

(MHRA) and the UK Commission on Human Medicines) issued an alert on the antiepileptic drug (AED) phenytoin (PHT) regarding an increased risk of Steven–Johnson syndrome (SJS) associated with the presence of the HLA-B*1502 genetic variant in patients of Asian origin.¹ Likewise, the US Federal Drug Agency (FDA) recommended genotyping for the allele in all Asian patients before starting carbamazepine (CBZ).² We wanted to explore the implications of this for our clinical practice.

STRUCTURED CLINICAL QUESTION

In children with epilepsy who are known to be positive for HLA-B*1502 [patient], do we need to avoid PHT and CBZ for fear of severe skin reactions [intervention] and do we need to screen children of Asian origin for the specific allele before starting on the AEDs [outcome]?

SEARCH STRATEGY

Primary sources

EMBASE and PubMed were searched using the term 'HLA-B*1502 AND cutaneous reactions AND antiepileptic drugs'.

Secondary sources

Four case–control studies were identified and included for further appraisal (see table 2)

COMMENTARY

Epilepsy is the most common neurological condition affecting all ages, races and social classes and there are an estimated 50 million people with epilepsy

QUESTION 2

SHOULD PHENYTOIN AND CARBAMAZEPINE BE AVOIDED IN ASIAN POPULATIONS WITH THE HLA-B*1502 POSITIVE GENETIC VARIANT?

SCENARIO

Recently, *Drug Safety Update* (a monthly newsletter from the Medicines and Healthcare products Regulatory Agency

Table 2 Should phenytoin and carbamazepine be avoided in Asian populations with the HLA-B*1502 positive genetic variant?

Study	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Chung <i>et al</i> ⁹	Study group: 44 patients with carbamazepine-induced SJS/TEN Control group: 101 carbamazepine-tolerant patients	Case-control analysis (3b)	44 from the study group tested positive for HLA-B*1502 (100%) Three (3%) of the carbamazepine-tolerant controls tested positive		The study was carried out among Han Chinese subjects living in Taiwan between 1996 and 2003.
Man <i>et al</i> ⁸	Study group: 24 patients with antiepileptic drug (AED)-induced SJS/TEN who were tested for the allele Control group: 48 AED-tolerant controls (age range 10–53 years)	Case-control analysis (3b)	A significant number of patients with AED-induced severe cutaneous reactions had HLA-B*1502 compared with controls (75% vs 14.5%, $p=0.001$, OR 17.6, 95% CI 2.9 to 105.2)	HLA-B*1502 was found in all patients with AED-induced SJS/TEN	All cases and controls were ethnic Han Chinese subjects.
Locharernkul <i>et al</i> ¹⁰	Study group: 31 patients of Thai ethnic origin with epilepsy who developed SJS or maculopapular eruptions after AEDs Control group: 50 AED-tolerant patients without reactions (age range 12–45 years)	Case-control analysis (3b)	A strong association between HLA-B*1502 and PHT- and CBZ-induced SJS was found ($p=0.005$ to 0.0005)	Patients with PHT- and CBZ-induced SJS in the study group tested positive for the HLA-B*1502 allele. In the control group, eight tested positive for HLA-B*1502	
Tassaneeyakul <i>et al</i> ¹²	Study group: 42 patients with CBZ-induced SJS/TEN (mean age 42 ± 17 years) Control group: 42 carbamazepine-tolerant controls (mean age 44 ± 18 years)	Case-control analysis (3b)	37 (88%) of the study group had HLA-B*1502 compared with 11% of controls	The sensitivity and specificity of HLA-B*1502 for predicting CBZ-induced SJS/TEN were 88.1%	This study was carried out in a Thai population. The risk of CBZ-induced SJS/TEN was significantly higher in patients with HLA-B*1502, with OR 55.

worldwide. Epilepsy in children has a prevalence of about 0.5%. Convulsive status epilepticus (CSE), with an incidence of 17–23 episodes per 100 000 children per year, is the most common medical neurological emergency in children. Since there is significant associated morbidity and mortality, which may partly be related to seizure length, it is essential to treat CSE early with AEDs.³

CBZ and PHT are well established AEDs. Advanced Paediatric Life Support, Neonatal Life Support and International League Against Epilepsy guidelines recommend PHT as the choice of anticonvulsant in established status epilepticus.

