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RESEARCH ARTICLE

Lack of clinically relevant differences in safety and pharmacokinetics after second-dose administration of intranasal diazepam within 4 h for acute treatment of seizure clusters: A population analysis

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Abstract

Objective: Current diazepam nasal spray labeling requires waiting 4 h before administering a second dose. The objective of the current analyses was to examine safety and pharmacokinetic profiles of second doses of diazepam nasal spray given 0–4 h after the first dose.

Methods: Two datasets were analyzed. The first, a long-term, repeat-dose safety study of diazepam nasal spray, compared rates of treatment-emergent adverse events (TEAEs), serious TEAEs, and treatment-related TEAEs for patients receiving ≥1 second dose ≤4 h versus all second doses >4 h after the first. The second was a population pharmacokinetic analysis using data from three phase 1 studies to model drug exposure when a second dose of diazepam nasal spray was administered across multiple time points (1 min–4 h) following the first dose.

Results: In the repeat-dose safety study, a second dose of diazepam nasal spray was administered ≤24 h after the first to treat 485 seizure clusters in 79 patients. Rates of TEAEs were similar between patients receiving ≥1 second dose in ≤4 h (89.5%, $n = 38$) compared with >4–24 h only (80.5%, $n = 41$). The most common treatment-related TEAEs were associated with nasal discomfort, which was mild or moderate and transient. There were no reports of respiratory or cardiac depression. The pharmacokinetic simulations of second doses predicted comparable elevations of plasma diazepam concentrations with administrations across a range of intervals after the first dose (1 min–4 h).

Significance: These data indicate that the safety and pharmacokinetic profiles of a second dose of diazepam nasal spray administered within 4 h of the first dose are consistent with those associated with current labeling. This is potentially important for patients with seizure clusters who have a recurrent seizure within 4 h

of first treatment and might benefit from immediate retreatment to reduce the risk of progression to status epilepticus.

KEYWORDS
acute repetitive seizure, benzodiazepine, nasal spray, seizure emergency

1 | INTRODUCTION

Seizure clusters are characterized by multiple seizures separated by brief interictal periods that can occur over a span of 24 h.[1,2] Seizure clusters are associated with outcomes such as hospitalization and status epilepticus,[3] and they can exert a negative impact on independence, mood, and daily life of patients and care partners.[4] Approximately one third of seizure clusters may include a second seizure within 4 h of the first[2,5]; therefore, prompt treatment is critical.[6]

Approved by the US Food and Drug Administration in 1997,[7] diazepam rectal gel was the first treatment with an indication for seizure clusters that could be administered outside a hospital setting by a nonmedical caregiver or care partner.[6,8] Per prescribing information, if a second dose is needed, diazepam rectal gel should be given 4 to 12 h after the first dose.[8]

The 4-h period following diazepam rectal gel administration was not established using direct evidence, but rather it was based on conservative safety assumptions and variable results at the time. Small studies had reported that initial peaks in mean plasma concentrations seemed to enter a phase of slower decline at 4 h.[9,10] In addition, respiratory depression had been observed in patients following intravenous administration of benzodiazepines, which provides a rapid increase in plasma concentrations that occurs shortly after administration by that route, and newer routes were treated with similar caution.[11]

In one of the pivotal studies of diazepam rectal gel, a second dose was administered to adult and pediatric patients at a prespecified 4 h (no doses before 4 h) after the initial diazepam dose to maintain target plasma diazepam concentration between 150 and 300 ng/ml (a third dose was given to adults 8 h following the second dose),[5] and there were no reports of respiratory depression in patients receiving diazepam. The age- and weight-based dosing regimen resulted in an actual dose that ranged from 90% to 180% of the target dose, and the lack of adverse events of concern suggests a wide safety margin with a nonintravenous route of administration. Of note, the recurrence of seizures in the treatment group was most common before the second dose was given at 4 h, occurring in 15 of 45 treated patients.[5]

Intranasal administration represents a rapid, noninvasive means of drug delivery for acute treatment of intermittent, stereotypic episodes of frequent seizure activity in patients with epilepsy. In this indication, diazepam nasal spray (Valtoco) is approved for use in patients aged 6 years and older.[12] The approval of diazepam nasal spray was based on a clinical trial program that demonstrated similar bioavailability, safety, and tolerability compared with the reference drug, diazepam rectal gel.[13–17] As a result, the labeling information requiring ≥4 h between the time of second dose and first administration matches the directions from the reference drug.[12]

