Ranitidine and Risk of N-Nitrosodimethylamine (NDMA) Formation
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The US Food and Drug Administration (FDA) limits the amount of the probable carcinogen N-nitrosodimethylamine (NDMA) in a daily dose of medication to 96 ng. Chronic NDMA exposure has been shown to induce liver and lung cancer in animals, while high-dose acute NDMA poisoning can damage the liver and induce gastrointestinal and hepatic bleeding. Since 2019, NDMA exceeding this amount was found in numerous lots of several medications—such as angiotensin receptor blockers, sustained-release metformin, and ranitidine—and led to widespread recalls of several products and concern among patients and clinicians. On April 1, 2020, based on an ongoing investigation of NDMA in ranitidine, the FDA requested manufacturers of ranitidine to remove all over-the-counter and prescription ranitidine products from the market.

The FDA meticulously evaluated sources of NDMA and other nitrosamine contamination during the manufacturing process and established new procedures that manufacturers can take to prevent this issue from occurring in the future. By March 31, 2021, all manufacturers of chemically synthesized active pharmaceutical ingredients and finished pharmaceutical products that are FDA approved or pending approval had to conduct initial risk assessments for nitrosamine contamination.

However, the manufacturing facility is not the only place NDMA can be introduced into medications. Ranitidine forms NDMA as the product degrades on the store shelf and in the medicine cabinet, especially when exposed to heat and humidity. According to a laboratory study from 2011, several dimethylamine-containing drugs bound to an electron-rich moiety (such as ranitidine, doxylamine and chlorpheniramine, sumatriptan, nizatidine, diliazem, and tetracycline) form NDMA when exposed to chloramine, a commonly used drinking water disinfectant. Of these, ranitidine produced the highest amounts of NDMA by far. These alternate production sources bypass the safety procedures just enacted by the FDA to prevent excessive NDMA exposure.

Before the middle of May 2021, the available literature suggested that ranitidine could be a potential source of NDMA creation in the body. In 2016, a small unblinded study by Zeng and Mitch found more than 40 000 ng of NDMA in the urine of 10 people taking ranitidine. In January 2021, an in vitro human stomach simulation study by Braunstein et al found that 947 ng and 320 000 ng of NDMA were created when 100 mL of 1000 μmol/L and 50 000 μmol/L sodium nitrite, respectively, were intermingled with ranitidine in an acidic medium. According to the World Health Organization, long-term total daily ingested NDMA amounts from all sources in an average male adult should remain below 200 ng, because the 70-year estimated risk of cancer for this ingested amount would be less than 1 in 100 000. However, it is estimated that the average adult consumes 100 to 110 ng of NDMA daily in the water and food supply. This means that exceeding 100 ng of NDMA daily from prescription drugs (either in the product at ingestion or converted in the stomach) would increase the risk of cancer beyond negligible and supports the FDA’s limit of 96 ng. With this backdrop, the new FDA studies by Gao et al reported in JAMA Network Open and Florian et al in this issue of JAMA are reassuring.

The study by Gao et al involved an in vitro stomach model with ranitidine using the same 2-hour nitrite intermingling time as the study by Braunstein et al but assessed sodium nitrite concentrations ranging from 100 to 10 000 μmol/L in acidic media. The authors found that 250 mL of an acidic medium with sodium nitrite concentrations of 100 to 1000 μmol/L yielded negligible NDMA creation, but NDMA amounts of 7353 ng and 23 453 ng occurred when sodium nitrite concentrations were at 5000 μmol/L and 10 000 μmol/L, respectively. When only 50 mL of 5000 μmol/L or 10 000 μmol/L sodium nitrite was used (20% of the available nitrite vs 250 mL), NDMA creation went to a negligible amount and to 15 067 ng, respectively.

