Effect of Oral Ranitidine on Urinary Excretion of N-Nitrosodimethylamine (NDMA)
A Randomized Clinical Trial

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**IMPORTANCE** In 2019, the US Food and Drug Administration (FDA) received a citizen petition indicating that ranitidine contained the probable human carcinogen N-nitrosodimethylamine (NDMA). In addition, the petitioner proposed that ranitidine could convert to NDMA in humans; however, this was primarily based on a small clinical study that detected an increase in urinary excretion of NDMA after oral ranitidine consumption.

**OBJECTIVE** To evaluate the 24-hour urinary excretion of NDMA after oral administration of ranitidine compared with placebo.

**DESIGN, SETTING, AND PARTICIPANTS** Randomized, double-blind, placebo-controlled, crossover clinical trial at a clinical pharmacology unit (West Bend, Wisconsin) conducted in 18 healthy participants. The study began in June 2020, and the end of participant follow-up was July 1, 2020.

**INTERVENTIONS** Participants were randomized to 1 of 4 treatment sequences and over 4 periods received ranitidine (300 mg) and placebo (randomized order) with a noncured-meats diet and then a cured-meats diet. The cured-meats diet was designed to have higher nitrites, nitrates (nitrate-reducing bacteria can convert nitrates to nitrites), and NDMA.

**MAIN OUTCOME AND MEASURE** Twenty-four-hour urinary excretion of NDMA.

**RESULTS** Among 18 randomized participants (median age, 33.0 [interquartile range (IQR), 28.3 to 42.8] years; 9 women [50%]; 7 White [39%], 11 African American [61%]; and 3 Hispanic or Latino ethnicity [17%]), 17 (94%) completed the trial. The median 24-hour NDMA urinary excretion values for ranitidine and placebo were 0.6 ng (IQR, 0 to 29.7) and 10.5 ng (IQR, 0 to 17.8), respectively, with a noncured-meats diet and 11.9 ng (IQR, 5.6 to 48.6) and 23.4 ng (IQR, 8.6 to 36.7), respectively, with a cured-meats diet. There was no statistically significant difference between ranitidine and placebo in 24-hour urinary excretion of NDMA with a noncured-meats diet (median of the paired differences, 0 [IQR, −6.9 to 0] ng; \( P = .54 \)) or a cured-meats diet (median of the paired differences, −11.1 [IQR, −9.1 to 11.5] ng; \( P = .71 \)). No drug-related serious adverse events were reported.

**CONCLUSIONS AND RELEVANCE** In this trial that included 18 healthy participants, oral ranitidine (300 mg), compared with placebo, did not significantly increase 24-hour urinary excretion of NDMA when participants consumed noncured-meats or cured-meats diets. The findings do not support that ranitidine is converted to NDMA in a general, healthy population.

**TRIAL REGISTRATION** ClinicalTrials.gov Identifier: NCT04397445
ranitidine, a histamine 2 (H₂) receptor blocker, was approved in the US in 1983 and became widely used as an over-the-counter drug for heartburn. In September 2019, the US Food and Drug Administration (FDA) received a citizen petition indicating that high levels of N-nitrosodimethylamine (NDMA), a probable human carcinogen,¹ had been detected in specific lots of ranitidine.² The petitioner also proposed that ranitidine could convert to NDMA in vivo by nitrite and statistical analysis plan are available in Supplement 1. Participants provided written informed consent. The protocol and statistical analysis plan are available in Supplement 1.

Methods

Study Setting and Dates
A randomized clinical trial with healthy participants was performed in a clinical pharmacology unit (West Bend, Wisconsin). This study was approved by the local institutional review board (Advvarra [https://www.advarra.com]). All participants provided written informed consent. The protocol and statistical analysis plan are available in Supplement 1.

Recruitment
The study was conducted in June and July of 2020. Participants were recruited by standard approaches for a phase 1 healthy volunteer study (ie, online advertising and emails/texts to individuals in the site’s database of potential participants for healthy volunteer studies). Self-identified race and ethnicity were collected in an open-ended format by clinical staff as recommended by the FDA’s guidance document, Collection of Race and Ethnicity Data in Clinical Trials.¹² Participants remained in the clinic for 10 days. Key inclusion criteria were age 18 to 50 years, nonsmoking, and negative test results for alcohol or drugs of abuse. Key exclusion criteria were a positive Helicobacter pylori test at screening or a history of H pylori or ulcer disease.

