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ASSESSMENT AND MONITORING OF ADVERSE EFFECT OF RANITIDINE WITH PHARMACOVIGILANCE STUDY

[1]Sanika Kate, *[2]Vishal Bodke, [3]Ruchita Badekar, [4]Paresh Bagul, [5]Prajval Birajdar and [6]Pavankumar Dhoble

[1]M.S. In Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Ahmedabad, India.

[2,3,5,6]M. Pharm. In Department of Pharmaceutics, Konkan Gyanpeeth Rahul Dharkar Coleege of Pharmacy and Research Institute, Karjat Maharashtra, India.

[4]M. Pharm. Department of Clinical Research, National Institute of Pharmaceutical Education and Research Mohali. India.

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***Corresponding Author**
Vishal Bodke
M. Pharm. In Department of Pharmaceutics, Konkan Gyanpeeth Rahul Dharkar Coleege of Pharmacy and Research Institute, Karjat Maharashtra, India.

ABSTRACT

In pharmacy profession Pharmacovigilance (PV) is essential in the healthcare profession because this examines, monitors, and identifies medication interactions and their impacts on individuals. Biotechnological and pharmaceutical treatments are designed to treat, prevent, or cure diseases, but they come with risks, chief among them the potential for adverse drug reactions (ADRs), which can be significantly detrimental to patients. As a result, it is crucial to keep an eye on pharmaceutical adverse drug reactions (ADRs) for every medicine throughout the course of its development, including in early stages of substance development, clinical studies, and post-marketing surveillance. The identification, assessment, understanding, and avoidance of ADRs are all things that PV is concerned with. Ranitidine is a drug used to reduce the formation of stomach acid and is marketed under the brand nam es Zantac and others.[4] It is frequently employed in the treatment of Zollinger-Ellison syndrome, gastroesophageal reflux disease and peptic ulcer disease.[4] It can be administered orally, intravenously, or intramuscularly. Ranitidine products from several manufacturers were recalled in September 2019 after the possible carcinogenic N-nitroso dimethylamine (NDMA) was found in them.

KEYWORDS: Pharmacovigilance, Ranitidine, Antacid, Zantac.

INTRODUCTION

Concept of Pharmacovigilance

The World Health Organization (WHO) characterizes pharmacovigilance as "The science and actions connected to The identification, assessment, monitoring and treatment of adverse effects and any other possible drug-associated Problem.".[1,2,15]

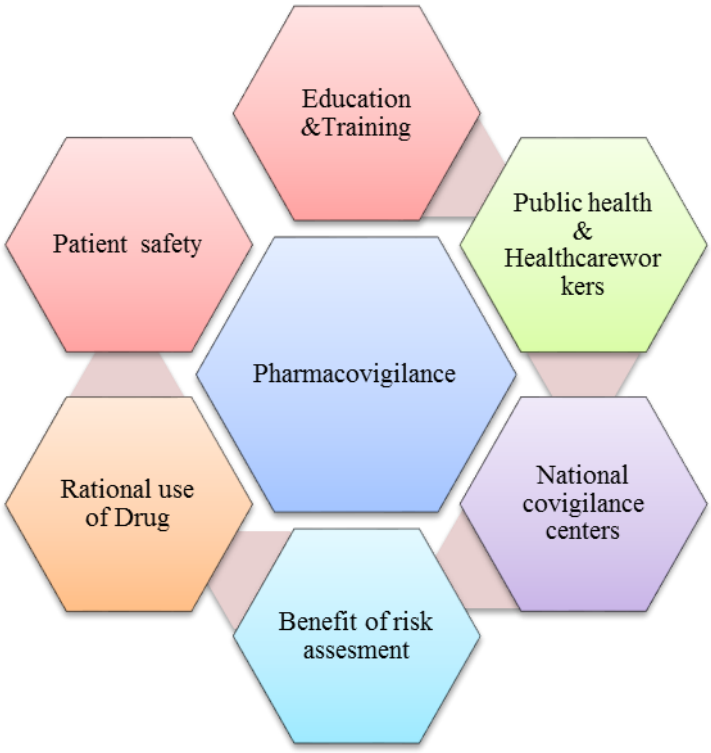


Fig.no 1: Pharmacovigilance Roles and uses.[3]

OBJECTIVE

1) Establish a national system for reporting patient safety.

