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Lack of observed tolerance to diazepam nasal spray (Valtoco®) after long-term rescue therapy in patients with epilepsy: Interim results from a phase 3, open-label, repeat-dose safety study.

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Lack of observed tolerance to diazepam nasal spray (Valtoco®) after long-term rescue therapy in patients with epilepsy: Interim results from a phase 3, open-label, repeat-dose safety study

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ABSTRACT

Objective: Tolerance is a known consideration for maintenance use of benzodiazepines and other antiseizure drugs; however, clinical experience suggests that tolerance may not be anticipated with long-term intermittent use of benzodiazepines as rescue therapy. Diazepam nasal spray (Valtoco®) is a proprietary intranasal formulation approved for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) in patients with epilepsy aged ≥6 years. Reported here are exploratory analyses investigating whether there was evidence of development of tolerance in an interim analysis of a long-term, phase 3, open-label safety study of diazepam nasal spray.

Methods: Patients and care partners were trained to administer 5, 10, 15, or 20 mg of diazepam nasal spray (age- and weight-based dosing), with a second dose administered 4–12 hours later if needed. A series of analyses were performed to assess evidence of tolerance using 2 equal, adjacent time periods and data for each patient to compare the proportion of events for which second doses of diazepam nasal spray (as a proxy for effectiveness) were administered in period 1 compared with period 2.

Results: A total of 175 patients were enrolled at interim cutoff, and 158 were treated with diazepam nasal spray for 3370 seizure-cluster events. For 73.4% of patients, duration of exposure to diazepam nasal spray was ≥12 months. A total of 191 analyses were conducted; the proportion of analyses in which second doses in period 2 were lower than in period 1 was 72.8%. Only 5 analyses showed nominally statistically significant changes ($P < 0.05$); this is fewer than expected by chance, and these differences were not directionally consistent. There was no safety signal with continued use.

Conclusions: These analyses found no statistical evidence of tolerance with the use of diazepam nasal spray over time based on use of a second dose in an initial period of the study compared with a subsequent period for each patient. These results are in agreement with prior studies of benzodiazepine rescue therapy.

1. Introduction

Reduced response to a drug after repeated administration (ie, tolerance) is a known consideration for maintenance use of benzodiazepines and other antiseizure drugs [1,2]. Although tolerance is

Abbreviation: TEAE, treatment-emergent adverse event.

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typically associated with prolonged treatment and high doses of antiseizure drugs [2], it may be associated with a number of other factors, key of which are pharmacokinetic and pharmacodynamic properties of the drug [1,2], as well as other factors that may occur acutely. Tolerance may also vary with seizure type, even with the same agent, as illustrated by studies of clobazam showing higher levels of tolerance in patients with temporal lobe epilepsy (27% at 1 year [3]) compared with Lennox-Gastaut syndrome (12% at 2 years [4]). Those studies defined tolerance as the development of partial or complete loss of therapeutic effectiveness [3] or a dosage increase ≥40% plus loss of response [4].

Benzodiazepines are the key treatment for seizure clusters [5–7], also referred to as acute repetitive seizures, which are seizure emergencies that contribute to the considerable burden of epilepsy on affected patients and their care partners [8]. Seizure clusters are associated with an increased risk of status epilepticus [9,10], hospitalization [11], increased mortality [12], decreased quality of life, and negative personal and financial impacts [8]. Seizure clusters may occur at irregular intervals, so treatment must be readily available for use as needed.

Given the importance of benzodiazepines in treatment of seizure clusters, understanding tolerance in this role is important. Clinical experience suggests that tolerance might not be anticipated with long-term intermittent use of benzodiazepines; intermittent usage is one strategy to overcome or prevent tolerance [2]. Although there are few formal analyses of tolerance in the treatment of seizure clusters [13,14], they have not found evidence of tolerance.

Diazepam nasal spray (Valtoco®), a proprietary intranasal formulation of diazepam approved by the US Food and Drug Administration for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) in patients with epilepsy aged ≥6 years, is designed to provide a rapid, noninvasive, and socially acceptable route of administration. It is formulated with n-dodecyl-beta-D-maltoside (Intravail® A3), which is a nonionic surfactant used as a mucosal absorption enhancement agent to promote increased bioavailability [15] and vitamin E to enhance solubility of diazepam.

This exploratory analysis of a long-term, open-label safety study of diazepam nasal spray investigated whether there was evidence of development of tolerance. For this analysis, tolerance was based on the proportion of events for which administration of a second dose of diazepam nasal spray (as a proxy for effectiveness) was administered for each patient in 2 time periods during the study.

