Title

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Journal

Epilepsia, 64(2)

ISSN

0013-9580

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Publication Date

2023-02-01

DOI

10.1111/epi.17459

Received: 7 September 2022 | Revised: 2 November 2022 | Accepted: 7 November 2022

DOI: 10.1111/epi.17459

Epilepsia®

RESEARCH ARTICLE

A randomized, open-label, two-treatment crossover study to evaluate the effect of food on the pharmacokinetics of diazepam nasal spray in healthy adults

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Abstract

Objective: The pharmacokinetics of oral diazepam are affected by food, but food-effect studies have not been conducted for diazepam nasal spray because it is believed that most absorption occurs via the nasal mucosa. However, gastrointestinal side effects reported with nasal diazepam suggest that at least a portion of the drug may be absorbed enterally and thus subject to food effects. The objective of this study was to evaluate the possible effects of food on the pharmacokinetics of diazepam nasal spray in healthy adults.

Methods: This randomized, open-label crossover study compared equal doses of diazepam nasal spray after an overnight fast and after a standardized high-fat, high-calorie breakfast. Each participant served as their own control, and there was a washout period of at least 21 days between treatments.

Results: Twenty-four healthy adults enrolled in this study. Two participants withdrew consent, and two had pre-dose diazepam concentrations that exceeded the protocol-defined minimum after the washout period and were excluded from the final analysis population of 20 participants. Under fed conditions, the mean maximum plasma diazepam concentration was decreased by 48% ($p < .0001$) and the overall diazepam exposure during the first 4 h was reduced by 57% ($p < .0001$) compared with fasted conditions. The time to maximum plasma concentration was 4.0 h in the fed state compared with 2.0 h in the fasted state ($p < .0001$). At 2 h post-dose, diazepam concentrations were ≥150 ng/mL for 100% of the participants when in the fasted state and 30% when in the fed state. Significantly more participants experienced adverse events under fasted conditions (83.3%) than under fed conditions (54.5%; $p = .0340$).

Significance: This study in healthy volunteers demonstrated that food significantly decreases and delays the absorption of diazepam dosed via nasal spray. Patients using diazepam nasal spray after eating may obtain diazepam concentrations that are below those needed for seizure control.

KEYWORDS
absorption, enteral, fasted, fed

1 | INTRODUCTION

Diazepam, first approved by the US Food and Drug Administration (FDA) in 1963, is now indicated for the management of anxiety, relief of the symptoms of acute alcohol withdrawal, alleviation of muscle spasms and spasticity, and the adjunct treatment of convulsive disorders, specifically the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern.[1,2] To support this range of indications, diazepam is currently available in the United States as an injectable solution, oral tablet, oral solution/concentrate, nasal spray, and rectal gel.[3]

The pharmacokinetics of diazepam depend on the route of administration. In particular, the absorption of orally administered diazepam is known to be delayed and decreased in the first few hours after dosing by the presence of food in the stomach.[1,4] Greenblatt et al. demonstrated that, in healthy volunteers taking 5-mg oral diazepam tablets, the average time to maximum diazepam plasma concentration (T_{max}) nearly doubled from 1.25 h when administered in the fasted state to 2.41 h after a standardized breakfast. In these participants, the maximum diazepam plasma concentration (C_{max}) decreased by an average of 27%, and the total exposure to diazepam (area under the curve [AUC]) from 0 to 4 h post-dose decreased by 16% in the fed vs the fasted state.[4]

To date, no studies have evaluated the effect of food on the pharmacokinetics of diazepam administered by non-oral routes of administration, and a recent review article on seizure clusters noted that the effect of food on the rate or extent of absorption of intranasal benzodiazepines is unknown.[5] The small liquid volume delivered by nasal spray formulations is believed to be absorbed by transport across the nasal mucosa and uptake into the mucosal capillary bed. However, gastrointestinal adverse events (AEs) reported in trials of diazepam nasal spray, such as dysgeusia and nausea, raise the possibility that at least some portion of the dose reaches the mouth, throat, and stomach.[6,7]

Studies of other nasal sprays where similar AEs were reported found evidence of enteral absorption. Midazolam nasal spray, which is also indicated for the acute treatment of intermittent seizure activity, can cause throat irritation and abnormal taste.[8] Pharmacokinetic studies comparing plasma concentrations of midazolam and midazolam's metabolite for different formulations found that a significant amount of the drug in the midazolam nasal spray is likely to be absorbed enterally rather than in the nasal cavity.[9] Similarly, the most common AEs for sumatriptan nasal spray (indicated for acute treatment of migraine) include throat discomfort, nausea and/or vomiting, and a bad/unusual taste.[10] Studies have estimated that only 10% of sumatriptan delivery occurs through the nasal cavity, with the majority of the administered dose being absorbed enterally.[11–13]

