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Authors

Misra, Sunita
Jarrar, Randa
Stern, John
et al.

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BRIEF REPORT

Rapid Rescue Treatment with Diazepam Nasal Spray Leads to Faster Seizure Cluster Termination in Epilepsy: An Exploratory Post Hoc Cohort Analysis

Sunita N. Misra · Randa Jarrar · John M. Stern · Danielle A. Becker · Enrique Carrazana · Adrian L. Rabinowicz

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ABSTRACT

Introduction: Although prompt treatment of status epilepticus is standard of care, the effect of timing of rescue therapy administration for seizure clusters in epilepsy remains unknown. Seizure clusters are a rare but clinically important condition, and benzodiazepines are the cornerstone rescue therapy for seizure clusters in epilepsy. We characterized temporal patterns from a large dataset of treated seizure clusters in the safety study of diazepam nasal spray.

Methods: This post hoc analysis used timing data of treated seizure clusters recorded by care partners and patients in seizure diaries during a 1-year safety study. Data analysis used time from seizure start to administration of diazepam.

Results: From 4466 observations, 3225 had data meeting criteria for analysis. Overall, median times from seizure start to dose administration, dose administration to seizure termination, and total seizure duration were 2, 3, and 7 min, respectively. In seizure clusters treated in < 5 min (median 1.0 min), median time from dose to seizure termination was 2.0 min, and median total seizure duration was

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S. N. Misra
Formerly of Clinical Development and Medical Affairs, Neurelis, Inc., San Diego, CA, USA
e-mail: sunita.n.misra@gmail.com

R. Jarrar
Department of Neurology, Phoenix Children's Hospital, Phoenix, AZ, USA
e-mail: rjarrar@phoenixchildrens.com

J. M. Stern
Department of Neurology, Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA
e-mail: jstern@ucla.edu

D. A. Becker
Department of Neurology, Ohio State University Wexner Medical Center, Columbus, OH, USA
e-mail: dbecker8@gmail.com

E. Carrazana · A. L. Rabinowicz (✉)
Clinical Development and Medical Affairs, Neurelis, Inc., 3430 Carmel Mountain Rd, Suite 300, San Diego, CA 92121, USA
e-mail: arabinowicz@neurelis.com

E. Carrazana
Department of Family Medicine, John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA
e-mail: ecarrazana@neurelis.com

4.0 min. Among seizure clusters treated in ≥ 5 min (median 10.0 min), median time to seizure termination was 10.0 min, and median total seizure duration was 23.0 min. Previously published safety results reported that over a mean participation of 1.5 years, 82.2% of patients had ≥ 1 treatment-emergent adverse events (TEAEs) irrespective of relationship to treatment, including 30.7% with serious TEAEs; 18.4% had TEAEs deemed at least possibly related to the study drug, none of which were serious. There were no events of cardiorespiratory depression.

Conclusion: Echoing the importance of early use of benzodiazepines in status epilepticus, the findings from this exploratory analysis of patients with refractory epilepsy and frequent seizure clusters identify a potential benefit of early diazepam nasal spray treatment leading to faster seizure resolution within the seizure cluster.Trial Registration Information: ClinicalTrials.gov identifier NCT02721069 (https://clinicaltrials.gov/ct2/show/NCT02721069).

PLAIN LANGUAGE SUMMARY

Some people with epilepsy who take daily antiseizure drugs might still have seizures. Some of these seizures may be emergencies that can be treated with rescue medicine. For status epilepticus, rescue treatment should be given as soon as this seizure emergency is recognized. Seizure clusters are rare and might also become emergencies, but until now it had not been clear if earlier treatment would be better. Diazepam nasal spray is a rescue medicine approved to treat seizure clusters. The report used data from a study of the safety of diazepam nasal spray in people needing treatment ≥ 6 times a year. We looked at the time the seizure in a seizure cluster started to the time rescue treatment was given. We also looked at the time from taking rescue treatment to the time when that specific seizure stopped. For some seizure clusters, rescue medicine was given in < 5 min after the seizure started; on average, these seizures stopped within 2 min after rescue treatment. The total time from the start of the seizure in the seizure cluster to when it stopped was 4 min. In contrast, for seizure clusters treated after 5 min, the seizures stopped in an average of 10 min after treatment. Overall, these seizures lasted 23 min. In conclusion, this analysis found that seizures in a seizure cluster ended more quickly when diazepam nasal spray was given sooner. These findings are suggestive that select patients and caregivers should not wait to treat a seizure cluster once it has been identified.