Randomization
Study participants were randomized to 1 of 4 treatment sequences using a random number generator in R statistical software and received 4 different combinations of study drug (ranitidine [300 mg] or placebo, randomized sequence) and diet (2 diets, fixed sequence) over 4 study periods (Figure 1). Randomization was conducted in block sizes of 4 for the first 16 participants enrolled, and the remaining 2 participants were randomly placed in 2 of the 4 treatment sequences. The study enrolled equal numbers of men and women, but randomization did not account for sex and treatment sequence interactions.

Interventions
The ranitidine lot was tested on 3 occasions and confirmed to have NDMA below the acceptable daily limit (6.3 and 7.5 ng prior to study start and 10.5 ng after study completion) (eTable 1 in Supplement 2). Each participant received a diet with noncured meats, organic vegetables/fruits and distilled water (noncured-meats diet) for 4 days and then cured meats, conventional vegetables/fruits, and tap water (cured-meats diet) for 4 days (Figure 1). The second diet was designed based on the literature to have higher nitrite, nitrate, and NDMA levels (eMethods 1 in Supplement 2).³⁹⁻¹¹

After consuming the same diet on the pretreatment day as the treatment day, participants received ranitidine or placebo at 0 hours (after overnight fast) on treatment days (days 1, 3, 5, and 7) and then began eating breakfast 1 minute afterward. This was done because the formation of NDMA is dependent on having nitrite and acidic conditions.¹³ Because gastric acidity is highest in the fasting state and then decreases after eating,¹³ this sequence was selected to maximize the 2 factors. Additional meals were provided at 4, 7.5, and 11.5 hours after dosing. Participants were
required to finish meals within 25 minutes (eTable 2 in Supplement 2). Participants were not allowed to take any prescription or nonprescription drugs, excluding contraceptives or acetaminophen, during the study unless prescribed by the study physician.

All urine voided over the 24 hours after drug administration was collected, weighed, and aliquoted to containers on ice with sodium hydroxide within 15 minutes and frozen on dry ice within 30 minutes (Urine Procedure Plan in Supplement 1). Void collection times were scheduled for 0- (predose), 3-, 6-, 9-, 12-, 15-, and 24-hours; unscheduled voids were also collected. Thirteen blood samples were collected on treatment days at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 11, 14, and 24 hours after treatment. NDMA, DMA, and ranitidine concentrations in urine and plasma were measured by validated liquid chromatographic tandem mass spectrometric methods (eMethod 2 in Supplement 2) per the FDA's Bioanalytical Method Validation Guidance for...
Outcomes
The primary outcome was 24-hour urinary excretion of NDMA. The exploratory outcomes included 24-hour urinary excretion of DMA and ranitidine; plasma pharmacokinetic parameters for NDMA, DMA, and ranitidine (including area under the plasma concentration vs time curve [AUC] and maximum concentration); and comparisons between cured-meat and noncured-meat diets. Adverse events were recorded by clinic staff and adjudicated by the principal investigator.

Statistical Analysis
A sample size of 14 participants was determined to have greater than 90% power to detect an increase in 24-hour urinary excretion of NDMA. The analysis assumed a 100% coefficient of variability, at least a 2-fold increase in NDMA, and 1-sided α of .05 because the primary objective was to determine if ranitidine increased urinary excretion of NDMA. A 2-fold difference was selected because it is a typical convention for pharmacokinetic studies, but it does not imply that a 2-fold increase in NDMA is clinically meaningful. Eighteen participants were randomized to account for dropouts without needing to enroll an additional cohort.

The analysis population included all participants who completed 2 paired treatment periods (ie, ranitidine and placebo with the same diet). Concentrations below the lower limit of quantitation (LLOQ) were considered zero. Missing data were not imputed. Because NDMA urine and plasma data were not normally distributed, a Wilcoxon signed-rank test was used for analyses per the statistical analysis plan (Supplement 1) without accounting for period or sequence. Because DMA and ranitidine data were log-normally distributed, analyses were based on a mixed-effects analysis of geometric means with terms for treatment, period, and sequence. A 1-sided lower P value <.05 was considered significant for the primary and exploratory analyses of ranitidine vs placebo because the study aim was to evaluate if ranitidine increased NDMA or DMA exposure. Comparisons were performed separately with each diet without adjustment for multiplicity. Exploratory analyses on the effect of diet used a 1-sided lower P value <.05 for NDMA because the cured-meats diet was designed to have higher NDMA, but a 2-sided P value <.05 for DMA and ranitidine because the diet was not designed to affect these outcomes. All analyses except for the primary outcome should be interpreted as exploratory because of the potential for type I error due to multiple comparisons. Pharmacokinetic and statistical analyses were performed in R version 3.6.3 (R Project for Statistical Computing).

