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Pharmacogenomics of lamotrigine: a possible link to serious cutaneous adverse reactions

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Abstract

Introduction: Lamotrigine's packaging contains a boxed warning for serious skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis. The purpose of this review is to summarize literature pertaining to HLA genetic polymorphisms that may increase susceptibility to serious skin reactions induced by lamotrigine.

Methods: A literature search of PubMed/MEDLINE and Ovid IPA was conducted using the following search terms: lamotrigine, genetic polymorphism, pharmacogenetics, pharmacogenomics, predictive genetic testing, anticonvulsants, hypersensitivity, and HLA-B.

Results: Three case-control studies were identified focusing on genetic polymorphisms that can cause direct susceptibility to serious skin reactions, such as HLA-B*1502. Other factors were also taken into consideration, such as age, concomitant medications, ethnicity, and smoking status. Most results were not statistically significant but rather hypothesis generating and were limited by small sample size and study design.

Discussion: Further studies are needed to better determine a relationship between genetic polymorphisms and lamotrigine-induced serious skin reactions. However, clinicians should exercise caution when prescribing lamotrigine to patients in whom relevant genetic polymorphisms, such as HLA-B*1502, may be present, such as those of Southeast Asian descent.

Keywords: lamotrigine, pharmacogenomics, cutaneous, adverse reactions

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Introduction

Lamotrigine (Lamictal®) is an antiepileptic drug (AED) and mood-stabilizing agent indicated for the treatment of partial seizures, primary generalized tonic-clonic seizures, Lennox-Gastaut syndrome, and bipolar I disorder.[1,2] Lamotrigine exerts its pharmacological effects primarily through inhibition of voltage-sensitive sodium channels, causing stabilization of neuronal membranes. It also inhibits release of glutamate and is a weak inhibitor of 5-HT_3 receptors.[1] These additional mechanisms help to explain its use in treating a wide variety of seizure disorders. Lamotrigine is primarily metabolized by glucuronic acid conjugation to the *2-N*-glucuronide and is then excreted in the urine. The normal half-life of lamotrigine is 25 to 33 hours in adults, but it increases 2-fold with concomitant valproic acid therapy to 48 to 70 hours. The initial dosing of lamotrigine must be decreased from 25 mg daily to 25 mg every other day in patients receiving

valproate. Some known adverse effects are nausea, dizziness, fatigue, somnolence, headache, and skin rash.[1,3]

In 1997, the US Food and Drug Administration added a boxed warning to the labeling of Lamictal® (GlaxoSmithKline, Research Triangle Park, NC) for life-threatening serious rashes.[2,3] These rashes are considered to be the result of a typical hypersensitivity reaction and can include Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). The reaction is usually delayed, beginning 1 to 3 weeks after initiation of therapy. According to Fernando et al, SJS and TEN are "distinguished arbitrarily by the extent of epidermal detachment." TEN causes > 30% epidermal detachment, and SJS causes < 10% epidermal detachment. Overlapping SJS and TEN causes 10% to 30% detachment. Mortality rates are high: 10% for SJS and 50% for cases of TEN.[4] Pediatric patients are at an increased risk of developing serious rashes from lamotrigine therapy as are patients receiving a higher dose or who have experienced rapid dose escalation.[2,5] Recent genomic research has identified several genetic polymorphisms that may confer susceptibility to severe skin reactions.[4] Perhaps the most well studied of these is the HLA-B*1502 allele, which has a strong association with carbamazepine-induced SJS and/or TEN. Although carbamazepine has been the primary focus of HLA-B research, other AEDs, such as phenytoin, oxcarbazepine, and lamotrigine, have been implicated.[6]

Lamotrigine's dual functioning as an AED and as a mood-stabilizing agent causes it to fit in to 2 categories of pharmacogenomic research. However, most anticonvulsant pharmacogenomic research focuses on carbamazepine and phenytoin, and psychiatric pharmacogenomic research is trending toward the antipsychotic agents and selective serotonin reuptake inhibitors. Currently, there is no comprehensive source of information focusing on the pharmacogenomic properties of lamotrigine alone. The purpose of this article is to summarize and analyze the current pharmacogenomic literature pertaining to lamotrigine or evaluating the effects of genetic polymorphisms on clinical outcomes of lamotrigine therapy. This article will investigate the gene polymorphisms that may make patients more susceptible to serious skin reactions. Gathering all of this information into one resource may be helpful for clinicians when determining courses of therapy for patients with epilepsy or bipolar disorder.

