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Adverse events of undiluted intravenous push levetiracetam

Jonathan A. Summerlin, PharmD [a,*], Nicholas Scaturo, PharmD [a], Jeremy A. Lund, PharmD [a], Kellie M. Wang, PharmD [a], Marshall A. Frank, DO [b]

[a] Department of Pharmacy, Sarasota Memorial Healthcare System, Sarasota, FL, USA
[b] Florida State University College of Medicine, Sarasota, FL, USA

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ABSTRACT

Background: In patients who experience a seizure, the seizure duration is a strong indicator of prognosis. Thus, reducing time to antiepileptic medications in patients who are actively seizing is critical. While findings from retrospective studies suggest that the rapid administration of undiluted intravenous (IV) levetiracetam may be safe, some gaps in the literature remain.
Objective: The purpose of this research study was to prospectively assess adverse events associated with the rapid administration of undiluted IV levetiracetam.
Methods: This was a prospective, observational cohort study of adult patients who received rapid administration of undiluted IV levetiracetam at doses up to 4500 mg in the emergency department (ED) of a large community, teaching hospital. The primary endpoint was the incidence of any pre-defined adverse event. Secondary endpoints included the incidence of each type of adverse event, the incidence of seizure termination, and the time to completion of drug administration in patients actively seizing at the time of study inclusion.
Results: A total of 321 doses of IV push levetiracetam were ordered for 318 patients and 250 patients were subsequently included. Fourteen (5.6%) patients experienced an adverse event, most commonly due to injection site reactions (9/14). Clinically relevant hypotension, tachycardia, and hypertension occurred in five patients. For actively seizing patients, 79% (15/19) achieved seizure termination and the median time from medication order to completion of therapy was 12 min.
Conclusion: This study found that the rapid administration of undiluted IV levetiracetam in ED patients was associated with few adverse events.

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1. Introduction

In patients who experience a seizure, the seizure duration is a strong indicator of prognosis. In status epilepticus (SE), mortality rates may reach up to 30%. Thus, reducing time to antiepileptic medications in patients who are actively seizing is critical [1]. Benzodiazepines are recommended as first line agents in SE, and additional treatments are often required [1,2].

Levetiracetam is an anticonvulsive medication commonly used for seizure prophylaxis and treatment. It is also recommended as a second line agent in SE at a dose of 60 mg/kg IV with a maximum of 4500 mg per the American Epilepsy Society Guidelines [1]. The Neurocritical Care Society recommends a dose of 1000 to 3000 mg IV for adults and 20 to 60 mg/kg IV for pediatric patients at a rate of 2 to 5 mg/kg/min [2]. Levetiracetam is associated with minimal adverse events, such as somnolence, dizziness, and behavioral abnormalities [3]. Due to its favorable safety profile and lack of required therapeutic drug monitoring, use of levetiracetam is increasing [4,5].

The package insert recommends dilution of levetiracetam with 100 mL of a compatible diluent and intravenous (IV) administration over 15 min [3]. Requirements for immediate-use compounding of sterile products limit emergency preparation of levetiracetam to a maximum of 1000 mg diluted in a single diluent bag [6]. Premixed doses up to 1500 mg are commercially available but are more costly than undiluted vials. Thus, doses of levetiracetam used for seizure or SE treatment are commonly prepared in the hospital IV room and may contribute to prolonged time to drug administration. Infusion times of 15 min also limit the ability to deliver therapeutic doses of levetiracetam quickly, which may be of particular interest when managing patients in SE.

Premarketing data suggested that the rapid administration of undiluted IV levetiracetam may cause local irritation. However, the original

* Corresponding author at: 1700 S Tamiami Trail, Sarasota, FL 34239, USA.
E-mail address: Jonathan-Summerlin@smh.com (J.A. Summerlin).

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formulation used was a 200 mg/ml unbuffered solution. Subsequently, a 100 mg/ml buffered formulation was developed and did not result in similar rates of local irritation when diluted [7]. Recent literature has evaluated the off-label usage of levetiracetam as an undiluted rapid administration to improve time to drug, decrease hospital IV room workloads, and curtail small volume fluid use [8-12]. While findings from these retrospective studies suggest that this practice may be associated with minimal adverse events, some gaps in the literature remain. Adverse events may be inherently underreported in retrospective data. Additionally, only one of these studies included doses >2000 mg, limiting the applicability of the conclusions to higher doses recommended in SE [9]. To date, there have been no prospective studies evaluating the safety of undiluted rapid administration of IV levetiracetam. The purpose of this study was to prospectively evaluate adverse events associated with rapid administration of undiluted IV levetiracetam at doses up to 4500 mg in the emergency department (ED).

