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Analyses of patients who self-administered diazepam nasal spray for acute treatment of seizure clusters

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ABSTRACT

For acute treatment of seizure clusters in patients with epilepsy, intranasal administration of acute seizure therapies has been shown to provide accessibility and ease of use to care partners as well as the potential for self-administration by patients. Diazepam nasal spray (Valtoco®) was approved by the US Food and Drug Administration for acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) in patients with epilepsy aged ≥6 years. Self-administration consistent with the prescribing information is feasible and was reported by a subgroup of patients (n = 27 of 163) in a long-term phase 3 safety study. Data regarding self-administration among these patients with seizure clusters are examined here to explore the safety profiles and measures of effectiveness, as well as the quality of life of those who self-treated. In addition, this focused look at patients who self-administered diazepam nasal spray may offer some insights into the characteristics of patients who may be appropriate for self-administration.

Introduction

The US Food and Drug Administration has noted that the intranasal route of administration of diazepam nasal spray provides significantly improved ease of use compared with its predecessor, diazepam gel rectal administration for seizure clusters [1]. Although the diazepam nasal spray label was based on that of rectal diazepam with no specific guidance about self-administration, self-administration has been shown to be feasible in patients who can participate in their own treatment and is consistent with the prescribing information [2]. Data regarding self-administration of diazepam nasal spray among patients with seizure clusters are examined here to explore the safety profile and proxies of effectiveness as well as patients' perceptions of self-administration and quality of life (QoL). Additionally, these patients' characteristics and responses to diazepam nasal spray may provide insights that assist clinicians in clarifying which patients may be appropriate for self-administration.

Materials and methods

These post hoc analyses use data from the phase 3 safety study of diazepam nasal spray (NCT02721069). Full methodology for the study

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has been published [3]. Briefly, included patients were aged 6 to 65 years, had a diagnosis of focal or generalized epilepsy with motor seizures or seizures with clear alteration of awareness, and were expected to need benzodiazepine treatment for seizure control despite daily antiseizure drugs. Participation of a care partner or medical professional who could administer treatment was required; this did not preclude self-administration. Patients and care partners were trained to administer age- and weight-based doses of 5 to 20 mg; a second dose was permitted if needed [3]. A diary was used to record seizure timing and drug administration (eg, time and date of dosing) [3,4]. Patients who reported self-administering ≥1 dose were included in the self-administration subgroup analysis.

Safety and effectiveness

Treatment-emergent adverse events (TEAEs) were recorded. Lower use of second doses in a 24-hour period to control a seizure cluster was a proxy for effectiveness of the first dose [3].

Seizure interval analysis

As a potential new measure of effectiveness beyond immediate termination of a cluster, patient diary data from the diazepam nasal spray phase 3 safety study were used to examine the interval in days between treated seizure clusters (SEIzure interVAL, SEIVAL) [5]. SEIVAL methods and results have been published, and use of diazepam nasal spray was associated with a substantial increase in time between treated clusters across a year. In patients who self-administered diazepam nasal spray, one SEIVAL analysis included all doses administered, and one excluded second doses for the same cluster to measure time between clusters. Ninety-day periods were used to evaluate SEIVAL over time, with four periods corresponding to 360 days, similar to the 12-month study treatment period. A consistent cohort of patients with data from each of these four periods addressed potential confounding that could result from a variable cohort over time. Additional potential confounders examined in the SEIVAL analysis included changes in drug or dose of concomitant antiseizure medications [5]. To better understand the results from this novel analysis, further investigation and corroboration is needed for validation.

Patient perceptions survey

To examine patient perceptions about use of diazepam nasal spray, surveys developed and face validated by the study investigators and a panel of epileptologists were given to patients and care partners near study end, and patients who had completed or discontinued the study received the survey by mail [2]. Questions assessed patients' experiences, including ease of being trained and training others, whether they self-administered diazepam nasal spray and their perceptions of doing so, and administration timing and return to baseline. Respondents did not need to answer all of the questions.