2. Materials and methods

2.1. Study design

This was a long-term, open-label, repeat-dose safety study of diazepam nasal spray in patients with epilepsy (NCT02721069). The treatment period was 12 months, after which patients could continue at the discretion of the Investigator. The investigators conducted the study in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The primary objective was to assess the safety of diazepam nasal spray after repeated administration in patients with epilepsy who experience frequent seizures. The study was approved by local institutional review boards and written informed consent was obtained for all patients.

2.2. Patients

The study enrolled male and female patients aged 6–65 years. Patients were required to have a diagnosis of epilepsy and to be experiencing frequent seizure episodes despite being on a stable antiseizure-drug regimen and, in the opinion of the investigator, may need benzodiazepine intervention for seizure control approximately 1 time every other month (ie, for an average of 6 times a year). Patients had either partial or generalized epilepsy with motor seizures or seizures with clear alteration of awareness and had a qualified care partner or medical professional available who could administer study medication in the event of a seizure. Other key inclusion criteria included absence of clinically significant abnormal findings in medical history or on physical examination, electrocardiogram, clinical laboratory results during screening, or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the patient. Female patients of childbearing potential agreed to use an approved method of birth control. Current concomitant benzodiazepine (eg, clobazam) use was permitted. Key exclusion criteria included history of major depression or a past suicide attempt or suicidal ideation or a clinically significant medical condition that would jeopardize the safety of the patient.

2.3. Treatment and assessments

Care partners and patients were trained to administer diazepam nasal spray. Doses were 5, 10, 15, or 20 mg based on patient age and weight (Supplementary Table 1), and a second dose was to be administered 4–12 h later if needed. Investigators could adjust doses if a different dose was necessary per their medical judgment and if there were no safety concerns associated with the dosing change.

Patients and care partners recorded seizures and use of diazepam nasal spray in diaries. Treatment-emergent adverse events (TEAEs) were collected.

2.4. Analyses

Because the occurrence of seizure clusters varies naturally over time and across individual patients—irrespective of treatment—a series of analyses of tolerance was planned to investigate overall trends across time of seizure-cluster response to diazepam nasal spray and administration of a second dose.

For each of the analyses, tolerance was assessed by defining 2 equal, adjacent periods (period 1 [initial] and period 2 [subsequent]). Data for each patient were analyzed to compare the proportion of events for which second doses were administered in periods 1 and 2, then mean second-dose usage in each period was calculated for all patients in that analysis. Two methods were used to define "initial" and "subsequent": (1) based on a minimum number of events in both periods (eg, 10 seizure clusters in each) and (2) based on a specific number of months (eg, 2 months in each) in both periods.

For all methods, consideration was restricted to patients with ≥8 events in the initial period, and all feasible combinations of time cutoffs and event cutoffs were considered. Seizure clusters were defined as including any seizures within 24 h of the initial event. The endpoint of interest was the proportion of events for which there was a seizure cluster for each patient, averaged across all patients in that specific analysis; this endpoint was assessed in both period 1 (initial) and period 2 (subsequent), with hypothetical examples illustrated in Table 1.

2.5. Statistics

For each of the analyses, the null hypothesis was that there is no difference between the first and second periods with respect to the proportion of events for which there was a seizure cluster, which was assessed using 2-sided Wilcoxon signed rank tests.

Table 1
Hypothetical illustration of analyses using a 4-month cutoff, 8-event minimum example.

	Period 1 (4 mo)			Period 2 (4 mo)			Difference
	1 Dose only	2nd Dose used	Proportion	1 Dose only	2nd Dose used	Proportion	
Patient A	8	1	12.5	7	0	0	12.5
Patient B	9	0	0	15	1	13.3	−13.3
Patient C	12	1	8.3	9	1	11.1	−2.8
Mean	—	—	—	—	—	—	−0.6

3. Results

As of October 31, 2019, the study had enrolled 175 patients; 158 received at least 1 dose of diazepam nasal spray, treating 3370 seizure-cluster events. Baseline characteristics are listed in Table 2.

3.1. Exposure to diazepam nasal spray

Overall, 11 (7.0%) patients had <6 months of exposure, 31 (19.6%) had 6 to <12 months of exposure, and 116 (73.4%) had ≥12 months of exposure. Median time on the study was 13.0 months (range, <1–36.6 months). Twenty-three (14.6%) patients received a total of 1–2 doses during the study, 49 (31.0%) received 3–10 doses, 24 (15.2%) received 11–20 doses, 36 (22.8%) received 21–40 doses, and 26 (16.5%) received >40 doses. There were 89 (56.3%) patients who used an average of 2 or more doses per month. The retention rate was 83% in this long-term study (47 patients completed the study and 84 were ongoing), with 27 patients discontinuing (lost to follow-up, $n = 3$; subject withdrawal, $n = 16$; other, $n = 8$). For each dose group, retention of ongoing patients as a function of study completion and discontinuations is shown in Fig. 1.