The purpose of the present analysis was to establish the safety, tolerability, and pharmacokinetics of a second dose of diazepam nasal spray administered ≤4 h from the first dose. This is of clinical importance because instruction for timing of a second dose is inherited from diazepam rectal gel and is based on the rectal gel clinical development program,[5] which needs to be considered in light of the urgency to terminate seizure activity to reduce the risk of progression to status epilepticus and the need for emergency care.[3] In the long-term safety study of diazepam nasal spray,[17] investigators could adjust dosing according to their judgment and perceived clinical need, and a number of second doses were administered by patients and care partners prior to the 4-h time period after the initial dose that is usually advised. Thus, because data existed for early use of diazepam nasal spray, the authors decided it would be useful to analyze the safety and effectiveness of this dosing to determine whether the 4-h time

Key Points

- Benzodiazepines, such as diazepam, are the mainstay rescue medications for the treatment of seizure clusters
- The current label for diazepam nasal spray requires a minimum of 4 h between consecutive treatments for seizure clusters
- A long-term safety study found similar adverse event rates for patients receiving ≥1 second dose ≤4 h or >4 h only after the first
- A pharmacokinetic model predicted that dosing intervals of <4 h and 4 h would result in comparable diazepam levels

window is appropriate, or if a shorter window could be recommended. This is important, as many patients experience a recurrent seizure before 4 h have elapsed since the first dose of diazepam nasal spray, and if additional treatment could be given sooner, this may prove beneficial. Here, two separate analyses were conducted: (1) second-dose usage and safety obtained from the long-term phase 3 safety study; and (2) a separate population pharmacokinetic model, based on three phase 1 studies, to assess the plasma profile of a second dose of diazepam nasal spray administered within 4 h of the first dose in patients with seizure clusters.

2 | MATERIALS AND METHODS

Safety and tolerability were assessed in a phase 3, repeat-dose, open-label, long-term study (NCT02721069).[17] Population pharmacokinetics were modeled using data from three phase 1 studies: two in healthy adult volunteers and one in pediatric and adult patients with epilepsy.[14–16]

2.1 | Phase 3 long-term safety study

The methods of this safety study have been described[17] and are summarized here. Patients were 6 to 65 years of age, with a diagnosis of epilepsy with motor seizures or seizures with altered awareness despite a stable antiseizure medication regimen, and were anticipated to require benzodiazepine intervention for seizure control an average of at least once every other month. Additional inclusion criteria were the participation of a qualified care partner to administer study medication in the event of a seizure; the use of an approved method of birth control for females of childbearing potential; and no clinically significant abnormal findings on medical history, physical examination, or electrocardiogram. Key exclusion criteria included active major depression, a past suicide attempt, or suicidal ideation, as well as a history of any clinically significant medical condition that would jeopardize the safety of the patient. Patients with concomitant use of benzodiazepines (e.g., clobazam), history of seasonal allergies or rhinitis, or history of status epilepticus were permitted to enroll.

Diazepam nasal spray was administered by care partners or patients in doses of 5, 10, 15, or 20 mg based on patient age and weight; a second dose was to be administered 4 to 12 h later if needed. Investigators could adjust dosing (e.g., total dose, time to second dose) for effectiveness or safety if needed and if there were no safety concerns. Second doses in a seizure cluster were defined as those given within 24 h of the initial dose. A diary was used to record timing of seizures and diazepam nasal spray administrations, and patients given a second dose within 4 h of the first dose were identified by time registration of the second dose. Treatment-emergent adverse events (TEAEs) were recorded throughout the study.

2.2 | Population pharmacokinetic model

Pharmacokinetic assessments from three phase 1 studies of diazepam nasal spray were used to develop the model.[14–16] Briefly, the two crossover studies included healthy adult volunteers; the first used three single-dose periods (5, 10, 20 mg) followed by a two-dose period (2 × 10 mg given 4 h apart) with a ≥28-day washout period between treatments,[14] whereas the second study used a single-dose, three-treatment, three-period, six-sequence design that assessed bioavailability and pharmacokinetic profile of intranasal (15, 20 mg), rectal gel (15, 20 mg), and oral diazepam (10 mg) using weight-based dosing.[15] The study in patients with epilepsy was an open-label assessment of the pharmacokinetic and safety profiles of diazepam nasal spray administration (5, 10, 15, 20 mg) to pediatric and adult patients during seizure (ictal/perictal) and nonseizure (interictal) periods.[16] In all, participants received ≥1 dose of diazepam nasal spray (5, 10, 15, or 20 mg) based on age and weight (.3 mg/kg for participants aged 6–11 years; .2 mg/kg for participants aged ≥12 years).[12,14–16]

2.3 | Analysis

The safety profile of diazepam nasal spray in the long-term safety study was evaluated in patients receiving any second dose ≤4 h after the first for ≥1 seizure cluster at any point during the study (≤4 h group) and compared with other patients who only used second doses >4 to 24 h after the first (4–24 h group; there was no overlap between groups).