Quality of life in epilepsy analysis

Patient perceptions of QoL during treatment with diazepam nasal spray were assessed using the Quality of Life in Epilepsy (QOLIE)-31-P, a self-reported tool for patients aged older than 18 years [6]. The total score is a weighted composite of seven subscales: Seizure Worry, Overall QoL, Emotional Well-Being, Energy/Fatigue, Cognitive Functioning, Medication Effects, and Social Functioning. Each scale/subscale is scored from 1 to 100; higher scores indicate better QoL [6]. The Seizure Worry and Social Functioning subscales were hypothesized to be most affected by acute seizure therapy and were the subscale focus for this analysis.

Results

Self-administrators subgroup

Of 158 pediatric and adult patients in the safety population at the time of the survey, 67 patients and 84 caregivers responded to the survey [2]. On the survey, 27 patients reported that they self-administered diazepam nasal spray at least once during the study (ie, yes response to "Did you self-administer?"). Median age was 34.0 years (range, 11–65 y; Table 1). Approximately half (55.6 %) had a college or higher educational level. A modest majority (63.0 %) had ≤ 10 seizures per month. Of the patients who self-administered, 23 (85.2 %) completed the study; 3 (11.1 %) withdrew (1 at day 224 and 2 after > 1 year); and 1 (3.7 %) discontinued at study closure.

Nearly all self-administering patients (26/27; 96.3 %) had duration of use of diazepam nasal spray ≥ 12 months. Twenty-five patients used 15- and 20-mg doses that required two applicators for a full dose; two patients used 10-mg doses requiring one applicator. A total of 1087 doses were administered in this group (by the patients or their care partners [patients were not asked to differentiate by whom specific doses were administered]); this was 24.8 % of the 4390 doses administered to the total safety population (N = 163). Monthly doses administered was a median of 6 doses at day 365 in the self-administrators group; across the entire study, self-administrators received a mean of 40 doses compared with 24 doses for patients treated by care partners only (n = 136) ($P = 0.07$). In the self-administrators group, second doses were used to control 135 of the total 923 seizure episodes (14.6 %; overall population: 485/3853 [12.6 %] [3]).

Table 1
Patient characteristics of self-administrators.

Characteristic, n (%)	Total (n = 27)
Sex, n (%)	
Male	12 (44.4)
Female	15 (55.6)
Age, y (range)	34.0 (11–65)
Education level, n	
Not completed high school	2 (7.4)[a]
High school	10 (37.0)[b]
College	9 (33.3)
Graduate school	6 (22.2)
Reported underlying disease (n = 13)	
Cortical dysplasia	2 (7.4)
Encephalitis	1 (3.7)
Genetic	1 (3.7)
Generalized epilepsy	3 (11.1)
Perisylvian syndrome	1 (3.7)
Stroke	3 (11.1)
Traumatic brain injury	2 (7.4)
Seizures per month	
1–10	17 (63.0)
11–20	5 (18.5)
>20	5 (18.5)
Range	1–60
Total doses used during the study	
1–2	3 (11.1)
3–10	2 (7.4)
11–20	6 (22.2)
21–40	8 (29.6)
>40	8 (29.6)
Diazepam nasal spray dose, mg	
5	0
10	2 (7.4)
15	10 (37.0)
20	15 (55.6)
Duration of exposure, mo	
<6	0
6–<12	1 (3.7)
≥12	26 (96.3)

[a]One of the two patients was pediatric, aged 11 y.
[b]One of the patients was pediatric, aged 16 y.

TEAEs were reported in 20 self-administering patients (74.1 %); TEAEs that were considered treatment related were reported for eight patients (29.6 %). Treatment-related TEAEs in ≥ 2 patients were nasal discomfort (n = 5) and migraine (n = 2). Serious TEAEs were reported for seven patients (25.9 %); only terms related to seizure were seen in ≥ 2 patients (4 patients). None were considered treatment related. None of these patients discontinued due to a TEAE.

Self-administrators' SEIVAL results

The increase in days from baseline in mean SEIVALs over time among self-administrators (n = 21) was similar to that observed in the overall population [5]. Among the self-administrators, statistically significant increases in mean SEIVAL vs Period 1 were observed at Periods 2 (mean difference, 6.3 d) and 3 (mean difference, 13.1 d) ($P < 0.05$). In the self-administrators consistent cohort with SEIVALs in all of Periods 1 through 4 (n = 18), the pattern of increases in mean SEIVAL over time with and without re-treatments eliminated (Fig. 1.) also was consistent with that observed in the overall population [5].