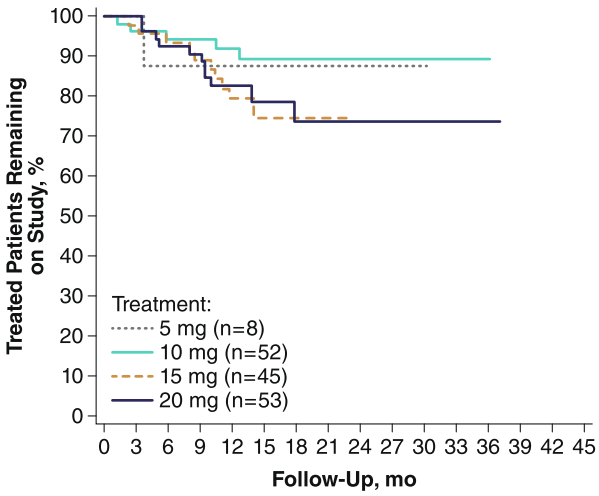

Fig. 1. Study retention (Ongoing patients as of October 31, 2019). For each dose group, retention of ongoing patients as a function of study completion ($n = 47$) and discontinuations ($n = 27$) is shown; 84 patients ongoing.

3.2. Measure of tolerance

Because the follow-up duration and patterns of usage varied widely among patients, all feasible combinations of time cutoffs and event cutoffs were considered for analysis. In total, 191 analyses were conducted with time cutoffs from 2 to 15 months in each period (totals of 4–30 months) and 1 to 18 events in each period (totals of 2–36 events). Thus, a 6-month time cutoff required that patients had two 6-month periods of data, for 12 months of data in total. A brief summary of these results, displaying the maximum number of events in each period, is shown in Table 3; all 191 analyses are presented in Supplementary Table 2.

Across all analyses, the rate of second doses was generally lower in period 2, with fewer second doses in period 2 in 139 (72.8%) analyses and fewer second doses in period 1 in 52 (27.2%) analyses (Fig. 2). For example, one high-use subgroup included patients with at least 12 months of data and at least 18 events in each of the two 6-month periods (Table 3, row 5). Among the 9 patients meeting these time and event thresholds, the mean use of second doses in the first period was 23%, whereas the second-period mean for retreatment was 19.4%, a reduction in use over time of 3.6% ($P = 0.129$). The mean lengths of first and second periods were similar at 26.1 and 26.0 months, respectively.

Only 5 (2.6%) of these 191 analyses showed nominally statistically significant changes ($P < 0.05$) between period 1 and period 2

Table 2
Demographic data, all patients (safety population).

Demographics	Diazepam nasal spray				
	5 mg ($n = 8$)	10 mg ($n = 52$)	15 mg ($n = 45$)	20 mg ($n = 53$)	Total ($n = 158$)
Sex, *n* (%)					
Male	2 (25.0)	27 (51.9)	15 (33.3)	29 (54.7)	73 (46.2)
Female	6 (75.0)	25 (48.1)	30 (66.7)	24 (45.3)	85 (53.8)
Age, y					
Mean (SD)	9.6 (6.93)	12.1 (9.16)	27.6 (13.73)	33.4 (13.03)	23.5 (15.13)
Range	6–26	6–65	10–59	11–59	6–65
Race, *n* (%)					
White	6 (75.0)	41 (78.8)	39 (86.7)	44 (83.0)	130 (82.3)
Black or African American	1 (12.5)	6 (11.5)	4 (8.9)	4 (7.5)	15 (9.5)
Asian	1 (12.5)	3 (5.8)	0	0	4 (2.5)
Native Hawaiian or Other Pacific Islanders	0	0	1 (2.2)	4 (7.5)	5 (3.2)
Other	0	2 (3.8)	1 (2.2)	1 (1.9)	4 (2.5)
Ethnicity					
Hispanic or Latino	0	10 (19.2)	3 (6.7)	4 (7.5)	17 (10.8)
Non-Hispanic or Latino	8 (100.0)	42 (80.8)	42 (93.3)	49 (92.5)	141 (89.2)

Table 3
Mean percentage of events treated with second doses, averaged over patients, based on the cutoff with the highest number of events analyzed in each time period.

