when an online pharmacy company named Valisure first in June 2019 claimed that the drug contains large amounts of a carcinogenic agent called NDMA (N-nitrosodimethyl amine) in the drug ranitidine. NDMA also is known as dimethylamine is an organic compound with the formula $(CH_3)_2NNO$. It is one of the simplest members of a large class of N-nitrosamines. NDMA has attracted wide attention as being highly hepatotoxic and a known carcinogen in lab animals. It has also been claimed that NDMA is also found as an environmental impurity which is also found in drinking water, food, including meat, dairy products, and vegetables in minimum amounts. The ban of the drug for a few days by the FDA and by other regulatory bodies. The research work conducted to re-verify the NDMA levels is being made by different universities and regulatory bodies from all over the world proved that the company claimed a false statement and again the drug was recalled all over the world and now in use as usual.

INTRODUCTION

History and development of the drug

Ranitidine was first developed by Glaxo (now GlaxoSmithKline) to match the success of Smith, Kline, and French (also now GlaxoSmithKline) with the first histamine H_2-receptor antagonist cimetidine. Ranitidine was the result of a rational drug-design process using what was by then a fairly refined model of the Histamine H_2 –receptor and quantitative structure-activity relationships (QSAR). Glaxo refined the model further by replacing the imidazole-ring of cimetidine with a furan-ring with a nitrogen-containing substituent, and in doing so developed Ranitidine. Ranitidine was found to have a far-improved tolerability profile (i.e., fewer adverse drug reactions), longer-lasting action, and ten times the activity of cimetidine. Ranitidine was introduced in 1981 and was the world's biggest-selling prescription drug by 1988. It has since largely been superseded by the even more effective proton pump inhibitors. Zantac is a medication that decreases stomach acid production. Commonly used in the treatment of peptic ulcer disease, gastroesophageal reflux disease, and Zollinger Ellison syndrome. It can be taken by mouth or injection through the intravenous route or intramuscular route.

It is an H_2 receptor blocker. Its chemical formula is $C_{13}H_{22}N_4O_3S$ representing a molecular weight of 350.87. Ranitidine HCl is white to pale yellow, crystalline, practically odorless powder, sensitive to light and moisture. Melts at about 140^0 C with decomposition. Each Ranitidine Tablet, 150 mg contains 168 mg of Ranitidine HCl which is equivalent to 150 mg of Ranitidine. Each tablet also contains the inactive ingredients microcrystalline cellulose, croscarmellose sodium, magnesium stearate. Common side effects of Ranitidine include headache, pain, or burning at the site if given by injection. Serious side effects include liver problems, slow heart rate, and pneumonia. Ranitidine is a schedule H drug and is a prescription drug in India.

Pharmacokinetics of Ranitidine

Absorption: 50% absorbed after oral administration, the administration is not significantly impaired by the administration of food or antacids.

Distribution: The volume of distribution is about 1.4L/kg. Serum protein binding averages 15%.

Metabolism: In humans, the N-oxide is the principal metabolite in the urine; however, this amounts to < 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl Ranitidine (1%). the remainder of the administered dose is found in the stool.

Excretion: The principal route of excretion is urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410mL/min, indicating active tubular excretion. The elimination half-life is 2.5 to 3 hours.

Pharmacodynamics of Ranitidine

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/ml.

In India, various drug makers such as Dr.Reddy's, sun pharma, Cadilapharma, GlaxoSmithKline, JB chemicals, and Zydus Cadila sell over 180 products based on Ranitidine. Below is the table 01 indicating the different brand names of Ranitidine manufactured in India in different pharmaceutical companies.

Table 01. Few brand names of ranitidine manufactured in India

Brand name	Composition	Company
Acibloc. tab	Ranitidine 150mg	Marc lab
Aciloc. tab	Ranitidine 150mg	Cadila
Advene. Tab	Ranitidine 150mg	Abbott
Zoran. tab	Ranitidine 150mg	Dr.reddy's lab
Histac. Tab	Ranitidine 150mg	Ranbaxy
Peploc. Tab	Ranitidine 150mg	Zydus Cadila
Zantac. Tab	Ranitidine 150mg	Glaxosmithkline
Helkos. tab	Ranitidine 150mg	Lupin

Misconceptions raised and ban of the drug:

