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Safety of intravenous lacosamide in critically ill children

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ABSTRACT

Purpose: Acute seizures are common in critically ill children. These patients would benefit from intravenous anti-seizure medications with few adverse effects. We reviewed the usage and effects of intravenous lacosamide in critically ill children with seizures or status epilepticus.
Methods: This retrospective series included consecutive patients who received at least one dose of intravenous lacosamide from April 2011 to February 2016 in the pediatric intensive care unit of a quaternary care children's hospital, including patients with new lacosamide initiation and continuation of outpatient oral lacosamide. Dosing and prescribing practices were reviewed. Adverse effects were defined by predefined criteria, and most were evaluated during the full admission.
Results: We identified 51 intensive care unit admissions (47 unique patients) with intravenous lacosamide administration. Lacosamide was utilized as a third or fourth-line anti-seizure medication for acute seizures or status epilepticus in the lacosamide-naïve cohort. One patient experienced bradycardia and one patient experienced a rash that were considered potentially related to lacosamide. No other adverse effects were identified, including no evidence of PR interval prolongation.
Conclusions: Lacosamide was well tolerated in critically ill children. Further study is warranted to evaluate the effectiveness of earlier lacosamide use for pediatric status epilepticus and acute seizures.

1. Introduction

Seizures are the most common reason for neurology consultation in the pediatric intensive care unit (PICU) [1,2]. Additionally, with increasing use of continuous electroencephalographic (EEG) monitoring in critically ill children with acute encephalopathy [3,4], electrographic seizures are often identified [5,6]. Since electrographic seizures are associated with unfavorable neurobehavioral outcomes [5–8], most physicians aim to terminate them by administering anti-seizure medications [9,10]. However, few data are available to guide evidence-based seizure management in critically ill children, particularly for seizures that are refractory to initial medications [10,11]. Critically ill children often have multisystem organ dysfunction and receive numerous medications. Thus, these patients would therefore benefit from intravenous anti-seizure medication options with few adverse effects or drug-drug interactions, leading to increasing use of newer anti-seizure medications such as lacosamide. Lacosamide has a novel mechanism of action involving augmentation of slow inactivation of voltage-gated sodium channels. Lacosamide was introduced in 2008 for epilepsy management in adults and is still not approved in children, although it is used for pediatric epilepsy management [12].While case series have described lacosamide as safe and sometimes effective in terminating or reducing seizures and status epilepticus in critically ill adults [13–28] only very limited data are available regarding the use of lacosamide for seizures and status epilepticus in critically ill children [29–31]. We aimed to evaluate the safety of intravenous lacosamide in critically ill children with seizures and status epilepticus.

2. Methods

We performed a single-center retrospective study of consecutive patients admitted to the PICU from April 2011 until February 2016 who received at least one dose of intravenous lacosamide. Lacosamide was introduced in the United States in 2008 for epilepsy management in adults, but we selected a start date after electronic medical record implementation at our site to ensure we could identify and collect data on consecutive patients. The study was approved by the institutional review board, and consent was not required since it was a retrospective study.

Data were abstracted from the electronic medical record and entered directly into the Research Electronic Data Capture

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(REDCap) system [32]. Two members of the study team reviewed patient demographics, prior medical history, pre-admission diagnoses, primary and additional problems at admission, functional scores at admission and hospital discharge, pre-admission medications, lacosamide data, specific predefined adverse events, in-hospital mortality, and EEG data. Lacosamide data included the use of lacosamide prior to admission, timing of administration relative to other anti-seizure medications, loading dose, whether maintenance dosing was initiated, the maximum total daily dose, whether the patient was discharged from the hospital on lacosamide, and the reasons for lacosamide discontinuation. We evaluated for predefined adverse events by reviewing all physician notes, nursing notes, vital sign documentation, laboratory tests, and electrocardiogram (ECG) results. Adverse event categories included cardiopulmonary events, laboratory abnormalities, and other adverse events. EEG data included the EEG background at the time of lacosamide administration, presence or absence of seizures, seizure characteristics prior to and after lacosamide administration, and the impact of lacosamide on seizures. Seizure improvement was defined as comments in progress notes or EEG reports that lacosamide had improved, reduced, or terminated seizures. The Pediatric Cerebral Performance Category (PCPC) score, a validated six-point scale categorizing degrees of functional impairment, was used to estimate pre-admission and discharge function. PCPC categories are (1) normal, (2) mild disability, (3) moderate disability, (4) severe disability, (5) coma and vegetative state, and (6) death [33,34].