Given the pronounced effect of food on oral diazepam,[1,4] the oropharyngeal AEs reported with diazepam nasal spray,[6,7] and the evidence of enteral absorption with other nasal sprays,[8,9,11–13] it is plausible that food could influence the pharmacokinetics of diazepam nasal spray. When diazepam nasal spray is used to treat acute repetitive seizures, a delay in absorption (prolonged T_{max}) or a reduction in peak concentration (suboptimal C_{max}) may adversely affect product performance. Although the concentration of diazepam needed for seizure rescue is not known precisely, a level of 70 ng/mL is required to elevate seizure threshold in animal models,[14] and several studies suggest that 150–200 ng/mL may be an appropriate therapeutic target for C_{max} in humans.[15–19]

The objective of this study was to evaluate the effect of food, if any, on the pharmacokinetics of diazepam nasal spray in healthy adult male and female participants.

Key points

- The pharmacokinetics of oral diazepam are affected by food, but food-effect studies have not been conducted for diazepam nasal spray.
- In this study of diazepam nasal spray, a high-fat, high-calorie meal decreased and delayed absorption compared with the fasted state.
- Two hours after dosing, 100% of participants in the fasted state but only 30% of participants in the fed state achieved plasma diazepam concentrations ≥150 ng/mL.
- Significantly more participants experienced adverse events when in the fasted state (83.3%) than when in the fed state (54.5%).
- Patients who use diazepam nasal spray after consuming a meal may have a greater likelihood of inadequate treatment.

2 | MATERIALS AND METHODS

2.1 | Study design

This phase 1, randomized, open-label, two-sequence, two-period, two-treatment crossover study compared equal doses of diazepam nasal spray (Valtoco, Neurelis, Inc.) under fasted and fed conditions in healthy adult male and female participants. Treatment consisted of diazepam nasal spray 15 mg (for participants weighing 50–75 kg) or 20 mg (for participants weighing at least 76 kg) administered as one 7.5 mg or 10 mg spray in each nostril while the participant was supine. The fasted treatment was administered following an overnight fast of at least 10 h, and the fed treatment was administered 30 min after the start of a standardized high-fat, high-calorie breakfast that was consumed in its entirety following an overnight fast of at least 10 h. Fluids, including water, were restricted from 1 h before to 1 h after treatment administration, except for the milk given with breakfast for the fed state. The order of treatments followed a two-sequence randomization schedule generated by the study biostatistician using SAS Version 9.4, and there was a washout period of at least 21 days between treatments.

Participants were confined to the research facility in Las Vegas, Nevada from 10.5 h before dosing until 24 h after dosing. All participants were instructed to abstain from alcohol- or grapefruit-containing food/beverages or energy drinks within 72 h before dosing and from caffeine- or xanthine-containing food/beverages within 24 h before dosing. No use of tobacco- or nicotine-containing products was permitted starting 6 months prior to the initial dose and throughout the study.

This study was conducted in accordance with the protocol approved by the Novum Independent Institutional Review Board and was compliant with the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use and Guidelines for Good Clinical Practice. All participants provided written informed consent before screening.

2.2 | Study population

Participants enrolled in this study were healthy male or female humans aged 18–55 years who weighed at least 51 kg and had a body mass index (BMI) of 18.5–29.9 kg/m^2. Included participants were in good health, had a systolic blood pressure between 90 and 140 mm Hg and/or a diastolic blood pressure between 50 and 90 mm Hg at screening and had a pulse between 50 and 100 beats per minute at screening.

Key exclusion criteria included a history of allergy or sensitivity to diazepam or an excipient in diazepam nasal spray; use of any inhalers, nasal sprays, or steam-inhalation-based practices within 7 days before dosing; nasal septum ulcers, nasal surgery, or nasal trauma within 3 months before initial dosing; sinus infection within 30 days of initial dosing or a history of chronic sinusitis; any signs or symptoms of ongoing influenza or common cold infection; significant history or current evidence of chronic postnasal drip; current and/or anticipated need for treatment of seasonal or perennial rhinitis within 30 days of initial study dosing or any time during the study; and difficulty with fasting or consuming standard meals that were part of the study.

Other exclusion criteria included a significant history or current evidence of chronic infectious disease, system disorder, or organ dysfunction, including gastrointestinal disease or malabsorption in the last year; a history of psychiatric disorders requiring medication or hospitalization; positive test results for HIV, hepatitis B surface antigen, or hepatitis C antibody; use of pharmacologic agents known to significantly induce or inhibit drug-metabolizing enzymes within 30 days before initial dosing; receipt of any drug as part of a research study within 30 days before initial dosing; use of recreational drugs within 12 months before initial dosing; any history of treatment for or current drug or alcohol addiction; history of excessive alcohol consumption in the 12 months prior to dosing; positive results for drugs of abuse or cotinine at screening; and use of any tobacco- or nicotine-containing products within 6 months before initial dosing.