2. Methods

2.1. Study design and setting

This was a prospective, observational cohort study of patients who received rapid administration of undiluted IV levetiracetam in the ED. The study institution is a 901-bed community teaching hospital with an ED census of approximately 90,000 patient visits per year. Rapid administration of undiluted levetiracetam for ED patients was approved at the institution's Pharmacy and Therapeutics Committee in August 2021 and was implemented in December 2021. The study was reviewed and granted approval by the local Institutional Review Board and informed consent was waived, as the practice of rapid administration of undiluted IV levetiracetam was established as the institution's standard of care in the ED.

2.2. Selection of participants

All patients located in the ED with an order for undiluted IV push levetiracetam were enrolled from December 2021 through October 2022. Patients were excluded if they were <18 years of age, received IV levetiracetam earlier in the same ED visit, or were transferred out of the ED prior to the collection of reassessment variables. Patients were also excluded if the research team was unable to collect baseline variables prior to levetiracetam administration or reassessment variables within 60 min of levetiracetam administration.

2.3. Interventions

Orders for undiluted IV push levetiracetam placed in the electronic health record (Sunrise™) generated an “evaluation alert” in the pharmacist order verification queue and an email to notify the emergency medicine (EM) pharmacist of the order. During the two weeks leading up to study enrollment, each EM pharmacist received training and practiced collecting preliminary data which was subsequently discarded and not included in the study. Upon order verification, the EM pharmacist reported to the bedside to collect data utilizing a standardized paper questionnaire created for the study and to assess that levetiracetam was administered properly. The baseline variables were collected within five minutes prior to drug administration. Reassessment variables were collected at a single time point between 30- and 60-min following drug administration. Baseline variables collected included age, sex, height, weight, time of levetiracetam administration, dose, IV site and gauge size, indication for levetiracetam, presence of seizure activity, blood pressure, heart rate, and Richmond Agitation Sedation Scale (RASS) score. The indication for levetiracetam and diagnosis of active seizure were determined by the bedside EM physician. Reassessment variables included blood pressure, heart rate, RASS score, whether the patient was intubated or still actively seizing, injection site reactions such as redness, swelling, pain, pruritus or burning, anaphylaxis, and bradycardia requiring intervention. If a severe adverse event, such as anaphylaxis, occurred prior to the collection of the reassessment variables, the bedside nurse was expected to report the timing of event to the research team. For patients actively seizing, the time from medication order to the completion of administration was retrospectively collected. The time of medication order was defined as either the time of medication removal from the medication dispensing cabinet or the time the order was placed in the electronic health record, whichever came first. Each dose was prepared emergently at the bedside in syringes with 500 mg/5 mL levetiracetam vials. To comply with immediate use compounding standards, a maximum of 3 vials or 1500 mg was prepared in a single syringe; each syringe was administered consecutively over 2 min. The institutional protocol allowed all doses up to 4500 mg to be administered as undiluted, IV push in the ED.

Prospective data collection occurred 24 h a day, as our institution has 24/7 EM pharmacist coverage. Upon completion of data collection, the questionnaire was transcribed by the EM pharmacist to a REDCap electronic data capture [13,14]. To eliminate the possibility of missing data, each field in REDCap required an answer prior to submission. Descriptive statistics were used to analyze data.

2.4. Outcomes

The primary endpoint was the incidence of any adverse event, defined as the composite of injection site reaction, anaphylaxis, and clinically relevant hypotension, hypertension, bradycardia, and tachycardia. Clinically relevant endpoints are defined in Table 1 and were derived by an EM physician member of the study group to capture significant and clinically impactful changes. Injection site reactions were determined by the EM pharmacist and comprised of objective endpoints such as redness and swelling, and subjective endpoints such as pain, pruritis or burning. Subjective infusion site reactions were determined via patient interview.

The Naranjo Adverse Drug Reaction Scale was used to objectively assess the likelihood of a causal relationship between adverse events and levetiracetam administration. The Naranjo Scale ranges from −4 to 13 and the adverse drug reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4 and doubtful if 0 or less [15]. Two study researchers independently assessed the electronic health record of each patient who experienced an adverse event and retrospectively assigned a Naranjo Scale score. Each score was then reviewed together by the two researchers and any difference in scoring was discussed until a consensus was reached.

Secondary endpoints included individual components of the composite primary endpoint, the incidence of seizure termination, and the time from medication order to completion of administration in patients actively seizing at the time of study inclusion. Seizure termination was determined by the bedside EM physician.

Table 1
Clinically relevant definitions.

