FDA Recommendations: Carbamazepine Patient Selection, Screening and Monitoring

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There have been instances during Facial Pain clinic where patients with neuropathic pain have been prescribed carbamazepine over a period of time without being advised on the screening protocol that accompanies use of this drug. Over the past 10 years the FDA has made connection between potentially fatal skin reactions (Stevens-Johnson-syndrome and toxic epidermal necrolysis) and the use of carbamazepine. This review will serve as a brief guideline on which patients require additional screening prior to use of this drug.

Carbamazepine has been found to be an important agent in the treatment of seizure disorders, bipolar disorders, trigeminal nerualgia and chronic pain. What has been found to be associated with use of this drug is hypersensitivity reactions that specific Asian populations are susceptible to, that range from benign urticaria to life-threatening cutaneous disorders like Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The importance of identifying these reactions are due to the 30% mortality rate that accompanies their presence. It's important to appreciate that these hypersensitivity reactions occur across a spectrum, at one end benign urticarial reactions are seen and at the other end SJS and TEN are found. Characteristically, SJS and TEN present as the following: erythematous, purpuric macules or flat atypical target like skin lesions. The difference between SJS and TEN relates to the amount of detachment of body surface area (BSA). SJS is seen with around ~10% BSA detachment, where TEN is seen with greater than ~30% BSA detachment. While these are usually found epidermally, increased mortality is associated when these conditions include gastrointestinal and tracheobronchial epithelium. The loss of epidermal attachment can lead to infection and sepsis. With no specific treatment modality identified for these conditions, the importance of identifying those who are at greater risk for this reaction is essential when prescribing this treatment to our patients.

It has been identified that those with the HLA-B*1502 gene are at increased risk, estimated to be ten times greater, for carbamazepine-induced SJS/TEN. During the study that found this relationship it was identified that the patients with this genotype were all of Han Chinese descent. This study has been reproduced multiple times, and

has reinforced the finding of a relatively high incidence of HLA-B*1502 in many Asian populations. Due to this, it is recommended that all Asian populations are genotyped prior to implementing Carbamazepine treatment. In the absence of Asian ancestry, the carbamazepine-induced SJS/TEN was not found. Due to the lack of evidence and infrequency of the HLA-B*1502 allele in non-Asian/Caucasian populations genotype screening is not recommended in these populations.

Another significant, however rare, side effect of the persistent use of carbamazepine was the finding of aplastic anemia and agranulocytosis. The risk of developing this reaction for all populations taking carbamazepine was five to eight times greater than those who are untreated (2-6 patients per 1 million per year). More commonly, patients on persistent carbamazepine treatment have been found to have transient or persistent decreased platelet or white blood cell counts. Due to the above, it has been recommended that pre-treatment hematological

testing be completed with CBC monitored periodically during treatment. The interval of monitoring has not been studied, however most sources recommend monthly testing.

Take Home Message:

The HLA-B*1502 allele, commonly found in Asian populations, is highly associated with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis; life threatening cutaneous disorders. Prior to implementing carbamazepine treatment in patients of Asian descent it is recommended that genotyping of these patients is performed to identify the presence of the HLA-B*1502 allele. Pre-treatment and regular hematological testing is also recommended to identify significant blood dyscrasias that can result due to carbamazepine treatment.

References:

1. Ferrell, P. B., Jr., & McLeod, H. L. (2008). Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenomics, 9*(10), 1543-1546. doi: 10.2217/14622416.9.10.1543