Demographics are reported with standard descriptive statistics. NDMA results are reported as median (interquartile range [IQR]). DMA and ranitidine results are reported as geometric means (coefficient of variation percent [CV %]). Comparisons between groups are reported as median (IQR) of the paired differences for NDMA (calculated by first determining the difference between 2 treatments for each individual participant and then determining the median and IQR of those values) and geometric mean ratios for DMA and ranitidine (with 90% CIs for DMA comparisons between ranitidine and placebo and 95% CIs for all other comparisons).

Two post hoc sensitivity analyses were performed for the primary outcome: (1) removing 1 participant who was an outlier for NDMA urinary excretion in 3 of the 4 treatment periods and (2) performing different imputations for NDMA urine values below the LLOQ (eg, assign all samples below the LLOQ of 0.0156 ng/mL to a value of 0.0156 ng/mL).

Results
Eighteen participants (median age, 33.0 [IQR, 28.3 to 42.8] years; 9 women [50%]; 7 White [39%], 11 African American [61%]; and 3 Hispanic or Latino ethnicity [17%]) (Table 1) were randomized to 4 different treatment sequences (Figure 1). One participant discontinued during period 2 (day 3) for personal reasons. The data from that participant were not included in summary tables or comparisons between treatment groups. Multiple samples were below the LLOQ for urine (NDMA LLOQ, 0.0156 ng/mL), 73% of samples; DMA [LLOQ, 0.50 μg/mL], <1% of samples; and ranitidine [LLOQ, 15.6 ng/mL], <1% of samples) and plasma (NDMA [LLOQ, 0.0156 ng/mL], 89% of samples; DMA...
Primary Outcome—Urinary Excretion of NDMA

Multiple participants had no quantifiable NDMA in urine (Figure 2; eFigure 1 in Supplement 2) when receiving the noncured-meats diet (8 with ranitidine and 7 with placebo) or the cured-meats diet (3 with ranitidine and 3 with placebo). The median 24-hour NDMA urinary excretion values for ranitidine and placebo were 0.6 ng (IQR, 0 to 29.7) and 10.5 ng (IQR, 0 to 17.8), respectively, with the noncured-meats diet and 11.9 ng (IQR, 5.6 to 48.6) and 23.4 ng (IQR, 8.6 to 36.7), respectively, with the cured-meats diet (Table 2 and Figure 2). There was no statistically significant difference between ranitidine and placebo in 24-hour urinary excretion of NDMA with a noncured-meats diet (median of the paired differences, 0 [IQR, −6.9 to 0] ng; ⨯ = .54) or a cured-meats diet (median of the paired differences, −1.1 [IQR, −9.1 to 11.5] ng; ⨯ = .71) (Table 2). Figure 3 shows these differences between treatment groups over 24 hours.

Exploratory Outcomes

Plasma NDMA

Multiple participants had no quantifiable NDMA in plasma when receiving the noncured-meats diet (6 with ranitidine and 6 with placebo) or the cured-meats diet (6 with ranitidine and 7 with placebo) (Figure 2). Plasma NDMA profiles (eFigures 2 and 3 in Supplement 2) did not show sustained quantifiable amounts of NDMA and thus did not support calculation of an AUC. Maximum plasma concentration data by group is shown in Figure 2 and Table 2 (additional pharmacokinetic parameters are reported in eTable 4 in Supplement 2). There were no statistically significant differences between ranitidine and placebo with the noncured-meats diet (median of the paired
DMANo participants had quantifiable DMA in plasma and urine across all treatment groups (Figure 2; eFigures 4-6 in Supplement 2). Across the 4 treatment groups, the geometric mean maximum plasma concentration range was 1.36 to 1.51 μg/mL (CV, 25%-27%), the geometric mean AUC range was 20.9 to 26.3 h·μg/mL (CV, 34%-53%), and the geometric mean amount excreted in urine range was 38.8 to 43.1 mg (CV, 33%-52%) (Table 2; additional pharmacokinetic parameters are reported in eTable 4 in Supplement 2). All comparisons between ranitidine and placebo had geometric mean ratio 90% CI crossing 1.