Variable	Definition
Hypotension	Change in mean arterial pressure of ≥20% and reassessment systolic blood pressure ≤ 90 mmHg
Hypertension	Change in mean arterial pressure of ≥20% and reassessment systolic blood pressure ≥ 180 mmHg
Bradycardia	Heart rate ≤ 60 beats/min and requiring intervention (atropine, vasopressors, or pacing)
Tachycardia	Change in heart rate of ≥20% and reassessment heart rate ≥ 100 beats/min

3. Results

3.1. Characteristics of study subjects

A total of 321 doses of IV push levetiracetam were ordered for 318 patients and 250 patients were subsequently included (Fig. 1). There were 63 (25.2%) patients that received a dose of levetiracetam >2000 mg (Fig. 2). Most patients received levetiracetam through a proximal upper extremity peripheral IV site (80.8%). Additional baseline characteristics are provided in Table 2.

3.2. Main results

Fourteen (5.6%) patients experienced an adverse event, most commonly due to injection site reactions (9/14). Clinically relevant hypotension, tachycardia, and hypertension were rare and occurred in five patients (Table 3). Four (6.3%) of the 63 patients that received a dose >2000 mg experienced an adverse event. Naranjo Scale scores for adverse events are listed in Table 4. Six patients had a score of 5–8, indicating a probable adverse reaction. Three of these patients received levetiracetam through an IV site located on the wrist or hand. Seven patients had a score of 1–4, indicating a possible adverse reaction. Of the 2 possible injection site reactions, one patient had IV potassium infusing in the peripheral site and the other complained of burning at multiple peripheral IV sites. The 5 possible hemodynamic adverse reactions had disease progression or were receiving propofol as a continuous infusion upon reassessment. Nineteen patients were actively seizing at the time of drug administration and 15 (79%) patients achieved seizure termination by the time of reassessment. For actively seizing patients, the median time from medication order to completion of levetiracetam administration was 12 min and the median dose of levetiracetam administered was 3000 mg. There was no change in median baseline and reassessment RASS scores. These scores were similar for intubated and non-intubated patients.

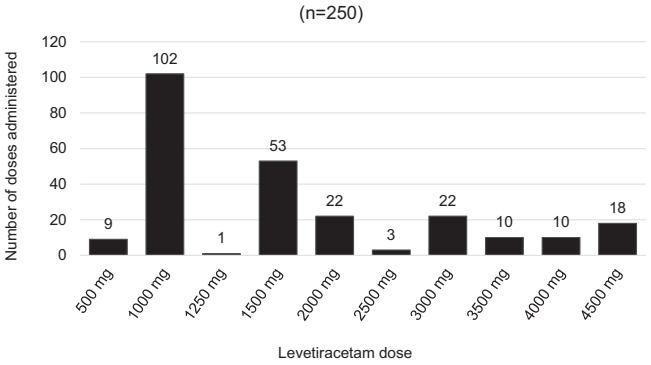

Fig. 2. Levetiracetam doses administered.

4. Discussion

Our study found that the rapid administration of undiluted IV levetiracetam was associated with a low incidence of adverse events, which primarily consisted of injection site reactions. To our knowledge, this is the first prospective study evaluating the safety of rapid administration of undiluted IV levetiracetam. Our results support findings from previous literature which suggest this is a safe practice; however, a higher incidence of adverse events than previously reported in retrospective studies was observed in our study [8-12]. Haller et al. reported