Population pharmacokinetic nonlinear mixed-effects modeling with first-order conditional maximum likelihood estimation with interaction was performed with NONMEM computer software (ICON Development Solutions). Population pharmacokinetic parameters (without covariates) were estimated. All relevant covariates with observed bias were tested separately, and all significant covariates were collectively added for the full model. Parameter–covariate relationships were tested with backward selection. The final population pharmacokinetic model was evaluated using diagnostic plots (goodness-of-fit) and visual predictive check. The model was tested for stability by the bootstrap resampling technique ($N = 500$) using Perl-speaks-NONMEM (PsN 3.5.3).

The effect of dosing interval of a second dose on overall diazepam exposure was examined by simulating the administration of a second dose of diazepam nasal spray at various time intervals (1, 5, 10, 30 min; 1, 2, 3, and 4 h) to predict drug exposure profiles in patients with epilepsy ($n = 250$ per dosing regimen).

2.4 | Exposure–response analysis

TEAEs of special interest were defined as respiratory distress, tachycardia, somnolence, ataxia, and epistaxis, based on the known safety profile of diazepam and the route of administration. An exposure–response analysis was planned for adverse events of special interest after single and repeated doses in patients with epilepsy.

3 | RESULTS

3.1 | Long-term safety study population

Of 175 enrolled patients, 163 received 4390 administrations of diazepam nasal spray (Table 1) to treat 3853 seizure clusters.[17] Median time on the study was 15.05 months, with patients receiving a mean (SD) of 2.3 (1.5) doses per month. Seventy-nine patients (48.5% of safety population) received second doses to treat a total of 485 seizure clusters (12.6% of all seizure clusters). One hundred fifty-two total second doses (31.3% of total second doses) of diazepam nasal spray were administered ≤4 h from the time of the first dose to 38 patients, with 9.1% of second doses administered within 10 min of the initial dose. Members of that group of 38 patients also received second doses >4 h after the initial dose at other time points during the study (total of 229 second doses). In addition, there were 41 patients who only received second doses >4 h after the initial dose (total of 104 second doses). Thus, overall, 333 second doses were received >4 h after initial dose during the study.

3.2 | Safety

The rates of TEAEs and serious TEAEs were similar between second-dose groups and the overall study population (Table 2). One discontinuation due to TEAEs and one death were reported in the >4 to 24 h group (neither deemed related to treatment), and no discontinuations due to TEAEs and no deaths occurred in the ≤4 h group. There were no serious treatment-related TEAEs in either group.

The most common treatment-related TEAE was nasal discomfort, which was mild or moderate and transient (Table 2). The rates of treatment-related TEAEs were 31.6% in the ≤4 h group and 17.1% in the >4 to 24 h group. The most common treatment-related TEAEs in the ≤4 h group were related to the route of administration: three patients (7.9%) each with epistaxis (two mild, one moderate severity) and nasal discomfort (one mild, two moderate severity). There were no reports of respiratory or cardiac depression. Overall, the safety profile across all patients receiving treatment was similar for those receiving ≥1 second dose in ≤4 h compared with all second doses >4 to 24 h after the first dose.

The TEAEs of special interest in the long-term safety study were respiratory distress (1/163, .6%), tachycardia (2/163, 1.2%), somnolence (11/163, 6.7%), ataxia (3/163, 1.8%), and epistaxis (4/163, 2.5%). Respiratory distress, tachycardia, and ataxia were all deemed unlikely to be

TABLE 1 Long-term study: Demographics and exposure to diazepam nasal spray in the second-dose subgroup and overall population