2) To increase the use of medications whose benefits can surpass their risks, protecting the patient population in the process.

3) To recognise and evaluate the data packet (ADR) from of the reported cases in order to evaluate the benefit-risk balance of commercially available drugs.

4) To produce data on the safety of medicines that is supported by evidence.

5) To assist regulatory bodies in making decisions about the usage of medications.

6) To reduce risk, stakeholders should be informed about the safety of using medications.

❖ **Selejction of Drug ClassRanitidine.**

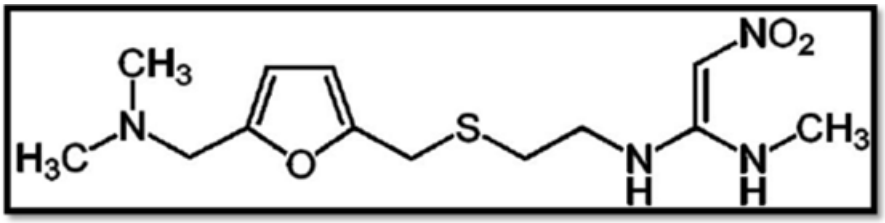


Fig No 2: Structure of Ranitidine.

Formula :- $C_{13}H_{23}ClN_4O_3S$

IUPAC Name:- 1-*N*'-[2-[[5-[(dimethylamino)methyl]furan-2 yl]methylsulfanyl]ethyl]-1-*N*-methyl-2-nitroethene-1,1-diamine.

Molecular weight:- 350.87

In the summer of 1977, John Bradshaw created ranitidine for the first time in England as AH19065 in the Ware research facilities of Allen and Hanburys, a division of the bigger Glaxo corporation. It was created in reaction to cimetidine, the first product of its kind to target the histamine H2 receptor, which was created by Sir James Black at Smith, Kline, and French and introduced as Tagamet in the UK in November 1976. Following a series of acquisitions and mergers, which began in 1979 with the combination of Glaxo and Allen and Hanbury's Ltd to become Glaxo Group Research, and ended in 2000 with the union of Glaxo Wellcome & SmithKline Beecham, both businesses eventually amalgamated to form GlaxoSmithKline (GSK). A quantitative structure-activity relationship model of the histamine H2 receptor and a rational drug-design process were used to create ranitidine.[8]

Since its release in 1981, ranitidine has become the most used prescription medication globally.

[Reference needed] It was thereafter largely replaced by the more efficient proton-pump inhibitor (PPI) category of medications, with omeprazole emerging as the top-selling medication for many years.[9]

Mechanism OF Action

Histamine H2-receptors are competitively inhibited by ranitidine. Both the volume and the concentration of stomach acid are decreased as a result of the inhibiting the activity of H2-receptors in the gastric parietal cells. The acid-lowering effect of ranitidine is stronger for basal and nighttime acid production than it is for acid secretion triggered by meals. Decreased

pepsin secretion and enhanced nitrate-reducing bacterial flora are two additional ranitidine side effects.

Pharmacological Actions

1. Histamine antagonists block bronchoconstriction and trigger the triple response. Falling blood pressure. Low dose blocked; high dose requires both H1 and H2 blockers.
2. Type I reactivity to an allergen is suppressed.
3. Partially prevented anaphylactic blood pressure drop Man's asthma is unaffected.
4. CNS: sedation, no sedation, restlessness; varied effect insomnia.
5. First-generation drugs have more anti-cholinergic effect
6. Local anaesthetic. not applied in medicine.
7. BP: only decline with IV admen, not p.o.

INDICATIONS

Due to nitroso dimethylamine contamination, the FDA requested that manufacturers remove every prescribed and the over (OTC) ranitidine medications from the market on April 1, 2020. (NDMA). There is solely historical value to this article.

The FDA has cleared ranitidine for use in both children and adults from 1 month to 16 years old. Only young generation than 12 years old were eligible for the FDA's approval of ranitidine, which is available over-the-counter without a prescription.

FDA-Approved Ranitidine Indications

• Treatment, maintenance, and short-term benign gastric and duodenal disease.
• Maintenance and short-term treatment for duodenal ulcer disease.
• Conditions that cause excessive secretion of mucus; (e.g., Zollinger-Ellison, systemic macrocytosis, multiple endocrine adenoma syndrome).
• GERD (gastrointestinal reflux disease) (GERD).
• Indigestion, heartburn, non-ulcer dyspepsia, and sour stomach.