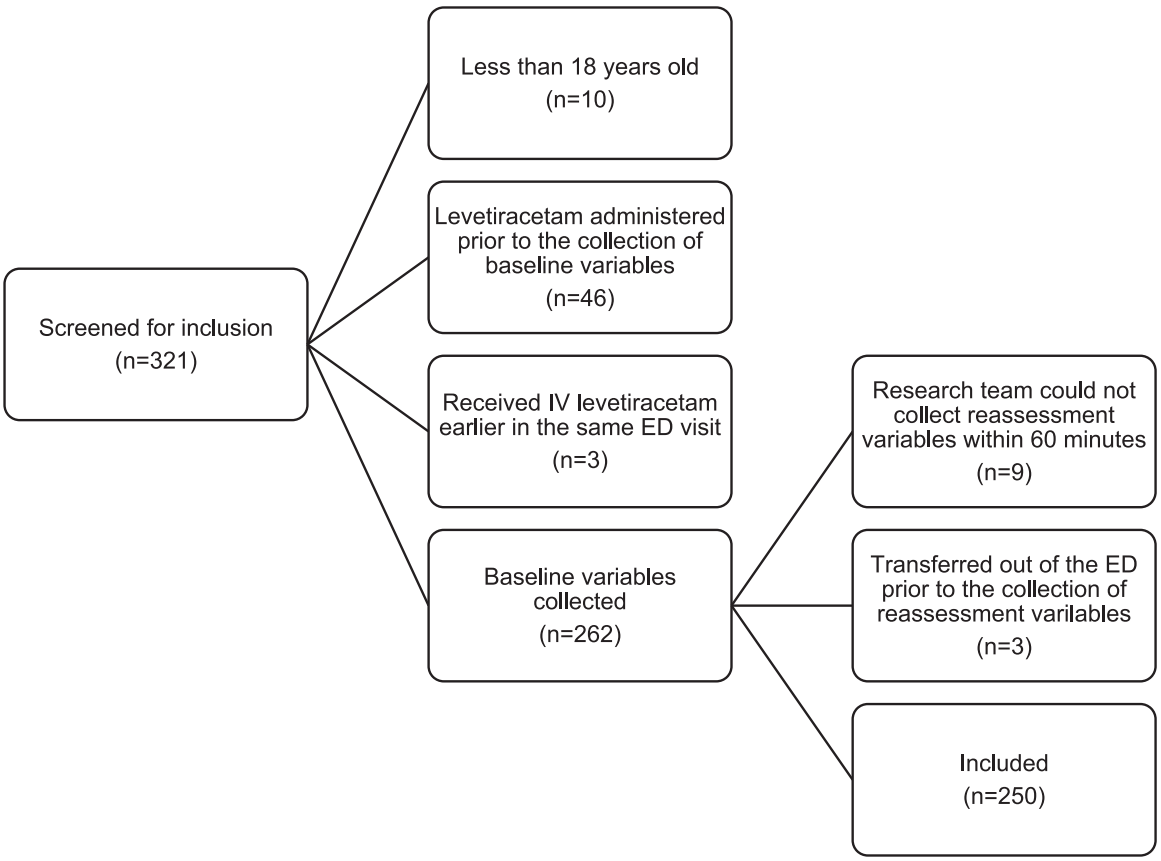

Fig. 1. Enrollment flow diagram.

Table 2
Baseline characteristics.

Variable	Value, $n = 250$
Age (years), mean (SD)	55 (19)
Female, No. (%)	124 (50)
Weight (kg), median [IQR]	74.5 [64–91]
Indication, No. (%)	
Witnessed or suspected seizure (non-status epilepticus)	177 (70.8)
Status epilepticus	33 (13.2)
Continuation of home medication	3 (1.2)
Seizure prophylaxis	37 (14.8)
Actively seizing at the time of levetiracetam administration, No. (%)	19 (7.6)
IV Access, No. (%)	
Peripheral - proximal upper extremity	202 (80.8)
Peripheral - wrist/hand	43 (17.2)
Central	5 (2)
Peripheral IV-gauge size, No. (%)[a]	
18 G	113 (46.1)
20 G	128 (52.2)
22 G	4 (1.6)
Intubated prior to levetiracetam administration	46 (18.4)

SD: standard deviation; IQR: interquartile range.
[a] $n = 245$.

Table 3
Outcomes.

Variable	Value, n = 250
Adverse event, No. (%)	14 (5.6)
Injection site reaction	9
Anaphylaxis	0
Hypotension	2
Hypertension	1
Bradycardia	0
Tachycardia	2
Seizure termination upon reassessment, No. (%)[ab]	15 (79)
Time from medication order to completion of administration (minutes), median [IQR][a]	12 [8–15]

IQR: interquartile range.
[a] n = 19, [b]Unable to determine seizure termination in 3 cases.

injection site reactions in 0.4% of patients who were administered undiluted levetiracetam, at doses up to 4500 mg over five minutes, compared to our 3.6% incidence rate [9]. Other studies had no findings of injection site reactions with administration of doses up to 2000 mg over two to five minutes [8,10-12]. Retrospective abstraction of data in these studies may have contributed to the differences in our findings.

Morgan et al. reported that 1.5% of patients experienced behavioral related adverse events and this was identified by searching for the term "agitation" in the electronic health record [8]. Our study did not include behavioral adverse events in our composite primary endpoint due to difficultly in objective assessment in patients actively seizing, postictal, or in those that had received benzodiazepines prior to the administration of levetiracetam. As a surrogate for behavior assessment, we collected RASS scores, and these were found to be similar upon collection of baseline and reassessment variables.

We included hemodynamic variables in our composite primary endpoint due to the association between sodium acetate, a buffering agent in levetiracetam injectable solution, and hypotension [16]. Findings from a recent retrospective study suggested that undiluted IV push levetiracetam was associated with a 12% incidence of hypotension or bradycardia [12]. These outcomes occurred less frequently in our study. However, variations in our outcome definitions may explain these differences.

