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CASE STUDY

Reintroduction of oxcarbazepine after allergic reaction in two pediatric patients with epilepsy

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Abstract

Allergic reactions are common reasons for withdrawal of oxcarbazepine treatment in patients with epilepsy. However, some patients are not responsive to other antiseizure medications. Herein, two pediatric patients with epilepsy and allergic to oxcarbazepine to whom oxcarbazepine therapy was successfully reintroduced are described. The reintroduction strategy used in this study was simple, feasible, and suitable for the reintroduction of oxcarbazepine in pediatric patients with epilepsy.

Introduction

Oxcarbazepine (OXC) is a new-generation antiseizure medication (ASM) that has been approved in several countries as monotherapy or adjunctive therapy for the treatment of partial seizures in pediatric patients.[1] OXC is among the first-choice options for the initial treatment of focal-onset seizures in the United States and China, with OXC use being progressively increase among Chinese pediatric patients with epilepsy.[2,3] Anaphylactic reaction is a common cause of withdrawal of OXC treatment; however, some patients still need this drug to manage their epilepsy manifestations, as the available therapeutic alternatives are ineffective.[4] In addition, the prevalence of cross-reactivity to other antiepileptic drugs in patients with allergy to OXC is reported to be 40%–58%.[5–7] Thus, reintroduction of OXC by desensitization may represent an important clinical option. Herein, two cases of successful reintroduction of OXC are reported.

Case Description

This study was approved by the ethics committee of the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China (20210003).

Patient 1 was a 195-day-old male who presented with seven seizures/day at the age 3 months. The patient weighed 11 kg. Electroencephalography (EEG) evaluation revealed epileptic discharges in the left posterior part. The patient was prescribed OXC (6.8 mg/kg/d) twice a day, resulting in seizure free. However, 1 week after treatment initiation, the patient had a skin rash throughout the whole body, presenting as a red urticaria rash. Given this

adverse reaction, OXC therapy was stopped and the rash subsided in 3 days without additional interventions. The Naranjo scale was used to assess the relationship between the adverse drug reactions and OXC therapy. The score was 6, suggesting a probable relationship. However, when the OXC was stopped, the frequency of the seizure episodes increased to 4–5 per day. Levetiracetam and lamotrigine were administered, but showed limited effect on seizure frequency. The test for HLA-B*1502, which is a risk biomarker of severe skin reactions to some drugs including OXC, was negative. Considering the clinical efficacy of OXC, the treatment was restarted at an initial dose of 1.7 mg/kg/d, which leads to a significant reduction in seizure frequency to only one seizure in nearly 2 days. Thus, the dose was doubled every week, and after 3 weeks, the patients had no seizure episodes at an OXC dosing of 13.64 mg/kg/day, which was higher than the original dose. Seizure was well controlled during 1 year, without dermatological adverse events, such as rash, being reported.

Patient 2 was an 11-year-old male who weighed 35 kg and presented seizure episodes lasting for nearly 2–3 min, approximately three times per day, since age 9 years. EEG showed epileptic discharges in the posterior left part of the brain, with normal cranial magnetic resonance imaging. Administration of OXC (8.6 mg/kg/d) was started, resulting in cessation of the seizures. However, 6 days after, a facial rash accompanied by itchiness appeared. As the Naranjo Scale score was 6, OXC therapy was stopped, and the rash subsided in 3 days without additional interventions. Treatment with levetiracetam and lamotrigine was then initiated, but the patient was still experiencing some seizure episodes. As the test for HLA-B*1502 was negative, OXC was restarted at a dose of 2.15 mg/kg/d, which was doubled every week up to 17.2 mg/kg/d (higher than the initial dose). The patient experienced only one seizure episode in approximately 3 days during the first 2 weeks of OXC reintroduction, and no seizure episode was reported for 1 year. Adverse reactions, such as rash and itching, were not reported during drug desensitization. The reintroduction process of these two cases are shown in Figure 1.

Discussion

This study describes the successful reintroduction of OXC in two pediatric patients who were allergic to OXC. The herein described OXC reintroduction strategy was simple and feasible, and proved to be safe and effective for the clinical management of epilepsy.

There are several reports on the desensitization of ASMs for patients at different ages, such as OXC, carbamazepine, and valproic acid.[4,8,9] However, desensitization should be considered for patients who show OXC-induced mild rashes and have no effective alternative drugs. Patients with history of severe cutaneous reactions are contraindicated for readministration. The herein presented cases were HLA-B*1502 negative, which indicated a low possibility of severe cutaneous reactions in Asian population.[10]

Selection of the initial dose for reintroduction is an important factor. A low restart dose may prolong the duration of the reintroduction protocol and delay the control of the seizures, but a high restart dose may cause reintroduction failure. There is no consensus on drug desensitization protocols for delayed-type hypersensitivity reactions, and the initial dose may vary from 1:8 to $1:10^6$ of the therapeutic daily dose.[11] The few studies available on OXC reintroduction often choose an initial dose of 0.1 mg.[12,13] Considering the low severity of the adverse reactions and the need for seizure control, the two patients were administered a quarter of the original dose as the restart dose. No allergic reactions occurred and the incidence of seizures decreased rapidly in both patients, suggesting that the restart dose was safe and suitable for reintroduction.

Another important issue of reintroduction is the dose increment protocol. The available literature describes an everyday increment strategy, which was proven safe and effective.[13,14] However, this procedure can be complex, being difficult for outpatients to follow the procedure without the help of a physician or pharmacist. In the present cases, a weekly double-dose strategy was used and the results proved that this increment protocol was suitable.