Ranitidine Non-FDA-Approved Indications

- Anaphylaxis.
- NSAID-induced ulcer prophylaxis.
- Stress ulcer prophylaxis.
- Taxane-related urticaria prophylaxis.

- Prevention of aspiration while under obstetric anaesthesia.

➢ ADVERSE EFFECTS

1. Following parenteral or oral treatment of ranitidine (frequency not specified), the following negative effects were identified in the earliest clinical trials.
2. First, the the central nervous system (CNS) Anxiety, agitation, confusion in the mind, somnolence, vertigo, and hallucinations.
3. 2. Cardiovascular: Increased heart rate, bradycardia, asystole, atrio - ventricular block, and ventricular beats that are too early. Rapid intravenous delivery with patients with cardiac rhythms disorders may make bradycardia more common.
4. Gastrointestinal (GI): nausea, vomiting, diarrhoea, constipation, and pancreatitis Hepatic: Hepatocellular, mixed, or cholestatic hepatitis; liver failure.
5. Arthralgia, myalgia, and musculoskeletal.
6. Anemia, granulocytopenia, thrombocytopenia, pancytopenia, and agranulocytosis are six hematologic disorders.
7. Endocrine: Impotence, decreased libido, galactorrhea, and gynecomastia.
8. Skin conditions: rashes, alopecia, and vasculitis
9. Reproductive: Pneumonia.
10. Enhanced serum creatinine and acute interstitial nephritis in the kidneys.
11. Other: Anaphylaxis and hypersensitivity responses.

It has been reported that intramuscular (IM) injection sites temporarily experience pain. Ranitidine intravenous (IV) injection has been associated with brief localised burning or itching.

Ranitidine is included as a medicine on the 2015 Beers Criteria list that could potentially cause or worsen delirium in persons over the age of 65. When administering ranitidine to elderly patients, caution should be exercised.

Ranitidine use for more than two years might also be linked to vitamin B12 insufficiency.

Pregnancy

Since it crosses the placenta, ranitidine is frequently prescribed to pregnant patients who need acid-suppressing medication. Notably, more research is showing a link between the usage of acid-suppressing medications during pregnancy and the emergence of childhood asthma.

Similar to how ranitidine is excreted in breast milk, it is important to consider the advantages and disadvantages of using it before beginning treatment.[27]

Interaction with Other Drugs

LIFE-THREATENING

- **Efavirenz**
- **Nevirapine**

SERIOUS

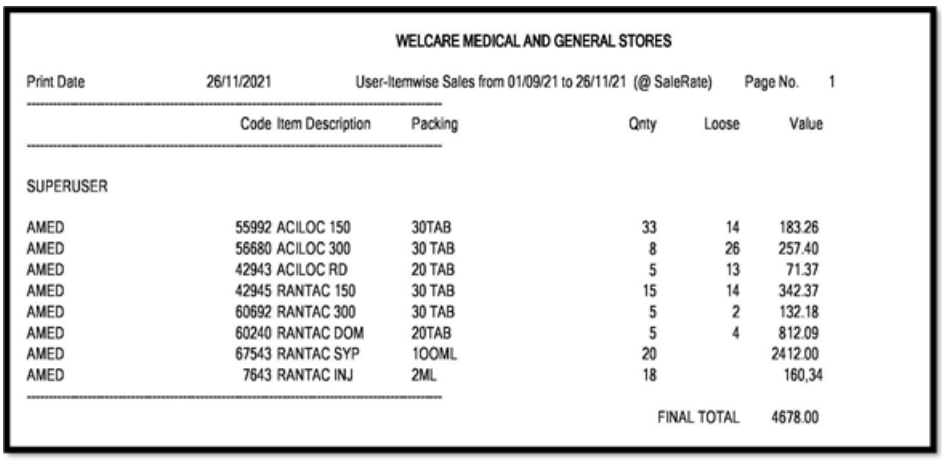
- **Acarbose**

• Patients who have previously had an allergic response to ranitidine or one of the product's ingredients should not take ranitidine. little set of cases.