Keywords: Benzodiazepine; Diazepam; Early Intervention; Epilepsy; Intranasal; Rescue Therapy; Seizure Cluster; Timing; Urgency

Key Summary Points

Why carry out the study?

The effect of timing of rescue therapy administration relative to the start of seizure clusters in epilepsy has been unknown.

We characterized temporal patterns from a large dataset of treated seizure clusters in the long-term safety study of diazepam nasal spray, with a focus on the impact of the time to dose administration.

What was learned from this study?

Treating a seizure in a seizure cluster within 5 min of seizure start was associated with a shorter time from dose to seizure termination (median 2.0 min) than waiting ≥ 5 min to administer rescue treatment (median time to seizure termination 10.0 min).

In select patients, there is a benefit to treating a seizure cluster soon after it starts, with faster seizure termination and shorter overall seizure duration.

These exploratory findings appear to suggest that an identified seizure cluster should be treated promptly and appropriately.

INTRODUCTION

Seizure clusters (SC) are acute seizure urgencies that might intensify [1, 2] to become emergencies associated with morbidity, emergency department usage, possible evolution to status epilepticus, and mortality [3–5]. Presentation of SCs, including seizure type, varies (but is definable on a patient by patient basis) and requires an individualized definition based on factors including number of seizures in a cluster, time between seizures within a cluster, time between clusters, length of the cluster, and patient perception [6]. Although universally accepted criteria have not been established [3, 5], practical definitions have been used for a quarter century [7, 8] and include a change in the number of seizures or the pattern of seizures within a certain period of time [5, 7], or ≥ 2 seizures in a 24-h period [9]. Seizure clusters, in which patients typically recover between seizures [7], are distinct from status epilepticus; however, the two conditions may overlap in the case of ongoing seizures without recovery between seizures. While the US Food and Drug Administration (FDA) recognizes SCs, this indication is not included in the current International League Against Epilepsy designations [10] and may not be recognized by regional regulatory authorities outside of the USA. In contrast, the European Union, the UK, Israel, and Japan have approved buccal midazolam for the treatment of prolonged seizures in children and adolescents, which is not approved in the USA [11–13].

Benzodiazepines are the cornerstone rescue therapy (RT) for SCs in epilepsy [14], which are classified as an orphan disease by the FDA and are thought to affect fewer than 200,000 [15] of the approximately 3.5 million patients with epilepsy in the USA [16]. In SC, prompt treatment with rectal diazepam gel has been associated with decreased emergency room visits [17]. However, rectal administration requires multiple steps, including partial disrobing of the patient and preparation of the device [14], which may delay treatment. Intranasal formulations of midazolam (Nayzilam®) [18] and diazepam (Valtoco®) [19] in prefilled unidose delivery systems offer potential benefits for ease of use that could facilitate rapid administration, including self-administration [20].

Benzodiazepines modulate γ-aminobutyric acid type A ($GABA_A$) receptor activity, and early RT is considered beneficial in the treatment of status epilepticus (SE) [21], which is characterized by the progressive internalization of GABA receptors during seizures [22]. Delayed or underdosed RT for SE is common [23–25], and multiple studies have linked suboptimal treatment and worse outcomes, including longer seizure duration, poorer functional status, and higher morbidity and mortality [24–26]. While considerable study has characterized aspects of the treatment of SE, the effect of timing of RT during an SC remains uncharacterized.

The objective of this exploratory post hoc analysis was to characterize temporal patterns of treated SCs from the pivotal long-term safety study of diazepam nasal spray, with a focus on the effect of timing of dose administration. Diazepam nasal spray is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., SCs, acute repetitive seizures) in patients with epilepsy aged ≥ 6 years [19]. No more than two doses are to be used for a single episode, and it is recommended to treat no more than one episode every 5 days and no more than five episodes per month [19]. The original single-arm, open-label study in a community setting enrolled patients with epilepsy who continue to experience SC despite daily antiseizure drug therapy [27]. The study evaluated the safety and effectiveness of diazepam nasal spray, but it also provided the largest dataset to date of treatment for SC, with 4390 administrations for 3853 clusters [27]. The dataset has proven to be a valuable tool for exploratory analyses of other questions related to temporality in the rescue treatment of SC [28].

