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Review

Efficacy of lacosamide in children and adolescents with drug-resistant epilepsy and refractory status epilepticus: A systematic review

Johann Sebastián Ortiz de la Rosa[a,*], Lady Diana Ladino[b], Paula Juliana Rodríguez[a], María Camila Rueda[a], Juan Pablo Polanía[a], Angie Catalina Castañeda[c]

[a] Universidad Nacional de Colombia, Bogotá DC, Colombia
[b] Epilepsy Program Hospital Pablo Tobón Uribe, University of Antioquia, Neuroclinica, Medellín, Colombia
[c] Universidad de la Sabana, Bogotá DC, Colombia

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ABSTRACT

Purpose: Lacosamide, is one of the newer antiepileptic drug approved for focal drug-resistant epilepsy as an add-on treatment in patients older than 16 years. However, there is growing evidence of its use, safety and efficacy in children. We aim to evaluate efficacy and tolerability of lacosamide in focal and generalized drug-resistant epilepsy and refractory status epilepticus in the pediatric population.
Methods: We conducted a systematic review on MEDLINE, EMBASE, COCHRANE, Google Scholar and Scielo from January 2008 to January 2017. The primary outcome was the efficacy of lacosamide in children with drug-resistant epilepsy and refractory status epilepticus. Efficacy and adverse events attributed to lacosamide were extracted from each publication and systematically reported. We performed no meta-analyses due to limited available data.
Results: Of 175 abstracts identified by the search, 82 were reviewed as full-text. Twenty-six articles fulfilled eligibility criteria and described outcomes in 797 patients (57% male). The majority of studies were retrospective (69%) small series (84%). On average 51% of patients had 50% or greater seizure reduction. The mean seizure freedom rate was 24%. Adverse effects occurred in 18–59% of patients. The main events were dizziness, sedation, gastrointestinal upset, mood and behavioral changes. Half of the patients with Lennox Gastaut syndrome showed 50% or greater seizure reduction, 32% did not response to lacosamide and 17% suffered seizure aggravation.
Conclusion: Current evidence shows lacosamide as a good option in pediatric patients with focal drug-resistant epilepsy and refractory status epilepticus as an add-on therapy given its efficacy on seizure control and safety profile. The use of lacosamide in Lennox-Gastaut syndrome shows conflicting data. Large randomized controlled studies in the pediatric population are necessary to substantiate these findings.

1. Introduction

Epilepsy is one of the most common neurological disorders, with an estimated annual incidence of 50/100.000 population and a prevalence of 700/100.000 population [1]. Some researchers suggest that 60% of patients might respond to standard medical treatment and achieve remission, however, 30–40% of patients will be refractory to current anti-epileptic drugs (AEDs) [2]. Those patients who failed to respond to at least two properly indicated and tolerated AEDs are referred as drug-resistant [3].

Newer AEDs have novel mechanisms of action designed to decrease drug–drug interactions and achieve seizure freedom [2]. Lacosamide is one of the newest medications and exhibits its function through selectively enhancing slow inactivation of voltage-gated sodium channels, without affecting fast inactivation; decreasing in this way pathologic neuronal hyperexcitability without affecting the physiological neuronal function [4]. Simultaneously, it seems that the drug binds to the collapsin response mediator protein 2, which partakes in a neurotrophic signal transduction. This is hypothesized to produce a neuroprotective effect preventing the formation of abnormal neuronal connections in the brain [5].

Currently, lacosamide is approved by the Food and Drug Administration to be used in patients older than 16 years [2,4]. Yet there is growing evidence suggesting that lacosamide is safe, well

* Corresponding author at: Universidad Nacional de Colombia, Carrera 45 # 26-85, Bogotá D.C, Colombia.
E-mail address: jsortizd@unal.edu.co (J.S. Ortiz de la Rosa).

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tolerated and effective in the pediatric population. In this study, we aim to evaluate the evidence regarding lacosamide use in drug-resistant epilepsy (DRE) and refractory status epilepticus (RSE) in children and adolescents.

2. Methods

2.1. Search methods

We performed a systematic review of the evidence on efficacy, safety and tolerability of lacosamide in pediatric epilepsy population. Three authors (JSO, PJR, and MCR) independently performed a literature search on MEDLINE, EMBASE, COCHRANE, Google Scholar and Scielo databases for articles published from January 2008 to January 2017. We used the following keywords: Lacosamide, "Vimpat", children, infants, child, childhood, focal epilepsy, generalized epilepsy, drug-resistant epilepsy, refractory epilepsy, Lennox Gastaut Syndrome, continuous spike and waves during slow sleep, and status epilepticus. We also searched bibliographies of pertinent reviews and relevant conference proceedings in order to find additional documents. When necessary we contacted study authors by e-mail. Additional studies were sought by searching the Internet for ongoing trials registers with preliminary published results (clinicaltrials.gov).