Methods

A primary literature search of PubMed/MEDLINE and Ovid IPA for articles describing pharmacogenomic studies of lamotrigine was conducted. The following search terms were used: lamotrigine, genetic polymorphism, pharmacogenetics, pharmacogenomics, predictive genetic testing, anticonvulsants, hypersensitivity, and HLA-B. Identified articles were included if they were available in English and investigated an association between lamotrigine and a specific genetic polymorphism. Articles were excluded if they did not specifically examine an association between lamotrigine and a genetic polymorphism. Relevant references in each article were scanned as well.

Results

Results from the literature search performed are presented below. There are 3 case-control studies focusing on HLA genotypes that may increase the likelihood of AED-induced serious skin reactions.

Man et al conducted a case-control study in Hong Kong looking at the association between the HLA-B*1502 allele and severe skin reactions that were induced by carbamazepine and other AEDs in the Han Chinese population. Patients at Prince of Wales Hospital were identified for this study through the hospital computer system. All were of Han Chinese descent. Patients who had experienced a severe skin reaction attributed to a recently started AED (within 8 weeks) were enrolled as cases and matched in a 1:2 case-control ratio with patients who had no history of drug-induced skin reactions. Cases and controls were matched according to age and AED prescribed. The study found 8 patients who had experienced SJS, TEN, or drug hypersensitivity syndrome (HSS) and 16 patients who had experienced mild maculopapular exanthema (MPE). The serious skin reaction patients (4 male, 4 female) had a mean age of 36 years. The MPE patients (9 male, 7 female) had a mean age of 40 years. These patients were matched against a total of 48 control patients. Of the control patients, 30 were male and 18 were female, and the mean age was 40 years. Six cases and 11 controls were taking lamotrigine. The researchers found that 75% of patients with AED-induced serious skin reactions had the HLA-B*1502 allele, and only 14.5% of controls had the HLA-B*1502 allele ($p = .001$). When the analysis was limited to patients experiencing SJS or TEN, the statistical significance was even more apparent with 100% of case patients being carriers of the HLA-B*1502 allele. Of the 8 patients who experienced serious skin reactions, 2 were taking lamotrigine. One was HLA-B*1502-positive and had TEN. The other was HLA-B*1502-negative and had HSS. The authors recognized that a level of cross-reactivity among the aromatic AEDs exists but stated that further research must be performed to assume the same for lamotrigine. It should be pointed out, however, that the HLA-B*1502-positive patient who had TEN had received lamotrigine on top of valproate therapy, which likely increased the serum concentration of the lamotrigine.[7]

Hung et al followed up on the Man et al study in 2010 by examining the cross-reactivity of 3 drugs similar in structure to carbamazepine through a case-control study. Their purpose was to determine if the HLA-B*1502 allele caused susceptibility to serious skin reactions induced by oxcarbazepine, phenytoin, and lamotrigine. For cases, the researchers used patients who had been hospitalized between 2002 and 2008, diagnosed with SJS or TEN induced by phenytoin (26 patients), oxcarbazepine (3 patients), or lamotrigine (6 patients). Controls for phenytoin (113 patients) and lamotrigine (67 patients) had been taking the specified drug for at least 3 months without experiencing any adverse drug reactions. For oxcarbazepine (93 patients), controls were healthy subjects randomly selected from a biobank used in a population study in Taiwan. All participants were residents of Taiwan who were of the Han Chinese ethnic group. The investigators performed HLA genotyping for the following alleles: A, B, Cw, and DRB1, specifically looking for HLA-B*1502. The lamotrigine patients had a mean age of 23.7 years in the case group and 33.2 years in the control group. Four males and 2 females had experienced SJS, and 39 men and 28 women had not. The case group had a mean drug exposure of 174 mg/day for 19.6 days; the control group, 297.4 mg/day for 42.1 months. Two of the 6 lamotrigine patients experiencing SJS were HLA-B*1502-positive. The overall risk for HLA-B*1502-positive patients to develop lamotrigine-induced SJS/TEN was 5.1, but this was not statistically significant ($p = .1266$). Having assessed these data, the authors concluded that although it may not be a statistically significant relationship, caution should be exercised when prescribing lamotrigine in patient populations that have a greater frequency of the HLA-B*1502 allele.[8]