Female participants who were pregnant, lactating, or likely to become pregnant during the study were excluded. Female participants of childbearing potential were required to abstain from sexual activity or use a non-hormonal double barrier method of contraception or a non-hormonal intrauterine device (IUD) for at least 14 days (3 months for an IUD) before initial dosing and throughout the study. Male participants who were sexually active with females of childbearing potential were required to use an approved method of highly effective contraception from the time of informed consent until the end of the study.

2.3 | Study endpoints

Blood samples were collected pre-dose (0 h) and at 10, 20, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 h post-dose. Samples were assayed for diazepam at a central laboratory using liquid chromatography and/or mass spectrometry methods validated according to international guidelines. Pharmacokinetic parameters

were computed using a non-compartmental model of Phoenix WinNonlin Version 8.1 or higher (Certara L.P.), and statistical analysis was performed using SAS (Version 9.4).

Other assessments included taste ("Do you taste or have sensation of the study drug in your throat or mouth?" at 15, 30, 45, and 60 min [±5 min] after dosing) and sedation (before dosing and at 1 and 2 h [±15 min] after dosing). Sedation was graded on a 6-point scale ranging from 0 (alert, not drowsy; normal conversation) to 5 (sleeping, cannot awaken). Participants were monitored for AEs throughout the study.

2.4 | Statistics

The safety population included all participants who received at least one dose of diazepam nasal spray. The pharmacokinetic population included all participants with data following administration of diazepam in both the fasted and fed states. The final analysis population excluded participants with pre-dose concentrations of diazepam >5% of the C_{max} for a particular study period. Formal power calculations were not performed. A sample size of 24 healthy participants was considered sufficient to meet the objectives of this study.

Descriptive statistics were calculated and reported for the pharmacokinetic parameters of diazepam. As the study was conducted in three groups, the ln-transformed pharmacokinetic parameters C_{max}, area under the curve $(AUC)_{0-4}$ and AUC_{0-24} were subjected to an analysis of variance (ANOVA) model that assessed group, sequence, and treatment (fed vs fasted). Each analysis of variance included calculation of least-squares means, the difference between the adjusted formulation means, and the standard error associated with this difference. The pharmacokinetic parameter T_{max} was assessed using the non-parametric Wilcoxon signed-rank test. Statistical analyses were performed using SAS (Version 9.4).

3 | RESULTS

3.1 | Study population

Twenty-four healthy adults (19 men, 5 women) were enrolled in this study between August and October 2021. During the washout period between treatments, two male participants withdrew consent and discontinued the study (Figure 1). The remaining 22 participants completed the study, but two male participants had pre-dose diazepam concentrations >5% of C_{max} after the washout period and were excluded from the final analysis population as prespecified in the statistical analysis plan. Both participants were administered diazepam while in the fasted state in the first part of the study.

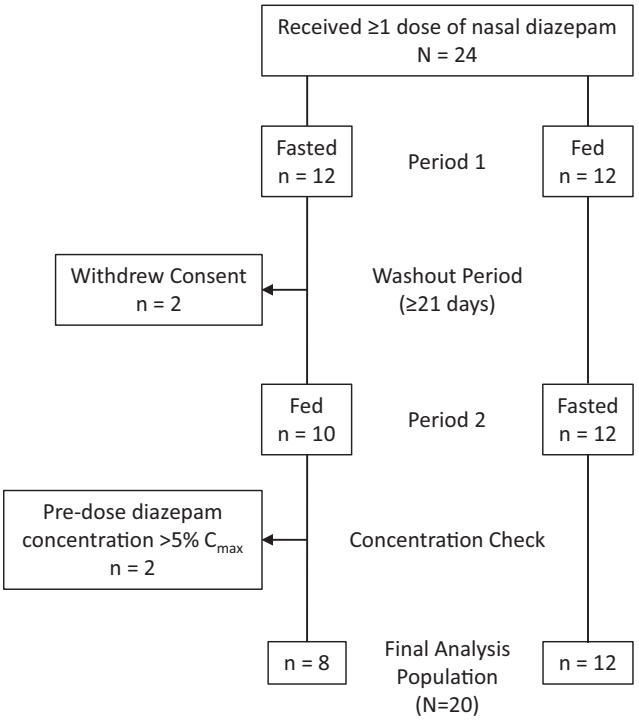


FIGURE 1 Participant flow diagram (healthy volunteers). C_{max}, maximum diazepam plasma concentration

The remaining 20 participants (15 men, 5 women) completed the study and are included in the pharmacokinetic analysis. The mean age was 38.0 years (standard deviation [SD] 8.94 years), and the mean (SD) BMI was 26.3 (2.55) kg/m^2. The mean body weights of the male and female participants were 80.1 kg and 63.7 kg, respectively. The racial identities of the participants were 45% Black/African American, 35% White, 15% multiple races, and 5% Native Hawaiian/Other Pacific Islander.

