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A Litrerature Review N-Nitrosodimethylamine Contaminated Ranitidine Long-Term Use May Produce Cancer Risk

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Abstract:- Ranitidine belongs is a histamine-2 blocker agent. Ranitidine is available in Tablet, Capsule, Syrup and Injection solution dosage form in market. Ranitidine is a prescription drug used to treat definite stomach and throat disease such as esophageal information, gastroesophageal reflux disease or GERD, and Zollinger-Ellison syndrome. It works by reducing the amount of gastric acid secretion . It relieves various symptoms such as chronic cough , stomach pain, heartburn, and painful blockage. It also used in treatment of stomach ulcers and intestineal ulcers. In April 2020, the United state Food and Drug Administration (FDA) publish a guidelines to manufacturers to withdraw all prescription and over-the-counter (OTC) ranitidine drugs from the market after find out the presence of the contaminants known as N-Nitrosodimethylamine (NDMA) in ranitidine medications in excess concentration (famous brand Zantac).This Literature reviews the indications, mechanism of action, pharmacokinetics, administration, adverse effects, contraindications, Mechanism of NDMA release, Regulatory Agencies Laboratory testing of Ranitidine for NDMA presence, the clinical study of NDMA generation in Angiotensin II Receptor Blockers (ARBs) and ranitidine were compared to find the current contamination evidence, and Effect of storage conditions, Stomach and intestine condition impact on NDMA generation, lastly we compare through which route NMDA produce lesser and in which greater.

I. INTRODUCTION

Ranitidine is easily accessible drug it act as a histamine H2-receptor antagonist, cimetidine and famotidine are the drugs which belongs to same class. The ranitidine is used to prevent/ treat the medical conditions occurred due to gastric acid, including ulcers, because it has ability to reduce the gastric acid secretion in stomach.(1)

N-nitrosodimethylamine (NDMA) is a organic compound belonging to the nitrosamines group having the molecular formula C2H6N2O, and has recently trending in the scientific community and researchers because of surprisingly detection as a pharmaceutical impurities in some formulations. NDMA is recognized as a cancer causing agent by the (IARC) International Agency for Research on Cancer Body.(2)

II. FDA-APPROVED RANITIDINE INDICATIONS AND USAGE.

- *Active duodenal ulcer is treating in very short period of time and observed that most of patients heal within 4 weeks after treatment initiation.*
- *The medication dose is reduced in continuous therapy after recovery of patients from duodenal ulcer until the affected area recover completely.*
- *It is used to treat hypersecretion of acid in stomach. (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).*
- *Short-term treatment of active, initial stage of gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated.*
- *Continuous therapy of gastric ulcer patients at decreased dose after recovery from acute ulcers.*
- *Treatment of GERD. The relief from symptoms mostly occurs within 24 hours after initiation of therapy with Ranitidine twice a day.*
- *Treatment of endoscopically diagnosed esophageal inflammation. The relief from Symptoms like heartburn commonly observed within 24 hours of therapy initiation with Ranitidine 4 times a day.*
- *Continuing of healing of esophageal inflammation. Placebo-controlled trials were carried out for 48 weeks to compare the effectiveness.*

Naturally accompanying antacids should be given as required to give relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.(8)

III. MECHANISM OF ACTION OF RANITIDINE

After having a meal a hormone name gastrin released by cells in linning of stomach which provoke the release of histamine then this histamine will binds with H2 receptors and this activity cause release of gastric acid. Ranitidine inhibit the activity of histamine H2-receptors. The reversible blocking of H2-receptors in gastric parietal cells results in a decreasing the gastric acid secretion. Ranitidine's acid-lowering effect is more pronounced for basal and nocturnal acid secretion than it is for food-stimulated acid secretion. Additional indirect effects of ranitidine are reduction of pepsin secretion and increased nitrate-reducing bacterial flora. (9)

