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Carbamazepine Cutaneous Adverse Reactions: The Importance of an Alternative Anticonvulsant

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Abstract

Antiepileptic drugs frequently provoke Cutaneous Adverse Drug Reactions (cADRs). The management of these reactions often requires discontinuation of the therapy. Cross reactivity among the most common antiepileptics (phenytoin, carbamazepine, and oxcarbazepine) is reported.

We described four patients with seizures who experienced cADRs secondary to carbamazepine (CBZ) treatment. Because of the failure of other alternative treatment, they underwent allergological work-up with CBZ and Oxcarbazepine (OXC).

Skin tests and patch tests were negative for CBZ and OXC in all patients. Our four patients tolerated OXC during the graduated oral tolerance test and no adverse reactions were observed in the follow-up period.

Introduction

Antiepileptic Drugs (AEDs) are frequently responsible of adverse drug reactions (cADRs) [1,2] that can be mild or life-threatening severe (Stevens–Johnson Syndrome, toxic epidermal necrolysis, hypersensitivity syndrome). Urticaria and/or maculopapular exanthema are relatively common in patients treated with aromatic anticonvulsants such as Carbamazepine (CBZ). The management of these reactions often requires discontinuation of the therapy. Cross reactivity among the most common antiepileptics (phenytoin, carbamazepine, and oxcarbazepine) is reported [3]. Allergological evaluation in a patient with suspected hypersensitivity is mandatory to rule out or confirm a cross-reactivity with an alternative anticonvulsant.

We report a retrospective case series of four patients with epilepsy who experienced cutaneous hypersesnitivity reactions secondary to CBZ treatment.

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Case reports

Patient 1

A 13-year-old female caucasic patient with right temporal ganglioglyoma developed generalized and itching erythema after 7 days of therapy with CBZ (5 mg/kg, daily). Aromatic antiepileptic was replaced with sodium valproate. Since the seizures progressively worsened and were not controlled by various associations of other AEDs such as topiramate, levetiracetam, valproate, benzodiazepine, a therapy with an analog of CBZ was tested. Oxcarbazepine (OXC) was mandatory for the child neuropsychiatric specialist.

Patient 2

A 18-year-old male suffering from symptomatic focal epilepsy, due to parietal poroencephalic cyst, was treated with CBZ (200 mg/day). Fourteen days later, the patient developed generalized maculopapular exanthema. The drug was immediately withdrawn and symptoms resolved in one week. CBZ was switched to topimarate and phenobarbital. Ten months later, frequent focal seizures, often followed by secondary generalization, prompted admission to the Neuropsychiatry dept.

Patient 3

A 9-year-old female patient affected by cortical dysplasia associated to partial epilepsy, developed generalized maculopapular eruption after 14 days of therapy with CBZ (6 mg/kg, daily). Drug administration was stopped and the lesions disappeared in 4 days. A new protocol with topiramate, levetiracetam, sodium valproate and phenytoin was started, but recurrent focal seizures (more than 50 seizures/day) occurred. The neurologist required an allergological evaluation.

Patient 4

A 8-year-old male, with a history of cryptogenic focal epilepsy, suffered seizures weekly. Initially, he received valproic acid, without seizure control. Then, this drug was replaced by CBZ (3 mg/kg, daily), increased after a week to 6 mg/kg. Ten days later, the patient developed a itching and erythematous maculopapular rash involving hands and legs. The drug was immediately discontinued and symptoms disappeared in one week. CZB was switched to clobazam, and then to levetiracetam. As he had frequent focal seizures often followed by secondary generalization, he was admitted to Neuropsychiatry department.

In all patients symptoms were treated with oral antihistamines and intramuscular corticosteroids. During drug reactions, all patients underwent both blood analysis (i.e. blood count, liver and kidney function tests, inflammation indexes) and urine analysis with normal results.