Variable	≥1 second dose ≤4 h, $n = 38$	All second doses >4 h, $n = 41$	Second-dose subgroup, $n = 79$	Overall population, $N = 163$
Sex, *n* (%)				
Male	17 (44.7)	22 (53.7)	39 (49.4)	74 (45.4)
Female	21 (55.3)	19 (46.3)	40 (50.6)	89 (54.6)
Age, years				
Mean (SD)	20.9 (15.23)	24.4 (15.00)	22.7 (15.1)	23.1 (15.1)
Range	6–55	6–59	6–59	6–65
Weight, kg, mean (SD)	53.3 (30.35)	66.3 (39.91)	60.0 (36.0)	60.2 (33.6)
Duration of exposure, *n* (%)				
<6 months	0	2 (4.9)	2 (2.5)	9 (5.5)
6–12 months	7 (18.4)	5 (12.2)	12 (15.2)	21 (12.9)
≥12 months	31 (81.6)	34 (82.9)	65 (82.3)	133 (81.6)

TABLE 2 Long-term study: TEAEs reported for the second dose in ≤4 h and >4 h groups

Category, *n* (%)	≥1 Second dose ≤4 h, *n* = 38	All Second doses >4 h, *n* = 41	All patients, *N* = 163
Patients with TEAEs	34 (89.5)	33 (80.5)	134 (82.2)
Patients with serious TEAEs	14 (36.8)	14 (34.1)	50 (30.7)
Required/prolonged hospitalization	13 (34.2)	12 (29.3)	44 (27.0)
Treatment-related	0	0	0
Death	0	1 (2.4)[a]	1 (.6)[a]
Discontinued owing to TEAE	0	1 (2.4)[a]	1 (.6)[a]
Patients with treatment-related TEAEs	12 (31.6)	7 (17.1)	30 (18.4)
Most common treatment-related TEAEs (≥2 patients in either second-dose group)			
Epistaxis[b]	3 (7.9)	0	3 (1.8)
Nasal discomfort	3 (7.9)	2 (4.9)	10 (6.1)
Headache	2 (5.3)	1 (2.4)	4 (2.5)
Rhinorrhea	2 (5.3)	0	2 (1.2)
Somnolence[b]	2 (5.3)	0	3 (1.8)
Eye irritation	0	2 (4.9)	2 (1.2)
Fatigue	0	2 (4.9)	2 (1.2)

Abbreviation: TEAE, treatment-emergent adverse event.

[a]Not considered treatment-related.

[b]Designated as a TEAE of special interest. There were no reports in either second-dose group of treatment-related TEAEs for other TEAEs of special interest: respiratory distress, tachycardia, and ataxia.

TABLE 3 Population pharmacokinetic analysis: Baseline demographics, dosing, and concomitant therapies with enzymatic interaction

Patient population	Healthy volunteers[a,b]	Patients with epilepsy[c]	Total
Patients (male, female), *n*	78 (45, 33)	48 (22, 26)	126 (67, 59)
Age, years (range)	36 (18–55)	27.5 (6–59)	33 (6–59)
Weight, kg (range)	85 (52–109)	67.6 (18.6–106)	79 (18.6–109)
BMI, kg/m^2 (range)	29.7 (19.5–44.3)	24.4 (13.8–37.7)	28.9 (13.8–44.3)
Dose strength; number of doses	5 mg; 31 (Study 1) 10 mg; 89 (Study 1) 15 mg; 17 (Study 2) 20 mg; 61 (32 in Study 1 and 29 in Study 2)	10 mg; 25 15 mg; 29 20 mg; 41	5 mg; 31 10 mg; 114 15 mg; 46 20 mg; 102

Abbreviation: BMI, body mass index.

[a]Study 1: Open-label, randomized, crossover study to assess the pharmacokinetics and dose proportionality of diazepam nasal spray.[30]

[b]Study 2: Open-label, randomized, single-dose, three-treatment, three-period, six-sequence crossover study to assess the bioavailability of diazepam after intranasal administration with respect to diazepam rectal gel and oral diazepam.[15]

[c]Study 3: Open-label assessment of similarity of pharmacokinetics and safety of diazepam nasal spray in patients with epilepsy during ictal/peri-ictal and interictal periods.[16]

related to treatment by the investigator. Three cases (1.8%) each of somnolence and epistaxis were the only TEAEs of special interest considered to be treatment-related by the investigator. All occurred after a single administration of diazepam nasal spray except for one case of epistaxis, which occurred after a second dose.