2.2. Type of studies

Original retrospective and prospective cohorts, series and case reports assessing the efficacy of lacosamide in patients <21 years of age were included, regardless of language or country of publication. For studies with multiple publications, all versions of the study were reviewed to ensure complete access to maximal trial data. Brief abstracts; mixed population cohorts (children and adults) not providing separate data on the pediatric participants, as well as repeated published populations were excluded. Full texts of all remaining articles were reviewed.

2.3. Data collection

Two authors (JSO, LDL) extracted relevant data and evaluated the methodological quality of documents. The following variables and outcomes were assessed: study design, number of patients, type of epilepsy, 50% or greater seizure reduction, seizure freedom, status epilepticus (SE) cessation, adverse effects, seizure aggravation, lacosamide dosing regimen, and time of follow-up. Using a standardized form data were systematically reported. Discrepancies were solved by consensus. Included studies were ranked on the basis of the quality of therapeutic evidence according to the American Academy of Neurology Classification of Evidence [6].

2.4. Statistical analysis

Categorical data were expressed as percentages and quantitative data as mean, standard deviation, and range. A weighted average calculator computed average of seizure cessation and seizure reduction. Categorical variables were analyzed using 2×2 contingency table using Fisher exact test. All statistical analyses were performed with SPSS statistical software package (SPSS for Mac, v.21, SPSS, Inc., Chicago, IL).

3. Results

Of 175 abstracts identified by the search, 82 were reviewed as full-text. Twenty-six articles fulfilled eligibility criteria and described outcomes in 797 patients (57% male) (Fig. 1). Majority of patients had focal epilepsy (75%), 20% had generalized epilepsy, and 5% of the population was on SE. Age ranged between 4 weeks and 21 years, but the majority of patients were 16 years old or younger (92%). All children or adolescents included in the study had DRE. All patients had failed at least to two AED trials and some had also trailed ketogenic diet, vagal nerve stimulation or epilepsy surgery.

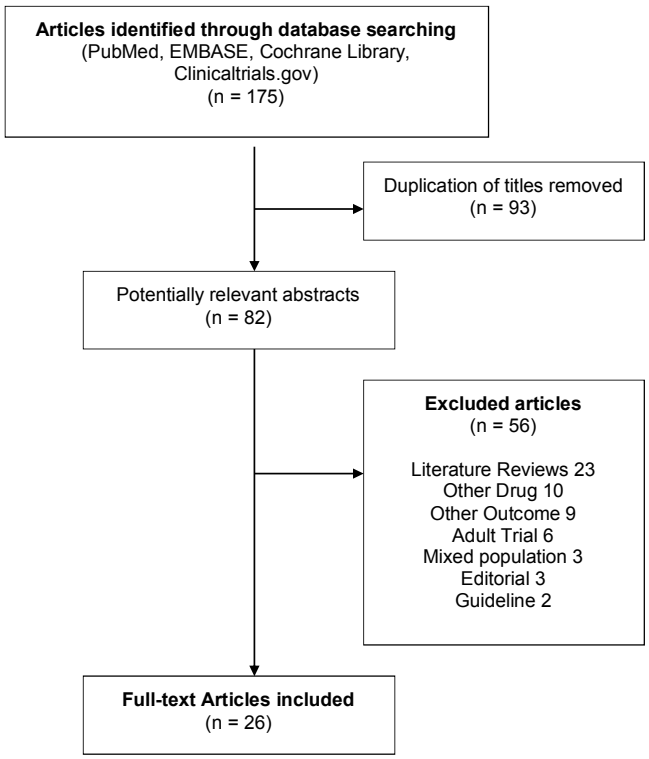

Fig. 1. Flowchart of the literature search and study inclusion.

3.1. Drug-resistant epilepsy

Seven hundred fifty-seven (57% male) patients had DRE. Seventy-nine percent had focal epilepsy and 21% generalized epilepsy. Forty cases had Lennox Gastaut Syndrome (LGS) and eight cases had continuous spike and waves during slow sleep (CSWS) syndrome. Lacosamide was administered orally in the form of syrup or tablets twice daily in all patients. Children were generally started on a low dose and titrated up weekly. The mean maintenance dose was 7.2 mg/kg/day (range 1–20 mg/kg/day).

Seizure frequency during 1–3 months preceding the drug initiation was used as baseline to calculate the seizure frequency reduction rate. Results were highly heterogeneous. Overall, mean follow-up was 10.23 (1–53) months, 50.07% of patients had ≥50% reduction in seizure frequency, and 23.62% of patients were seizure free. Rastogi et al. found a significant difference between generalized and focal epilepsy groups, in their cohort lacosamide was effective in treating 62% focal epilepsies but only 25% generalized epilepsies [7]. Two studies [8,9] compared the proportion of seizure reduction in the first and 12 months of treatment in the same population with focal epilepsy. They found a clear difference in the weighted average seizure reduction rate at 28 days (70%) when compared with the results at one year of follow-up (38%). See Table 1.

3.2. Adverse effects

Adverse effects occurred in 18–59% of cases. Few patients had lacosamide dose reduction because of side effects, but the drug was