3.2 | Pharmacokinetics

After a high-fat, high-calorie meal, administration of diazepam nasal spray to healthy volunteers led to reduced plasma diazepam concentrations compared with the fasted state (Figures 2 and 3). Fed administration of diazepam nasal spray resulted in a 48% lower C_{max} ($p < .0001$), a doubling of the median T_{max} from 2 h to 4 h ($p < .0001$), and a 57% lower diazepam AUC_{0-4} ($p < .0001$) vs fasted administration (Table 1). Over 24 h, food decreased total diazepam exposure (AUC_{0-24}) by 16% ($p = .0232$).

Similar fed/fasted ratios were obtained when data from the two participants who had pre-dose diazepam

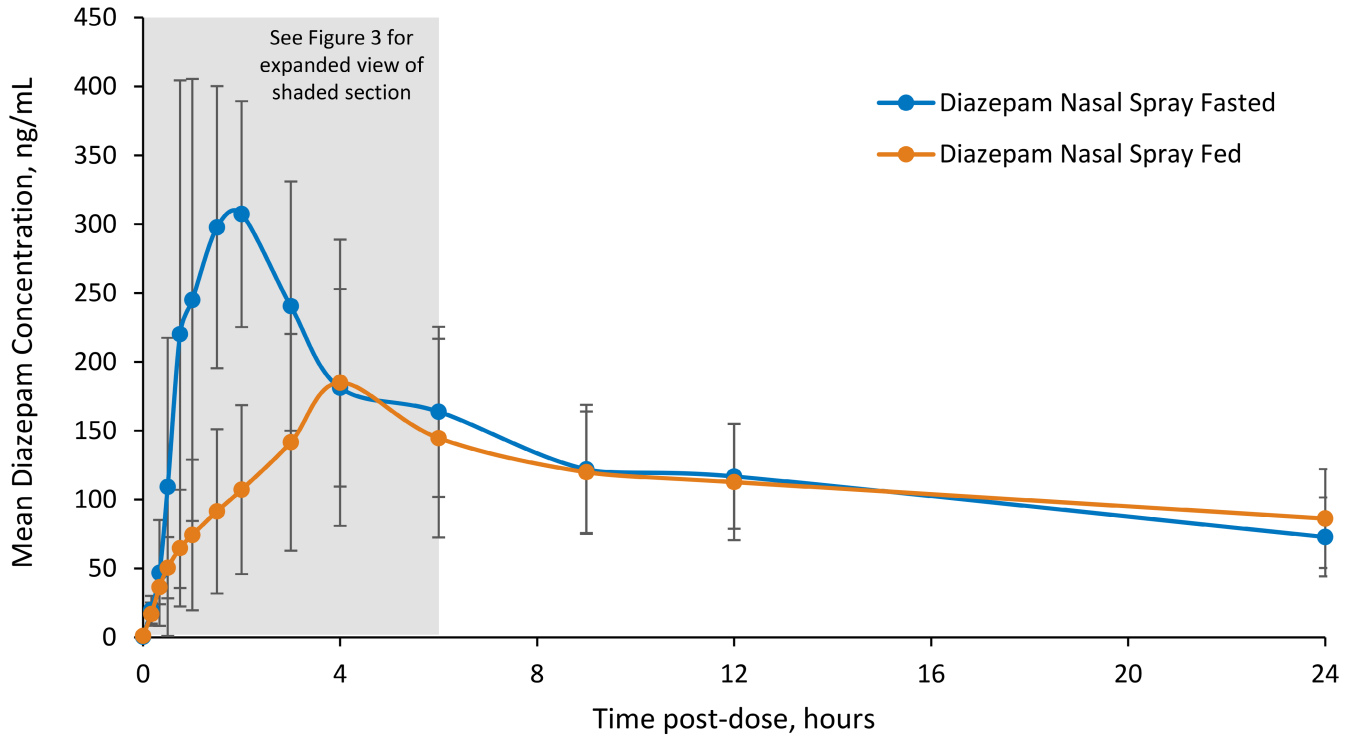


FIGURE 2 Mean diazepam plasma concentrations during the 24-h period after administration of diazepam nasal spray in the fasted or fed state. Each point represents the mean of plasma measurements from the 20 healthy volunteers in the final analysis population. Error bars represent standard deviations.

