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NLM Citation: Dean L. Lacosamide Therapy and *CYP2C19* Genotype. 2018 Apr 18. In: Pratt VM, Scott SA, Pirmohamed M, et al., editors. Medical Genetics Summaries [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2012-.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Lacosamide Therapy and *CYP2C19* Genotype

Laura Dean, MD[1]

Created: April 18, 2018.

Introduction

Lacosamide (brand name Vimpat) is an antiseizure drug indicated for adjunctive therapy for partial-onset seizures in pediatric and adult patients with epilepsy. Lacosamide is thought to work by selectively enhancing slow inactivation of voltage-dependent sodium channels. This stabilizes the neuronal membrane and suppresses the repetitive neuronal firing associated with seizures.

Several cytochrome P450 (CYP) enzymes are involved in metabolizing active lacosamide to an inactive metabolite, including CYP2C19. Individuals who have no CYP2C19 enzyme activity are known as "CYP2C19 poor metabolizers".

The FDA-approved drug label for lacosamide cites a small study that found plasma levels of lacosamide were similar in CYP2C19 poor metabolizers (n=4) and normal (extensive) metabolizers (n=8) (Table 1). Therefore, the recommended standard doses of lacosamide may be used for CYP2C19 poor metabolizers (1).

Table 1. FDA (2016) Drug Label for Lacosamide. Recommendations for CYP2C19 Phenotype. Pharmacokinetics.

Phenotype	Recommendations
CYP2C19 Poor metabolizer	There are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 poor metabolizers and extensive metabolizers.

This table is adapted from (1).

Drug: Lacosamide

Lacosamide is an antiseizure drug that is used in the treatment of partial-onset (focal) seizures. It may be used as monotherapy, or as an adjunctive therapy. When lacosamide is taken orally, it can be used in pediatric patients (from age 4), or if given intravenously, it is indicated for adult patients (from age 17) (1).

Over 50 million people worldwide suffer from epilepsy, which is characterized by spontaneous recurrent epileptic seizures classified as generalized or focal. Generalized seizures appear to originate in all regions of the cortex simultaneously and include absence seizures (sudden impaired consciousness and staring) and general tonic-clonic seizures (loss of consciousness, stiffening of limbs in the tonic phase, and twitching or jerking muscles in the clonic phase). In contrast, symptoms of focal seizures depend upon where the focus of the seizure originates in the brain (e.g., jerking of a limb indicates a focus in the contralateral motor cortex).

Author Affiliation: 1 NCBI; Email: mgs@ncbi.nlm.nih.gov.

Most currently available antiseizure medications target sodium channels (e.g., carbamazepine, phenytoin), calcium channels (e.g., ethosuximide), or the gamma-aminobutyric acid (GABA) system (e.g., clobazam). However, up to one-third of patients may not achieve seizure control, or they may not be able to tolerate the side effects. This has led to the development of newer antiseizure drugs with unconventional targets.

Lacosamide is a third-generation antiseizure drug that was designed to have a novel mechanism of action — it selectively enhances the slow inactivation of voltage-gated sodium channels. This leads to a stabilization of neuronal membranes and an inhibition of repetitive neuronal firing. This mode of action is fundamentally different to traditional sodium channel blocking drugs, which affect the fast inactivation of voltage-gated sodium channels (2, 3).

In adult patients (aged 17 and older), the recommended initial dose for lacosamide monotherapy is 100 mg twice daily (50 mg twice daily for adjunctive therapy), which may be increased to a maximum dose of 200 mg twice daily, for both monotherapy and adjunctive therapy. At these doses, randomized controlled trials have reported that lacosamide reduces the frequency of focal seizures significantly more than placebo, while also being well tolerated (4-7). The most common adverse drug effects of lacosamide are diplopia (double vision), headache, dizziness, and nausea (2, 3, 8, 9).

Lacosamide is metabolized to a major inactive O-desmethyl metabolite by several cytochrome P (CYP) enzymes, including CYP3A4, CYP2C9, and CYP2C19. The role of CYP2C19 in lacosamide metabolism has been the most thoroughly studied. According to the FDA drug label for lacosamide, individuals who harbor 2 nonfunctional *CYP2C19* variant alleles ("CYP2C19 poor metabolizers") have lower concentrations of the inactive O-desmethyl metabolite in their plasma, compared to normal (extensive) metabolizers with 2 functional *CYP2C19* alleles.

However, the plasma concentration of active lacosamide was similar in both poor metabolizers and normal (extensive) metabolizers. Therefore, the label states that there are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 poor and normal metabolizers (1).

The Cytochrome P450 Superfamily

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The CYP450 genes are highly polymorphic and can result in no, decreased, normal, or increased enzyme activity.