Month Cutoff	Number of Events Cutoff	Patients, *n*	Period 1	Period 2	Difference, % (P2–P1)	Events, *n*				*P* Value*
						Period 1		Period 2		
			Mean, %	Mean, %		Mean	Max	Mean	Max	
4	7	12	10.1	18.2	8.1	9.8	14	10.3	17	0.195
6	10	8	10.5	22.5	12.0	14.1	18	13.6	17	0.063
8	13	9	25.3	29.1	3.8	19.0	28	18.1	25	0.734
10	18	8	25.6	21.4	−4.2	24.4	32	23.1	38	0.195
12	18	9	23.0	19.4	−3.6	26.1	32	26.0	47	0.129
14	18	8	20.9	18.3	−2.6	27.6	36	29.0	53	0.547
16	17	8	13.6	12.3	−1.3	29.0	39	31.0	56	0.844
18	18	8	14.2	9.5	−4.7	32.5	52	34.4	64	0.156
20	18	8	16.8	14.9	−1.8	35.9	61	37.9	74	0.688
22	12	8	16.6	18.3	1.8	35.9	69	32.9	73	1.000
24	12	8	17.3	18.3	1.1	37.4	74	34.4	77	0.844
26	14	8	16.6	18.9	2.3	41.6	81	37.9	82	0.844
28	7	8	18.8	16.1	−2.6	39.5	82	41.8	99	0.375
30	9	8	18.6	16.5	−2.0	42.1	86	43.3	99	0.469

* Wilcoxon signed rank test.

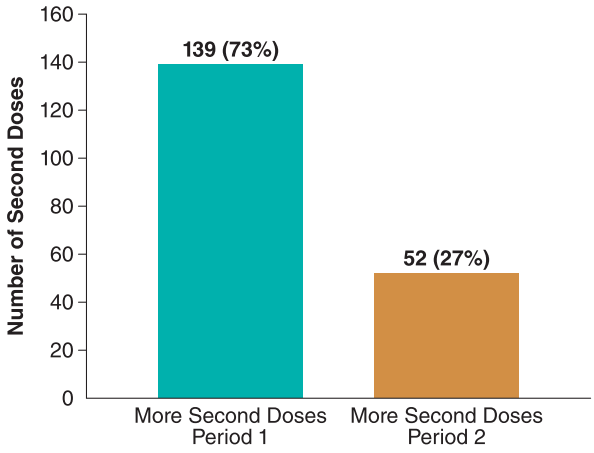

Fig. 2. Proportions of scenarios with increased or decreased use of second doses in period 1 compared with period 2.

in number of second doses, fewer than expected by chance (ie, a 95% confidence for 191 analyses would suggest that 10 instances would be expected to be nominally significant). Of the nominally significant changes, the period 2 mean rate was greater than period 1 in 3 instances and smaller in 2 instances.

3.3. Safety profile

A total of 119 (75.3%) patients experienced TEAEs. The most common nonseizure TEAEs (>5%) were nasopharyngitis (7.6%), upper respiratory tract infection (7.6%), pneumonia (7.0%), pyrexia (6.3%), and influenza (5.1%); no patients discontinued the study owing to TEAEs. Twenty-six (16.5%) patients had TEAEs that were considered at least possibly treatment related; of these, only nasal discomfort (5.7%) occurred in >5% of patients. This was reported in patients receiving 15 mg and 20 mg doses, which are given as 2 sprays, 1 in each nostril (ie, 7.5 mg × 2 or 10 mg × 2). Forty-five (28.5%) patients experienced serious adverse events; none were considered to be treatment related. There were no deaths recorded by the cutoff date of this analysis. However, one death was recorded after the cutoff date and was assessed as not being treatment related.

4. Discussion

Although tolerance limits the use of benzodiazepines in continuous therapy, intermittent use may eliminate or reduce the chances that patients develop tolerance [2]. The results of our analysis found no statistical evidence of tolerance with the use of diazepam nasal spray over time based on use of a second dose in an initial period of the study compared with a subsequent period for each patient. Across all analyses, the rate of second doses was generally lower in period 2 compared with period 1.

Only 5 (2.5%) of the 191 analyses showed nominally statistically significant changes ($P < 0.05$) between period 1 and period 2, fewer than expected by chance. Notably, the nominally statistically significant changes were not directionally consistent, with 3 increases in period 2 relative to period 1 and 2 decreases in period 2 relative to period 1.

