INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Review Article

RANITIDINE PUZZLE: CLEARING UP THE MUDDLE FROM MEDIA

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ABSTRACT

Ranitidine formulations were recently shown to contain carcinogens. This paper traces the history, pharmacology, toxicity and the possible synthetic origin of carcinogenic content and food and drug administration updates on ranitidine formulations.

Keywords: n-nitroso-dimethylamine (NDMA), carcinogenic, Ranitidine formulations, FDA updates.

INTRODUCTION

Ranitidine formulations are now being questioned for their carcinogenic effect. The current scenario has troubled many leading pharmaceutical companies and have made them withdraw their respective brands of ranitidine from the market.

Ranitidine, a competitive and reversible inhibitor of histamine H2-receptors on the parietal cells in the stomach, thereby inhibiting the normal and meal-stimulated secretion of stomach acid. In addition, H2 receptor blockade suppresses acid secretion by parietal cells when stimulated[1]. Ranitidine is widely used for treatment of acid-peptic disease. Ranitidine is both an over-the-counter (OTC) and a prescription drug. Rantac, Zinetac, Histac, Aciloc, zantac are common brand names of ranitidine formulations[2].

HISTORY OF RANITIDINE

Ranitidine was discovered in 1976 by John Bradshaw of Allen & Hanburys laboratory, under Glaxo- organisation and was available commercially since 1981[3].The first in class H2 blocker, namely Cimetidine, was the first to enter the market but incidence of gynecomastia pushed Ranitidine into the mainstream[4].

WHAT IS NDMA?

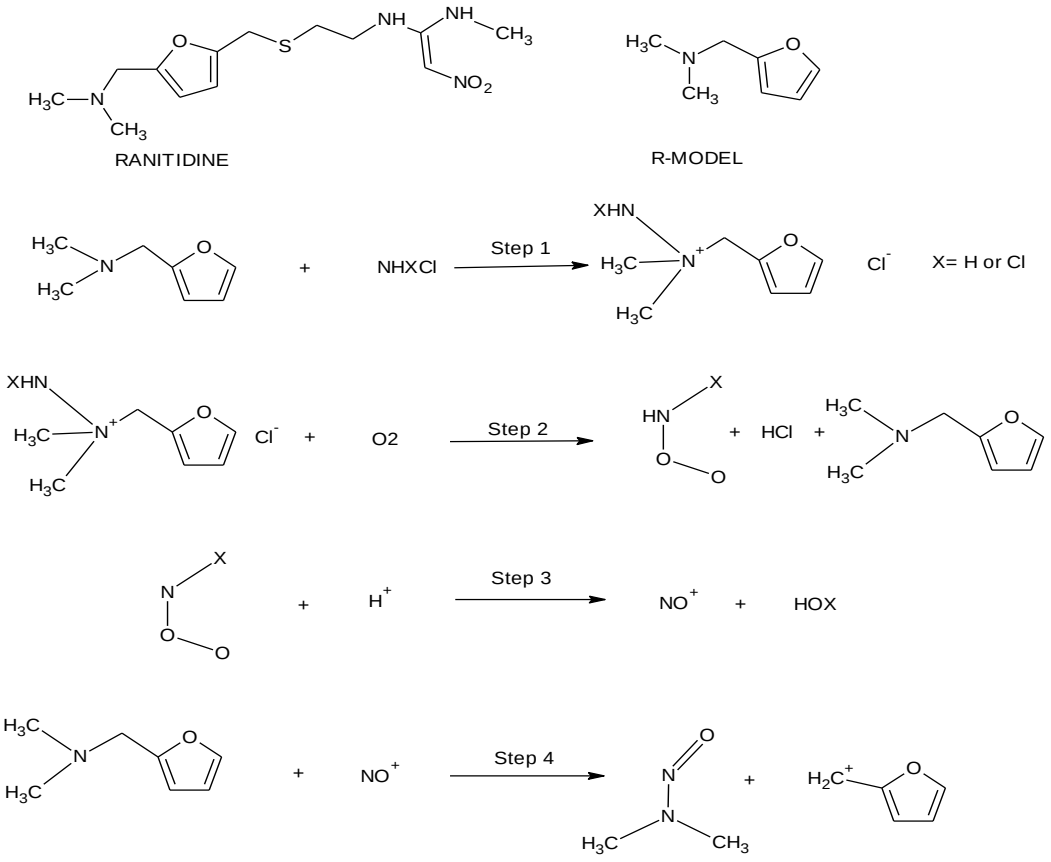
U.S FDA has identified an impurity named n-nitroso-dimethylamine (NDMA) in certain batches of ranitidine[5]. NDMA is an environmental toxin found in water (0.0007µg/L) and foods, including dairy products, vegetables, and grilled meats. Its classification as a probable carcinogen is built on studies in animals, although data on humans are very limited[6].