The issue surfaced when an online pharmacy company named Valisure first in June 2019 in the US alerted the regulators that their tests of samples revealed the drugs seem to contain cancer-causing impurity nitrosamine (N-nitrosodimethyl amine NDMA) beyond permissible levels (geotaxis). This company filed a detailed citizen petition to the FDA on SEP 13, 2019,

alleging it had found "extremely high levels of [NDMA] in every lot tested, across multiple manufacturers and dosage forms of the drug Ranitidine''. The petition states that Valisure detected levels greater than 3 million nanograms per tablet far exceeding the FDA's permissible daily intake of 96ng. Neither the FDA nor any other authorities received any reports of adverse reactions or events related to NDMA found in Ranitidine claim FDA. While many drug regulators across the globe have banned the sale and manufacturing of anti-acidic drug Ranitidine until its safety profile is verified and assured, the drug controller of India (DCGI) has only alerted the state drug authorities to direct the manufacturers to ensure patient safety in our country. FDA advised companies to conduct their laboratory testing for the findings of the levels of NDMA.

NMDA profile

N-nitrosodimethylamine: Also known as dimethylnitrosamine is an organic compound with the formula $(CH_3)_2NNO$. It is one of the simplest members of a large class of N-nitrosamines. NDMA has attracted wide attention as being highly hepatotoxic and a known carcinogen in lab animals. The boiling point of NDMA is 151^0C. The molar mass of NDMA is 74.0819 g/mol. The density of NDMA is $1g/cm^3$ Nitrosamines, or more correctly N-nitrosamines, refer to any molecule containing the nitroso functional group. These molecules are of concern because nitrosamine impurities are probable human carcinogens.

Truths of the drug

But these high levels have been a result of the testing method VALISURE used, which involves heating the sample. "That method is not suitable for testing Ranitidine because heating the sample generates NDMA", the FDA said in its OCT 2 statement. Instead, the agency recommends using one or two techniques: liquid chromatography- high-resolution mass spectrometry (LC-HRMS) or liquid chromatography-tandem mass spectrometry (LC-MS).NDMA is an environmental impurity that is also found in drinking water, food, including meat, dairy products, and vegetables. It is imp to know that the NDMA in Ranitidine products does not pose any immediate health risks. Although classified as probable carcinogen NDMA may cause cancer only after exposure to high doses over a long period. In many conditions, ranitidine is only recommended for short term use.

A 2016 study of Stanford University gave 10 healthy volunteers 150 milligrams of Zantac and found that subsequent NDMA levels in their urine exceeded 47,000 nanograms because

most of the NDMA would have been metabolized before reaching the urine, the actual amount in the body could have been much higher, the researchers wrote.

Another potential concern is that if Ranitidine breaks down into NDMA, it could enter the sewage treatment system and contaminate drinking water. NDMA from rocket fuels is also known as water contamination and VALISURE thinks the concentration of this chemical in Ranitidine medication could be large enough to pose a problem."If you throw away these pills (NDMA) can now enter the water supply," Valisure encourages people to take their medicines back to their doctor or pharmacy to dispose of them safely.

GSK says it had considered the potential formation of nitrosamines in the body during Ranitidine development, during its regulatory review, and in subsequent studies. Scientists had hypothesized that any drugs that raised the stomach's pH could increase the growth of bacteria that produces nitrites, which could interact with chemicals called amines to produce nitrosamines. Although several studies find that taking Ranitidine could increase the concentration of nitrites in the stomach and at least one found a statistically significant increase in nitrosamines that does not mean they cause cancer, GSK says. The company adds that Ranitidine was not carcinogenic in studies of rodents whose diet and bacterial metabolism was similar to that of humans and claims that "extensive Pharmacovigilance monitoring, regular safety reviews, and substantive epidemiological studies have not linked Ranitidine to raised cancer risks".

The Almada, California independent lab says that "our preliminary data indicate that NDMA accumulates in the Ranitidine containing drug products on exposure to elevated temperatures, which would be routinely reached during shipment and storage. More importantly, these conditions occur post-lot release by the manufacturer".

Recall of the drug

FDA is alerting patients and health care professionals to recall Ranitidine tablets (150mg), dated 1st January 2020. The medicines are being recalled because they may contain unacceptable levels of N-nitrosodimethylamine (NDMA). FDA also advised companies to recall their Ranitidine if testing shows levels of NDMA of daily intake ranging (96nanograms per day or 0.32 parts per million for Ranitidine).

SUMMARY

From the literature and the information gathered about the drug Ranitidine and the carcinogenic moiety NDMA. It has been proven that there was a misconception about the levels of the carcinogenic agent in the drug Ranitidine and later by testing the same drug in all the companies by the order of FDA the misconception raised was proven wrong and the drug is now again recalled and manufactured for the market by all the pharmaceutical companies and is prescribed by doctors as usual as a prescription drug to the patients.

Acknowledgement

I thank my co-author P.Tulasi for her support and strength for my research work.

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