METHODS

Study Design

The present analyses derive data from a pivotal single-arm long-term, phase 3, open-label,

repeat-dose safety study of diazepam nasal spray (11 April 2016 to 23 July 2020; ClinicalTrials.gov identifier: NCT02721069). The study design has been published [27]. Briefly, all enrolled patients (male or female, aged 6–65 years) had a diagnosis of focal or generalized epilepsy with motor seizures or seizures with clear alteration of awareness and, in the investigator's opinion, might need benzodiazepine treatment for seizure control ≥ 6 times a year on average despite a stable daily antiseizure drug regimen. Care partners or patients were trained to administer diazepam nasal spray as needed to treat SCs. Second doses were permitted 4–12 h later if needed, and investigators could adjust doses or timing of second doses (e.g., up to 24 h). Seizure timing and drug administration were tracked in seizure diaries. Tracking did not include seizure type or untreated seizures. Safety assessments included incidence and seriousness of treatment-emergent adverse events (TEAEs) and their potential relationship to therapy. Following the 12-month treatment period, patients could elect to remain on therapy as part of the study.

The ethics committees or institutional review boards of the study centers approved study procedures (see Electronic Supplementary Material). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All patients or parents/guardians provided written informed consent prior to participation.

Temporal Analysis

Researchers identified SCs from seizure diaries and calculated times from the seizure that prompted treatment to diazepam administration and to seizure termination. Data preparation included removal of observations with missing date/time, duplicate entries, SCs > 24 h in duration, and dose administration or seizure stop > 1 min before seizure start (e.g., perhaps in anticipation of an airplane flight rather than to treat an aura/seizure). Descriptive statistics defined temporal patterns. Owing to the substantial interpatient variability in both the timing and the number of events per patient (ranging from 1 to > 300), reliable statistical analyses of differences were not viable. To investigate the potential confounder of seizures that might have stopped spontaneously, irrespective of treatment, a sensitivity analysis was also conducted that censored seizure durations ≤ 2 min; a recent analysis of 11,919 video electroencephalography (EEG) recordings found that seizures lasting ≥ 2 min were uncommon for any type of epileptic seizure [29]. Data reporting as per Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [30].

RESULTS

Overall Study

Study results, including overall safety and effectiveness, have been published [27]. Of 175 enrolled patients, 163 received ≥ 1 dose of diazepam nasal spray (safety population). A total of 3853 SCs were treated with 4390 doses of diazepam nasal spray [27]. More than 80% of patients elected to continue beyond the initial 12-month treatment period (range 2 months to > 3 years) [27]. An in-study survey found that approximately 80% of responding caregivers typically administered diazepam nasal spray during the seizure [31]. Twenty-five patients reported self-administered rescue, and about half reported using medication at the first sign an SC may be coming [31]. Second doses were given within 24 h of the initial dose for only 485 SCs (12.6%) [27]. A post hoc analysis found that the interval between treated SCs approximately doubled during the course of 1 year of treatment; this result is under active investigation [28].

With respect to safety, over a mean exposure of approximately 1.5 years (2 months to > 3 years), 134 (82.2%) of 163 patients had ≥ 1 TEAE irrespective of relationship to treatment and 50 (30.7%) had serious TEAEs. TEAEs deemed at least possibly related to the study drug occurred in 30 (18.4%) patients, with primarily (> 2%) nasal discomfort (6.1%) and headache (2.5%) reported [27]. No serious TEAEs considered to be treatment related

occurred, and no cases of respiratory depression were reported. The study included one discontinuation (due to major depression) and one death (sudden unexpected death in epilepsy); both were deemed unlikely to be related to treatment [27]. There were no cases of cardiorespiratory depression.

