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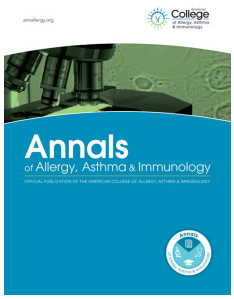

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Slow graded reintroduction of oxcarbazepine for delayed maculopapular eruption

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Abbreviations/Acronyms:

AED: antiepileptic drug

DHR: drug hypersensitivity reaction

DRESS: drug reaction with eosinophilia and systemic symptoms

MPE: maculopapular eruption

SCARs: severe cutaneous adverse reactions

SJS: Stevens-Johnson syndrome

TEN: toxic epidermal necrolysis

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Antiepileptic drugs (AED) are known to be associated with delayed T-cell mediated hypersensitivity reactions that range from maculopapular eruptions to severe cutaneous and systemic reactions. Approximately 2-16% of patients taking AEDs will develop a skin rash.[1, 2] Conditions requiring AEDs are often difficult to treat and may require multiple medication trials before the optimal treatment is determined. Complicating the matter, prior and concurrent use of multiple AEDs heightens the risk of developing a drug hypersensitivity reaction (DHR). Antiepileptic drugs are frequent culprits of the most concerning form of DHRs, severe cutaneous adverse reactions (SCARs).[2] When a reaction does occur, it is especially difficult to find an alternative due to cross-reactivity amongst aromatic amine AEDs including carbamazepine, oxcarbazepine, phenytoin, phenobarbital and lamotrigine.[1]

Pharmacogenetic studies have identified *HLA-B*15:02* as a risk factor for carbamazepine and oxcarbazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in certain Asian populations.[3] Moon et al. reported higher frequency of *HLA-B*40:02* and *HLA-DRB1*04:03* in Korean patients with oxcarbazepine-induced maculopapular eruptions (MPE).[4] In European populations, *HLA-A*31:01* is a risk factor for cutaneous hypersensitivity reactions to carbamazepine and oxcarbazepine including MPE, drug eruption with eosinophilia and systemic symptoms (DRESS) and SJS/TEN.[5, 6] Risk stratification to guide future management such as strict avoidance, direct re-challenge or graded reintroduction is based on history, but patch testing and HLA genotyping may also aid in cross-reactivity and guide future management.

A 16-year-old female of European decent with paroxysmal kinesiogenic dyskinesia presented to the outpatient allergy clinic for evaluation of multiple drug reactions. Paroxysmal kinesiogenic

dyskinesia is a condition with involuntary muscle spasms usually triggered by sudden movements or changes in position[7] which interfered with the patient's daily activities and had been refractory to several AEDs including lamotrigine, tetrabenazine, and levetiracetam. She trialed oxcarbazepine which provided "life changing" symptom control. Approximately 1 week after starting, she developed a pruritic, maculopapular eruption on medial thighs, popliteal and antecubital fossae without associated systemic symptoms. Photographs provided by the family revealed small maculopapular patches. Oxcarbazepine was stopped and eruption subsided over 3-4 days without intervention. No laboratory studies were available. At the time of presentation, she was not taking medications for paroxysmal kinesiogenic dyskinesia and had made lifestyle adaptations to minimize interference with daily activities. There was no evidence of skin lesions or residual markings at the time of presentation. A similar eruption had occurred several weeks after starting lamotrigine and self-resolved several days after cessation of the medication. She had no other occurrences of a similar rash.

Patch testing was performed using previously published and non-irritating concentrations of 10% and 30% oxcarbazepine and potentially cross-reactive drugs carbamazepine, phenobarbital, phenytoin and lamotrigine all formulated from commercially available product.[8] All readings were negative at 48 hours, 96 hours and 1 week. Pharmacogenetic testing revealed the presence of *HLA-A*02:01, HLA-A*11:01, HLA-B*15:01, HLA-B*35:01, HLA-DRB1*11:03, HLA-DRB1*12:01,* none of which are consistent with known risk alleles for carbamazepine, oxcarbazepine, lamotrigine or other anti-epileptic drug cutaneous hypersensitivity reactions. The benign nature of the eruption, negative patch testing and the absence of known risk alleles supported the decision to proceed with graded reintroduction.