The pathogenesis of ASM-induced hypersensitivity is believed to result from toxic drug metabolites that either directly cause cell death or act as prohaptens to evoke an immune response by binding to T cells.[14] However, the specific immune mechanism by which tolerance can occur with slow reintroduction of the drugs in the setting of delayed T-cell-mediated reactions remains unclear; thus, the reported reintroduction strategy, as well as that applied in previously reported cases, was empirical.[15] A better understanding of the underlying hypersensitivity mechanism can help define a mechanism-guided reintroduction strategy.

Conclusions

For patients who are allergic to OXC but not responsive to other ASMs, reintroduction of OXC by desensitization can be cautiously considered as a clinical valuable alternative. The reintroduction strategy used in this study was simple, feasible, and suitable for the reintroduction of OXC in pediatric patients with epilepsy.

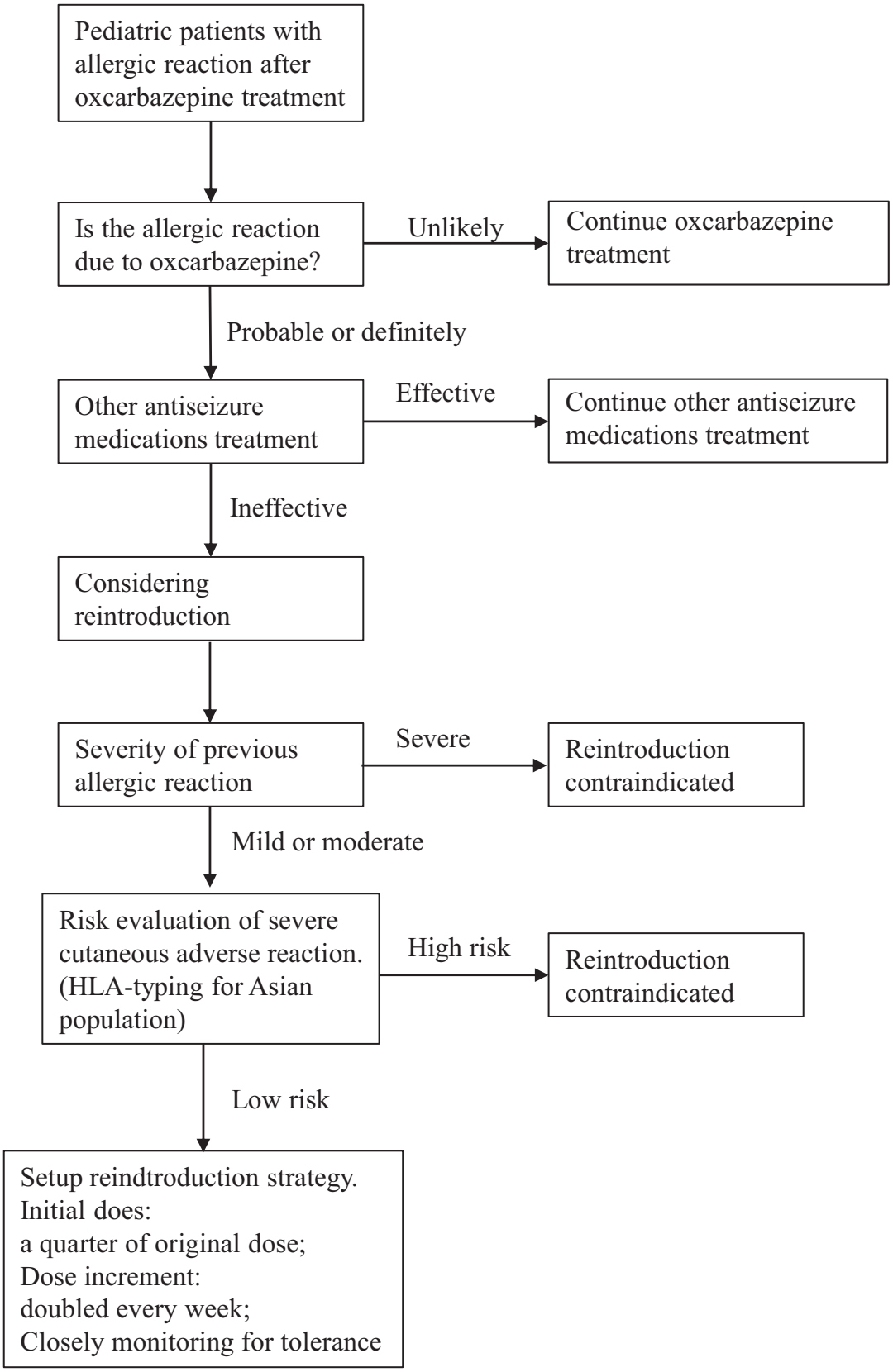

FIGURE 1. Flowchart illustrating the reintroduction process of oxcarbazepine after allergic reaction in two pediatric patients.

Author Contributions

Conceptualization, LY and JF; Data curation, LY and ZW; Formal analysis, LY, ZW, and ZY; Investigation, LY, ZW, and ZY; Methodology, LY; Project administration, HD; Resources, LY and JF; Supervision, JF and HD; Validation, HD; Roles/Writing – original draft, LY and ZW; Writing – review and editing, JF and HD. All authors had read and approved the final article.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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