Analyses show contradictory results regarding the cross-sensitivity of H2-receptor antagonists, therefore care should be used. There is hypothesis that some H2 blockers have a lower risk of cross-reactivity than others because to variations and similarities in their chemical structures. Additionally, individuals with any background of acute hemochromatosis should avoid ranitidine since it may provoke porphyria episodes.

• Clinicians advise against using the over-the-counter medication if a patient experiences pain or difficulty swallowing, or if they have blood in their stool or vomit. With other acid-reducing medications, kidney illness, or in patients under the age of 12, concurrent usage is not advised.

➢ **Consummation Report of Ranitidine**



WELCARE MEDICAL AND GENERAL STORES

Print Date 26/11/2021 User-Itemwise Sales from 01/09/21 to 26/11/21 (@ SaleRate) Page No. 1

	Code	Item Description	Packing	Qnty	Loose	Value
SUPERUSER						
AMED	55992	ACILOC 150	30TAB	33	14	183.26
AMED	56680	ACILOC 300	30 TAB	8	26	257.40
AMED	42943	ACILOC RD	20 TAB	5	13	71.37
AMED	42945	RANTAC 150	30 TAB	15	14	342.37
AMED	60692	RANTAC 300	30 TAB	5	2	132.18
AMED	60240	RANTAC DOM	20TAB	5	4	812.09
AMED	67543	RANTAC SYP	1OOML	20		2412.00
AMED	7643	RANTAC INJ	2ML	18		160,34
					FINAL TOTAL	4678.00

- **Identification of Adverse Effects of a Selected Drug Side effects of Ranitidine include**[23]

1. Headache.
2. Abdominal pain.
3. Agitation.
4. Hair loss.
5. Confusion.
6. Constipation.
7. Diarrhea.
8. Dizzineess.

- **Hospital Visit**

Fig no 3. Hospital Visit (Friday).

1. Name of Doctor:- **Dr. Jitendra Kapre.**
2. Qualification:- M.B.B.S.
3. How much time you work in this place:- 3 year.
4. Specialist of doctor:- Physician & Consultant, Family Physician & Surgeon.
5. Name of Doctor**:- Dr. Rajani M. Pandit.**
6. Qualification:- B.A.M.S., M.D.

7. How much time you work in this place:- 5 year.
8. Specialty of doctor:- Physician & Consultant, Family Physician.

➢ **Patient Interview**

Fig no-4 Patient Interview (Friday).

➢ Name of patient :-**Mr. Amol Bharade,** Age-28, Sex- Male.

1. In which condition you start the treatment.

Ans- High G.I.T Disturbance, Heart burn

2. How long you take this Drug/medicineAns-20 days, Aciloc 150.
3. You feel any discomfartness/side effect of this drugAns-No.
4. Tell me about your medication history.

Ans- No any specially medication

5. Did you suggest this treatment for another person which suffer from same conditionAns- yes its helpful.
6. What other medicine do you take with this medicineAns- NO.

❖ Name of patient **:- Ms.Kavita Das** Age-36 Sex-Female

1. In which condition you start the treatment ?

Ans :- Upset Stomach, Heart burn, Acid reflux

2. How long you take this Drug/medicine ?Ans:-from 90days
3. You feel any discomfartness/side effect of this drug ?

Ans:-No

4. Tell me about your medication history

Ans- he has diabetes, he takes Glycomet 0.5 medicine from 3 year

5. Did you suggest this treatment for another person which suffer from same condition ?

Ans- yess its helpful & feel good

6. What other medicine do you take with this medicine ?

Ans- zincovit tab

❖ Name of patient **:- Mr.Dhruv Pathak,** Age-65, Sex-Male.

1. In which condition you start the treatment ?Ans- Stomach Pain, GI Ulcer.
2. How long you take this Drug/medicine?

Ans-from 2Months Rantac 150

3. You feel any discomfartness/side effect of this drug ?Ans-No.
4. Tell me about your medication history.

Ans-he has Diabetics

5. Did you suggest this treatment for another person which suffer from same condition ?

Ans- yess its helpful & feel good.

6. What other medicine do you take with this medicine?.

Ans- Glycomet 0.5 tab.

❖ Name of patient **:- Pooja Jadhav,** Age-18, Sex-Female.