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A protocol for slow graded reintroduction of oxcarbazepine was developed after review of available literature.[1, 9] The protocol began with an in clinic graded challenge of oxcarbazepine 0.06mg (1/10,000th the final daily dose) followed by 30 minutes of observation then 0.6mg (1/1,000th the final daily dose) followed by 60 minutes of observation. She tolerated both challenge doses and was discharged home asymptomatic with instructions for slow graded reintroduction. The daily dose was doubled every 48 hours. She successfully reached the maintenance dose without adverse events through a 27-day slow graded reintroduction of oxcarbazepine (Table 1). Several months after reintroduction, she was able to increase the maintenance dose to 450mg twice a day without further build up and has achieved significantly improved quality of life with minimal episodes of involuntary movements.

Suspected drug hypersensitivity reactions to AEDS are challenging because diagnostic testing is not standardized and has poor sensitivity and specificity.[2] This is the first case in the United States to report successful reintroduction of oxcarbazepine using a graded protocol over several days for benign nonimmediate rash which allowed our patient to reach a therapeutic dose faster than previously published protocols.[9] The decision for re-exposure is based on careful history, available diagnostic testing, knowledge of cross-reactivity and available alternatives. In this case, cutaneous symptoms were mild and benign without systemic symptoms. The patient had a similar reaction to lamotrigine suggesting potential cross-reactivity among aromatic AEDs and there were few known effective alternatives. In patients with a severe reaction to one aromatic AED, avoidance of other aromatic AEDs is a cautious approach based on the possibility of clinical cross-reactivity.[3] Therefore, patch testing to evaluate cross-reactive aromatic AEDs was

applied. Delayed intradermal testing could have been considered but the known testing concentration is not well established. Current guidelines recommend testing for *HLA-B*15:02* prior to initiating carbamazepine and in the countries where this has been implemented, such as Singapore and Taiwan, there has been a significant reduction in carbamazepine SJS/TEN.[3] Prior to initiating other AEDs, pharmacogenomic testing could be considered.[3, 6] HLA testing in this European patient did not reveal the presence of known risk alleles.

Slow graded reintroduction after negative patch testing was utilized due to the delayed nature of the reaction and protocol was based on available published case reports[9]. There has been advancement in knowledge of the immunopathogenesis of T-cell mediated adverse drug reactions. However, the specific immune mechanism by which tolerance can occur with slow reintroduction of drug in the setting of delayed T-cell mediated reactions is not known. In the setting of desensitization for fixed drug eruption, a shift from CD25+ CD8+ T cells to CD25+ CD4+ T cells has been reported suggesting that expansion of regulatory T cells in the skin may be one mechanism.[10]

Conditions requiring AEDs can be difficult to treat and may require trials of several medications before the optimal treatment is determined and effective alternatives may not be available. This case highlights the importance of an accurate clinical history, a comprehensive evaluation of delayed drug reactions, understanding the potential for cross-reactivity of AEDs, risk stratification to determine re-exposure or avoidance and novel re-introduction protocols for nonimmediate mild reactions. More importantly, this case was motivated by patient driven care and the instrumental role allergists play in improving quality of life.

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Table 1. Slow graded oxcarbazepine reintroduction protocol

Days	Dose Volume (mL)	Actual Dose Given (mg)
	Solution concentration 0.6 mg/mL	
In clinic followed by 30 minutes of observation	0.1 mL	0.06 mg
In clinic followed by 60 minutes of observation	1 mL	0.6 mg
1-2	1 mL	0.6 mg daily
3-4	2 mL	1.2 mg daily
5-6	4 mL	2.4 mg daily
	Solution concentration 6 mg/mL	
7-8	0.8 mL	4.8 mg daily
9-10	1.6 mL	9.6 mg daily
11-12	3.2 mL	19.2 mg daily
13-14	6.4 mL	38.4 mg daily
	Solution concentration 60mg/mL	
15-16	1.2 mL	75 mg daily
17-18	1.2 mL	75 mg daily
19-20	1.2 mL twice daily	75 mg twice daily
21-22	2.5 mL twice daily	150 mg twice daily
23-24	2.5 mL twice daily	150 mg twice daily
25-26	5 mL twice daily	300 mg twice daily
27 days onwards	5 mL twice daily	300 mg twice daily

mg, milligram; mL, milliliter

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