

COMMENTARY

Medicine and Media: The Ranitidine Debate

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Ranitidine has been the topic of recent media reports. Current findings, confirmed by the US Food and Drug Administration, indicate that some ranitidine products contain a substance that may be carcinogenic. Providers and patients require additional information on the risks of continuing therapy vs. the benefits of the medication. This article comments on what is currently known about the evolving situation of elevated N-nitrosodimethylamine levels in ranitidine and the limits of the existing information to assess best practices.

In September 2019, a petition was sent to the US Food and Drug Administration (FDA) reporting routine testing had detected N-nitrosodimethylamine (NDMA), a likely human carcinogen, in excess of 3,000 micrograms (μg) per ranitidine tablet, over 30,000 times the FDA's permissible daily intake limit.¹ The petitioner suggested that ranitidine is an unstable molecule capable of reacting with itself in standard analysis conditions to produce excessive NDMA levels and requested the FDA take actions to include robust independent chemical testing and verification of pharmaceuticals. The FDA confirmed some ranitidine products contained NDMA but categorized the levels as low and further recommended a liquid chromatography-high-resolution mass spectrometry testing protocol specific for ranitidine, as there was concern by the FDA that the elevated levels reported by the petitioner were produced as a direct by-product of elevated temperatures used in the analysis.²

Ranitidine, an H₂-receptor antagonist (H₂RA), is very commonly prescribed for the treatment of gastroesophageal reflux disease (GERD). It is also used for the treatment of peptic ulcer disease, hypersecretory states, such as Zollinger-Ellison syndrome, systemic mastocytosis, and prophylaxis of stress ulceration and gastrointestinal bleeding. GERD is a chronic disorder where gastric contents move from the stomach back into the esophagus and cause symptoms such as regurgitation, vomiting, feeding refusal, and poor weight gain in infants and epigastric pain, chest pain, heartburn, and regurgitation in older children and adults. Without treatment, GERD can negatively impact quality of life and is a risk factor for the development of erosive esophagitis, esophageal strictures, and Barrett's esophagus, a precancerous lesion. Pediatric and adult GERD clinical practice guidelines suggest nonpharmacologic treatments as first-line therapy; however, if these treatments fail, medications such as H₂RAs and/or proton pump inhibitors (PPIs) are recommended. H₂RAs selectively block the histamine-2

receptor in gastric parietal cells, resulting in the decreased production of gastric acid. H₂RAs are more effective than placebo in improving symptoms, increasing intragastric pH, and improving histologic changes due to acid reflux.

Average NDMA levels found in 7 of the 14 ranitidine products tested by the FDA yielded ranges from 0.15–0.86 μg per tablet or standard dose of syrup formulation, noted to be above the acceptable daily intake (ADI) level of 0.096 μg set forth by the FDA,² but significantly lower than reported by the petitioner. Several ranitidine products contained well below the recommended maximum daily intake levels. Various formulations of nizatidine, a structurally similar H₂-receptor antagonist, contained NDMA but below threshold levels. The FDA initially asked manufacturers to conduct their own laboratory testing to examine levels of NDMA in ranitidine and nizatidine and send samples to be tested by the FDA. The agency asked for voluntary recalls by manufacturers of products with elevated levels, although many manufacturers had already begun recalls while several retailers discontinued ranitidine sales. The agency has since asked for manufacturers to test all lots of ranitidine and nizatidine before releasing to consumers and to retain lots with levels above the ADI and report those to the FDA. Furthermore, the FDA reported that no additional NDMA was generated when the products were subjected to the agency's simulated gastric and intestinal fluid models but that testing the drugs in the human body is required to fully understand if ranitidine forms NDMA.² This was in contrast to the petitioner's claims that high levels of NDMA resulted when ranitidine was exposed to a simulated gastric fluid model with the addition of various concentrations of sodium nitrite, although the amounts of sodium nitrite added may not support the claim of biologically relevant conditions.³ The FDA has reiterated that levels in affected ranitidine are similar to those expected from ingestion of common nitrite-rich foods, such as grilled or smoked meats.

In 2018, the FDA confirmed NDMA contamination in valsartan, an angiotensin II receptor blocker leading to recalls. Valsartan products contained as much as 20 μg per tablet of NDMA likely resulting from a change in the manufacturing process. In December 2019, several metformin products marketed by Singapore-based manufacturers were found to contain elevated NDMA levels. The FDA is investigating, but currently has not recalled metformin on the US market.

