Journal of Medical Toxicology (2019) 15:271–275
https://doi.org/10.1007/s13181-019-00717-y

ORIGINAL ARTICLE

Lacosamide: a Study of Exposures Reported to US Poison Centers over a 9-Year Period

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Received: 14 February 2019 / Revised: 6 June 2019 / Accepted: 10 June 2019 / Published online: 8 July 2019

Abstract

Background Lacosamide (Vimpat®) is an anticonvulsant used to treat partial-onset seizures. Little is known about the characteristics and outcomes of patients exposed to lacosamide.

Objective To characterize lacosamide exposures reported to US poison centers with regard to patient demographics, clinical effects, and outcomes.

Methods This retrospective observational study queried the National Poison Data System (NPDS) for single substance lacosamide exposures from January 2008 to December 2016. Variables of interest included age, gender, medical outcome, management site, level of healthcare facility, reason for exposure, and clinical effects.

Results Lacosamide exposures were identified in 1124 patients, ranging from ages 2 months to 99 years. Six hundred and twenty-two patients (55.3%) were female. Nine hundred and seventy-six patients (86.8%) had minimal or no toxic effects. Life-threatening exposures numbered 30 cases (2.7%). There was one death. Five hundred and forty-eight patients (48.8%) did not require healthcare management while 537 (47.7%) were either referred to or already at a hospital. Among those treated at a healthcare facility, 269 (50.1%) did not require admission. Thirty-three patients (6.1%) were admitted to a psychiatric facility, 68 (12.7%) to a non-critical care unit, and 93 (17.3%) to a critical care unit. Six hundred and thirty-two exposures (56.2%) were due to therapeutic error. Suicide attempts numbered 168 (14.9%). Neurologic, gastrointestinal, and cardiovascular symptoms were commonly encountered.

Conclusion Lacosamide exposures infrequently cause death or disability; however, a considerable proportion of the study population required intensive care. Exposed patients with symptoms require healthcare evaluation.

Keywords Lacosamide · National Poison Data System · Overdose · Vimpat

Introduction

Lacosamide (*R*-2-acetamido-*N*-benzyl-3-methoxypropionamide) is an anticonvulsant used to treat partial seizures [1]. Though the exact mechanism is unknown, binding studies have revealed that lacosamide produces slow inactivation of voltage-gated sodium channels. [2] Its side effects include blurred vision, dizziness, nausea/vomiting, and headache. Lacosamide is reported to have cardiotoxicity including atrioventricular blockade, PR prolongation, atrial flutter, atrial fibrillation, sinus pauses, ventricular tachycardia, and cardiac arrests [2–9]. The objective of this study is to evaluate exposures to lacosamide as reported to US poison centers with regard to patient demographics, clinical effects, and outcomes.

Materials and Methods

We performed a retrospective observational study of all exposures to lacosamide reported to the National Poison Data System (NPDS) for a 9-year period. Inclusion criteria included

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ingestion of lacosamide in humans and the exposure was within the timeframe of January 1, 2008, and December 31, 2016. Exclusions included multiple substance exposure.

Data was provided by NPDS in a password-protected electronic spreadsheet (Microsoft Excel; Microsoft Corporation, Redmond WA, 2007). Excel was used to collect and organize the data and to determine mean age, median age, and age range. Other data points examined included gender, reason for exposure, clinical effects, management site, level of healthcare facility, treatments provided, and medical outcome. The overall purpose of the analysis was to organize these data points and identify trends with regard to patient demographics, clinical effects, and patient outcomes. Descriptive statistics were used. Specific dosages ingested were not available in most cases.

Calls reported to US poison centers are handled by specialists in poison information who are nurses, physicians, physician assistants, or pharmacists [10]. All cases are documented in a standardized electronic data collection format that is maintained by the American Association of Poison Control Centers [10, 11]. The NPDS database of calls from all US poison centers is updated in real time [12]. In 2016, human exposures added to the databases numbered 2,159,032. It now contains data on over 66 million human exposures collected since 1985. All data is published annually in December by the American Association of Poison Control Centers [10]. This study was approved by the Concordia University Wisconsin institutional review board. All data was de-identified.

Definitions for reason for exposure, clinical effects, and medical outcome categories are standards used by all poison centers who submitted data to the NPDS [10, 11]. Dose ingested was obtained by patient history and electronic medical record documentation. Individual notes from the medical record were not available for review.

The American Association of Poison Control Centers (AAPCC) maintains the national database of information logged by the country's poison control centers [10, 11]. Case records in this database are from self-reported calls. They reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, inhalation, or topical exposure) or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to verify the accuracy of every report made to member centers. Additional exposures may go unreported to poison centers, and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance [10].