NDMA in ranitidine formulations does not pose any immediate health risks. Neither the FDA nor Novartis/Sandoz or Apotex have received any reports of adverse events related to NDMA found in ranitidine. Although classified as a probable carcinogen, NDMA may cause cancer only after exposure to high doses over a long period of time. Laboratories have detected up to 300µg/kgNDMA per tablet. However, the permissible upper limit is 0.096µg/kg. NDMA is also among the impurities found in many other medicines too, for e.g. valsartan[7].

How does NDMA form in the ranitidine products?

Drinking water undergoes disinfection when treated with chloramine by the process chloramination. When administered ranitidine react with chloramine, NDMA is formed. The formation of NDMA is four-step pathway. The first step involves a nucleophilic substitution reaction between NHXCl (X = H or Cl) and R-Model and produces a Complex I. In the second step, an elimination reaction of hydrogen chloride from Complex I (X = H or Cl) first occurs and simultaneously forms an active intermediate [XN-

R-Model], which is then easily trapped by oxygen molecule. With the oxygen approaching the nitrogen atom of NX moiety, an N–O bond forms and N–N bond cleaves, and then produces a nitrosating agent OONX as well as R-Model again. In the third step, OONX (X = H or Cl) traps a proton and then dehydrates to generate a NO+ cation. Therefore, it can be concluded that monochloramine (NH2Cl) is preferable to dichloramine (NHCl2) in generating NO+. Monochloramine rather than dichloramine is responsible for NDMA formation from ranitidine. NO+ is a well-known active nitrosating agent, and immediately after its formation, NO+ can react with the amine[8].



IS NDMA TROUBLESOME IN RANITIDINE FORMULATIONS??

This question should strike in one's mind whether only ranitidine is prone to be life risking? Is NDMA found in any other medicines or products we use in routine? Let us start off with the basic element of life: drinking water. Researchers have found the presence of NDMA in drinking water with a quantity of0.0007µg/L. Food and edible products like cereals, potatoes, and beans consist 1.71µg/kg NDMA.A maximumof 6.1µg/kg and a minimum of 4.9µg/kg NDMA was detected in fresh vegetables and mushrooms. 1µg/kg NDMA was detected in bread, rice cake, pickled vegetables and doughnut. NDMA of cheese showed 0.72µg/kg. Cake and ice-cream showed an amount of 0.56µg/kg of NDMA. NDMA showed the highest value of 0.3-1.54µg /kg in meat and meat products. Almost all seafood such as tuna, frog, shellfish, salted fish, etc. contain NDMA in the concentration of 0.12-322.92µg/kg. Edible oil namely olive oil, sunflower, vegetable oilholds0.98-23µg/kgNDMA. Beverages such as beer, vodka, whisky cover 0.22-2.5µg/kgNDMA[9]. Despite of all these facts the intake of these food has drastically increased. Now we should rethink as the food we take is also carcinogenic. Is ranitidine more unsafe or the food we consume dangerous?

REPORTED SIDE EFFECTS OF RANITIDINE

Hepatotoxicity

Chronic therapy with ranitidine has been associated with minor elevations in serum aminotransferase levels in 1% to 4% of patients, but similar rates were reported in placebo recipients. Rare instances of clinically apparent liver injury have been reported in patients receiving ranitidine, but the time to onset and pattern of injury has varied greatly (Cases 1-3). The pattern of serum enzyme elevation varies from hepatocellular to cholestatic, most cases being "mixed" hepatocellular-cholestatic. The injury is rarely severe and usually resolves with discontinuation, within 4 to 12 weeks. Liver biopsy histology often shows prominent centrolobular necrosis. Ranitidine has been linked to rare instances of clinically apparent acute liver injury [10].