This analysis is in agreement with prior studies of benzodiazepine rescue therapy. In an open-label extension trial, no tolerance was observed with long-term use of midazolam nasal spray [14]. A total of 161 patients ≥12 years old with seizure clusters were rolled over from a randomized controlled phase 3 trial to the extension trial. In that study, a second dose was required in 797 of 1998 seizure episodes (39.9%). Tolerance was examined by the number of second doses required relative to how many episodes had been treated for individual patients. No change was observed in the proportion of patients requiring a second dose based on number of treated episodes, to ≥50 episodes [14].

Similarly, no evidence of tolerance was observed in a long-term study of diazepam rectal gel [13]. In that study, 149 patients, aged 2–76 years, from 1 of 2 randomized controlled trials enrolled into an extension study. Extension patients recorded 1578 seizures, and the effect of first and last dose was assessed for loss of efficacy. The efficacy in terminating seizure clusters was similar for both first and last administrations; 63% of patients had no subsequent seizures after the first administration, and 69% had no subsequent seizures after the last administration. Patients with low utilization (2–7 treatments) compared with high utilization (8–78 treatments) also showed similar levels of seizure control.

In the present study, safety was consistent with that of rectal diazepam, and the retention rate was high, which suggests that patients and care partners may have believed that the safety/effectiveness profile was favorable. There were no reports of cardiac or respiratory depression, no life-threatening adverse events, and no discontinuations due to diazepam nasal spray.

This study has several considerations for interpretation. This was an open-label design in which physicians were free to revise

maintenance medications, and seizures and use of rescue was monitored indirectly (via review of seizure diaries). Also, a clear explanation for the lower numbers of second doses in period 2 compared with period 1 has not been identified. For example, while it is possible that adverse events led to increasingly restricted use of the study drug, the reported safety profile does not support this interpretation. Strengths of the study include a large patient population, number of seizures analyzed, and long mean duration of treatment. The analysis of retreatment is robust and shows consistent results for both calendar and event cutoffs. Furthermore, there were a large number of analyses conducted, which provides a detailed picture of retreatment over time. In conclusion, in this analysis of a long-term, open-label, repeat-dose study, no tolerance was seen with intermittent repeat dosing of diazepam nasal spray to control seizure clusters in patients with epilepsy.

5. Disclosures

Dr. Cascino has nothing to disclose. **Dr. Tarquinio** has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Avexis; Marinus; and Neurelis, Inc. **Dr. Wheless** has served as an advisor or consultant for CombiMatrix; Eisai, Inc.; GW Pharmaceuticals; Lundbeck, Inc.; Neurelis, Inc; NeuroPace, Inc.; Supernus Pharmaceuticals, Inc.; and Upsher-Smith Laboratories, Inc. Dr Wheless has served as a speaker or a member of a speakers bureau for Cyberonics, Inc.; Eisai, Inc.; Lundbeck, Inc.; Mallinckrodt; Neurelis, Inc., Supernus Pharmaceuticals, Inc.; Upsher-Smith Laboratories, Inc., and has received grants for clinical research from Acorda Therapeutics; GW Pharmaceuticals; Insys Therapeutics, Inc.; Lundbeck, Inc.; Mallinckrodt; Neurelis, Inc.; NeuroPace, Inc.; Upsher-Smith Laboratories, Inc.; and Zogenix, Inc. **Dr. Hogan** has received research support from UCB Pharmaceuticals, Neurelis, Inc; and Biogen, Inc., and is an advisor for Neurelis, Inc. **Dr. Sperling** has received personal compensation for speaking from Neurology Live and Eisai, Inc., is an advisor for Neurelis, Inc., and consulting with payments to Thomas Jefferson University from Medtronic. Dr Sperling has received research support from Eisai, Inc.; Medtronic; Neurelis, Inc.; SK Life Science; Takeda; Sunovion; UCB Pharmaceuticals; Xenon; and Engage Pharmaceuticals. **Dr. Liow** has received research support from Intracellular Therapies, SK Life Science, Genentech, Biotie Therapies, Monosol, Aquestive Therapeutics, Engage Therapeutics, Xenon, Lundbeck, Biogen, Inc., Eli Lilly, Pfizer, Novartis, Sunovion, Acorda, Eisai, Inc., UCB, Livanova, Axsome, and Acadia. **Dr. Desai** has received research funding from the Epilepsy Foundation of Greater Los Angeles; Neurelis, Inc.; Novartis; Ovid; Aquestive; and UCB Pharmaceuticals. **Dr. Davis** is a consultant to Neurelis, Inc. **Dr. Rabinowicz** is an employee of and has received stock options from Neurelis, Inc.

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Appendix A. Supplementary data

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