Descriptive statistics are presented including means (standard deviation) and medians (interquartile ranges, IQR). Two subgroups were delineated for analysis: (1) patients who had not received lacosamide prior to PICU admission, and (2) patients who were receiving oral lacosamide prior to PICU admission.

Table 1
Patient Characteristics.

Variable	Full Cohort (N = 51) N (%)	Lacosamide initiated during PICU admission (N = 29) N (%)	Taking lacosamide prior to PICU admission (N = 22) N (%)
Age on admission (years)			
0–4	22 (43%)	14 (48%)	8 (36%)
4–12	17 (33%)	8 (28%)	9 (41%)
>12	12 (24%)	7 (24%)	5 (23%)
Gender Male	33 (65%)	17 (59%)	16 (73%)
Weight (kg)			
<5	1 (2%)	1 (3%)	0 (0%)
5–10	11 (22%)	7 (25%)	4 (18%)
10.1–40	26 (50%)	13 (45%)	13 (59%)
>40	13 (26%)	8 (27%)	5 (23%)
Neurodevelopmental problems prior to admission	34 (67%)	13 (45%)	21 (95%)
Diagnosis of epilepsy prior to admission	32 (63%)	12 (41%)	22 (100%)
Admitted to PICU on hospital day 1	44 (86%)	27 (93%)	18 (82%)
Admission PCPC score			
1 (Normal)	12 (23%)	12 (41%)	0 (0%)
2 (Mild Disability)	5 (10%)	2 (7%)	3 (14%)
3 (Moderate Disability)	9 (17%)	2 (7%)	7 (32%)
4 (Severe Disability)	22 (44%)	11 (38%)	11 (50%)
5 (Coma or Vegetative State)	3 (6%)	2 (7%)	1 (5%)
Discharge PCPC score			
1 (Normal)	0 (0%)	0 (0%)	0 (0%)
2 (Mild Disability)	6 (12%)	4 (14%)	2 (9%)
3 (Moderate Disability)	9 (18%)	2 (7%)	7 (32%)
4 (Severe Disability)	24 (47%)	15 (52%)	9 (41%)
5 (Coma or Vegetative State)	1 (2%)	1 (3%)	0 (0%)
6 (Death)	11 (22%)	7 (24%)	4 (18%)
Seizures (clinical and/or EEG) ongoing at Lacosamide Administration	37 (73%)	26 (90%)	11 (50%)
Seizure Characteristics at Lacosamide AdministrationClinical Correlate			
Unknown	4 (11%)	0 (0%)	4 (36%)
All Clinical	5 (14%)	3 (12%)	2 (18%)
EEG-Only	13 (35%)	13 (50%)	0 (0%)
Clinical and EEG-Only	15 (41%)	10 (38%)	5 (45%)
Seizure Type			
Unknown	4 (11%)	0 (0%)	4 (36%)
Independent Recurrent Seizures	15 (41%)	11 (41%)	4 (36%)
Continuous Seizure	9 (24%)	8 (31%)	1 (9%)
Ictal-Interictal Continuum	9 (24%)	7 (27%)	2 (18%)
EEG Category at Lacosamide Administration (N = 38 with EEG data available)			
Ongoing status epilepticus	16 (42%)	15 (54%)	1 (10%)
Slow-Disorganized	15 (39%)	11 (39%)	4 (40%)
Discontinuous	2 (5%)	1 (4%)	1 (10%)
Attenuated	2 (5%)	0 (0%)	2 (20%)
Epileptic Encephalopathy	3 (8%)	1 (4%)	2 (20%)
Seizures Improvement after Lacosamide Initiation among Patients Experiencing Seizures at Time of Administration (N = 37)	7 (19%)	4 (15%)	3 (27%)

EEG, electroencephalogram; PCPC, Pediatric Cerebral Performance Category; PICU, pediatric intensive care unit.