Ranitidine

Geometric mean ranitidine 24-hour urinary excretion was 91.7 mg (CV, 29%) for the noncured-meats diet and 74.1 mg (CV, 39%) for the cured-meats diet (median of the paired differences, 0 [IQR, −6.9 to 0] ng; P = .54) or the cured-meats diet (median of the paired differences, 2.2 [IQR, −9.4 to 9.1] ng; P = .23)(Table 2).

Table 2. Effect of Ranitidine on NDMA and DMA 24-Hour Urinary Excretion and Plasma Measurements (Primary and Exploratory Outcomes)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Diet</th>
<th>Ranitidine, median (IQR)</th>
<th>Placebo, median (IQR)</th>
<th>Paired differences, median (IQR)*</th>
<th>P valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDMA 24-h urinary excretion, ng</td>
<td>Noncured meats</td>
<td>0.6 (0-29.7)</td>
<td>10.5 (0-17.8)</td>
<td>0 (−6.9 to 0)</td>
<td>.54</td>
</tr>
<tr>
<td></td>
<td>Cured meats</td>
<td>11.9 (5.6-48.6)</td>
<td>23.4 (8.6-36.7)</td>
<td>−1.1 (−9.1 to 11.5)</td>
<td>.71</td>
</tr>
<tr>
<td></td>
<td>Placebo, median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cured meats</td>
<td>23.4 (8.6-36.7)</td>
<td>23.4 (8.6-36.7)</td>
<td>0 (−6.9 to 0)</td>
<td>.54</td>
</tr>
<tr>
<td>Exploratory outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum NDMA plasma concentration, pg/mL</td>
<td>Noncured meats</td>
<td>18.9 (0-25.7)</td>
<td>20.3 (0-33.5)</td>
<td>0 (−20.5 to 13.6)</td>
<td>.79</td>
</tr>
<tr>
<td></td>
<td>Cured meats</td>
<td>29.0 (0-34.5)</td>
<td>16.2 (0-27.4)</td>
<td>2.2 (−8.4 to 9.1)</td>
<td>.23</td>
</tr>
<tr>
<td>DMA 24-h urinary excretion, mg</td>
<td>Noncured meats</td>
<td>38.8 (38)</td>
<td>41.1 (33)</td>
<td>0.94 (0.87 to 1.01)</td>
<td>.92</td>
</tr>
<tr>
<td></td>
<td>Cured meats</td>
<td>40.7 (52)</td>
<td>43.1 (34)</td>
<td>0.95 (0.81 to 1.10)</td>
<td>.74</td>
</tr>
<tr>
<td></td>
<td>Placebo, geometric mean (CV %)</td>
<td>Placebo, geometric mean (CV %)</td>
<td>Geometric mean ratio (90% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum DMA plasma concentration, μg/mL</td>
<td>Noncured meats</td>
<td>1.51 (25)</td>
<td>1.48 (27)</td>
<td>1.02 (0.97 to 1.08)</td>
<td>.26</td>
</tr>
<tr>
<td></td>
<td>Cured meats</td>
<td>1.36 (27)</td>
<td>1.41 (26)</td>
<td>0.97 (0.91 to 1.03)</td>
<td>.82</td>
</tr>
<tr>
<td>24-h plasma DMA area under the curve, h·μg/mL</td>
<td>Noncured meats</td>
<td>26.3 (34)</td>
<td>26.2 (35)</td>
<td>1.00 (0.91 to 1.11)</td>
<td>.46</td>
</tr>
<tr>
<td></td>
<td>Cured meats</td>
<td>20.9 (53)</td>
<td>20.9 (46)</td>
<td>1.00 (0.80 to 1.25)</td>
<td>.49</td>
</tr>
</tbody>
</table>

Abbreviations: CV, coefficient of variation; DMA, dimethylamine; IQR, interquartile range; NDMA, N-nitrosodimethylamine.

* Calculated by first determining the difference between the 2 treatments for each individual participant and then determining the median of those values. The Wilcoxon signed-rank test used for NDMA analyses is also based on first determining the difference between the treatment groups for each individual participant.

b A 1-sided lower P value <.05 was considered significant for the primary and exploratory analyses of ranitidine vs placebo because the study aim was to evaluate if ranitidine increased NDMA or DMA exposure.

