Hypersensitivity to Antiepileptic Drugs

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KEYWORDS

- Antiepileptic drugs • Drug hypersensitivity • Pharmacogenetics
- Severe cutaneous adverse reactions

KEY POINTS

- Antiepileptic drug allergy is a rare but potentially fatal adverse reaction, associated most commonly with phenytoin, carbamazepine, and lamotrigine.
- Antiepileptic drug allergy generally occurs on first exposure to the drug, with symptoms such as skin rash, fever, and internal organ involvement that develop within several weeks of drug exposure.
- Early diagnosis is essential because primary treatment starts with cessation of the implicated drug.
- Avoidance of other aromatic anticonvulsants (eg, phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, and lamotrigine) is recommended in patients who develop allergic reactions to any one of these agents due to a high degree of cross-reactivity among them.
- Pharmacogenetic testing for HLA allele B*1502 should be considered before commencing carbamazepine in Han Chinese, South Asian, and East Indian patients.

INTRODUCTION

Adverse reactions to antiepileptic drugs (AEDs) may lead to treatment failure, morbidity, and mortality from both epilepsy and the adverse drug reaction (ADR).[1,2] It may also impair the quality of life for epilepsy patients.[1] Most adverse reactions to AEDs are predictable, dose-dependent, and pharmacologic-associated type A ADRs, which are usually reversible after discontinuation of the offending drugs. However, type B ADRs occur unexpectedly in susceptible patients and are pathogenically unrelated to the mechanism of action of the drugs. Despite the relatively low

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incidence, drug hypersensitivity reactions (DHRs) that are type B may result in potentially fatal outcomes.[3] As for antibiotics, conventional aromatic AEDs are a common cause of drug allergy (immunologic-mediated DHRs) in hospitalized and general populations.[4,5] AED DHRs present with a variety of different clinical manifestations ranging from skin rashes and mucosal involvement to systemic involvement (fever, hepatitis, lymphadenopathy, eosinophilia, and blood dyscrasias). Cutaneous eruptions are the more common manifestation. However, severe cutaneous adverse reactions (SCARs) are not rare in AED users.[2] These include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug-induced hypersensitivity syndrome (DIHS), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). The pathogenesis of AED DHR has not been fully elucidated. Bioactivation, detoxification, covalent adduct formation, presentation to the immune system, and consequent formation of antibody and T-cell immune effectors have been suggested.[6] The incidence and severity of AED DHRs may be affected by various factors that include age, gender, genetics, and the drug itself.[2] Identifying susceptible individuals and risk factors, as well as close clinical monitoring during the latent period are key to the prevention of AED DHR. This article summarizes the epidemiology, pathogenic mechanisms, risk factors, clinical features, and management of allergic reactions to the aromatic AEDs carbamazepine (CBZ), phenytoin (PHT), and lamotrigine (LTG).

EPIDEMIOLOGY

The prevalence of DHRs to AEDs varies according to the populations enrolled, offending drugs, and study design. Skin rash is a common adverse reaction of AEDs and is a leading cause of withdrawal from some AED trials.[7]

A retrospective chart review reported that the average rate of AED-associated rash was 2.8%, resulting in a rate of AED discontinuation of 2.1%.[8] Most reports on ADRs to AEDs have shown higher rates of rash with CBZ (5%–17% of the patients taking CBZ), PHT (5%–7%), and LTG (5%–10%).[8] Severe mucocutaneous reactions with internal organ involvement such as DIHS-DRESS and SJS-TEN are estimated between 1 in 1000 and 1 in 10,000 exposures.[9] The incidence of AED DHRs in patients with head injuries increases to 1 in 100.[10]

SJS-TEN can lead to significant disability or mortality (ranging from 10% to 40%) despite the low incidence.[11] Aromatic AEDs (including CBZ, PHT, phenobarbital, and LTG) are also associated with these SCARs.[9] In addition, aromatic AEDs are significantly associated with IgE-mediated (immediate) type I and cell-mediated (non-immediate or delayed) type IV DHRs, with a reported odds ratio of 2.15 and 6.06, respectively.[12]

Cross-sensitivity among aromatic AEDs (particularly high in female patients) is reported to be 30% to 58%.[8,13] Among various AEDs, PHT and CBZ were reported as the two drugs with the most frequent cross-reactivity.[13] In addition, cross-reactivity between CBZ and tricyclic antidepressant agents has also been reported based on their structural similarity with the tricyclic nucleus.[14]

RISK FACTORS

Genetic Factors

Genetic markers are useful to predict individuals susceptible to AED DHR (**Box 1**). HLA alleles represent a major determinant of AED DHR since 2004 when Chung and colleagues[15] first reported a strong association of HLA-B*1502 in Han Chinese patients with CBZ-induced SCARs. This strong association was further confirmed by other