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Letter to the Editor

Ranitidine: recent regulatory issues

Sir,

Ranitidine is histamine 2 receptor blocker which became commercial in 1981 as an antacid by Glaxosmithkline Pharamceuticals by the brand name of Zantac in various formulations. The drug accelerated in the market as amongst most commonly used drug for peptic ulcer disease, acid reflux and sooner than later it became available as an over-the-counter drug in 1996 for adults and children. Ranitidine's mechanism of action involves competitive block of histamine 2 receptor leading to decrease cAMP formation which reduces acid secretion from parietal cells of stomach thereby healing the peptic ulcer.

The drug came into limelight, when in a routine testing of by Valisure Pharmacy, N-nitrosodimethylamine (NDMA) was discovered in ranitidine Syrup for which valisure first notified the US-FDA in June 2019. On September 13th 2019, valisure filed a detailed petition with the Food and Drug Administration asking the agency to recall all products containing ranitidine.[1] Ranitidine recall happened due to presence of unacceptable levels of NDMA which is >96 nanograms/0.32 ppm. The calculated acceptable intake for NDMA in drugs is based on methods described in the 2018 International Council for Harmonisation Guidance M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.[2]

NDMA is one of the simplest members of dialky-lnitroamine with the chemical formula $(CH3)_2NNO$. NDMA is known to be a by-product of alkylamines, pesticides production, dyes and rubber tyres.[3]

NDMA is categorized as a probable carcinogen (group 2A) by International Agency For Research on Cancer (IARC) implying that NDMA should be considered carcinogenic in humans for all practical purposes.[4] Today the only role that NDMA plays is to induce cancer in animals as a part of lab experiments. Mechanism of cancer causation can be attributed to oxidative demethylation of NDMA and formation of reactive intermediates. Alkylation of guanine and cytosine to 7-methylguanlic acid and 3-methylcytosine respectively are thought to be the reason for NDMA-induces carcinogenesis.[5]

USFDA has been testing H2 blockers and PPIs and NDMA is detected in ranitidine and nizanitidine. FDA's tests of samples of alternatives like pepcid (famotidine), nexium (esomeprazole), prevacid (lansoprazole) and prilosec (omeprazole) show no NDMA impurities in the medicines.[2]

Actions have been taken across the globe including ban, suspended registration, recalls on ranitidine products by many pharmaceutical companies and advising the physicians not to prescribe the drug ranitidine and seek other alternative medications like famotidine, esomeprazole, omeprazole as no NDMA has been detected in these, as suggested by US-FDA.

US-FDA is alerting the patients and physicians on voluntary recalls of ranitidine tablets and capsules 150mg, 300 mg, syrup 15 mg/ml by various pharmaceuticals like Aurobindo pharma, Amneal, Lannett, Novitium, Dr Reddy's, GlaxoSmithKline Pharmaceuticals and Perrigo.[6]

In a previous related development, FDA learnt about the impurities of NDMA in angiotensin II receptor blockers, valsartan and losartan in 2018. Elaborate testing revealed that the raw materials used in some of the batches of these medicines were contaminated and the respective batches were withdrawn. But the scenario with ranitidine is different and appears to be more than just the contaminants. The presence of NDMA in ranitidine might be attributed two plausible mechanisms i.e. metabolic by-product in human's body and molecular structure of ranitidine.

In-vitro studies show that NDMA can be a metabolic by-product of ranitidine. FDA developed simulates gastric fluid (SGF) and simulated intestinal fluid (SIF) to estimate the significance of these in-vitro findings and found no additional production of NDMA in the stomach.[7]

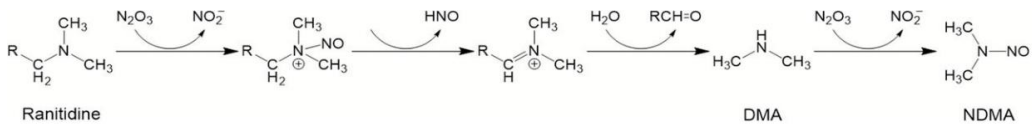

Figure 1: Chemical reaction mechanism for the formation of NDMA from ranitidine in gastric conditions.
Source: https://www.ncbi.nlm.nih.gov/pubmed/26992900

A detailed chemical reaction mechanism for the formation of NDMA from ranitidine in gastric conditions is proposed from a Stanford University paper published in 2016 (Figure 1).[8]

In addition to gastric fluid mechanism, a possible enzymatic reaction via dimethylarginine dimethyl-aminohydrolase (DDAH) enzyme for liberation of dimethylamine (DMA) group of ranitidine can occur. This liberated DMA can form NDMA when combined with nitrite present on ranitidine molecule, and free nitrite in the body.[9]

DDAH enzyme is present in every cell and degrades asymmetric dimethylarginine (ADMA), the endogenous inhibitor of nitric oxide (NO) synthase.[10] DDAH metabolizes endogenous ADMA which is also a putative marker of cardiovascular disease.

These results suggest that the enzyme DDAH-1 may increase formation of NDMA in the human body when ranitidine is present. DDAH-1 gene is expressed in many organs mainly in kidneys, small intestine and colon.[11] This offers a general mechanism for NDMA formation in the human body from ranitidine.

The structure of ranitidine molecule may also play an important role in NDMA production. Ranitidine contains nitrite group and dimethylamine (DMA) group which can combine and form NDMA (Figure 2).[12]

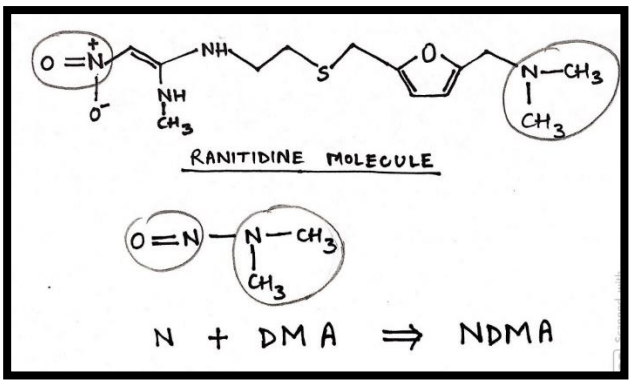

Figure 2: Ranitidine molecule.

Though the amount of NDMA in ranitidine according to USFDA is almost similar to that of smoked chicken, grilled food, cured meats,[7] tests are still going on to come to a final conclusion of the amount and source of NDMA production from ranitidine.

We have tried to compile all the recent information regarding ranitidine and finding out the plausible mechanism of NDMA production from ranitidine, which may be related to its molecular structure. Patients are to be alerted for the known carcinogen in their medicine ranitidine and that any amount of carcinogen consumption is harmful. The voluntary recalls by pharmaceuticals are increasing day by day since September 13th, 2019 and many countries have stopped the sale of ranitidine until the drug regulatory bodies give a go flag. Few countries (Canada, Bangladesh and Egypt) have banned ranitidine.

USFDA has now determined that the impurity in some ranitidine products increases over time and when stored at higher than room temperatures and may result in consumer exposure to unacceptable levels of this impurity.

Hence, on 01 April 2020, USFDA requested the manufacturers to withdraw prescription and over the counter ranitidine drugs from the market for patient safety.[13]

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