Figure 3. Effect of Ranitidine and Diet on Cumulative Excretion of NDMA in Urine Over 24 Hours

Paired differences in cumulative excretion of N-nitrosodimethylamine (NDMA) in urine over 24 hours. At each listed time point on the x-axis since study drug administration (ie, 0 [pre-dose], 3, 6, 9, 12, 15, and 24 hours), the y-axis shows the median (point) and interquartile range (lines) of the paired differences in cumulative NDMA excretion between the 2 specific treatment groups up until that time point. Note that the median and interquartile range of the paired differences is calculated by first determining the difference between 2 treatments for each individual participant and then determining the median and interquartile range of those values. Ranitidine or placebo was administered at 0 hours. Meals were administered at 0, 4, 7.5, and 11.5 hours. Individual participant profiles for each treatment group are shown in eFigure 1 in Supplement 2.

Differences, 0 [IQR, −20.5 to 13.6] ng; P = .79) or the cured-meats diet (median of the paired differences, 2.2 [IQR, −9.4 to 9.1] ng; P = .23) (Table 2).
The cured-meats diet was associated with significantly higher 24-hour urinary excretion of NDMA (median of the paired differences, 9.3 [IQR, 3.8 to 25.0]; \( P = .005 \)) (Figure 3 and Table 3). Comparisons between diets for ranitidine and placebo revealed no statistically significant difference in 24-hour urinary excretion of NDMA (Table 3 in Supplement 2).

**Adverse Events**

No serious drug-related adverse events were reported. The most common adverse event was vessel puncture site pain, which developed in 2 participants (eTable 9 in Supplement 2).

**Discussion**

In this randomized, placebo-controlled study in healthy participants, oral administration of ranitidine (300 mg) did not significantly increase 24-hour urinary excretion of NDMA. The lack of a significant increase occurred even when participants were served a diet designed to be higher in nitrates, which in vitro studies have suggested can potentiate NDMA formation. Furthermore, exploratory analyses did not reveal any significant difference between ranitidine and placebo for NDMA in plasma or DMA in urine or plasma.

This study was designed and conducted to further investigate the findings from a prior clinical study that observed an approximately 400-fold increase in 24-hour urinary excretion of NDMA and an approximately 2.5-fold increase in DMA level after ranitidine administration. After completion of this study and submission of this report for publication, the prior study was retracted at the request of the authors, citing that an analytical artifact could have contributed to the levels of NDMA measured. The analytical artifact was likely the primary factor; however, other factors could have contributed to falsely high NDMA levels in the prior study (summarized in eTable 10 in Supplement 2). Furthermore, the absence of a significant increase in NDMA for the cured-meats diet. Additional urine and plasma data are reported in eTable 5 and eFigures 7-11 in Supplement 2.

**Comparisons Between Diets for Ranitidine and Placebo**

The cured-meats diet compared with the noncured-meats diet was associated with significantly higher 24-hour urinary excretion of NDMA with placebo (median of the paired differences, 6.4 [IQR, 0 to 23.4]; \( P = .007 \)) and ranitidine (median of the paired differences, 9.3 [IQR, 3.8 to 25.0]; \( P = .005 \)) (Figure 3 and Table 3). In addition, the cured-meats diet, compared with the noncured-meats diet, was associated with significantly lower plasma DMA AUC geometric mean ratios with both placebo and ranitidine (0.80 [95% CI, 0.65 to 0.98]; \( P = .03 \) with placebo and 0.80 [95% CI, 0.67 to 0.95]; \( P = .02 \) with ranitidine) and maximum plasma concentration with ranitidine (0.90 [95% CI, 0.84 to 0.97]; \( P = .009 \)) but not placebo (0.95 [95% CI, 0.86 to 1.06]; \( P = .33 \)) (Table 3). Comparisons between diets for 24-hour DMA urinary excretion had 95% CIs crossing 1 (Table 3).

