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Original Article

Human Leukocyte Antigen Genotypes and Trial of Desensitization in Patients With Oxcarbazepine-Induced Skin Rash: A Pilot Study

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ABSTRACT

BACKGROUND: Skin rash associated with specific antiepileptic drugs occurs not infrequently and it usually necessitates discontinuation of the causative drugs. An alternative strategy is to desensitize the individual to the offending drug. We checked the human leukocyte antigen genotypes and conducted a pilot study to investigate the usefulness and safety of desensitization in pediatric patients with skin rash associated with oxcarbazepine. **METHODS:** We enrolled 19 patients with epilepsy who had discontinued oxcarbazepine because of skin rash despite an initial good response and then became refractory to other antiepileptic drugs along with an individual with paroxysmal kinesigenic dyskinesia with a similar situation. High-resolution *HLA-A* and *-B* genotyping was performed to investigate the genetic risk. The desensitization began with 0.1 mg daily reaching 120 mg on the thirty-first day. Thereafter, the dose was increased at a rate of 12 mg/day. **RESULTS:** Nineteen patients completed the desensitization protocol to a target dosage over 2-5 months. Five patients developed itching and erythema during desensitization, but the symptoms disappeared after withholding a dose increment transiently. There were no human leukocyte antigen genotypes relevant to aromatic antiepileptic drug–induced severe hypersensitivity reactions. The seizure frequency was reduced to less than at baseline in 18 individuals. **CONCLUSION:** This study demonstrated 95% efficacy, including 42% seizure-free patients and the favorable tolerability of desensitization to oxcarbazepine in patients with intractable epilepsy and one patient with paroxysmal kinesigenic dyskinesia. Screening for sensitive human leukocyte antigen types and exclusion of severe hypersensitivity reactions should precede desensitization.

Keywords: desensitization, oxcarbazepine, children, rash, human leukocyte antigen, drug allergy

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Introduction

Skin rash associated with antiepileptic drugs (AEDs) is common with an average rate of 2.8%, and the risk is higher with aromatic AEDs such as phenytoin, phenobarbital, carbamazepine, and oxcarbazepine.[1,2] Skin rash occurs mostly as maculopapular erythema and typically resolves within a few days after drug discontinuation; however, it can progress to life-threatening reactions such as drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, and toxic epidermal necrosis.[2] The risk of rash was reported to be increased approximately threefold to fivefold in patients who experienced rash with another AED.[1-3] Therefore, once skin rash occurs, the choice of AEDs can be very limited.[2]

Antiepileptic drug–induced rash is the most frequent idiosyncratic reaction and clinically can be assumed as drug

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hypersensitivity or drug allergy although it is not determined via thorough evaluation by an allergist or immunologist, which appears to be dependent on individual inherent susceptibility.[2,4] Recent pharmacogenetic studies have uncovered a strong association between carbamazepine-induced severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, and *HLA-B**1502*, a human leukocyte antigen (HLA) belonging to a major histocompatibility complex class I, in Asian populations.[5-7] Further studies suggested that *HLA-B**1502* was also a common risk allele in aromatic AEDs such as oxcarbazepine, phenytoin, and lamotrigine, which have structural similarity to carbamazepine, when causing Stevens-Johnson syndrome and toxic epidermal necrosis.[8,9] However, this pharmacogenetic association does not always coincide, especially in AED-induced maculopapular erythema.[10-12]

The usual recommendation for drug-induced rash is to avoid the causative drug because it occasionally causes severe cutaneous adverse reactions. However, drug desensitization can be cautiously considered where no better alternative drugs are available for treatment of the underlying condition and where the benefits of desensitization outweigh the risks.[13,14] There have been several reports of desensitization to drugs such as antibiotics, aspirin, and allopurinol.[13-15] Similarly, desensitization of the causative AEDs deserves careful consideration if the drugs have effectively controlled refractory seizures. There have been few reports about desensitization of oxcarbazepine, carbamazepine, or phenytoin.[16-20] Therefore we conducted a pilot study to investigate the efficacy and safety of desensitization of oxcarbazepine after mild cutaneous adverse reactions. The secondary objective of this study was to investigate the association between *HLA-A* and *-B* genotypes and oxcarbazepine-related skin rash.