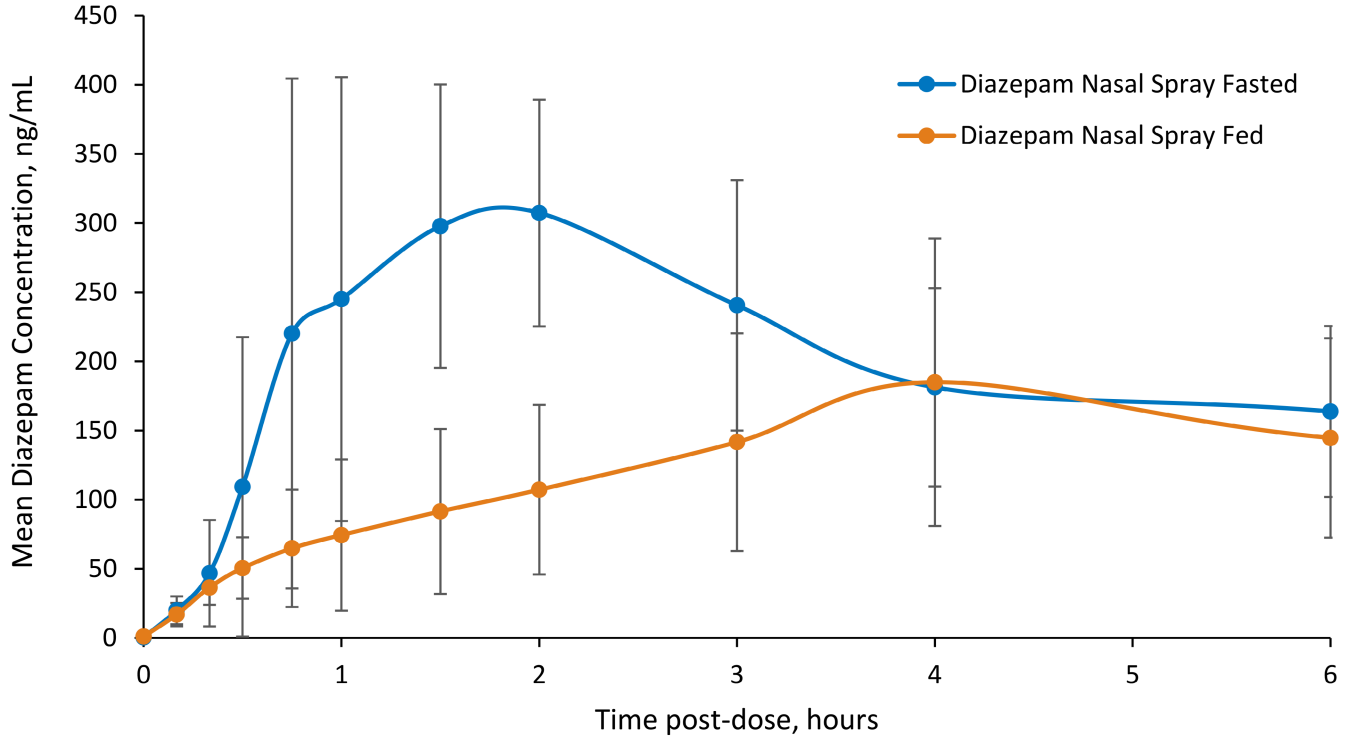


FIGURE 3 Mean diazepam plasma concentrations during the 6-h period after administration of diazepam nasal spray in the fasted or fed state. The data are the same as in Figure 2 but shown on an expanded time scale.

concentrations >5% of C_{max} after the washout period were included in the analysis (fed/fasted ratio of 50.2% for C_{max}, 41.7% for AUC_{0-4}, and 83.2% for AUC_{0-24}).

The effect of food on the pharmacokinetics of diazepam may be affected by sex and race. In a post hoc analysis, female participants had lower geometric mean values than

TABLE 1 Pharmacokinetic parameters, with fed/fasted ratios, 90% confidence intervals, and *p*-values where appropriate, for the 20 participants in the pharmacokinetic analysis population

Parameter	Diazepam – Fasted	Diazepam – Fed	Fed/fasted ratio, %	90% confidence interval	*p*-Value
Geometric least squares mean					
C_{max}, ng/mL	358.1	185.0	51.7	43.6, 61.7	<.0001
AUC_{0-4}, ng.h/mL	845.0	366.5	43.4	35.7, 52.7	<.0001
AUC_{0-24}, ng.h/mL	3007.7	2514.4	83.6	73.8, 94.7	.0232
Median (range)					
T_{max}, hours	2.0 (0.75–3.0)	4.0 (1.0–24.0)			<.0001

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; T_{max}, time to maximum concentration.

male participants for C_{max}, AUC_{0-4}, and AUC_{0-24} in both the fasted and fed states (Table 2). The fed/fasted ratios for C_{max} and AUC_{0-4} were also lower for females than males, demonstrating that the effect of food was more pronounced in females. Statistical comparisons were not made because of the small number of female participants in this study. Numerical differences in pharmacokinetic values were also observed between races, with Black/African American participants and participants from other races (multiple races or Native Hawaiian/Other Pacific Islander) having greater mean values for C_{max}, AUC_{0-4}, and AUC_{0-24} than White participants. Given the small number of participants in each group and the unequal distribution of females between races (3/7 Whites, 2/9 Black/African Americans, and 0/4 other races), statistical analyses were not performed.