**Post Hoc Assessments**

One participant’s 24-hour NDMA urinary excretion was an outlier in periods 2 through 4 (ranitidine/noncured-meats diet, 512 ng; ranitidine/cured-meats diet, 649 ng; and placebo/cured-meats diet, 746 ng) but not in period 1 (placebo/noncured-meats diet, 29 ng). The participant’s maximum plasma concentration for NDMA did not follow this pattern; however, the NDMA amount in predose urine samples followed the same pattern (eTable 6 in Supplement 2). Clinical staff noted that the participant began menstruating between study periods 1 and 2, continuing through study period 4, and blood was detected and visible in urine samples. When removing this participant from the analysis, ranitidine, compared with placebo, still did not significantly increase 24-hour NDMA urinary excretion (eTable 7 in Supplement 2). In addition, when performing the second set of sensitivity analyses (imputations for samples below the LLOQ), there was still no statistically significant difference in 24-hour urinary excretion of NDMA (eTable 8 in Supplement 2).

**Table 3. Effect of Diet on NDMA and DMA 24-Hour Urinary Excretion and Plasma Measurements (Exploratory Outcomes)**

<table>
<thead>
<tr>
<th>Study drug</th>
<th>Cured-meats diet, median (IQR)</th>
<th>Noncured-meats diet, median (IQR)</th>
<th>Paired differences, median (IQR)*</th>
<th>( P ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NDMA 24-h excretion</strong>, ng</td>
<td>Ranitidine 11.9 (5.6-48.6)</td>
<td>0.6 (0-29.7)</td>
<td>9.3 (3.8 to 25.0)</td>
<td>.005</td>
</tr>
<tr>
<td><strong>Maximum NDMA plasma concentration, pg/mL</strong></td>
<td>Ranitidine 29.0 (0-34.5)</td>
<td>18.9 (0-25.7)</td>
<td>0.4 (-5.1 to 32.6)</td>
<td>.15</td>
</tr>
<tr>
<td></td>
<td>Placebo 16.2 (0-27.4)</td>
<td>20.3 (0-33.5)</td>
<td>0 (-18.8 to 8.1)</td>
<td>.74</td>
</tr>
<tr>
<td><strong>DMA 24-h excretion, mg</strong></td>
<td>Ranitidine 40.7 (52)</td>
<td>38.8 (38)</td>
<td>1.05 (0.90 to 1.23)</td>
<td>.52</td>
</tr>
<tr>
<td></td>
<td>Placebo 43.1 (34)</td>
<td>41.1 (33)</td>
<td>1.05 (0.93 to 1.19)</td>
<td>.42</td>
</tr>
<tr>
<td><strong>Maximum DMA plasma concentration, pg/mL</strong></td>
<td>Ranitidine 1.36 (27)</td>
<td>1.51 (25)</td>
<td>0.90 (0.84 to 0.97)</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>Placebo 1.41 (26)</td>
<td>1.48 (27)</td>
<td>0.95 (0.86 to 1.06)</td>
<td>.33</td>
</tr>
<tr>
<td><strong>24-h plasma DMA area under the curve, h pg/mL</strong></td>
<td>Ranitidine 20.9 (53)</td>
<td>26.3 (34)</td>
<td>0.80 (0.67 to 0.95)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Placebo 20.9 (46)</td>
<td>26.2 (35)</td>
<td>0.80 (0.65 to 0.98)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviations: CV, coefficient of variation; DMA, dimethylamine; IQR, interquartile range; NDMA, N-nitrosodimethylamine.

* Calculated by first determining the difference between the 2 treatments for each individual participant and then determining the median of those values. The Wilcoxon signed-rank test used for NDMA analyses is also based on first determining the difference between the treatment groups for each individual participant.

\( * \) Exploratory analyses on the effect of diet used a 1-sided lower \( P \) value < .05 for DMA, as the cured-meats diet was designed to have higher DMA but used \( P < .05 \) (2-sided) for DMA, as the effect of diet on these outcomes was not known.
levels in the present study occurred despite using a higher ranitidine dose (300 mg vs 150 mg) and having participants consume a diet with higher nitrite and nitrate content for at least 24 hours before and after administration of ranitidine or placebo.

The 24-hour urinary excretion of NDMA with placebo in this study was within the range of previously reported results. While ranitidine did not have a significant effect on NDMA or DMA values, the cured-meats diet was associated with a significant increase in NDMA urinary excretion, suggesting that the study design and methods were sufficiently sensitive to detect the relatively small effect of diet on NDMA urinary excretion. Regarding DMA, the cured-meats diet was associated with significantly lower DMA plasma exposure. DMA content in foods is known to differ. There was a consistent level of DMA in plasma throughout the day, with approximately 40 mg excreted in urine daily across all treatment groups. This demonstrated that the human body is constantly exposed to large amounts of DMA.