Human NDMA exposure occurs through both exogenous and endogenous pathways. NDMA is a known byproduct from pesticide manufacturing, tanneries, and tire plants, and is found in multiple food and beverages, including

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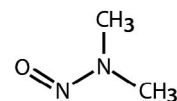
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processed/cured meats and smoked/salted fish, as well as malt beverages. Additional sources include toiletry products, cigarette smoke, and drinking water. In animal studies, ingested NDMA is absorbed extensively, distributed widely, cleared rapidly via hepatic and extrahepatic metabolism, and excreted in the urine or exhaled. Intra-gastric formation of NDMA in humans has been reported to occur *in vitro* under physiological conditions.⁴ Various animal species have developed cancers in the liver, lung, stomach, respiratory tract, kidney, and blood vessels secondary to NDMA, and the International Agency for Research on Cancer has classified NDMA as group 2A, “probably carcinogenic to humans.”⁵ Three studies have reported that NDMA increases the risk of gastrointestinal cancer in humans,⁶ yet additional evidence of carcinogenicity in humans is sparse.

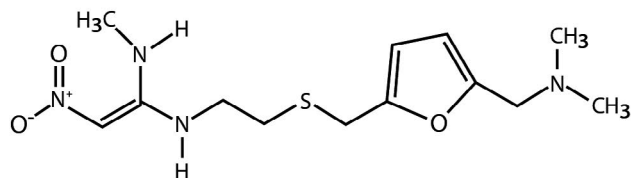
Generally, standard risk assessments of carcinogens assume that cancer risk increases as a function of cumulative dose. The NDMA ADI limit set by the FDA is a daily exposure at a theoretically calculated level that approximates a 1:100,000 cancer risk after 70 years of exposure. These risk levels represent a small theoretical increase in risk when compared with overall human lifetime incidence of developing any type of cancer, which is > 1 in 3. For certain medications, calculation of a higher daily intake of impurities can be considered for brief exposures because the cumulative dose would be significantly less than a daily treatment regimen of 70 years at the ADI limit. Average daily dietary intake of NDMA for US adults aged 20–49 is an estimated 0.06 µg.⁷

The agency has stopped short of recommending discontinuation of ranitidine, instead suggesting that concerned patients should discuss other treatment options with their providers, or if taking an over the counter ranitidine product, to consider using other over the counter medications. Suggested ranitidine treatment duration for GERD is only 4–8 weeks with symptom reassessment to avoid unnecessary long-term use, and tachyphylaxis does occur with prolonged use sometimes rendering it ineffective. Alternatives to ranitidine include other H₂RAs (cimetidine and famotidine) and PPIs (omeprazole, lansoprazole, and esomeprazole). Ranitidine and famotidine seem to be equally effective. Current clinical practice guidelines indicate that H₂RAs play a secondary role in the treatment of GERD; PPIs have become the mainstay of treatment.⁸ Notably, neither the FDA nor the petitioner detected NDMA in structurally dissimilar H₂RAs famotidine and cimetidine (Figure 1) or in several PPIs.

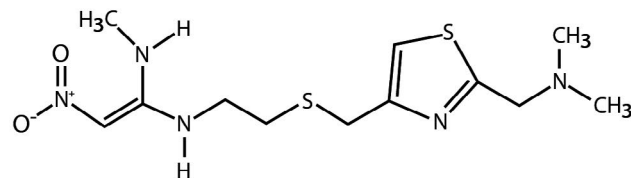
Little evidence is available to interpret associations among NDMA, ranitidine, and carcinogenicity. High doses of ranitidine in combination with nitrite was found to produce DNA fragmentation in the liver and gastric mucosa in rodents.⁹ A recent study conducted in humans found that urinary NDMA excretion over a 24-hour period following an orally administered dose of ranitidine increased from an average baseline of 0.11 µg/24 hour to a range of 19.5–47.6 µg/24 hour.¹⁰ The authors argue the urinary measurement represents a lower bound estimate to systemic NDMA exposure. Additionally, the researchers documented production of NDMA by nitrosation of ranitidine under stomach-relevant pH conditions *in vitro* and proposed a mechanism of NDMA formation from ranitidine (Figure 2).