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IV. PHARMACOKINETICS

When dosed by oral route, ranitidine has a bioavailability of 50%, which is not affected by food. After administration by oral route the peak concentration of Ranitidine takes 2 to 3 hours and but in case of intramuscular route it takes 15 minutes after administration. Ranitidine is usually excreted unchanged in the urine, with a half-life ranging from 2.5 to 3 hours, and because of the elimination by renal route, the half-life possibly increase to 4 to 5 hours in patients with renal disorder.(10)

V. ROUTES OF ADMINISTRATION

- *Oral*

Ranitidine is available as tablets, capsules, or syrup. Ranitidine solution may be mixed with select enteral tube feeding solutions. [10]

- *Intramuscular (IM)*

Administer solution without dilution.

- *Intravenous (IV)*

Intermittent IV bolus: Dilute it in a compatible IV solution before administrator upto a maximum concentration of 2.5 mg/mL. Then the solution may be administered at a maximum rate of 10 mg per minute.

- *Intermittent IV infusion*

Dilute with a compatible IV solution before administration at concentration of 0.5 mg/mL. Then the solution may be administered at a rate of 2.5 to 3.5 mg per minute.

- *Continuous IV infusion*

150 mg ranitidine is diluted with a compatible IV solution of 250ml. Then this solution can be administered at a rate of 6.25 mg per hour. The patients suffering from Zollinger-Ellison disease, a relatively high infusion rate will be required. The rate of infusion may vary 1 mg/kg per hour to a maximum dose of 2.5 mg/kg per hour. (9)

VI. POTENTIAL MECHANISM OF NDMA GENERATION FROM RANITIDINE AND IT'S IMPACT

- In 2 January 2020 Emery Pharma filed a Petition with the FDA concerning the Ranitidine. Emery Pharma found in its tests that the Ranitidine is a "Time- and temperature-sensitive (TTSPP)"drug , which produces a known cancer causing agent named N-Nitrosodimethylamine (NDMA) when exposed to high temperature environment. The study perform by them established that 150 mg strength ranitidine tablets USP contained 18 ng of NDMA initially, but after storing it at specified condition i.e., 25 °C for 12 days, NDMA level reaches to 25 ng concentration, and then storing the same strength tablet of Ranitidine at 70 °C cause an increased concentration of NDMA i.e, 142 ng. Ranitidine 150 mg.(3) Figure 1 and Table 1.

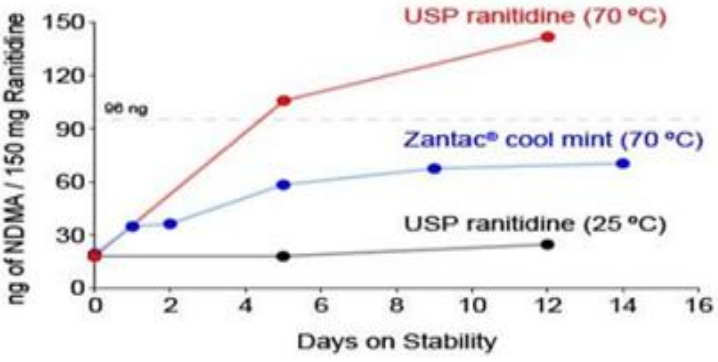

Figure 1. Preliminary stability study with USP ranitidine standard at 25 °C (black), USP ranitidine standard at 70 °C (red), and Zantac® cool mint, lot# 18G542 at 70 °C (blue). NDMA analysis performed via LC-MS/MS (*vide infra*), and quantified based on a calibration curve generated using an NDMA reference standard.

Dotted line approximately indicates the daily intake limit of 96 ng for NDMA.

Table 1. A preliminary stability study (n=2) was performed using USP Ranitidine, lot# MKCH3111 (at 25 °C and 70 °C) and Zantac® cool mint, lot# 18G542 (at 70 °C). Average results from NDMA analysis by LC-MS/MS are reported.