Temporal Analysis

From an initial 4466 observations, 3225 composed the full set for analysis (Fig. 1). Second doses were not censored because the analysis included all seizures that met criteria (i.e., each dose was considered to be used to treat a separate seizure within the seizure cluster); seizure type was not recorded in diaries. Overall, median time to dose administration was 2 min, and median time from dose administration to seizure termination was 3 min (Fig. 2a). In SCs treated in < 5 min (median 1.0 min), the median time from dose administration to seizure termination was 2.0 min (Fig. 2b), whereas among SCs treated in ≥ 5 min (median 10.0 min), median time to seizure termination was 10.0 min.

Given the range of temporal patterns within the ≥ 5-min group, all data were re-analyzed using three time categories: < 5, 5–15, and > 15 min to dose administration (Fig. 3a). The sensitivity analysis removing observations with seizure durations of 0–2 min, which reduced potential confounding by seizures that may have resolved spontaneously [29], produced comparable results (Fig. 3b). Distribution of observations by time to seizure termination in each of the three time categories revealed that the majority of observations in the < 5-min group terminated in < 5 min with a sharp decrease in the proportion of observations terminating ≥ 5 min after dose. Higher

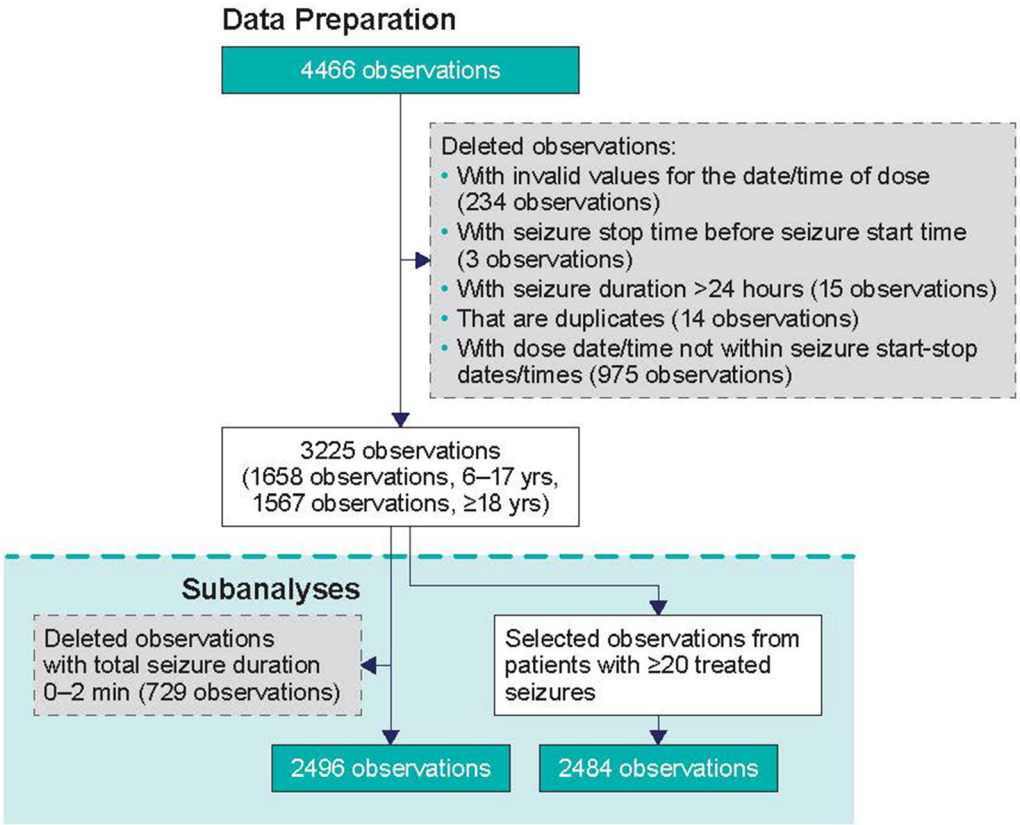

Fig. 1 Data preparation for treated seizure observations used in temporal analysis

proportions of observations in the 5- to 15- and > 15-min groups had longer times to termination following dosing (Fig. 4). Finally, analyses of patients with ≥ 20 observations (Fig. 5), and of pediatric (aged 6–17 years) and adult (aged ≥ 18 years) patients (Fig. 6) yielded similar patterns to the main analyses. The weight- and age-based dosing strategy of diazepam nasal spray is similar to that of diazepam rectal gel, which aims to maintain plasma drug concentrations within the target therapeutic range [8].