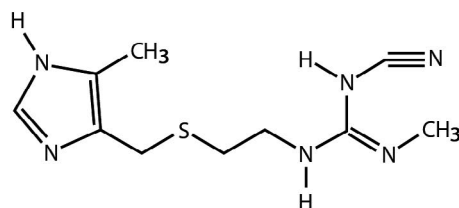
N-nitrosodimethylamine (NDMA)



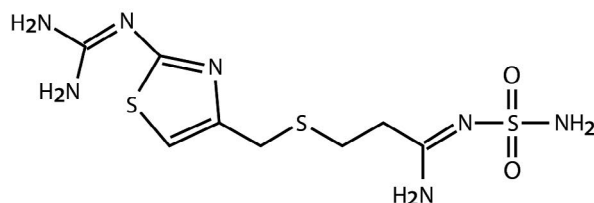
Ranitidine



Nizatidine



Cimetidine



Famotidine

Figure 1 Structures of N-nitrosodimethylamine and H₂-receptor antagonists.

The FDA requires extensive safety data be produced prior to any new drug approval, but cancer risks are difficult to determine in studies that are inherently short and conducted

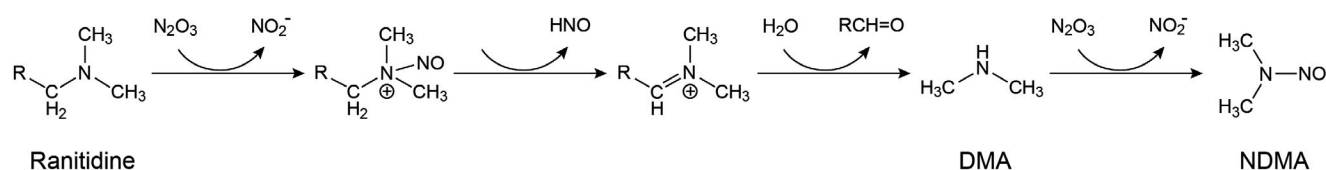


Figure 2 Proposed mechanism for the formation of N-nitrosodimethylamine (NDMA) from ranitidine in gastric conditions (Zeng & Mitch¹⁰. Used by permission of Oxford University Press).

primarily in animals. Moreover, drugs that have been on the market for many decades were originally dependent on testing methodologies that may be outdated. Elevated NDMA levels were observed in both tablet and syrup formulations, which lends further evidence that the NDMA formation is a result of an issue intrinsic to the active pharmaceutical ingredient. Regardless of the controversy that exists regarding the source and amounts of NDMA measured in ranitidine, the FDA has documented levels higher than its own recommended limit in some products. However, guidance on ADI limits as related to traditionally prescribed length of treatment courses (significantly less than lifetime exposure) may allow the prescriber to have a more thorough appreciation of risk. Setting the ADI equal to the maximum amount allowed in a standard dose does not allow for any exposures from additional sources. Additionally, whether or not ranitidine can react with itself, theoretically any nitroso donor reacting with ranitidine may be capable of producing NDMA under favorable conditions. Clearly, the potential cancer risk of various treatment lengths of ranitidine should be balanced against its benefits of therapeutic use, but complete data for a comprehensive risk assessment are lacking.

Additional studies, such as measuring NDMA concentrations in body fluids following ranitidine or radiolabeled ranitidine administration, to understand the load of NDMA would be beneficial, and epidemiological studies evaluating cancer risk attributable to long-term use of ranitidine and NDMA are necessary. Research examining production of NDMA is imperative, and manufacturers and the FDA should have a high index of suspicion of elevated levels in additional pharmaceuticals given NDMA may result from production processes or potentially from endogenous processes. In the meantime, with acceptable alternatives both in the same class and in additional classes, the benefits of continuing treatment with ranitidine may not clearly outweigh the risks.

As the FDA continues to investigate NDMA's association to ranitidine and provide clear and actionable information, the actions of the manufacturers and retailers may limit patients' and providers' medication treatment options. Media coverage to consumers may be misinterpreted as clear evidence of potential harm with continued use. However, removing medications from the market prematurely can result in critical drug shortages of alternative medications and may pose greater harm to patients who require these medications. Additionally, prescribing alternative medications may be difficult given insurance medication coverage

and may delay necessary treatment. Manufacturers, regulators, and providers must help families understand the risks and benefits when considering treatment with ranitidine and continuously evaluate the efficacy and safety of the medications prescribed using the most accurate available information, but current resolution of the various issues involved may take considerable time leaving providers lacking necessary information to quickly and accurately counsel patients.

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