Other side effects

Reversible mental confusion, agitation, mental depression, and hallucinations have occurred, mainly in debilitated geriatric patients. A child who was receiving prolonged, high-dose oral ranitidine therapy developed altered consciousness, drowsiness, dysarthria, hyporeflexia, positive Babinski's sign, diaphoresis, and bradycardia, which resolved within 24 hr after discontinuance of the drug.

Constipation, nausea, vomiting, and abdominal discomfort or pain have occurred in patients receiving ranitidine. Pancreatitis has been reported rarely. Rash, which may be urticarial, maculopapular, and/or pruritic, has been reported during ranitidine therapy.Leukopenia, granulocytopenia, agranulocytosis, thrombocytopenia, aplastic anaemia, acquired immune hemolytic anaemia, and pancytopenia, which may be accompanied by bone marrow hypoplasia, have been reported rarely in patients receiving ranitidine[11].

Non-Human Toxicity Excerpts

In vitro tests have generally not revealed ranitidine or its N-oxide, S-oxide, and desmethyl metabolites to be mutagenic. No evidence of carcinogenicity was seen in long-term studies in dogs, mice, or rats receiving ranitidine dosages up to 2 g/kg daily; evidence of gastric neoplasm or premalignant gastric changes was not observed in these studies. From the findings, it was concluded that renal dysfunction is a risk factor for ranitidine neurotoxicity, and this increased risk results from increase in the drug concentration in plasma and brain as a result of impaired renal excretion. No apparent effect of acute hepatic dysfunction was observed on both the pharmacokinetic and pharmacodynamic behaviour of the drug[12].

FDA STATEMENTS ON RANITIDINE

Director - Centre for Drug Evaluation and Research Janet Woodcock M.D on 13th September 2019 posted a Statement alerting patients and health care professionals of NDMA found in samples of ranitidine. The U.S. Food and Drug Administration has learned that some ranitidine medicines, with following brand-name Zantac, Rantac, Aciloc, Histac contain NDMA at low levels. The FDA was evaluating whether the low levels of NDMA in ranitidine pose a risk to patients. The levels the FDA found in ranitidine from preliminary tests barely exceed amounts expected to be found in common foods (13). FDA announced on 24th September 2019 for voluntary recall of Sandoz ranitidine capsules for the presence of NDMA[14]. On 26th September 2019 U.S. Food and Drug Administration alerted health care professionals and patients for voluntary recall of over-the-counter (OTC) ranitidine tablets (75 mg and 150 mg), labelled by Walgreens, Walmart, and Rite-Aid and manufactured byApotex Corp. FDA recommended LC-HRMS as testing protocol to test samples of ranitidine[15]. On 2nd October 2019 FDA stated that their investigation of NDMA was carried out in ranitidine oral solution and other H2 blockers and level of NDMA was unacceptable[16].

While the very first alert of FDA regarding ranitidine was posted, many countries have immediately taken action by recalling the marketed ranitidine. Singapore was among the first, when on 16th of September 2019they halted sales of eight brands containing NDMA above internationally acceptable levels[17]. Similarly, Health Canada on 17th of September 2019informed Canadians regarding NDMA in ranitidine and requested companies to stop distribution of ranitidine formulations until NDMA was determined to be within acceptable levels[18]. India, well known for its pharmaceutical output didn't take any certain action. Instead they tried to bury it. Later, health care professionals themselves stopped prescribing ranitidine because of international updates. FDA updated on 23rd October 2019 that Dr. Reddy's Laboratories Ltd had voluntary recalled all prescription and over-the-counter (OTC) ranitidine tablets and capsules manufactured by the company[19].

CONCLUSION

FDA statements have confused both health care professionals and common people regarding ranitidine, ranitidine formulations and NDMA. A prominent conclusion is not yet derived to stop the usage of ranitidine which is why even now there are patients who take ranitidine under prescription. Why ranitidine formulation only to be in trouble when NDMA is also found in drinking water other edible products. All this chaos handled to misconception and anxiety towards the use of modern medicine by a common man. However, ranitidine confusions have largely affected the pharmaceutical industries and over all market and economy.

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