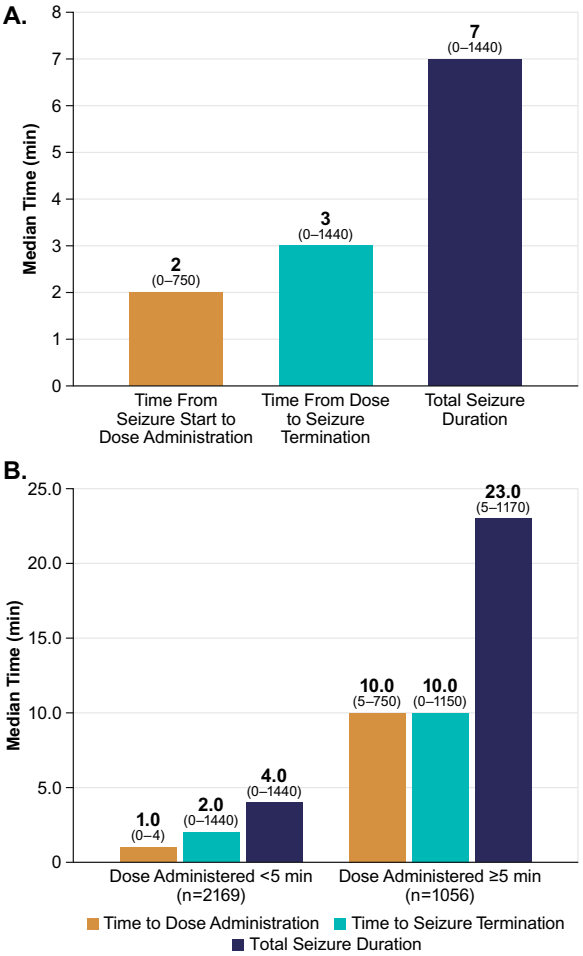

Fig. 2 Median time (range) to dose administration, time to seizure termination, and total seizure duration for seizures treated with diazepam nasal spray. **a** All observations (N = 3225), **b** observations based on time to dose administration: < 5 min and ≥ 5 min

DISCUSSION

Caregivers and patients typically recognize the onset of SC by their consistent, patient-specific presentation [7]. In this long-term study of SC RT in a real-world setting among patients with epilepsy expected to need benzodiazepine treatment for seizure control ≥ 6 times a year, half of treated seizures were treated within 2 min of the seizure that prompted treatment and half of these terminated within 3 min after administration. In multiple analyses, earlier administration of RT was associated with shorter time to seizure termination and overall seizure duration in an SC. Diazepam nasal spray use was based on stereotypic seizures for clusters in individual patients; thus, RT was not limited to a specific seizure type. In this study of patients with frequent SC, these findings are strongly suggestive of a benefit to treating appropriate patients with diazepam nasal spray within 5 min of onset to shorten seizure duration, which is consistent with the prescribing information for the approved benzodiazepine RTs [18, 19, 32].

Unnecessary delay in administration of RT for SC may have several sources, including a lack of or delayed recognition of the episode [23]; the practice of waiting before treating the related condition SE [21]; a history in which rectal RT was the only option, which caregivers may have been reluctant to administer [14]; concerns over adverse events of respiratory depression or excessive sedation [17–19, 21, 27, 32]; and a historical (but unfounded [17]) concern of tolerance with repeated benzodiazepine RT [27]. At the same time, earlier treatment of SCs may minimize morbidity. Also, current knowledge of cellular mechanisms of benzodiazepine activity, including changes in $GABA_A$ receptor localization and configuration during seizure and decreased benzodiazepine effectiveness with longer SE seizure times, supports earlier intervention [33]. Finally, the emotional stress and burden experienced by caregivers standing by and watching loved ones seize is a consideration.