Self-administrators' survey responses

Of self-administering patients who responded to the survey, most (85.2 %) responded that it was very (n = 7) or extremely (n = 16) easy to be trained to use diazepam nasal spray; regarding training others, 88.9 % responded that it was very (n = 8) or extremely (n = 8) easy. Twenty-one respondents (77.8 %) reported that self-administration was very (n = 10) or extremely (n = 11) easy. Nearly half of these patients (48.0 %) reported primarily administering a dose at the first sign that a seizure may be coming, and more than half (51.9 %) reported returning to baseline within 30 min. The majority of the patients (70.4 %) were very or extremely likely to ask their healthcare provider about continuing diazepam nasal spray at study completion.

Self-administrators' QOLIE-31-P data

Twenty-five of the self-administrators were adults with at least some QOLIE-31-P data. Two self-administrators were pediatric patients, aged 11 and 16 years, and were not eligible to complete the QOLIE-31-P. Overall QOLIE-31-P scores for self-administrators did not change over the course of 1 year [6]. Seizure Worry and Social Functioning subscale scores also were maintained over time (data not shown) [6].

Discussion

These analyses suggest that self-administration of diazepam nasal spray has safety and effectiveness profiles similar to those reported in the overall study [3] and that self-administering patients' survey responses indicate positive perceptions of using this rescue therapy. No disadvantages of self-administration were identified. Patients who self-administered at least once had low second-dose usage, which was comparable to the overall study population (12.6 %) [3], demonstrating single-dose effectiveness. Increases in SEIVAL among self-administrators during the study showed a pattern similar to the overall population [5]. In the survey, self-administrators expressed ease and comfort of using and training to use diazepam nasal spray that was supported by QoL data, which remained stable over time, a welcome finding.

The diazepam nasal spray label allows the possibility of self-administration. Self-administrators in the phase 3 safety study of diazepam nasal spray were mostly adults, with majorities having a college education, using doses that required administration of two applicators (ie, 15 or 20 mg), and experiencing ≤ 10 seizures per month. Notably, these patients were generally capable of administering two applicators and appeared to be higher functioning, including two mature children, and more than half had > 20 doses. In addition, nearly half of patients administered at the first sign of a seizure, suggesting that patients with prodromes, auras, or focal-aware onset may be ideal candidates for self-administration.

Approximate doubling in mean SEIVAL over time was shown in self-administrators' data with and without re-treatments eliminated. The cause for such increases in patients with epilepsy administering diazepam nasal spray needs further elucidation. Hypotheses regarding potential biological or behavioral changes or regression to the mean have been discussed in a previous publication [5]. In the overall population, SEIVAL was similar over time regardless of changes to concomitant antiseizure medication drug or dose [5].

A previous analysis of QoL in the self-administrators (n = 25) vs patients with only care partner administration (n = 47) in this study found the overall QOLIE-31-P scores of adult patients in the self-administrators subgroup were numerically higher at all time points and had significantly higher scores in the Seizure Worry and Social Functioning subscales [6]. Similarly, in a recent analysis, it was shown that adults who took part in self-management activities had significantly higher QOLIE-31-P scores compared with a control group [7].

As discussed here, QOLIE-31-P scores among those who self-administered were maintained through study end. The QOLIE-31-P

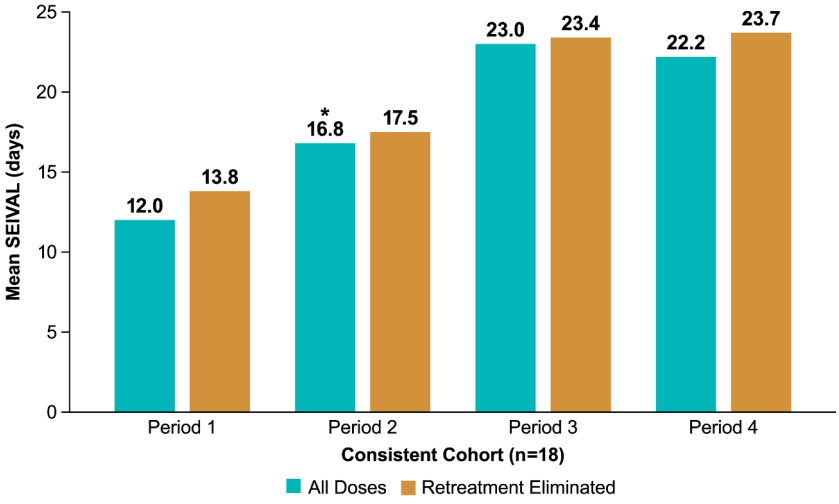

Fig. 1. SEIVAL in self-administrators consistent cohort.
*$P<0.05$.
SEIVAL, SEIzure interVAL.