3.3 | Population pharmacokinetic model

The final dataset included pharmacokinetic measurements from 126 individuals who participated in the phase 1 studies,[14–16] some receiving >1 dose of diazepam nasal spray (Table 3). A two-compartment open

pharmacokinetic model with first-order input and first-order elimination adequately fit the data. Model parameters included clearance (CL), volume of distribution in central (V2) or peripheral compartments (V3), intercompartmental clearance (Q), and first-order absorption rate constant (k_a). Weight was added to the pharmacokinetic model as an allometric covariate. Population (volunteers or patients) was included as a covariate for determining k_a. Point estimates of interindividual variability were 41.8% for CL, 45.5% for V2, 47.1% for V3, 66.2% for Q, and 36.2% for k_a. The final model was deemed adequate because >90% of the observed data fell within the range of the 5th and 95th percentiles of the model-predicted data using the visual predictive check method.

Simulation studies using the final model were conducted to examine the effect of dosing interval on the overall exposure of diazepam. For second doses, maximum plasma concentration (C_{max}) was predicted to increase by approximately 65% (Figure 1) and mean area under the concentration–time curve (AUC) was predicted to increase approximately twofold (Figure 2) compared with a single dose. Predicted exposures of dosing interval regimens between 1 min and 4 h overlapped and were predicted to result in comparable diazepam levels (C_{max} and AUC). As noted above, there was no observed relationship between TEAEs of special interest and number of doses (exposure–response) in the long-term safety study.

4 | DISCUSSION

In the long-term safety study, the safety profile of a second dose of diazepam nasal spray did not differ between patients who received ≥1 second dose in ≤4 h compared with all second doses >4 to 24 h after the first dose, with similar frequencies of overall and serious TEAEs in both groups. Although the rate of treatment-related TEAEs was higher in the ≤4 h group, events were mild or moderate in severity, and early repeat dosing was not associated with respiratory depression. Likewise, the population pharmacokinetic analysis did not find evidence of substantive differences in pharmacokinetic profiles across second doses of diazepam nasal spray given ≤4 h after the first dose.

Approved diazepam formulations for seizure clusters permit a second dose if needed to control a seizure cluster to reduce the risk of morbidity due to uncontrolled seizures. In the long-term safety study, a total of 4390 doses were administered to treat 3853 seizure clusters.[17] A single dose was administered for 3368 (87.4%) of these seizure clusters, and a second dose was given within 24 h of the first dose in 485 events (12.6% of seizure clusters). Of these second doses, 152 (31.3% of second-dose events, 3.9% of seizure clusters) were administered between 0 and 4 h after the initial dose, highlighting the clinical urgency of treatment in a subset of patients. The proportion of second doses administered within 4 h of the initial event was consistent with previous findings of similar proportions of