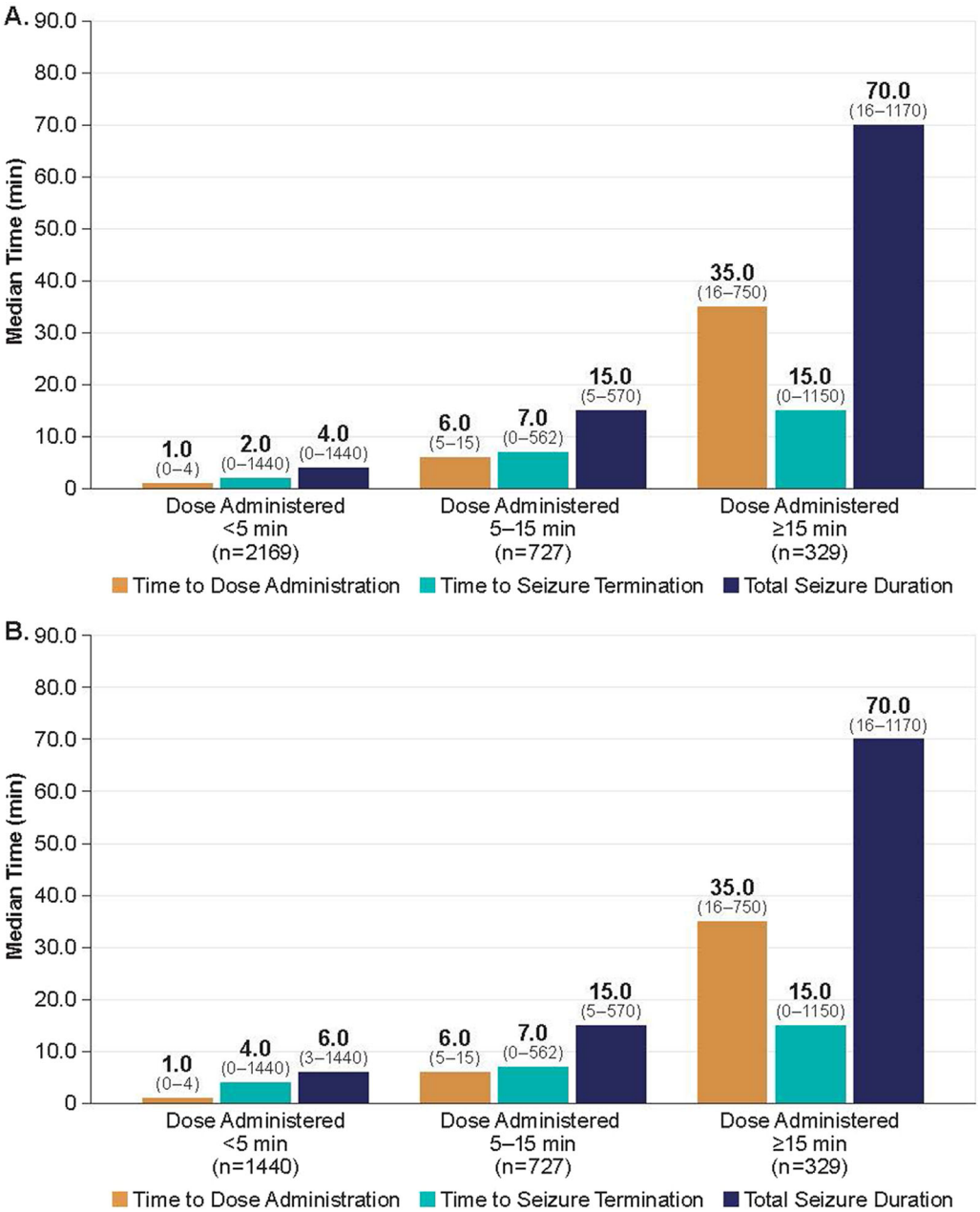

Fig. 3 Median (range) time to dose administration, time to seizure termination, and total seizure duration based on time to dose administration for seizures treated with diazepam nasal spray. **a** All observations (N = 3225), **b** observations after removing observations of seizure duration 0–2 min (N = 2496)

Limitations of this post hoc analysis include the main study being an open-label safety study with no placebo control, in which patients and caregivers, not healthcare professionals, recorded data. There were nine documented histories of "status epilepticus," but other baseline data characterizing untreated seizures or seizure type or severity in the clusters were not prospectively captured. In addition, measures of potential overuse were not included in the original safety study. However, although this was not specifically tested, earlier analyses did not find any