The B*1502 allele is observed more frequently in Southeast Asians compared to those of European ancestry. Kazeem et al conducted a case-control study in patients of European descent to evaluate the association with HLA genetic variants and severe cutaneous adverse reactions (SCAR) from lamotrigine. Case patients were those who developed SJS, TEN, or hypersensitivity reaction within the 8-week treatment with lamotrigine. Controls were those patients who also received lamotrigine for at least 8 weeks but did not develop SCAR. Patients self-reported ancestral origin with 93% of patients reporting European ancestry; the remaining 7% reported African and Hispanic ancestry. Cases and controls were matched in a 1:2 ratio by age, race, and concurrent use of valproic acid. HLA genotyping was performed for 22 cases and for 43 controls. The mean age in the case group was 32 years and 36 years in the control group. There was also a majority of females in each group, with 59% in the cases and 53% in the controls. There were 5 risk alleles carried by those with European ancestry that had a significant association with SCAR: A*6801, B*5801, Cw*0718, DQB1*0609, and DRB1*1301. Correlations were also seen between these alleles. Each of the 3 cases that carried the Cw*0718 allele also carried B*5801, which was also correlated with DQB1*0609. No correlation was observed, however, between B*5801 and A*6801. Of note, alleles A*6801 and DRB1*1301 were present in non-European cases, yet none of the risk alleles were carried by the non-European controls. Also of interest, the B*1502 allele was not carried in cases in this study. The authors concluded that there was evidence of association with the risk alleles and lamotrigine-induced SCARs; however, further research is needed with a larger sample to investigate the impact of this association.[9]

Discussion

The articles presented above represent a broad view of the pharmacogenomic properties of lamotrigine. Although there were some significant limitations in research, each study made at least one hypothesis-generating point for further studies.

The primary limitation of research was the lack of focus on lamotrigine itself. Only 1 of the studies (the Kazeem et al study) used lamotrigine as the sole focus. The others included lamotrigine as one of many drugs examined, often secondary to other AEDs, such as carbamazepine and phenytoin. As a result, sample sizes were small. This may have contributed to the lack of significance in some of the results. Unfortunately, it is likely that small sample size will continue to be a problem with further research, at least when investigating the relationship between lamotrigine-induced serious skin reactions and the HLA-B*1502 allele. This allele does not exist in high frequencies in Caucasian, African, or Japanese populations, so no association between the polymorphism and AED-induced skin reactions has yet been established in these populations.[4,8]

There are multiple factors to consider when assessing the relationship between lamotrigine and serious skin reactions, including comedication with valproate or other enzyme-inducing AEDs, smoking, age, and ethnicity. Ethnicity was a major factor in the Man et al and Hung et al studies, which investigated direct relationships between genetic polymorphisms and AED-induced serious skin reactions. All patients included in these 2 studies were Han Chinese.[7,8] It is difficult to determine statistical significance when there are so many variables to consider. However, this is a true-to-life scenario, which paints a better picture of the general public.

The methodology for each study was generally good, and patient demographics were well matched for cases and controls in each of the 3 studies. Assuming that the SJS/

TEN developed by case patients was truly AED-induced, there seemed to be a good association between serious skin reactions and gene polymorphisms.

The association of genetic polymorphisms and lamotrigine-induced serious skin reactions is one that could possibly be of clinical importance when prescribing new therapy for patients with epilepsy or bipolar disorder. Studies discussed in this article explored the relationship between genetic polymorphisms and direct susceptibility to lamotrigine-induced serious skin reactions. Although the literature presented here does not point to any clear relationships between genetic polymorphisms and lamotrigine-induced serious skin reactions, clinicians should exercise caution when prescribing this medication to patients in whom relevant genetic polymorphisms such as HLA-B*1502 may be present, such as those of Southeast Asian descent. Further studies are needed to better understand the likelihood of lamotrigine-induced SJS or TEN.

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