scores reported suggest that the 25 adult patients able to self-administer diazepam nasal spray per their survey responses may be a high-functioning subgroup at baseline. Because the instrument was to be completed without care partner assistance, this observation might be expected in self-administrators.

Limitations

The analysis of when or why those in this group chose to self-administer is limited by the details captured in the diary record, which was designed to support a safety analysis. In addition, this safety study was not powered to test statistical differences. Also, because there was a small number of self-administrators, the generalizability to a larger group may only be inferred. Only 5 of 21 study sites had $\geq$2 self-administrating patients, and 70% of all self-administrators were from only three sites; however, additional self-administrators may not have completed the survey. Additionally, the affirmative response to self-administering only indicated that the patient did so at least once; a care partner may have administered doses on other occasions. Also, a patient who self-administered may not have administered a second dose if needed due to variables such as postictal confusion.

Conclusions

Self-administration with diazepam nasal spray has been shown to be feasible for adults and some children and is consistent with the prescribing information. Additional research in pediatric patients may be beneficial. The potential for self-administration in patients with varying etiologies and seizure burdens may be a benefit of diazepam nasal spray compared with other routes of administration, which require administration by a care partner, potentially allowing for changes in behavior consistent with the label and administration instructions. The use of two applicators to achieve the total dose was not a barrier to self-administration. Adults have historically had low rates of use of rescue medication, self-management programs, and seizure action plans. Self-administration of rescue treatment may empower more independence and possible improved QoL. The safety profile of patients who self-administered was consistent with overall phase 3 safety study and the profile reported for diazepam.

CRediT authorship contribution statement

Sunita N Misra: Conceptualization, Writing – review & editing. **Michael R. Sperling:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Vikram R. Rao:** Conceptualization, Writing – review & editing. **Jurriaan M. Peters:** Conceptualization, Writing – review & editing. **Patricia Penovich:** Conceptualization, Investigation, Methodology, Writing – review & editing. **James Wheless:** Conceptualization, Investigation, Methodology, Writing – review & editing. **R. Edward Hogan:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Charles S. Davis:** Conceptualization, Formal Analysis, Writing – review & editing. **Enrique Carrazana:** Conceptualization, Methodology, Writing – review & editing. **Adrian L. Rabinowicz:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Dr Misra** was an employee of Neurelis, Inc., at the time of the development of this manuscript and has received stock options from Neurelis, Inc. **Dr Sperling** has received compensation for speaking at continuing medical education programs from Medscape, Projects for Knowledge, International Medical Press, and UCB Pharma. He has consulted for Medtronic; Neurelis, Inc.; and Johnson & Johnson. He has received research support from Eisai; Medtronic; Neurelis, Inc.; SK Life Science; Takeda; Xenon; Cerevel; UCB Pharma; Janssen; and Engage Pharmaceuticals. He receives royalties from Oxford University Press and Cambridge University Press. **Dr Rao** has served as a consultant for NeuroPace, Inc., manufacturer of the RNS® System. **Dr Peters** has served as a speaker and consultant for Neurelis, Inc.; SK Life Science; and Jazz Pharmaceuticals. **Dr Penovich** has served on speakers bureaus for Jazz Pharmaceuticals; Neurelis, Inc.; and UCB Pharma, and is an advisor to LVIS Corporation 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; and INSYS. **Dr Hogan** has received research support from UCB Pharmaceuticals, Neurelis, Inc; and Biogen Inc, and is an advisor for Neurelis, Inc. **Dr Davis** is a consultant to Neurelis, Inc. **Dr Carrazana** is an employee of and received stock and stock options from Neurelis, Inc. **Dr Rabinowicz** is an employee of and has received stock options from Neurelis, Inc.

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