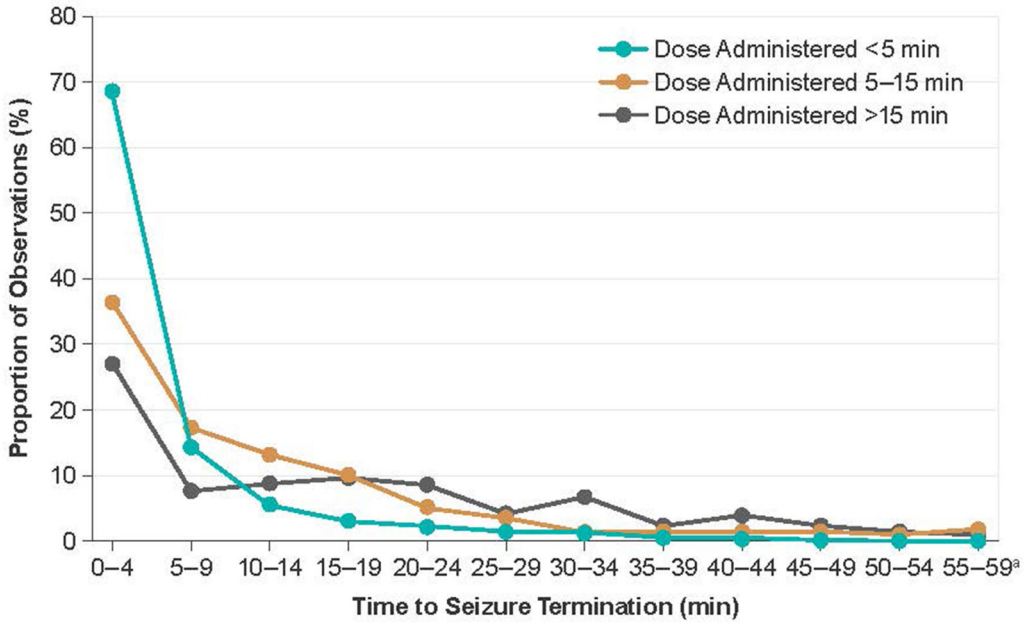

Fig. 4 Distribution (across 5-min periods) of treated seizure observations ($N = 3225$) by time from dose administration to seizure termination based on time to dose administration: < 5 min, 5–15 min, > 15 min ($N = 3225$). [a]40/2169 (1.8%), 39/727 (5.4%), and 53/329 (16.1%) of observation with dose administered < 5 min, 5–15 min, > 15 min, respectively, terminated ≥ 60 min after dose administration

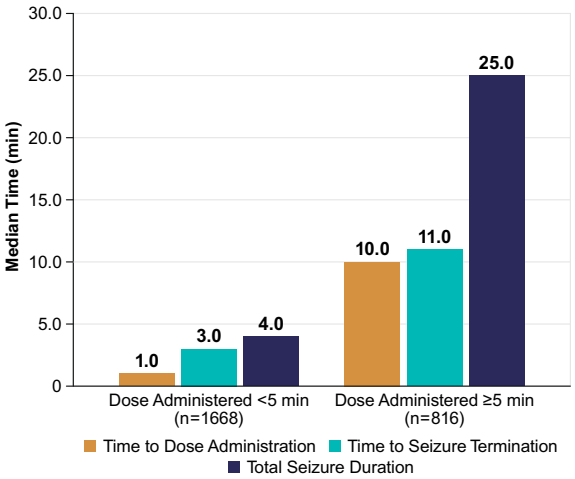

Fig. 5 Median time to dose administration, time to seizure termination, and total seizure duration based on time to dose administration for seizures among patients with ≥ 20 seizures ($N = 2484$ observations) treated with diazepam nasal spray

indication of increasing use over time [28, 34]. Indeed, during the study's 12-month treatment period, a post hoc analysis found that time between treated SCs increased, reflecting lower usage [28]. This analysis also does not test statistical significance, as an appropriate statistical analysis cannot be carried out on a per-subject basis (owing to wide variation in seizures), nor does it account for multiple seizures per subject, which is not a viable approach with this dataset. However, temporal patterns were similar after removal of the possible confounder of seizures spontaneously resolving within 2 min and regardless of age or high-frequency usage. Future research may define temporal patterns, such as duration of postictal recovery, and evaluate other possible reasons for these observations. Ultimately, results of research could impact guidance to clinicians and patients on the appropriate use of RT for seizure clusters.