1. In which condition you start the treatment ?

Ans- Stomach Pain, Acidity, Duodenal ulcer

2. How long you take this Drug/medicine ?Ans-from 15 Days Rantac syrup
3. You feel any discomfartness/side effect of this drug

Ans-No

4. Tell me about your medication historyAns-normal Cold & Flu
5. Did you suggest this treatment for another person which suffer from same condition?

Ans- yess its helpful & feel good

6. What other medicine do you take with this medicine?Ans- Sinarest syrup,

❖ **Assessment of ADR**

Naranjo Scale

The Naranjo Scale was developed by Naranjo et al. to assess the chance that an adverse drug reaction (ADR) is caused by the drug itself rather than by other factors. A score is used to categorise probability as certain, probable, possible, or doubtful. Peer reviews frequently use the values from this algorithm to validate the accuracy of an author's conclusions about adverse drug reactions. That Naranjo Scale and Naranjo Score are other names for it.[20.,21,22]

Scoring

- ≥ 9 = definite ADR
- 5-8 = probable ADR
- 1-4 = possible ADR
- 0 = doubtful ADR[20]

Histamine H2 antagonists ranitidine is a well-tolerated over-the-counter medication has adverse effects as low and around 2% that is frequently used to treat gastritis. Headache, fatigue, disorientation, drowsiness, stomach discomfort, alopecia, constipation, diarrhoea, impotence, gastritis, and pancytopenia are additional adverse effects of H2 enzyme inhibitor., etc.[20]

On the Naranjo's severity assessment scale, the adverse event was 5 indicating a probable reaction to ranitidine.

Naranjo score of Rantac is = 5.

➢ Ranitidine contain '**Zantac**' banned

- The Health Ministry joined other nations, notably the United States, in taking any action against by the salt which has been a source of worry abroad earlier this week by removing ranitidine from of the listing of Essential Medicines.[25]
- There have been questions raised about the salt's potential to cause cancer, despite its widespread use in medications like Rantac and Zintac.
- The Health Ministry has unveiled the 384-drug National Listing of Essential Medicines (NLEM). Ranitidine is one of a number of 26 medications that have been omitted off the list.
- The US Food and Drug Association (FDA) has been looking into Zintac heartburn

treatment since 2019 after discovering a possible cancer-causing contaminant in the medication. India was the most recent country to remove these medications from the market.[25,26,27]

- Most cancerous cases by zantac:- Zantac may increase your risk of developing cancer outside of your digestive system. The prevalence of bladder cancer among ranitidine users and nonusers was examined in a 2021 study. It was shown that ranitidine users had a greater incidence of bladder cancer, particularly if they had used the drug for more than three years 2. For persons who regularly take ranitidine, valsartan, or related drugs, NDMA exposure presents a possible carcinogenic risk of uncertain effect.[26,27]

U.S. Food and Drug Administration demanded that producers remove all prescription and over-the-counter (OTC) ranitidine medications from the market right now. This is the most recent development in an ongoing research of a contaminant known as N-Nitrosodimethylamine (NDMA) found in drugs that contain ranitidine (typically marketed under the trade name Zantac). The EPA has found that some ranitidine products have prohibited quantities of this contaminant, which can rise over time and when stored at temperatures above room temperature. Products containing ranitidine won't be available in the United States for new or current prescriptions or OTC usage as a result of this emergency market withdrawal request. NDMA is a chemical that has the potential to cause cancer in humans.[29]

In April 2020, the FDA recommended that Zantac (ranitidine) be taken off the market. All ranitidine Zantac products were recalled by the manufacturers because they may have been contaminated with NDMA, a substance known to cause cancer.[28]

CONCLUSION

The most commonly used antacid is ranitidine. An antihistamine that blocks H2 receptors, ranitidine lowers stomach acid production. In terms of lowering heartburn, treating erosive esophagitis, reducing discomfort, and enhancing quality of life, effervescent ranitidine was noticeably superior to antacids. Overall, there were no appreciable differences between the two groups' incidences of adverse events; however, 12% of the antacid group and 3% of the ranitidine group experienced gastrointestinal-related adverse events (nausea, vomiting, diarrhoea, constipation, gas, and faecal incontinence), while 1% of the antacid group and 4% of the ranitidine group experienced central nervous-system-related adverse events (headache, dizziness, insomnia, malaise.

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