HLA-B*1502 Increases the Risk of Phenytoin or Lamotrigine Induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: Evidence from a Meta-analysis of Nine Case-control Studies

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Key words
- phenytoin
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Abstract

Background and Study aims: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are fatal adverse cutaneous drug reactions which may be induced by phenytoin (PHT) or lamotrigine (LTG). The objective of this study was to analyze the association of human leukocyte antigen (HLA)-B*1502 and PHT or LTG induced SJS/TEN.

Patients and Methods: All the participants were epileptic patients and the SJS/TEN were induced by PHT or LTG. The presence or absence of the HLA-B*1502 allele of all the patients was determined. ISI Web of Knowledge, PubMed, ScienceDirect, EMBASE, and Cochrane Register of Controlled Trials (CENTRAL) data were searched for the literature published before April 2014. Meta-analysis was performed using Review Manager 5.2 software.

Results: From 256 citations, 6 English studies were included that involved 480 epilepsy patients. Meta-analysis showed that odd ratio (OR) of PHT and LTG were 5.65 [95% CI: 2.76–11.57] and 4.51 [95% CI: 1.57–12.98], respectively. Funnel plot analysis showed symmetry, indicting less possible publication bias and the results were partly reliable.

Conclusion: There is a significant association between HLA-B*1502 and PHT or LTG-induced SJS/TEN.

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Introduction

Serious adverse drug reactions are a major cause of morbidity and mortality worldwide. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare immune-mediated severe cutaneous adverse reactions that predominantly involve the skin and mucous membranes [1]. The symptoms of SJS begin with fever and tiredness, followed by a rash, severe skin wounds, and shedding of the skin. Up to 10% of the skin can be affected. Wounds may also appear in other tissues that cover the eyes, mouth, and genitals. Up to 5% of SJS cases are fatal. TEN is more severe than SJS, and can be life threatening. It also begins with fever and tiredness followed by a rash and skin wounds that may resemble extensive burns [2]. However 30% or more of the skin may be affected. Between 25% and 35% of TEN cases are fatal.

SJS/TEN are severe adverse cutaneous drug reactions with incidence rate of 0.05–2 persons per million populations per year. Drugs are the most commonly implicated in 95% of cases. Antiepileptic drugs were more often associated with serious form of adverse reaction (TEN: 81.8%) than other drugs [3]. In the U.S. Food and Drug Administration (FDA) post-marketing adverse events reports, the frequencies of SJS/TEN were more than 10 times higher in some Asian people (from Malaysia, Thailand, Taiwan, the Philippines) than those in Caucasians [4,5]. The cumulative estimate report by Novartis (carbamazepine (CBZ) manufacturer), between 2000 and 2006, revealed an SJS/TEN incidence of 4.1–5.9 per 10000 patient year exposure in some Asian countries, whereas only 0.2–0.9 per 10000 were reported in USA and European countries [6]. The occurrence of adverse cutaneous drug reactions among new CBZ users was 1–6 per 10000 in Caucasian patients [7], compared to 17–25 per 10000 in Thailand and Taiwan [8,9]. This confirms an approximately 3-fold to 25-fold higher frequency in Asian populations than in Caucasians.

HLA-B is part of a family of genes called the human leukocyte antigen complex. It provides instructions for making a protein that plays a critical role in the immune system. The frequency of the HLA-B*1502 allele is reportedly

vation was consistent with the clinical symptoms. Nassif's [29] results strongly suggested that drug-specific, major histocompatibility complex (MHC) class I-restricted, perforin/granzyme-mediated cytotoxicity probably had a primary role in TEN.

However, there are several limitations in this meta-analysis that must be addressed. First, only published data were brought into this eligible study, preexisting publication bias would reflect our results. Second, the lack of original data from the included studies limited the further evaluation of potential interaction, such as the interactions among gene-gene, gene-environment. Last, the sample size of most studies was not big enough, and this may reduce the statistical power to detect associations.

Conclusions

In summary, the most important implication of this study is that HLA-B*1502 is significantly associated with PHT or LTG-induced SJS/TEN. It is necessary to determine HLA-B*1502 before starting the 2 drugs. As the prodrug of PHT, fosphenytoin-induced SJS/TEN may be associated with HLA-B*1502 allele. Except for HLA-B*1502, other alleles may be potential risk factors which need to be studied further.

Conflict of Interest

All authors of the article declare no conflict of interests in relation to this study.

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