As shown in Table 3, most participants (90%, 18/20) had fed/fasted ratios for C_{max} and AUC_{0-4} values <80%. However fewer participants (45%, 9/20) had fed/fasted AUC_{0-24} values <80%. This analysis is consistent with the results of Table 1, which demonstrate that the major effect of food is to blunt and delay early (<4 h) absorption but to have a lesser effect on overall bioavailability.

The presence or absence of food resulted in significant differences in the proportion of participants reaching diazepam concentrations of 100, 150, and 200 ng/mL at different time points (Figure 4). Sixty minutes post-dose, plasma diazepam concentrations were ≥150 ng/mL for 55% (11/20) of participants in the fasted state and 5% (1/20) of participants in the fed state. At 2 h post-dose, concentrations were ≥150 ng/mL for all (20/20) participants when in the fasted state and 30% (6/20) of participants when in the fed state.

3.3 | Adverse events

A total of 47 AEs occurred in 87.5% (21/24) of participants during the study. Significantly more participants experienced AEs during fasted administration (83.3% [20/24]) compared with fed administration (54.5% [12/22]; $p = .0340$). Most AEs (44/47) were mild, and all three moderate events were somnolence (two after fasted administration and one after fed administration).

AEs occurring in more than one participant were somnolence (75%), dizziness (16.7%), headache (12.5%), dry mouth (8.3%), and euphoric mood (8.3%). Each of these AEs was more common in the fasted state than in the fed state, and the difference was statistically significant for somnolence (70.8% of participants when in the fasted state vs 40.9% of the participants when in the fed state, $p = .0408$). There were no deaths, serious AEs, or significant AEs during the conduct of the study.

Fifteen minutes after dosing, almost all participants (85%) reported having a sensation or taste of the study drug. The sensation or taste decreased over time, with 20% of participants reporting it 1 h after dosing.

4 | DISCUSSION

In this study of healthy volunteers, the pharmacokinetics of diazepam nasal spray were significantly different when it was dosed 30 min after the start of a high-fat, high-calorie meal compared with when dosed in a fasted state. Median T_{max} doubled, mean diazepam C_{max} decreased by 48%, and AUC_{0-4} decreased by 57% in the fed vs fasted state. However, AUC_{0-24} decreased by only 16%, indicating that food slows the absorption of intranasal diazepam but has a lesser impact on overall bioavailability.

The effect of food on the pharmacokinetics of diazepam nasal spray reported in this study is comparable to that described previously for oral diazepam tablets.[4] In both studies, the presence of food caused T_{max} to double and C_{max} and AUC_{0-4} to decrease significantly. There are numerical differences in the C_{max} and AUC_{0-4} fed/fasted ratios between the studies, but comparisons should be approached cautiously given the methodological differences that include the diazepam doses used, the character of the meals, and the duration of the period monitored.

TABLE 2 Pharmacokinetic parameters and fed/fasted ratios by sex and race

		Geometric mean – Fasted			Geometric mean – Fed			Fed/fasted ratio, %		
	n	C_{max}, ng/mL	AUC_{0-4}, ng.h/mL	AUC_{0-24}, ng.h/mL	C_{max}, ng/mL	AUC_{0-4}, ng.h/ml	AUC_{0-24}, ng.h/ml	C_{max}	AUC_{0-4}	AUC_{0-24}
Sex										
Male	15	372.0	876.2	3131.0	202.3	438.8	2634.5	54.4	50.1	84.1
Female	5	326.3	789.2	2667.5	144.5	236.2	2168.4	44.3	29.9	81.3
Male/female ratio	—	1.14	1.11	1.17	1.40	1.86	1.21	1.23	1.67	1.04
Race										
Black/African American	9	375.0	859.7	2946.5	166.6	371.2	2316.7	44.4	43.2	78.6
White	7	317.4	751.4	2486.1	171.2	351.4	2248.7	53.9	46.8	90.4
Other[a]	4	409.5	1049.8	4398.8	275.7	434.8	3638.8	67.3	41.4	82.7

Note: Participants weighing 75 kg or less (seven males and four females) received diazepam nasal spray 15 mg, and participants weighing ≥76 kg (eight males and one female) received diazepam nasal spray 20 mg.

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration; *n*, number of participants in the population subgroup (total $N = 20$).

[a]Includes three multiple-race males and one male Native Hawaiian/Other Pacific Islander.

Diazepam nasal spray is indicated for the acute treatment of seizure activity,[2] and any delay or failure in reaching a therapeutic plasma concentration of diazepam may affect the likelihood of reducing recurrent seizures. The therapeutic concentration for control of seizures by diazepam, which the literature suggests is 150–200 ng/mL,[15–19] was reached by 2 h in only 30% of participants in the fed state who were administered nasal diazepam in this study. Clinically, this finding may explain why diazepam nasal spray sometimes fails to control acute repetitive seizures and may require repeat dosing. In a phase 3 trial of diazepam nasal spray by Sperling et al.,[20] 12.6% of the 3853 seizure clusters treated during the study required a second dose. About half (51.5%) of the 163 enrolled patients never needed a second dose of diazepam, 26.3% required a second dose to treat one or two seizure clusters, and 22.1% needed repeat dosing at least three times. Although a dose adjustment may have benefited some of these patients (and 18 patients did have their dose increased during the study), some of the failures may have been the result of food intake prior to administration of diazepam nasal spray.