Table 1 Demographics of patients meeting inclusion criteria

Demographics	
Total number of patients	1124
Males	500 (44.5%)
Females	622 (55.3%)
Unknown gender	2 (0.2%)
Pediatric patients (< 18 years)	443 (39.4%)
Mean age	30 years
Median age	26 years
Age range	2 months–99 years

Table 2 Breakdown of management sites

Management site	
On site	548 (48.8%)
At or en route to HFC	422 (37.5%)
Poison center referred patient to HFC	115 (10.2%)
Other	26 (2.3%)
Unknown	13 (1.2%)

On site: non-healthcare facility such as at home or at school
HCF healthcare facility

Results

The database search returned records of 1124 patients, all of which met inclusion criteria. The ages of patients ranged from 2 months to 99 years (mean = 30 years, median = 26 years, standard deviation = 22 years), and 622 were females while 500 were male (55.3% and 44.5%, respectively; 2 patients of unknown gender). Pediatric patients defined as less than age 18 accounted for 39.4% of the exposures (see Table 1).

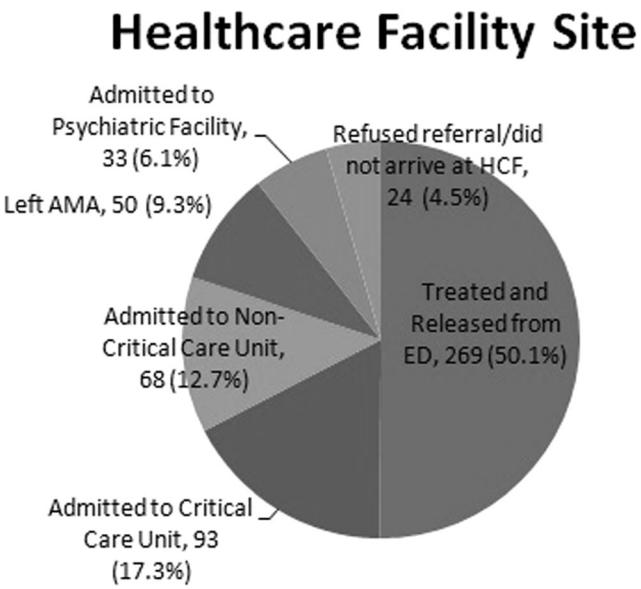

Fig. 1 Breakdown of healthcare facility site where treatment took place. AMA against medical advice, ED emergency department, HCF healthcare facility

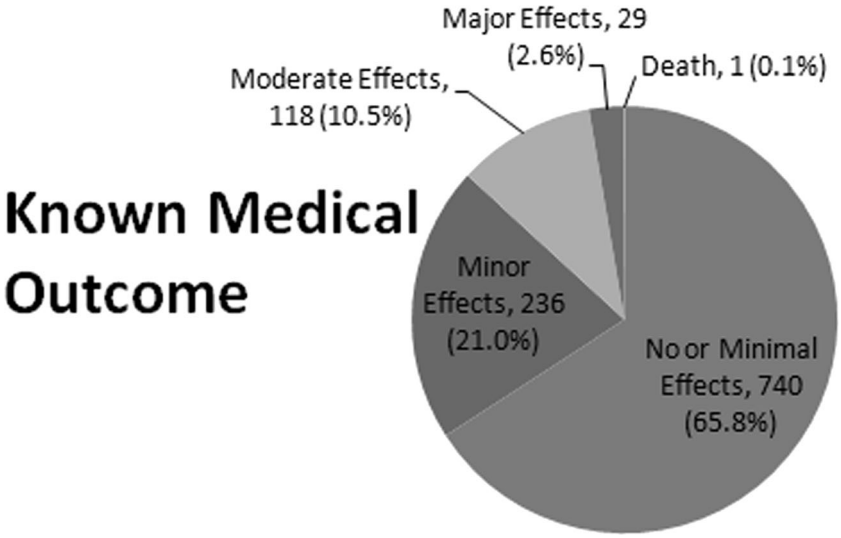

Fig. 2 Breakdown of healthcare facility site where treatment took place

Of all exposures to lacosamide, 837 (84.5%) of them were unintentional, and 632 (56.2%) were noted to be therapeutic errors. Two hundred and twenty-two of the exposures (20%) were intentional, 168 (14.9%) were suicide attempts, and 67 (5.9%) of the exposures were either labeled as for an unknown reason or labeled as an "other" exposure.

Five hundred and forty-eight patients (48.8%) were managed outside of a healthcare facility such as at home. Five hundred and thirty-seven patients (47.7%) were managed at a healthcare facility while the remaining 39 patients did not have a listed treatment location. Among those patients treated at a healthcare facility, 269 (50.1%) were treated and released from the emergency department, 93 (17.3%) were admitted to a critical care unit, 68 (12.7%) were admitted to a non-critical care unit, 33 (6.1%) were admitted to a psychiatric care facility, and 74 (13.8%) either did not follow up as prescribed, left against medical advice, or refused transfer to a healthcare facility (see Table 2 and Fig. 1).