Allergological work-up

Patients were admitted to the Day Hospital of Allergy Unit of Fondazione Policlinico A. Gemelli (Rome, Italy) to undergo allergological evaluation four weeks after their symptoms were disappeared and they had stopped antihistamines and corticosteroids. In all cases, treatment with OXC was suggested. Therefore, after obtaining informed consent, skin tests (prick tests) and patch tests were performed with CBZ and OXC. Skin tests were carried out on the volar surface of the forearm using the tablet powder of each drug (i.e. CBZ, Tegretol® 400 mg and OXC, Tolep® 300 mg), diluted in saline solution; readings were made after 20 minutes. Patch tests were performed for both drugs diluted in petrolatum at the concentration of 10% [4], applied in occlusion on the back and removed after 48 hours; readings were made at 48 and 72 hours.

Oral provocation test with CBZ were not performed for the risk of more severe systemic reactions also in case of negative skin and patch test results.

We planned a graduated oral tolerance test with OXC at increasing dilutions (the tablet powder was dissolved in water), until the final dose of 300 mg (Table 1). Dose increases were made unless symptoms occurred. Each patient took four daily doses for four consecutive days. The total dose achieved was adapted for each patient according to his/her own therapeutic regimen. The schedule was followed at home with gradual increase of the dose according to the prescription. Patients were monitored for 48 hours after the last dose received.

Results

Skin prick and patch tests were negative for CBZ and OXC in all patients. All patients tolerated OXC during the oral tolerance test and no adverse reactions were reported during the follow-up.

Then, all patients continued at home anticonvulsant therapy (Table 2).

Every 6 months, for two years we made a telephonic follow-up. Any reaction was reported.

Table 1: Protocol of oral tolerance test with OXC.

DAY	DOSES
I	0.3 mg, 0.6 mg, 0.9 mg, 1.2 mg
II	3 mg, 6 mg, 9 mg, 12mg
III	30 mg, 60 mg, 90mg
IV	300 mg (one tablet)

Table 2: Protocol of continuation of OXC therapy at home.

Patients	Dose Increases	Final Dose Reached
1	25 mg/day, in fifty days	1400 mg/day
2	30 mg/every two days, in eighty days	1500 mg/day
3	25 mg/day, in ninety days	900 mg/day
4	25 mg/day, in eighty days	600 mg/day

Discussion

OXC is an alternative for patients unable to tolerate CBZ, that generally is the first-line antiepileptic drug treatment for patients with partial onset seizures [5].

OXC causes less skin reactions than CBZ owing to its different metabolic pathway. OXC is almost completely metabolized through reduction and conjugation to yield an active monohydroxy derivative (MHD), which is glucuronidated and excreted in the urine. In contrast, the oxidation of CBZ to 10, 11- epoxide is regarded as the most common cause of side effects [6].

Nevertheless, cross-sensitivities with OXC in patients with known rashes from CBZ have been found in the range of 25-30% [7].

Patch test is useful for the diagnosis of anticonvulsant hypersensitivity; the positive responses to patch tests with CBZ range from 18.9% [8] to 76.5% [9]. Previous studies showed that positive predictive value of patch test to CBZ is relatively useful for the diagnosis [10-12], even if negative results of patch test cannot exclude the possibility of hypersensitivity reaction.

The underlying mechanisms of these manifestations are not yet completely understood. A toxic pathogenic mechanism related to reactive metabolites, as well as an immunological T-cell mediated mechanism, or a combination of both has been hypothesized [13]. The role of viral infections (naïve OR reactived) has also been involved in the pathogenesis of adverse drug reactions.

All our patients showed a negative results to patch test for CBZ as well as to skin tests; thus, we ruled out a diagnosis of allergic hypersensitivity.

An alternative management of these patients could be the desensitization to CBZ, as described in the literature [14,15]. We did not performed desensitization with CBZ for the risk of more severe reactions in patients with compromised physical conditions.

In our group of patients, OXC was the drug of choice since alternative strategy was not successful to control seizures. Allergological evalution (skin test, patch test and graduated oral tolerance test) for OXC allowed us to rule out hypersensitivity mechanisms; thus, our patients benefited from the treatment with OXC that, due to potential cross-reactivity, was initially excluded.

Conclusions

Our case series showed that a careful allergological evaluation is important in the management of patients with skin rashes associated to aromatic anticonvulsant agents, to avoid ineffective alternative treatments.

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