Enzymes CYP2C19, CYP2C9, and CYP3A4 are involved in the metabolism of lacosamide to a major inactive O-desmethyl metabolite. The role of CYP2C19 in lacosamide metabolism has been the most thoroughly studied (10). According to the FDA drug label for lacosamide, individuals who harbor 2 nonfunctional *CYP2C19* variant alleles ("CYP2C19 poor metabolizers") have lower concentrations of the inactive O-desmethyl metabolite in their plasma and excreted in the urine compared with normal (extensive) metabolizers with 2 functional *CYP2C19* alleles.

Genetic Testing

The National Institutes of Health (NIH) Genetic Testing Registry (GTR) displays genetic tests that are currently available for the *CYP2C19* gene.

Given that currently there are no clinically significant differences in lacosamide pharmacokinetics between CYP2C19 poor and normal metabolizers, there is no evidence supporting clinical CYP2C19 pharmacogenetic testing prior to initiating lacosamide, and testing has not been addressed by currently available professional society practice guidelines.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2016 Statement from the US Food and Drug Administration (FDA):

CYP2C19 Polymorphism

There are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 poor metabolizers and extensive metabolizers. Results from a trial in poor metabolizers (PM) (N=4) and extensive metabolizers (EM) (N=8) of cytochrome P450 (CYP) 2C19 showed that lacosamide plasma concentrations were similar in PMs and EMs, but plasma concentrations and the amount excreted into urine of the O-desmethyl metabolite were about 70% reduced in PMs compared to EMs.

Please review the complete therapeutic recommendations that are located here: (1).

Acknowledgments

The author would like to thank Ben Kong, PharmD, BCPS, Clinical Pharmacist, Oregon Health & Science University, Portland, OR, USA; Gouri Mukerjee, Scientific Officer at Geneyouin Inc., Toronto, Canada; and Stuart A. Scott, Assistant Professor of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; for reviewing this summary.

References

1. VIMPAT-lacosamide tablet, film coated; VIMPAT- lacosamide; VIMPAT- lacosamide injection; VIMPAT-lacosamide solution [Packet insert]. Smyrna, GA; November, 2017. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9e79b42c-38a3-4b2c-a196-a5a1948250e2
2. de Biase S., Valente M., Gigli G.L., Merlino G. Pharmacokinetic drug evaluation of lacosamide for the treatment of partial-onset seizures. Expert Opin Drug Metab Toxicol. 2017 Sep;13(9):997–1005. PubMed PMID: 28750560.
3. Bauer S., Willems L.M., Paule E., Petschow C., et al. The efficacy of lacosamide as monotherapy and adjunctive therapy in focal epilepsy and its use in status epilepticus: clinical trial evidence and experience. Ther Adv Neurol Disord. 2017 Feb;10(2):103–126. PubMed PMID: 28382109.
4. Ben-Menachem E., Biton V., Jatuzis D., Abou-Khalil B., et al. Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia. 2007 Jul;48(7):1308–17. PubMed PMID: 17635557.
5. Chung S., Sperling M.R., Biton V., Krauss G., et al. Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial. Epilepsia. 2010 Jun;51(6):958–67. PubMed PMID: 20132285.
6. Halász P., Kalviainen R., Mazurkiewicz-Beldzinska M., Rosenow F., et al. Adjunctive lacosamide for partial-onset seizures: Efficacy and safety results from a randomized controlled trial. Epilepsia. 2009 Mar;50(3):443–53. PubMed PMID: 19183227.
7. Kwok C.S., Johnson E.L., Krauss G.L. Comparing Safety and Efficacy of "Third-Generation" Antiepileptic Drugs: Long-Term Extension and Post-marketing Treatment. CNS Drugs. 2017 Nov;31(11):959–974. PubMed PMID: 29204953.
8. Elger C.E., Rademacher M., Brandt C., Elmoufti S., et al. Changes in hormone and lipid levels in male patients with focal seizures when switched from carbamazepine to lacosamide as adjunctive treatment to

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

levetiracetam: A small phase IIIb, prospective, multicenter, open-label trial. Epilepsy Behav. 2016 Sep;62:1–5. PubMed PMID: 27423106.
9. Liu H., Xu X. Influence of adjunctive lacosamide in patients with seizures: a systematic review and meta-analysis. Int J Neurosci. 2017 Dec 17.:1–7. PubMed PMID: 29172828.
10. Cawello W., Mueller-Voessing C., Fichtner A. Pharmacokinetics of lacosamide and omeprazole coadministration in healthy volunteers: results from a phase I, randomized, crossover trial. Clin Drug Investig. 2014 May;34(5):317–25. PubMed PMID: 24567279.

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