PHT and CBZ can be associated with hypersensitivity reactions that range from urticaria to life-threatening severe adverse cutaneous drug reaction (ACDR), which includes SJS and toxic epidermal necrolysis (TEN).^{4–5} ACDR is common, comprising 10–30% of all reported adverse drug reactions and 2–3% of all hospitalisations,⁶ but the more severe forms of ACDR (SJS and TEN) are relatively rare with one to two cases per million population per year.⁷ TEN and SJS have been observed worldwide and occur in all age groups including children, infants and newborns.⁷

The exact incidence of ACDR in children among new users of AEDs in the UK is not known. The incidence of SJS in European patients prescribed CBZ is approximately 1/10 000 drug exposures.⁸

SJS and TEN are immune complex-mediated, potentially fatal, hypersensitivity reactions. Mortality is 1–5% for SJS and 25–35% for TEN.⁸ Survivors of SJS/TEN may experience numerous long-term sequelae, the most disabling of which involve the eye. When the drugs are used long term, the greatest risk of SJS/TEN occurs in the first 3 months of use.⁶ The mechanism by which AEDs cause ACDR is not well understood.

In 2004, Chung *et al* from Taiwan reported a strong association between CBZ-induced SJS and HLA-B*1502 in their Han Chinese patients.⁹ CBZ- and PHT-induced SJS, but not maculopapular eruptions, is associated with the HLA-B*1502 allele in the Thai population.¹⁰ The strong linkage suggests that the product of this gene may have a direct functional role in a specific type of drug hypersensitivity. Two studies have failed to show a correlation between allele status and SJS/TEN in Caucasians.²

Reports across Asia have shown that the prevalence of HLA B*1502 is high among Han Chinese (5–15%), Malay (12–15%) and Thai subjects (8–27%), but low among the Japanese, Korean, Sri Lankan populations and most ethnic groups in India.^{6–9} The prevalence of HLA-B*1502 is extremely low among Caucasians (1–2%).¹ HLA B*1502 is not a universal marker for SJS/TEN, but is ethnicity specific for Asians.¹¹ The sensitivity and specificity of this HLA marker,

Clinical bottom line

- ▶ There is insufficient evidence to support routine HLA typing of all Asian patients prior to the commencement of antiepileptic drugs (AEDs). (Grade C)
- ▶ In Han Chinese, Malay and Thai patients, it is necessary to carry out HLA typing where feasible due to the higher risk of an adverse cutaneous drug reaction or use an alternative AED. (Grade C)
- ▶ Further clinical studies are needed for patients of Asian and non-Asian origin to determine the prevalence of the allele and the risk of Steven–Johnson syndrome/toxic epidermal necrolysis in patients on AEDs who test positive for HLA-B*1502. (Grade C)

the mechanism by which the HLA complex pharmacologically interacts with drugs to cause SJS and whether there are other factors such as age, puberty or environment, is not clearly understood. The current recommendations for genotyping all Asians is based on the strong correlation between HLA-B*1502 and CBZ/PHT-induced SJS/TEN in Han Chinese patients. Adequate information about the risk association for patients of other ethnic origins is not currently available.

Although treatment with PHT and CBZ may be associated with an increased risk of developing SJS/TEN in susceptible patients with the typical genetic allele, decisions can be taken on an individual basis. In emergencies, PHT is still considered an effective drug for controlling CSE and the benefits are thought to outweigh the risks. In controlled situations, one can wait for genotyping results in case of a rare life-threatening skin reaction and alternative AEDs can be prescribed where needed. Although the current available case-control studies included a few paediatric patients, it is not possible to directly extrapolate these results to children. Based on the current evidence, we disagree with the suggestion of the FDA and MHRA that it is necessary to screen all Asian children for the allele before starting antiepileptic medication. Further robust clinical studies that include large cohorts of children on CBZ and PHT are needed in both Asian and non-Asian populations for safer treatment of epilepsy in the future.

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