A recent study by Braunstein et al reported that ranitidine converted to NDMA under simulated physiological conditions in gastric fluid. However, in an article by Gao et al, comparison to clinical studies measuring human gastric nitrite concentrations and pH suggested that in the study by Braunstein et al the tested gastric fluid conditions did not represent physiologic nitrite concentrations. Gao et al included physiologic nitrite concentrations in simulated gastric fluid experiments and found that NDMA did not form until nitrite concentrations were approximately 50-fold higher than the upper range of physiologic nitrite at pH less than 6. Furthermore, at more acidic pH, where NDMA formation is favored, the difference compared with the 95th percentile of the study population was approximately 9000-fold for fasting patients undergoing upper endoscopy and 600-fold from a study with 24-hour gastric nitrite and pH measurements (fed and fasting) with patients with precancerous conditions.

The importance of assessing physiologic relevance extends to other settings. A rodent study reported as preliminary evidence of ranitidine being associated with cancer. While that study found that co-dosing ranitidine and sodium nitrite to 2-month old rats could be genotoxic, it involved extremely high ranitidine (175 or 350 mg/kg) and sodium nitrite (80 mg/kg) doses while fasting animals for 60 hours to reduce gastric pH. This vastly exceeds human ranitidine doses (~2-4 mg/kg), and the sodium nitrite dose was close to the median lethal dose in rats. Regarding human studies, a recent commentary also referenced an observational study as preliminary evidence of ranitidine being associated with cancer. The study found that current ranitidine users had an increased risk of ductal carcinoma (breast cancer); however, the study did not control for cancer risk factors and performed more than 40 comparisons without adjustment for multiple comparisons, and 4 other studies found no relationship between ranitidine and breast cancer. When considering all cancer types, while each study had limitations (e.g., confounding by indication, residual confounding, multiple comparisons), no consistent signals emerged across studies, and studies with comparison to active controls found no association between ranitidine and overall or specific cancer risk.

Ranitidine products were withdrawn from the US market in April 2020 because of higher than acceptable NDMA amounts being detected in the drug product that could increase over time during storage. However, the approvals were not withdrawn, and the FDA may consider allowing ranitidine product back on the market if a specific product is stable and NDMA amounts do not increase to unsafe levels over time during storage. When considering the potential risk to patients who may have taken ranitidine with NDMA amounts above the acceptable daily limit, it is important to note that this is the amount predicted to result in a cancer risk of 1 in 100 000 if taken daily for a lifetime (i.e., 70 years of 96 ng/d of NDMA for a 50-kg person).

Limitations
This study has several limitations. First, 1 participant was an outlier for 24-hour NDMA urinary excretion in 3 treatment periods; however, the data suggest that this was not due to ranitidine or an in vivo effect because (1) the outlier values occurred when the participant was menstruating, (2) blood was visible and detected in urine samples, and (3) predose urine sample NDMA amounts followed the same pattern while maximum plasma concentration of NDMA did not. Because red blood cells contain high intracellular nitrite concentration, it is possible that ex vivo lysis of red blood cells in acidic urine samples facilitated conversion of DMA to NDMA. Second, the study included many urine samples with NDMA levels below the LLOQ. However, the NDMA assay was very sensitive (LLOQ, 0.0156 ng/mL) and there was no notable difference between ranitidine and placebo in the number of participants with all sample below the LLOQ. Sensitivity analyses for each of the first 2 limitations did not change the study results. Third, the exact dietary amount of nitrite, nitrate, and NDMA is not known. However, ranitidine did not significantly increase NDMA values with either diet, including the cured-meats diet designed to have high nitrite content. Fourth, this study only included healthy participants and did not exclude formation of NDMA in the gastrointestinal tract that was not absorbed and detected in plasma or urine. However, the results support that ranitidine did not significantly increase levels of NDMA or DMA detected in plasma or urine using highly sensitive assays, and the accompanying in vitro gastric fluid study indicated that NDMA was not formed until nitrite concentrations were substantially higher than those seen in patients.

Conclusions
In this trial that included 18 healthy participants, oral ranitidine (300 mg), compared with placebo, did not significantly increase 24-hour urinary excretion of NDMA when participants consumed noncured-meats or cured-meats diets. These findings do not support that ranitidine is converted to NDMA in a general, healthy population.
Effect of Oral Ranitidine on Urinary Excretion of N-Nitrosodimethylamine (NDMA)