The main result of the current study (food delays and decreases the absorption of diazepam when delivered via nasal spray) was consistent across sex and race subgroups. Although the magnitude of the effect differed between male and female participants and between races in some comparisons, the small sample sizes within the subgroups necessitate that the results be interpreted only as an indication that future studies of this topic should include pre-specified analyses by sex and race.

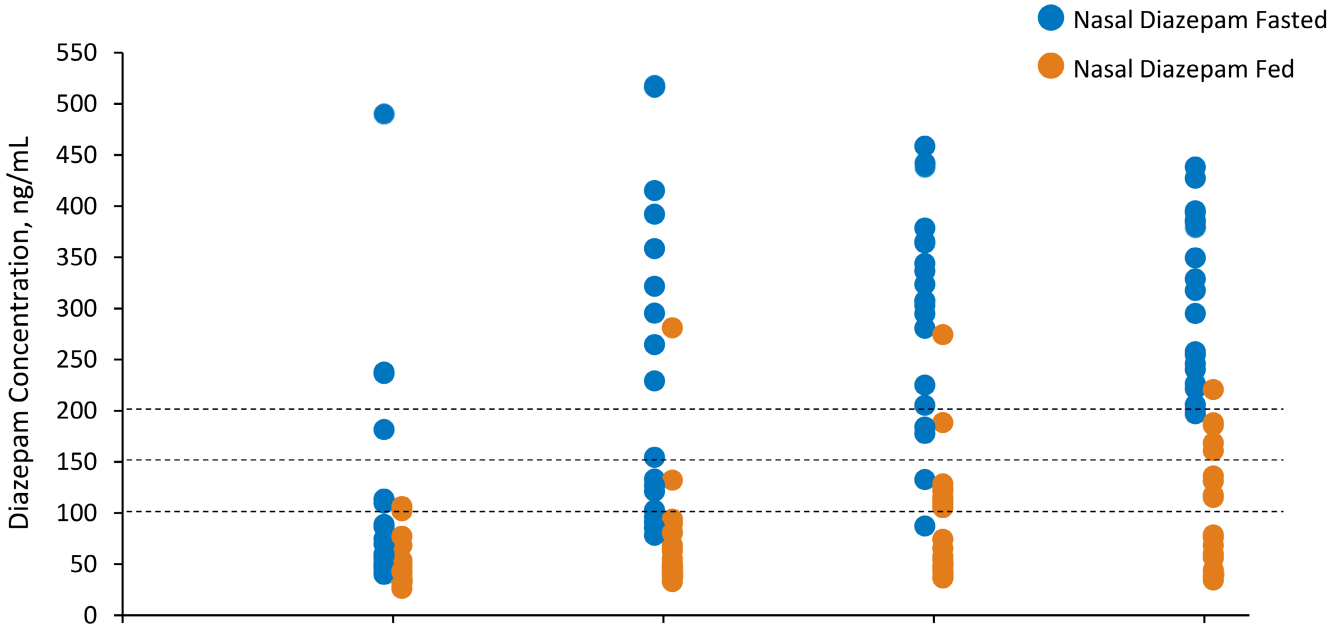
Acknowledging the need for cautious interpretation, further comment on the comparison of male and female participants is warranted. Female participants had lower levels of C_{max}, AUC_{0-4}, and AUC_{0-24} than male participants in both the fed and fasted states. This difference may be due in part to the well-documented greater volume of distribution of diazepam in females compared with males.[21,22] In addition, diazepam nasal spray was dosed according to body weight in this study. Although a larger proportion of female (80%) vs male (47%) participants received the lower 15-mg diazepam dose, the lower body mass of those participants likely balanced out most of the effect on the pharmacokinetic parameters. More interestingly, the fed/fasted ratios for C_{max} and AUC_{0-4} were lower in female vs male participants, indicating that females may be more susceptible than males to a food effect. If this observation is confirmed in a larger study, it will indicate that females are at greater risk than males of inadequate performance of diazepam nasal spray following a meal.

The results of the current study challenge the conventional view that most diazepam absorption from a nasal

TABLE 3 Percentage of participants in the final analysis population with low, equivalent, and high fed/fasted ratios

Parameter	Participants with fed/fasted ratio <80%	Participants with fed/fasted ratio 80%–125%	Participants with fed/fasted ratio > 125%
C_{max}, ng/mL	90%	5%	5%
AUC_{0-4}, ng.h/mL	90%	5%	5%
AUC_{0-24}, ng.h/mL	45%	45%	10%

Abbreviations: AUC, area under the curve; C_{max}, maximum concentration.



