Study protocol

Risks of arrhythmias reporting with antiepileptics including Lamotrigine: a pharmacovigilance study in VigiBase®

Lisa Orts[1, 2], François Montastruc[1, 2*]

1. Department of Medical and Clinical Pharmacology, Centre of PharmacoVigilance and Pharmacoepidemiology, Toulouse University Hospital (CHU), Faculty of Medicine, Toulouse, France.
2. Centre d'Investigation Clinique 1436, Team PEPSS « Pharmacologie En Population cohorteS et biobanqueS », Toulouse University Hospital, France

*Lead Investigator:

Dr François Montastruc, Department of Medical and Clinical Pharmacology, 37 Allées Jules Guesde, 31000 Toulouse, France. francois.montastruc@univ-tlse3.fr

Introduction

On March 3, 2021, the FDA issued an alert about increased risks of arrhythmias when taking Lamotrigine, a drug treating epilepsy and people with mental disorders.[1,2,3]

Lamotrigine is a voltage-dependant sodium channel blocker, decreasing the high-frequency sustained repetitive firing of sodium action potentials, which may lead to stabilization of presynaptic neuronal membranes and therefore decrease presynaptic glutamate release.[4,5] Antiepileptics help control electrical activity when it gets carried away. There are four major classes of antiepileptics.[6,7] 1. Those which block voltage-dependent ion channels (sodium, calcium and potassium) and thus reduce excitatory transmission. 2. Those that enhance GABA-mediated inhibitory neurotransmission. 3. Those that attenuate glutamate-mediated excitatory neurotransmission. 4. Those that modulate the release of neurotransmitters via presynaptic action. Some of these antiepileptics could be (via their mechanisms of action) involved in the genesis of arrhythmias.

The question of arrhythmia risk with lamotrigine remains unclear. Indeed, the studies that have come out on this subject are sometimes contradictory. Some studies suggest this risk of arrhythmias with slowing of ventricular conduction (widening of the QRS) inducing pro-arrhythmias.[8,9,10,11] While others contradict these risks by demonstrating that Lamotrigine would have no effects on the widening of the QRS.[8,12]

Given that there is currently uncertainty on this subject, we wanted to better characterize these risks of arrhythmias with Lamotrigine. The aim of this study was therefore to compare the risks of arrhythmias with lamotrigine compared with other antiepileptics, to know if these risks are characteristic of lamotrigine or not.

Methods

Data source

We will perform a case-non-case study using Vigibase®, World Health Organization's unique global database of reported potential side effects of drugs. It is the largest such database in the world, which contains the WHO's Global Individual Case Safety Reports (ICSR), which includes over 28 million anonymous reports of Suspected adverse drug reactions (at September 2021) reported to the WHO Uppsala Surveillance Center by national pharmacovigilance systems from over 130 countries around the world since 1968. It is always updated with

incoming reports. The ICSRs are spontaneously generated accounts of adverse drug reactions describing a suspected causative agent, as reported by health professionals, consumers, or the drug manufacturers.

Study population

We will include all ICSRs registered between January 1, 1994, and December 31, 2020, with known age and sex. Those of unknown sex and age were excluded. All patients aged 18 or over on the date of the declarations and treated with an antiepileptic (listed in the definition of exposure) were included. The starting date for the collection of reports is concomitant with the approval of Lamotrigine® in the United States in 1994.

Case and non-case definitions

Cases were all patients in the study population who reported arrhythmias recorded in VigiBase® defined by the following MedDRA High Level Terms (HLTs) : "Supraventricular Arrhythmias (HLT)", "Cardiac Conduction Disorders (HLT)", "Heart rhythm and rate disorders NEC (HLT)", "Ventricular rhythm disorders and cardiac arrest (HLT)" and being exposed to lamotrigine or the comparator antiepileptic. Non-cases will be all control reports reporting no arrhythmias and being exposed to lamotrigine or the comparator antiepileptic during the same period of interest.

Outcomes

The main outcome of interest will be the risk of declaring a rhythm disorder (as defined by the previous MedDRA terms).

Exposure definition

For all cases and non-cases, we will identify patients exposed to different types of antiepileptics. Sodium channel modulators (phenytoin, carbamazepine, eslicarbazepine, lamotrigine, oxcarbazepine, rufinamide, lacosamide), calcium channel blockers (ethosuximide, zonisamide) and calcium channel modulators (gabapentin, pregabalin). But also, GABA-Enhancing (Tiagabine, Stiripentol, Vigabatrin), glutamate receptor antagonists (Perampanel), potassium channel modulators (Ezogabine), 2A synaptic vesicle modulators (Levetiracetam, Brivaracetam) and mechanisms of action mixed (Topiramate and valproate). For the analysis, the drugs will therefore be separated into seven groups. (Table 1)

The list of antiepileptic drugs was built from Smith's text in the Goodman and Gilman's reference textbook.[13] Benzodiazepines (Gaba-Enhancing drugs) were excluded since they are also used in non-epileptic patients.

