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NDMA as an Impurity of Ranitidine: A Carcinogenic Moiety

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INTRODUCTION

Ranitidine, an H2-receptor antagonist, is widely used to treat gastroesophageal reflux disease (GERD). It is also used to treat peptic ulcer disease, hypersecretory states such as Zollinger-Ellison syndrome, systemic mastocytosis, and the prevention of stress ulcers and gastrointestinal bleeding [1]. It was approved for use in the United States in 1983, and by 1988, it had become the best-selling drug on the planet. Ranitidine was approved for over-the-counter use in 2004 and was previously marketed under the brand name Zantac [2]. In September 2019, a petition was submitted to the US Food and Drug Administration (FDA) stating that routine testing had revealed N-nitrosodimethylamine (NDMA), a likely human carcinogen, in Zantac, a brand name for ranitidine. NDMA is classified as a probable human carcinogen, which means it has the potential to cause cancer. It is a known environmental contaminant that can be found in water as well as foods such as meat, dairy products, and vegetables [3]. N-nitrosodimethylamine (NDMA) is a chemical that has been shown to cause tumors in the gastrointestinal tract, liver, lungs, and kidneys. NDMA directly activates RAS oncogenes, and its methylated metabolite, methyl diazonium, is also a mutagen. NDMA has been classified as a probable carcinogen by international organizations ranging from the Environmental Protection Agency to the World Health Organization's International Agency for Research on Cancer [4]. On September 13, 2019, the FDA issued a warning to consumers that some ranitidine products contain unacceptable levels of NDMA and are being recalled. Because of the high levels of NDMA, many manufacturers, including Apotex Corporation, Sandoz, Sanofi, Aurobindo, and Dr Reddy Labs, have had to recall products containing ranitidine. The FDA announced in April 2020 that ranitidine would be withdrawn from the market and advised consumers to stop using the product. Ranitidine is the second medication linked to NDMA impurities. The first was the therapeutic class known as Angiotensin II Receptor Blockers (ARBs), which were found to contain NDMA and other nitrosamines in 2018. The published NDMA levels detected in ranitidine are lower on average than in ARBs, and detection necessitates the use of highly accurate and sensitive methods [5]. The Valisure pharmacy reported in 2019 that ranitidine (the over-the-counter brand Zantac) used to treat gastric hyperacidity and reflux contained unsafe levels of NDMA [6]. According to their findings, the spontaneous breakdown of the ranitidine molecule could produce dimethylamine and nitrites, resulting in the formation of NDMA. The acceptable daily intake limit for NDMA was set by the FDA at 0.096 micrograms or 0.32 ppm for ranitidine. However, NDMA levels in ranitidine products were found to be up to nine times higher than the FDA's recommended limit. As a result, many manufacturers and retailers have completely recalled ranitidine around the world [7]. Liquid Chromatography-Mass Spectrometry (LC-MS) and Liquid Chromatography High-Resolution Mass Spectrometry (LC–HRMS) are two published analytical methods for NDMA analysis in ranitidine (LC-HRMS). A third-party laboratory also used Gas Chromatography-Mass Spectrometry (GC–MS) to detect NDMA concentrations in ranitidine samples [5]. According to the FDA, the high temperature (266°F) gas chromatography/mass spectrophotometry method used in Valisure's laboratory is unsuitable because heating the sample produces NDMA. The FDA's preferred method, liquid chromatography-high-resolution mass spectrometry, does not use heating, and while it discovered significantly lower NDMA doses per tablet for ranitidine, it still discovered unacceptable doses [6].

The current study's positive association between ranitidine and pancreatic cancer was consistent with the findings of Habel [8] who found a statistically significant 2.6-fold increased risk associated with ranitidine use for the combined outcome of stomach/esophageal cancer [8,9]. Discovered a statistical link between occupational NDMA exposure and

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pancreatic cancer deaths [9,10] reported site-specific results for the proximal and distal colon and rectum in their study of NDMA and colorectal cancer [10]. The findings revealed a statistically significant link between dietary NDMA exposure and rectal cancer. The FDA has acted appropriately thus far, but there may be more that can be done to improve our understanding of this issue and limit human exposure to NDMA through prescription drugs. Current ranitidine users were found to have a significantly increased risk of ductal carcinoma, but neither cimetidine nor famotidine were. While these studies are far from conclusive, there are less risky options.

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