	25 °C	70 °C	
	USP Ranitidine (ng of NDMA/150 mg Ranitidine)	USP Ranitidine (ng of NDMA/150 mg Ranitidine)	Zantac® Cool Mint (ng of NDMA/150 mg Ranitidine)
Day 0	18	18	19
Day 1	*	*	35
Day 2	*	*	36
Day 5	18	106	58
Day 9	*	*	67
Day 12	25	142	*
Day 14	*	*	70

**Timepoints were not assessed.*

The above observation concluded that having an lower or acceptable concentration of NDMA impurities at the time of manufacturing does not assure this will be the case on the day an individual ingests it.

- From 1 June 2019 to 31 August 2020 Braunstein et al conduct the study to find the posible reason of NDMA generation by In-vitro study. For this he prepares a sodium chloride in water solutiom of 2g/L concentration at different pH range and nitrite concentration and add ranitidine into it. He found that by fixing the sodium nitrite concentration at 50 mmol/L and varying pH from 1.2 to 5.5 ranging in the presence of 150- or 300-mg ranitidine tablets demonstrated raised in NDMA impurities generation under acidic environment (198 000 ng of NDMA impurities generate at pH 1.2) with diminishing NDMA yields at higher pH (3310 ng NDMA impurities generate at pH 5.5).(4)

- The Brambilla et al, perform a study on rodants observed the chemicaly conversation of NDMA impurities in rats and mice stomach after administring high single doses of this histamine H 2 receptor antagonist along with NaNO 2 Liver DNA fragmentation, as revealed in rats by both DNA alkaline elution and DNA alkaline denaturation followed by hydroxylapatite chromatography, was found to be dependent either on the molar ratio drug/nitrite or on the gastric pH. He observed that with decreasing the pH level increase the rate of damages of DNA segments and vice versa. His study shows a positive correlation between the dose of Ranitidine and pH of stomach in production of NDMA. impurities. Higher the Dose and lower the gastric acid pH cause increase in level of NDMA impurities generate. (5)

- Mathes et al, perform a study to check that is the H2-Receptor Antagonist Medications can cause the Brest Cancer in patients or not. His study shows that Some H2 blockers, specifically cimetidine and ranitidine, also increase serum prolactin concentrations combined cause an increase the risk of breast cancer. His study shows a positive relationship between prolactin levels and postmenopausal breast cancer risk, use of H2 blockers is a potential breast cancer risk factor in lactating womens.

He collects the data from two population-based case-control studies conducted in western Washington and combine them, and try to form a clear picture of relationship of H2 blockers like Ranitidine and risk of development of different types of Brest Cancer in women's among 1,941 reported cases and 1,476 controls volenture of age range of 55 to 79 years old. Odds ratios and 95% confidence interval were calculated using polytomous logistic regression.

He concluded that the Use of H2 blockers in general is not associated with an increased risk of breast cancer but the use of ranitidine may be increase the risk of hormone receptor–positive ductal carcinoma. Further studies has to be done to relate the Ranitidine with Brest Cancer.(6,7).

VII. REGULATORY AGENCIES LABORATORY TESTING OF RANITIDINE MEDICINE FOR NDMA PRESENCE

A. TGA(Therapeutic Goods Administration):

After checking the report and evidences which shows the drug name Ranitidine is contaminated with a impurity N-nitrosodimethylamine(NDMA) which can cause a cancer to the patients if present above the safe concentration in body, the TGA labs have collected and analysed the samples from the batches currently available in market for sales in Australia to check that is these are rumours or actually the Ranitidine carrying the NDMA impurity beyond the daily exposure limit.

The TGA Labs used the publically available test method of US Food and Drug Administration i.e detection of NDMA impurities in Ranitidine sames by liquid chromatography with high resolution mass spectroscopy (LC-HRMS). This method has a limit of quantitative analysis of 0.1 parts per million (ppm) NDMA is equivalent to 0.1 microgram of NDMA per gram of ranitidine active ingredient. Their is a safe limit of NDMA in the Ranitidine products which is 0.3 ppm which is following at international level.