The report by Gao et al includes references to 27 studies to substantiate that nitrite concentrations in a physiologic stomach environment would be unlikely to exceed 100 μmol/L. Even with the additive effects of dietary nitrates being converted to nitrites by saliva and mouth flora and having nitrates and nitrites from previous meals being stored and then released from salivary glands, achieving a nitrite concentration of 1000 μmol/L in the stomach at an acidic pH has not been substantiated. However, the vast differences in NDMA production between 50 mL vs 250 mL of 5000 μmol/L sodium nitrite in the study Gao et al clearly shows that the amount rather than the concentration of nitrite in contact with ranitidine is the driver of NDMA production. Since the human stomach of a person with obesity can reasonably hold approximately 2 L of volume, it cannot be excluded that ranitidine use with a large acidic and nitrite-rich meal could drive appreciable NDMA production. Importantly, at higher nitrite concentrations, both Braunstein et al and Gao et al found much greater production of NDMA at lower pH levels, suggesting that little conversion of ranitidine to NDMA would occur in the intestines or the bloodstream.
In the report by Florian et al in this issue of JAMA, the investigators report findings from a phase 1 randomized crossover trial that evaluated urinary NDMA excretion for 24 hours after consumption of ranitidine or placebo. Eighteen healthy volunteers (median age, 33 years; 50% women) fasted overnight, consumed ranitidine (300 mg) or placebo, and then immediately ate a breakfast that was lower or higher in nitrate/nitrite, based on consumption of a diet with a noncured-meats diet and a cured-meats diet. The authors did not find overall increases in urinary NDMA concentration with ranitidine use vs placebo in either the high- or low-nitrate/nitrite meal environment.

However, Florian et al gave the participants ranitidine after a 12-hour fast and then gave them breakfast. By giving ranitidine with breakfast instead of dinner, the investigators might have missed a saliva source of nitrates. Breakfast was consumed over a 25-minute period after ranitidine was taken, but it is uncertain whether consumption was fast enough to ensure that enough nitrate was released from the food, converted to nitrite, and intermingled with dissolved ranitidine. The package labeling for ranitidine suggests that once-daily dosing should occur after the evening meal or before bedtime, not immediately before breakfast. It is unclear whether ranitidine administration around dinner would yield greater stomach nitrite concentrations than when it is given before breakfast. However, a study with a large-volume, acidic, and nitrite-rich dinner would need to be conducted to assess this issue.

Florian et al also gave participants distilled water (as part of the noncured-meats diet) and tap water (as part of the cured-meats diet). The lack of chloramine in distilled water might have eliminated an alternate but complementary pathway to ranitidine creation of NDMA, and this needs to be explored. The study by Florian et al also enrolled healthy volunteers, not people with chronic reflux disease or ulcers. These disorders affect gastric pH and flora and may not mimic the effects seen in these healthy volunteers.

The most important part of the study by Florian et al may be that the investigators devised and validated a process to ensure that the NDMA quantified in a urine sample represented what was created in the body and not what was subsequently created ex vivo. By not using these FDA-developed stabilization and analytic techniques on their urine samples, it is likely that Zeng and Mitch in their study on urinary NDMA did not detect NDMA produced in the body. Their study was retracted at the end of May 2021 as a result. These methods are complicated and only recently established, but future studies should incorporate these contemporary collection and analytic methods.

With the retraction of the study on urinary NDMA by Zeng and Mitch and the likelihood that the nitrite concentrations in the study by Braustein et al were not physiological, the 2 new FDA studies in JAMA Network Open and JAMA13 would serve to alleviate much of the previous concern about NDMA production of dimethylamine drugs in the human body. However, an in vitro study and a small phase 1 normal-participant study are far from definitive evidence. The in vitro stomach model used by Gao et al still does not include numerous variables that can exist in a human stomach and may not reflect the scenario after a large acidic meal or one that includes chloramine-treated water. The study by Florian et al provides rigorous evidence, although additional studies will be needed to address several remaining unknown factors and better refine understanding of this area.

Even with the reassuring data from these 2 FDA studies, patients and clinicians should not expect the return of ranitidine to the market anytime soon. Ranitidine is not needed when other similarly effective H2 antagonists exist without the ability to form NDMA as they degrade in the medicine cabinet or enter the water supply. The extent to which the other dimethylamine-containing drugs form NDMA when they degrade is still unknown and will require additional research to evaluate whether this occurs and if this risk is of concern with these products.

**REFERENCES**

10. Braustein LZ, Kantor ED, O’Connell K, et al. Analysis of ranitidine-associated N-nitrosodimethylamine production under...