Methods

Patients

We recruited children with mild cutaneous adverse reactions to oxcarbazepine in the Samsung Medical Center (Seoul, Korea) from July 2009 to August 2012. This study was approved by the Ethics Committee of Samsung Medical Center, and informed consent was acquired from the parents. All patients were thoroughly reviewed for clinical manifestations and confirmed to have oxcarbazepine-induced hypersensitivity if the onset of rash occurred within one or three weeks of exposure without any other drug modification in that period and if the symptoms resolved after the discontinuation of oxcarbazepine. The severity and extents of rash were described by the physicians based on examination. A careful reintroduction of smaller doses of oxcarbazepine was tried if a rash was thought to be unrelated. However, if the skin rash reappeared, the patient was confirmed to have oxcarbazepine-induced hypersensitivity. Clinical data included age, gender, seizure etiology, type of seizure, cross-sensitivity with other AEDs, and clinical course of seizures. Features of allergic reactions other than cutaneous manifestations were also analyzed. These included hepatitis, bone marrow toxicity (including leukopenia, thrombocytopenia, and anemia), fever, or lymphadenopathy. The extents of rash were described as maculopapular erythema when the patients developed cutaneous itchy and erythematous macules or papules without systemic symptoms after administration of drug.[4] In addition, the allergic reactions were classified as generalized rash if they had mild associated systemic adverse reactions.

For the desensitization of oxcarbazepine, patients with the following indications were included in this study: (1) patients with an initial positive effect of seizure control with oxcarbazepine before the appearance of rash and (2) patients with poorly tolerated alternative AEDs or with noncontrolled seizures with more than two other AEDs. We excluded patients if oxcarbazepine caused severe cutaneous adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrosis, hemolytic anemia, or exfoliative dermatitis, because a reintroduction could induce dangerous and life-threatening reactions.[14,15]

HLA-A *and* -B *genotyping*

Deoxyribonucleic acid extraction

Genomic DNA was extracted from 200 μL of an ethylenediaminetetraacetic acid–treated whole blood sample using a QuickGene DNA whole blood kit S and QuickGene-Mini80 (Fujifilm Corp, Tokyo, Japan) according to the manufacturer's instructions. This extracted DNA was used for both sequencing-based typing. The concentration and purity of the DNA samples were measured as the optical density at 260 nm and the ratio of the optical densities at 260/280 nm, r, using a NanoDrop (Thermo Fisher Scientific, Wilmington, DE). The required concentration was 20-50 ng/μL and the purity was 1.7-1.9.

Sequencing-based typing

To type *HLA-A* and *-B* loci, genomic DNA was amplified using SeCore Sequencing Kits (Invitrogen Corp, Madison, WI). A master mix (20 μL) containing either *HLA-A* or *-B* locus–specific primers and FastStart Taq DNA polymerase (Roche Diagnostics Korea, Seoul, Korea) was added to the DNA sample (5 μL). The same volume of master mix was added to 5 μL of deionized water as a negative control. The DNA amplification was performed according to the program parameters in an ABI 9700 thermal cycler (Applied Biosystems Inc, Foster City, CA). After the primary amplification, the polymerase chain reaction products were sequenced using three separate sequencing primers for both *HLA-A* and *-B* loci (forward and reverse of exons 2, 3, and 4). After 25 cycles of the sequencing reaction, the DNA was purified, denatured, and sequenced using an ABI 3130 genetic analyzer (Applied Biosystems). Sequence data were analyzed using Assign-SBT 3.5+ software (Conexio Genomics, Fremantle, Western Australia, Australia).

Desensitization protocol

During desensitization, we used a solution form of oxcarbazepine for dilution. Each original solution was diluted with normal saline into three different concentrations (Table 1). Using the diluted suspensions, we gradually increased the dosage until the effect was optimal for seizure control or the dosage reached its upper limit. The desensitization protocol for this study was set up with modifications of a method described in a previous report about oxcarbazepine desensitization.[19] The present study schedule adapted a slower increment of dose than the previous protocol. At the beginning, the patients were recommended to stay at the hospital for 2 hours after the first dose because of the possible risk of acute allergic reactions. All patients were cautioned about a possible severe cutaneous adverse reaction and were instructed to discontinue desensitization and to consult our center if an adverse reaction, such as fever, pruritus, or skin eruption, appears. If the patients experienced localized skin rash without generalized symptoms during desensitization, the next step was to withhold the medication, and all patients were educated to take antihistamine until the rash had resolved. After that, the desensitization was cautiously reintroduced at lower dosage and the rate of dose increment was slowed. Neither drug modification, such as prescription of other AEDs, nor dose increment of coadministered agents was performed during desensitization.

Outcome assessment

Success or failure of desensitization, seizure control, and the occurrence of recurrent rash during desensitization were documented for the assessment of primary outcomes. Successful desensitization was defined as a state where the patient could tolerate oxcarbazepine at a dosage of 10 mg/kg/day without any allergic reactions. The seizure outcome was evaluated by comparing the 3-month seizure frequency between the initial period and the last follow-up. In addition, the time taken to reach the target dosage and the extent of cutaneous adverse reactions or other adverse events were appraised.