The TGA tests 135 different batches with Different types of dosage forms including Syrups, Injection (Ampoules), tablets and effervescent tablets in their Labs. They publish their Labs results after which they only allowed to sales in market those products which are having the NDMA concentration in acceptance limit i.e., 0.3 ppm and those products who are not complying with the standards are removed from shelves of the stores to ensure public health. The NDMA value above 3 ppm is just a estimated.

Value because during analysis it was observed that this method does not provide linear response above the 3ppm, hence we can say that the test results above 3 ppm are unreliable.(11)

- *USFDA* :

The lab testing done by FDA samples included 12 tablets batches, two syrups batches , and four nizatidine products with multiple batches. The maximum NDMA concentration observed in syrups were 1.37 ppm, as we compared it with tablet which produces 2.85 ppm NDMA. Not only Ranitidine the USFDA has tested some another drugs of H2 blocker class which is chemically similar to ranitidine to find that is they are also producing same impurities as Ranitidine does. The observed NDMA levels in other H2 blocker agents were lower than that of ranitidine observed concentration.

After the researches FDA has set the acceptable daily exposure limit for NDMA at 0.096 micrograms or 0.32 ppm for ranitidine. Despite the fact that many Ranitidine manufacturers have already stated recalling of ranitidine from market to minimise the risk of cancer due to their products and to save their brand value in market, FDA will

recommended manufacturers to recall their products who carry the NDMA levels above the safe daily intake limit.(12)

➢ *Adverse effects*

- Central nervous system (CNS):⁚ Headache, choreoathetosis, dizziness, insomnia, mental confusion, agitation, and hallucinations.
- Endocrine: Hypoactive Sexual Desire Disorder, impotence,gynecomastia
- Cardiovascular: It cause increase or decrease in hreat rate of patients i.e, tachycardia or bradycardia after administration
- Gastrointestinal (GI): stomach pain, loss of appetite, Constipation, diarrhea, nausea, vomiting.
- Respiratory: cause infection in lungs
- Hepatic: Hepatic Injury
- Musculoskeletal: Myalgia, arthralgia
- Hematologic: Leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, agranulocytosis
- Integumentary: Rashes on skin, hairfall and Angiitis.
- Renal: Increased serum creatinine level, inflammation in Kidney, dark urine.
- Other: Allergic reactions in patients, anaphylaxis

Pain observed at the site of intramuscular (IM) injection has been reported for shorter duration. Initially burning or itching sensation has been reported with of at the site of administration of IV of Ranitidine.(9)

In 2015 Beers Criteria list identifies ranitidine as a therapy that may potentially trigger or exacerbate delirium in adults older than 65 years of age. Caution should be used when treating the elderly with ranitidine.(13)

Long-term use of ranitidine for greater than 2 years may also be associated with vitamin B12 deficiency.(14)

VIII. PREGNANCY

Ranitidine is known to cross the placenta; however, it is still commonly used when pregnant patients require acid release reduction therapy. Of note, increasing studies are revealing a correlation between acid release reduction therapy use during pregnancy and the raise in asthma cases in children.(15)

IX. CONCLUSION

Ranitidine is a medicine used to treat a wide range of diseases like peptic ulcer, gastroesophageal reflux disease, and Zollinger–Ellison syndrome. But after the finding of NDMA (Probable human carcinogen) led to a massive interest related to its benefits over Risks. Researchers need to check that if the Ranitidine produces NDMA concentration is the same in all the dosage forms available or its higher only in Tablets, also researchers need to identify others drugs which can generate NDMA impurities. Till time their is no strong evidence that can prove Ranitidine induce cancer case, because Ranitidine available in market from very long time and very wide variety of population administrator it. Still as per TGA they allow Ranitidine of some manufacturers which produce a low amount of NDMA impurities i.e, less than 0.096 micrograms concentration of NDMA per day.

Further strategies to be mitigated to control the NDMA production in ranitidine, or to develop a method to completely remove the NDMA impurities from its manufacturing stages to save this clinically effective medicine.

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