Adverse events occurred at a rate of 6.3% in patients who received doses >2000 mg compared to 4.3% for doses 2000 mg or less. While numerically higher, this is unlikely to be clinically significant. Of the six patients who had a Naranjo Scale score of 5–8, indicating a probable adverse event, only one patient received a dose >2000 mg. Previous literature reported 40 total doses >2000 mg but did not delineate the rate of adverse events in this cohort compared to lower doses [9]. To date, our study contains the largest cohort of patients who received doses >2000 mg, adding to the body of literature supporting this practice in all recommended doses.

Additionally, there were no differences in probable adverse events when comparing patients that were administered IV levetiracetam through an 18-gauge and a 20-guage peripheral IV site. Peripheral administration utilizing other IV-gauge sizes and central administration of the drug were minimal and could not be adequately assessed. Adverse events occurred at a rate of 7% for patients administered levetiracetam through a peripheral IV site located on the wrist or hand compared to 1.5% for patients with a proximal upper extremity IV site. Based on these results, a proximal upper extremity IV site may be preferred over the wrist or hand to administer undiluted levetiracetam.

Approximately three quarters of the patients actively seizing during levetiracetam administration achieved seizure termination upon reassessment. These patients received the entirety of the levetiracetam dose in a median time of <15 min from medication order. The ESETT trial reported seizure termination in 47% of patients following levetiracetam administration over 10 min [17]. Their inclusion criteria required a diagnosis of status epilepticus, whereas our study did not. Additionally, their definition of seizure termination included improved responsive-

Table 4
Naranjo Scale scores for adverse drug reactions.

Adverse event	Dose (mg)	IV site	IV-gauge size	Naranjo scale score
Probable adverse drug reaction				
Injection site reaction	4500	Wrist/hand	20	6
Injection site reaction	1500	Wrist/hand	18	6
Injection site reaction	1000	Wrist/hand	20	6
Injection site reaction	500	Proximal upper extremity	20	6
Injection site reaction	1500	Proximal upper extremity	18	5
Injection site reaction	1500	Proximal upper extremity	20	5
Possible adverse drug reaction				
Injection site reaction	1500	Proximal upper extremity	20	3
Injection site reaction	1500	Proximal upper extremity	20	2
Hypotension	3000	Proximal upper extremity	20	2
Hypotension	1000	Proximal upper extremity	18	2
Tachycardia	4000	Proximal upper extremity	18	2
Tachycardia	3000	Central line	N/A	2
Hypertension	1000	Wrist/hand	20	2
Doubtful adverse drug reaction				
Injection site reaction	1500	Proximal upper extremity	20	−1

ness at 60 min without the need for additional anticonvulsants. In our study, seizure termination was assessed 30–60 min following administration, did not require improved responsiveness, and did not consider if the patient received additional anticonvulsants. These findings warrant further investigation to determine if a quicker administration time of levetiracetam is associated with higher incidences of seizure termination.

5. Limitations

This study has several limitations which warrant discussion. First, the reassessment time frame of between 30 and 60 min may have missed vital sign deviations that occurred shortly after administration and did not persist to the time of reassessment. Multiple reassessment time points would have been ideal; however, this was not feasible in the workflow of the EM pharmacists who collected the data. Additionally, confounding factors, such as other drugs administered, recurrent seizures, or intubation, may have contributed to reported adverse events. A Naranjo Scale score was calculated for each adverse drug reaction to account for this limitation. Forty-eight patients were intubated, and one additional patient was actively seizing upon collection of reassessment variables. These patients were unable to self-report injection site reactions such as pain, pruritus, or burning. The IV site, however, was still assessed for redness and swelling. Finally, seizure termination was determined based on physician assessment which may have relied on visible termination of a tonic-clonic seizure, rather than evaluation via an electroencephalogram. This may have resulted in a falsely elevated incidence rate of seizure termination.

6. Conclusion

This study found that the rapid administration of undiluted IV levetiracetam in ED patients was associated with few adverse events. Adverse events were seen at a variety of doses, suggesting larger doses of levetiracetam may not pose additional risk when given as undiluted IV push.

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Meetings

Study design and results were presented in poster format at the Florida Society of Health System Pharmacists 56th Annual Meeting in Orlando, Florida on August 6th, 2022.

CRediT authorship contribution statement

Jonathan A. Summerlin: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nicholas Scaturo:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Jeremy A. Lund:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Kellie M. Wang:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Marshall A. Frank:** Writing – review & editing, Methodology, Conceptualization.

Declaration of Competing Interest

Authors of this study have no conflicts of interest to report.

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