Diazepam Concentration	Through 30 mins post-dose		Through 60 mins post-dose		Through 90 min post-dose		Through 120 min post-dose	
	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
≥200 ng/mL	15%	0	50%	5%	80%	5%	95%	5%
≥150 ng/mL	20%	0	55%	5%	90%	10%	100%	30%
≥100 ng/mL	30%	10%	75%	10%	95%	45%	100%	50%

FIGURE 4 Diazepam plasma concentration values for each of the 20 participants in the final analysis population at 30, 60, 90, and 120 min after administration of diazepam nasal spray in the fasted or fed state. The cumulative percentage achieving the specified diazepam concentration at each of the time points is shown in the table.

spray preparation occurs within the nasal cavity. To our knowledge, no pharmacokinetic study has attempted to assess enteral absorption of diazepam following nasal delivery. Other pharmacokinetic studies of diazepam nasal spray occurred under fasted conditions or did not control for the presence of food.[6,7] The significant food effect demonstrated in the current study and the observation that most participants reported tasting the medication following nasal administration suggests that a substantial portion of the diazepam dose is swallowed. Further studies are required to determine the precise fraction absorbed via the gastrointestinal route.

The current results are consistent with studies of other orally bioavailable medications delivered by the nasal route, including midazolam nasal spray and sumatriptan nasal spray, which also reported substantial enteral absorption.[9,11–13] It is apparent that a relevant fraction of the drug substance in liquid nasal sprays is swallowed.

4.1 | Limitations

Diazepam nasal spray is intended as an acute treatment for frequent seizures. Its label specifies that a second

dose may be administered if required for a single seizure episode, and that it may be used to treat subsequent episodes as frequently as every 5 days for up to five episodes per month.[2] The present study evaluated only a single dose and provides no information on any pharmacokinetic differences that may be obtained with repeated administration.

This study was conducted in healthy volunteers. Diazepam levels in people with epilepsy tend to be lower than in healthy people[7,23] and, therefore, the absolute levels of diazepam may not be representative of what would be observed in clinical practice. The analysis population in this study was 75% male and 25% female. Although an effort was made to enroll a balanced distribution of participants by sex, the need to avoid pregnancy during the study using a non-hormonal double barrier method of contraception or a non-hormonal IUD limited the number of eligible women.

Study participants were required to have a BMI between 18.5 and 29.9 kg/m^2 (normal or overweight). The mean BMI of participants in this study was 26.3 kg/m^2, which is consistent with the mean BMI of adults in the United States (26.6 kg/m^2 for men and 26.5 kg/m^2 for women).[24] Because this study was the first to investigate the effect of food on the pharmacokinetics of diazepam nasal spray, an effort was made to avoid potentially confounding factors. Adults with BMI ≥30 kg/m^2 (obese) were excluded from this study because the diazepam volume of distribution has been shown to be markedly higher in obese compared with normal-weight people.[25] In addition, diazepam nasal spray is dosed by weight, with the maximum dose of 20 mg given to adults weighing at least 76 kg.[2] Together, these two factors suggest that the risk of underdosing diazepam is greater in people with higher BMIs, and the presence of food may only exacerbate the issue. However, further study in obese individuals is required before conclusions can be drawn.

5 | CONCLUSIONS

This study in healthy volunteers found that food significantly altered the absorption of diazepam delivered via nasal spray. When compared with the fasted state, the maximum plasma diazepam concentration in the fed state was nearly halved, the time to maximum concentration was doubled, and the total exposure to diazepam in the first 4 h was reduced by 57%. This effect appeared to be more pronounced in females then in males. Physicians should be aware that some patients using diazepam nasal spray after eating may obtain diazepam exposures that are below those considered to be required for seizure control.

AUTHOR CONTRIBUTIONS

Dr. Rogawski—data analysis and interpretation, manuscript writing and revision; Dr. Slatko—study design, data analysis and interpretation, and manuscript writing.

ACKNOWLEDGMENTS

This study was funded by Aquestive Therapeutics. Medical writing support, also funded by Aquestive Therapeutics, was provided by Katherine A. DeBruin, PhD, of Kodiak Consulting Group, Inc.

FUNDING INFORMATION

This study was funded by Aquestive Therapeutics.

CONFLICT OF INTEREST

Dr. Rogawski has served as a paid consultant to Aquestive Therapeutics. Dr. Slatko is an employee of Aquestive Therapeutics. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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How to cite this article: Rogawski MA, Slatko G. A randomized, open-label, two-treatment crossover study to evaluate the effect of food on the pharmacokinetics of diazepam nasal spray in healthy adults. Epilepsia. 2023;64:364–373. https://doi.org/10.1111/epi.17459