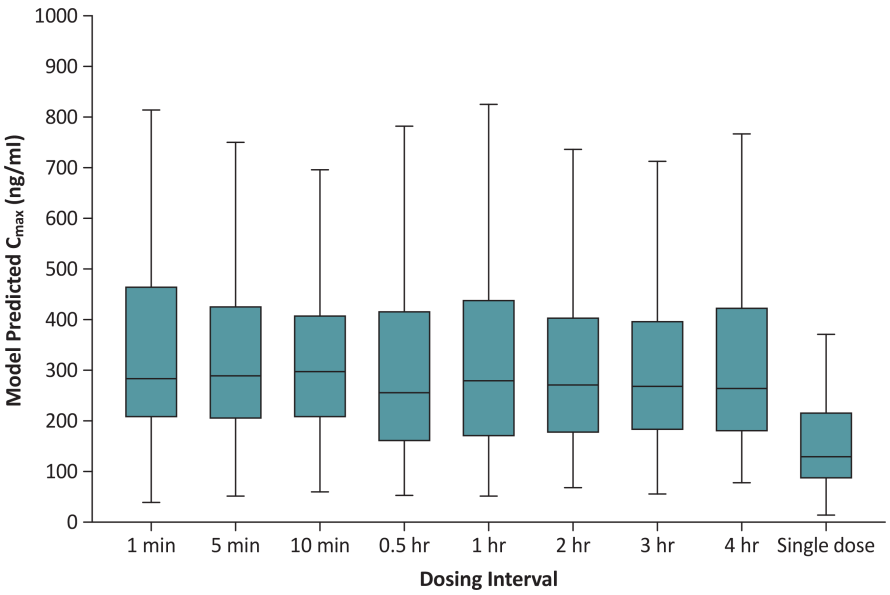

FIGURE 1 Population pharmacokinetic analysis: 20 mg in patients aged ≥12 years with median body weight of 90 kg. Simulations were performed for 250 patients per dosing regimen using the final pharmacokinetic model. Patients received either a single dose or two consecutive doses at different dosing intervals ranging from 1 min to 4 h. The bottom and top of the box represent the first (Q1, 25th percentile) and third (Q3, 75th percentile) quartiles, whereas the line inside the box represents the median (Q2, 50th percentile). The length of the box is the interquartile range (IQR = Q3–Q1). The two lines that come out of the box represent the minimum and maximum values, as defined by Q1 – 1.5*IQR and Q3 + 1.5*IQR, respectively. C_{max}, maximum plasma concentration