CONCLUSION

In a group of patients who were expected to need RT ≥ 6 times a year, diazepam nasal spray rescue was administered in real-world settings soon after recognition of an SC, with successful

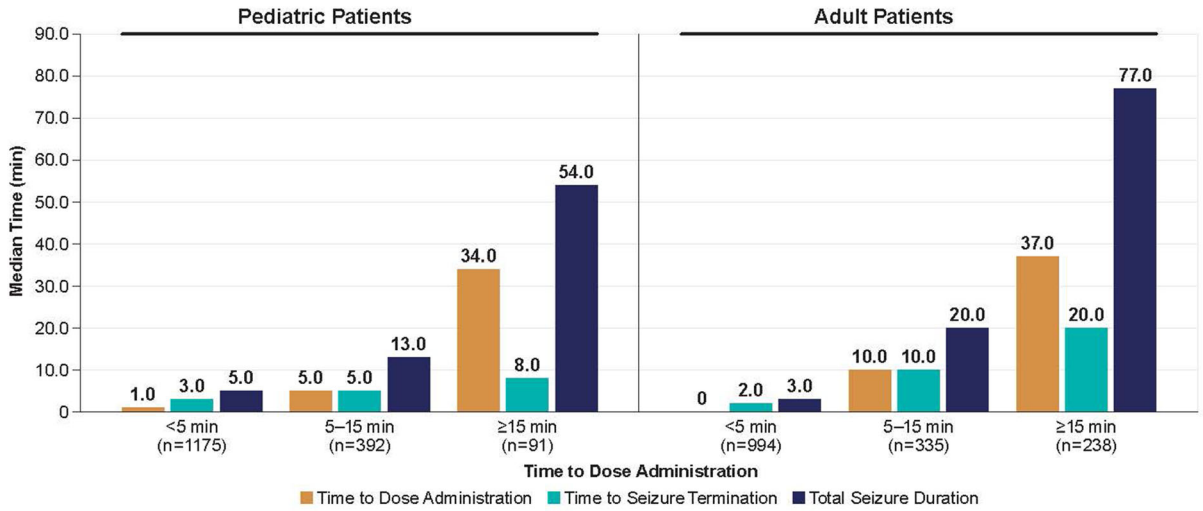

Fig. 6 Median (range) time to dose administration, time to seizure termination, and total seizure duration based on time to dose administration for seizures treated with diazepam nasal spray for pediatric patients aged 6–17 years (N = 1658 observations) and adult patients aged ≥ 18 years (N = 1567 observations)

termination of seizures within minutes. In this exploratory analysis, results were strongly suggestive that earlier RT (< 5 min) with diazepam nasal spray following appropriate dosing and usage for the treatment of SC is likely associated with shorter time to seizure termination and overall seizure duration. This study adds to the increasing evidence of the benefits of early RT with different benzodiazepines for a range of seizure emergencies (i.e., SC, prolonged seizures, and SE). These findings provide support for an approach in which identified SCs in appropriate patients should be treated promptly and appropriately to help limit seizure duration.

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Author Contributions. Design or conceptualization of the study: Sunita N Misra, Enrique Carrazana, Adrian L Rabinowicz. Major role in the acquisition of data: Randa Jarrar, Danielle A Becker, John M Stern. Analysis or interpretation of the data: all authors. Drafting or revising the manuscript for intellectual content: all authors.

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Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to commercial restrictions.

Declarations

Conflict of Interest. At the time of this study, Sunita N Misra was an employee of and had received stock options from Neurelis, Inc. Randa Jarrar is an advisor for Neurelis, Inc. John N Stern is a consultant for Eisai, Jazz, Neurelis, Inc., SK Life Science, and UCB. Danielle A Becker is a consultant/speaker for Neurelis, Inc., SK Life Science, UCB, and Jazz Pharmaceuticals. Enrique Carrazana is an employee of and has received stock and stock options from Neurelis,

Inc. Adrian L Rabinowicz is an employee of and has received stock options from Neurelis, Inc.

Ethical Approval. The ethics committees or institutional review boards of the study centers approved study procedures. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All patients or parents/guardians provided written informed consent prior to participation.

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