Nine hundred seventy-six patients (87%) had no symptoms or had minor effects, defined as symptoms which are minimally bothersome and resolved rapidly [11]. Moderate effects, which are defined as more pronounced and prolonged than minor effects without being life-threatening or causing disability, occurred in 118 (10.5%) patients [11]. Major clinical effects, which are life-threatening, occurred in 29 (2.5%) patients, and one patient died (see Fig. 2). [11]

The primary clinical signs and symptoms experienced by patients were gastrointestinal and neurological. The most commonly experienced symptoms among patients ages 17 years and younger were drowsiness (53), nausea or vomiting (46), dizziness or vertigo (13), agitation (8), ataxia (7), cardiac conduction disturbance (5), coma (4), confusion (4), headache (4), and slurred speech (1). The most common clinical effects among patients greater than age 17 years were similar including nausea or vomiting (167), drowsiness (149), dizziness or vertigo (121), ataxia (44), agitation (40), cardiac conduction disturbance (37), headache (33), slurred speech (31), and confusion (30) (see Table 3).

Multiple treatments were noted, most commonly intravenous fluids for 134 patients (12%), supportive oxygen therapy for 50 patients (4.4%), benzodiazepines for 44 patients (3.9%), activated charcoal for 43 patients (3.8%), and antiemetics for 41 patients (3.6%). Forty patients were intubated (3.5%), 8 patients required vasopressors (0.7%), and 5 patients required hemodialysis (0.4%).

Discussion

Although its exact mechanism is not known, lacosamide is thought to act by enhancing slow inactivation of voltage-gated sodium channels [13, 14]. Oral formulations are absorbed between 1 and 4 h. Hepatic CYP2C19 metabolizes lacosamide to an inactive form, O-desmetyl-lacosamide [15].

Table 3 Clinical signs and symptoms broken down by age group

Clinical sign/symptom	Total patients	0–17 years	> 17 years
Drowsiness	202	53 (26%)	149 (74%)
Nausea or vomiting	213	46 (22%)	167 (78%)
Agitation	48	8 (17%)	40 (83%)
Ataxia	51	7 (14%)	44 (86%)
Coma	4	4 (100%)	0
Dizziness/vertigo	134	13 (10%)	121 (90%)
Conduction disturbance	42	5 (12%)	37 (88%)
Confusion	34	4 (12%)	30 (88%)
Headache	37	4 (11%)	33 (89%)
Slurred speech	32	1 (3%)	31 (97%)

The molecule's half-life is 13 h and elimination is primarily renal [2].

The data presented here demonstrates that exposures to lacosamide rarely develop symptoms of any consequence, but those that do, although few, often required healthcare facility treatment. Among patients who were admitted, 17.3% required critical care admission. Most clinical effects described were minor and included gastrointestinal and neurological symptoms; however, the more critically ill patients in this study population had cardiac conduction disturbances and respiratory failure, required intubation, and had depressed mental status.

In the event that a lacosamide exposure produces life-threatening toxicity, the primary systems of concern are cardiovascular, gastrointestinal, and neurological. With regard to cardiovascular toxicity of lacosamide, there are case reports of fatal lacosamide-related cardiovascular effects. One case demonstrated an initial junctional rhythm, bi-bundle branch block, and wide QRS corrected with hypertonic sodium bicarbonate infusion. [7] This suggests that cardiac arrhythmias in lacosamide exposure may be related to its sodium channel blockade. This is important for providers to keep in mind especially in multi-drug overdoses. Many antiepileptic medications cause sodium channel blockade, and there is no data characterizing the additive effects of these drugs on sodium channel blockade when in combination [7]. In addition there are case reports showing symptomatic bradycardia, syncope, atrial fibrillation, and ventricular arrhythmias [3, 5, 6, 8, 15, 16]. In this study, 37 adult and 5 pediatric patients were reported to have conduction disturbances. No studies have been published that provide a direct mechanistic description of cardiac toxicity of lacosamide.

Limitations

There are several limitations to this study. This study is retrospective which limits the ability to control for confounding factors. The data is self-reported to national poison centers, and therefore it is a reflection only of that information provided by the public or by healthcare professionals. Confirmatory testing was not done to verify exposures. The data presented represents all exposures, but not necessarily overdoses. Underreporting is a limitation of poison center studies. In addition, because this is a voluntary reporting system, there are several inherent biases. Selection bias likely occurred as low-dose exposures may have been judged as minimally concerning and without need to report especially if the patient was asymptomatic. Many elements of the case histories and presentations may be incomplete or inaccurate.

Conclusion

Exposures to lacosamide rarely cause death or disability. There is a low occurrence of moderate and major effects. A short monitoring period and supportive care may be all that is needed, but morbidity is a possibility in few cases due to agitation, sedation, gastrointestinal symptoms, and cardiac conduction disturbances. Patients who present with lacosamide exposures who have symptoms likely require evaluation in a healthcare facility, but the overall morbidity and mortality from lacosamide is low.

Source of Funding None.

Compliance with Ethical Standards

This study was approved by the Concordia University Wisconsin institutional review board.

Conflict of Interest None.

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