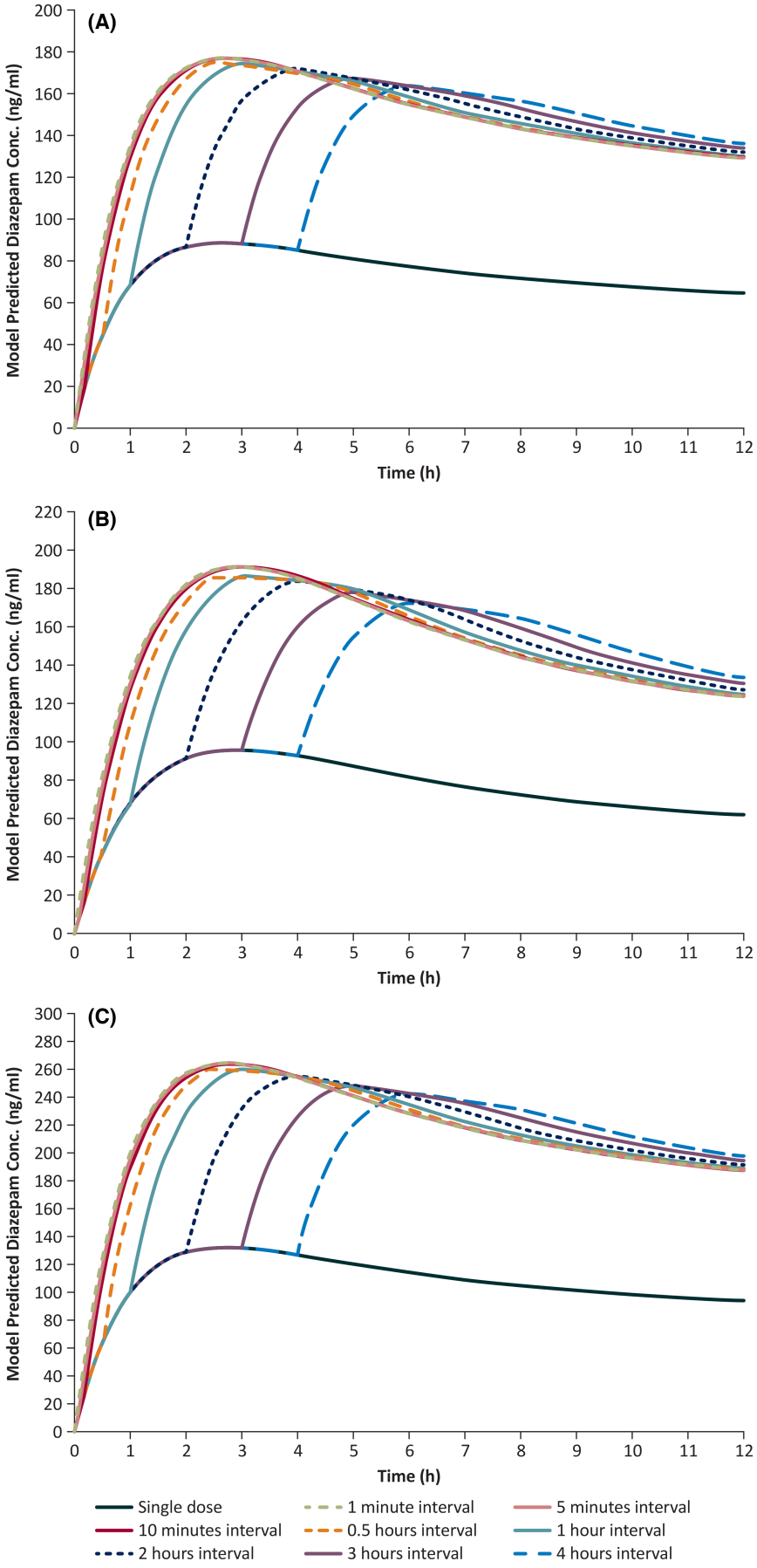

FIGURE 2 Population pharmacokinetic analysis: model-predicted population diazepam concentration (Conc.)–time profiles following administration of diazepam nasal spray. (A) Five milligrams intranasal diazepam in typical 20-kg patient ≥12 years old. (B) Twenty milligrams intranasal diazepam in typical 90-kg patient ≥12 years old. (C) Ten milligrams intranasal diazepam in typical 28-kg patient <12 years old. Simulations were performed for 250 patients per dosing regimen using the final pharmacokinetic model. Patients received either a single dose or two consecutive doses at different dosing intervals ranging from 1 min to 4 h

untreated and treated patients (33.7% and 33.3%, respectively) who experienced recurrent seizures within 4 h of the initial event.[2,5]

In the long-term safety study of diazepam nasal spray, 333 of 485 second doses (69%) were administered between 4 and 24 h: 72 second doses between 4 and 6 h, 94 second doses between 6 and 12 h, and 167 second doses between 12 and 24 h. Of second doses administered sooner than 4 h after the first dose, 44 events (9.1% of all 485 second doses) were given between 0 and 10 min. The therapeutic need for second dosing within 10 min further highlights the clinical urgency of treatment experienced by some patients.

Although respiratory depression is associated with a rapid rise in plasma levels after intravenous administration of benzodiazepines, this adverse event has not been observed following rectal or intranasal administration.[11,14,16] Data from early diazepam studies have not identified long-term effects with earlier second doses or high plasma levels of diazepam. In one, during 2 years after introduction of home oral or rectal diazepam rescue treatment with second doses permitted after 3 h, status/seizure cluster patients ($n = 76$) reported no instances of respiratory depression or noteworthy adverse events.[18] Another study of patients given larger-than-recommended doses of diazepam rectal gel (>180% of recommended dose, mean overdose of 214%, 51 total overdoses examined) reported that about 78% experienced no adverse events, and those that did occur (22%) resolved without incident.[19] No respiratory/cardiac depression was observed. Other studies found that accidental overdoses with diazepam levels as high as 330% of the recommended dose resolved without incident or observed clinical consequences.[20–22] Therefore, concerns about the safety of early second intranasal doses do not appear warranted as long as established weight-based doses are given.

Somnolence has been reported in diazepam rectal gel studies.[11] However, normal postictal sedation is not clearly distinguished from diazepam-associated sedation.[11] All cases of sedation, including those in the placebo group, were assessed as treatment-related in one study.[23] Therefore, this suggests to some authors that treatment-related somnolence may be somewhat less common than has been reported, and this somnolence is often not clinically relevant.[11,22]

Together, these two analyses investigated use of a second dose of diazepam nasal spray within 4 h of the first dose, based on four clinical studies[14–17] and using two separate, complementary methodologies. Although the original studies were not designed to test the safety, efficacy, or pharmacokinetics of second doses within 4 h after the first dose, together, these results present a consistent profile for use of second doses of diazepam nasal spray in this time frame. Limitations of the individual clinical studies, including the absence of a control group in the long-term safety study to determine the degree to which TEAEs are related to treatment, are provided in their respective primary publications.[14–17] In addition, the low use of second doses in the long-term study may have constrained statistical power; however, the concordant results of two independent analyses support the clinical relevance of these findings.

In conclusion, this analysis did not find clinical evidence that a second dose should be delayed until ≥4 h have elapsed after the first dose if there is a need to administer the second dose sooner. Dosing intervals ranging from 1 min to 4 h had comparable diazepam exposures as later doses and did not affect safety. Hence, a second dose of diazepam nasal spray might safely be used, if needed, within 4 h of the first dose to treat seizure clusters. Risks associated with underdosing of benzodiazepines in status epilepticus—and not adequately treating status epilepticus—are generally considered greater than benzodiazepine overdosing,[11,19,24,25] and the rate of respiratory depression has been observed to be lower in treated than in untreated status epilepticus.[26] This supports the concept of administering second doses based on individual need to prevent further seizures that might lead to physical injury, neuronal injury, use of emergency services, status epilepticus, and sudden unexplained death in epilepsy.[1,3,27–29]

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CONFLICT OF INTEREST

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