Data Analysis

Descriptive statistics will be used to compare characteristics between reports. Using a case/non-case design, we will perform univariate logistic regression to estimate the odds ratios (RORs) with their 95% confidence intervals (CIs). Reporting odds ratios (RORs) are the odds of exposure among reported cases of arrhythmias relative to the odds of exposure among reported non-cases.

We will perform several sensitivities analyzes to assess the robustness of our study. First, we will restrict the analyzes to the reports of physicians because the observations will have a lower risk of error. In a second step, we will carry out temporal analyzes every 5 years from 1994 to see if the signal appears from the start of the marketing of lamotrigine. Thirdly, we will carry out analyzes just before the publication of the FDA alert on March 3, 2021, to ensure the presence of the signal before the media event and to limit the temporality bias. Next, analyzes will be performed separately on the four MedDRA high-level terms (HLTs) mentioned in the "case and non-case definitions" section. Fifth, the serious criteria will be analyzed compared to the non-serious ones to avoid an underestimation of the ROR and limit the temporal bias. Finally, analyzes will be carried out by stratifying the data according to age (18 to 44, 45 to 64, 65 to 74 and over 75) or sex (male or female).

Data extraction

Data extraction of reports (ICSRs) of interest was done in February 2022.

Ethics

As all data from VigiBase® were deidentified, patient informed consent will be not necessary.

Amendments and deviations

Any future amendments or deviations will be recorded here.

References:

1. 03-31-2021 FDA Drug Safety Communication
2. Ahmed Naguy, Najah Al-Enezi, « Lamotrigine Uses in Psychiatric Practice » Am J Ther. Jan/Feb 2019;26(1):e96-e102. doi: 10.1097/MJT.0000000000000535.
3. Alessandro Cuomo et al, "[Lamotrigine in bipolar disorder: preventing depression to treat the disease] », Riv Psichiatr. Jan-Feb 2021;56(1): 1-11.doi: 10.1708/3546.35215.
4. Nicholas T. Betchel et al, « Lamotrigine » Treasure Island (FL): StatPearls Publishing; 2022 Jan-.
5. R L Macdonald, K M Kelly, « Antiepileptic drug mechanisms of action » Epilepsia. 1995 ;36 Suppl 2: S2-12.doi: 10.1111/j.1528-1157. 1995.tb05996. x.
6. Graeme J Sills, Michael A Rogawski, "Mechanisms of action of currently used antiseizure drugs » Neuropharmacology. 2020 May 15;168: 107966.doi: 10.1016/j.neuropharm.2020.107966. Epub 2020 Jan 14.
7. J A Davies, « Mechanisms of action of antiepileptic drugs » eizure. 1995 Dec;4(4): 267-71.doi: 10.1016/s1059-1311(95)80003-4.
8. Jacqueline A. French et al, « FDA safety warning on the cardiac effects of lamotrigine: An advisory from the Ad Hoc ILAE/AES Task Force », Epilepsia Open. 2021 Mar; 6(1): 45–48.
9. Diane S Aschenbrenner, « Lamotrigine may Increase Risk of Arrythmias », American Journal of Nursing, 2021 Aug 1;121(8):23. doi: 10.1097/01.NAJ.0000767792.01749.bd.
10. Simon P Hagley et al, "Lamotrigine Toxicosis Treated with Intravenous Lipid Emulsion Therapy in a Dog" Jul/Aug 2020;56(4): 226-230.doi: 10.5326/JAAHA-MS-6815. Epub 2020 May 15.
11. Andrew Dream et al, "Refractory ventricular fibrillation in patient taking Lamictal". 2018 Jul;36(7): 1324.e1-1324.e2.doi: 10.1016/j.ajem.2018.04.008. Epub 2018 Apr 5.
12. Ruth Dixon et al, "Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects. » Copyright © 2008 The Authors Journal compilation © 2008 Blackwell Publishing Ltd
13. Smith MD, Metcalf CS, Wilcox RS. Pharmacotherapy of the Epilepsies. In Goodman and Gilman's, the pharmacological basis of therapeutics. 13th edition. Brunton L.L. & Hilal-Dandan R, & Knollmann B.C.(Eds.) Mc graw Hill, New York, 2018, 302-326

Table 1: Classification of antiepileptics studied

Sodium channel modulators	Phénytoïne
	Carbamazepine
	Eslicarbazepine
	Lamotrigine
	Oxcarbazepine
	Rufinamide
	Lacosamide
Calcium Channel Blockers	Ethosuximide
	Zonisamide
Calcium Channel Modulators	Gabapentine
	Pregabalin
GABA-Enhancing Drugs	Tiagabine
	Stiripentol
	Vigabatrin
Glutamate Receptor Antagonists	Perampanel
Potassium Channel Modulators	Ezogabine
Synaptic Vesicle 2A Modulators	Levetiracetam
	Brivaracetam
Mixed Mechanisms of Action	Topiramate
	Valproate