CASE SERIES
Oxcarbazepine-induced skin reactions – A case series

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Received: February 04, 2023; Accepted: March 03, 2023

ABSTRACT
Oxcarbazepine, an antiepileptic medication, can cause adverse drug reactions (ADRs). These rashes can range in severity and present as maculopapular, urticarial, or as a fixed drug eruption. The onset of the rash can occur within a few days to several weeks after starting the medication. We report three cases of ADRs in the form of series of skin reactions in patients who were prescribed Oxcarbazepine. In addition, the series also depicts the importance of stopping Oxcarbazepine use and seek medical attention if a rash is suspected to be drug-induced. Proper knowledge, recognition, and management of this adverse reaction can help minimize the risk of further harm.

KEY WORDS: Oxcarbazepine; Acute Urticaria; Maculopapular Rash; Erythematous Papules

INTRODUCTION
Harmful and unintended reactions to medicines that occur at doses normally used for treatment are called adverse drug reactions (ADRs).

Oxcarbazepine is an antiepileptic drug (AED) commonly used for treating seizures and neuropathic pain. ADRs related to oxcarbazepine can occur within a few days to several weeks after initiation of therapy and can range from mild to severe. The rash can present as maculopapular,[2] urticarial, or even as a fixed drug eruption. Furthermore, there are reports of adverse events in form of eosinophilia and systemic involvement in the form of dermatitis.[3] It is important to recognize and report any suspicious adverse reactions to a health-care provider to ensure proper management and to minimize risk of further harm.

CASE REPORTS
Case 1
A 52-year-old female patient had a single episode of seizure, for which she was prescribed Tab. Levetiracetam 500 mg once daily. Missing the dose for a few days, she suffered from another episode of seizure, after which, Tab. Sodium Valproate 250 mg and Tab. Oxcarbazepine 300 mg twice daily were added along with Tab. Levetiracetam 500 mg. After 10–15 days, the patient suddenly started developing red, itchy lesions, initially over the neck and face, which progressed to involve the entire trunk and both the upper and lower limbs. There were multiple red lesions associated with itching. On examination, multiple erythematous papules and coalescing to form plaques were present on the face, involving both ears, along with exfoliation present over both the cheeks and lower half of the face. A diffuse, ill-defined, and mildly blanchable erythema was present over the anterior
and posterior aspects of the trunk, with relative sparing of the folds. Furthermore, multiple erythematous to violaceous colored papules coalescing to form plaques were present over bilateral upper limbs extending to forearms, bilateral thighs, and lower limbs [Figure 1]. A pathology test was done on the left arm, which came out to be negative. Tab. Oxcarbazepine was stopped, and the patient was prescribed Inj. Pheniramine Maleate I.V. stat and Tab. Fexofenadine 180 mg for 2 days, along with Inj. Hydrocortisone 100 mg IV stat for 1 day. After continued observation in the hospital and treatment, the patient demonstrated stabilization of the reaction with no further progression. The patient had been taking Tab. Levetiracetam and Tab. Sodium Valproate for several days before the onset of skin reactions, but only developed the reactions after the introduction of Tab. Oxcarbazepine. In addition, the skin reactions improved after discontinuation of Tab. Oxcarbazepine and treatment with antihistamines and corticosteroids. Finally, there were no other plausible causes for the skin reactions in this case. This patient had no history of drug reactions in the past. Skin reactions are a known adverse drug reaction (ADR) due to the use of Oxcarbazepine. This case has been reported to the Indian Pharmacopoeia Commission with the unique ID number IN-IPC-300728537. Causality assessment for the drug is probable.

Case 2
A 61-year-old female patient suffering from Trigeminal neuralgia was prescribed Tab. Oxcarbazepine 300 mg. After taking a single dose, within 10 min, the patient started having a sudden onset of red, itchy lesions over the thighs associated with itching. The lesions gradually started spreading over the trunk and then to both the upper limbs within the next 1–2 h. On examination, there were ill defined irregular blanchable erythematous patches present over the trunk, B/L axilla, and B/L palms [Figure 2]. Furthermore, on taking the further history of patient, she had the same episode of this kind of reaction in the past from the same medication, she was prescribed for the seizure. The patient was asked to stop the Tab. Oxcarbazepine immediately and was given Tab. Levocetirizine twice daily for 5 days and calamine lotion. After 5 days of hospitalization, the patient showed signs of improvement through continued observation and treatment in the hospital, displaying stability without any further deterioration of her reaction. In this case, the patient had no history of taking any other drugs along with Tab. Oxcarbazepine. The rashes resolved after stopping Tab. Oxcarbazepine and continued observation. This case has been reported to the Indian Pharmacopoeia Commission with the unique ID number IN-IPC-300691412. Causality assessment for the drug is probable.

Case 3
A 20-year-old male patient suffering from seizures due to cerebral venous sinus thrombosis was prescribed Tab. Oxcarbazepine 450 mg along with Tab. Sodium Valproate 500 mg. After 2 days of continued medication, the patient started having skin reactions in the form of red and itchy lesions, which initially were present over both the legs and trunk. On examination, multiple, discrete, and blanchable erythematous papules and macules were present on the trunk, back, abdomen, and both upper and lower limbs except the palms and soles. The patient was asked to stop the Tab. Oxcarbazepine immediately and was managed using Tab. Levocetirizine 5 mg, calamine lotion, Inj. Dexamethasone 1.5 cc I.V., and Inj. Pheniramine Maleate stat. In this case the patient was taking Tab. Sodium Valproate for seizures but developed skin reactions only after the introduction of Tab. Oxcarbazepine. This case has been reported to the Indian Pharmacopoeia Commission with the unique ID number IN-IPC-300691412. Causality assessment for the drug is probable.

DISCUSSION
Oxcarbazepine is a new AED, a 10-keto derivative of Carbamazepine. Similar to carbamazepine in terms of clinical efficacy, oxcarbazepine due to the different metabolic pathways, has fewer side-effects. Although less common, Oxcarbazepine has some of the same side effects as Carbamazepine, including fatigue, headache, nausea, and vomiting, as well
as serious skin reactions in the form of Stevens-Johnson syndrome.\textsuperscript{[6-8]} However, unlike carbamazepine, oxcarbazepine is less associated with cutaneous ADRs.

Although the precise process by which Oxcarbazepine triggers rashes is not entirely known, it is believed to be connected to the drug’s effects on the immune system and genetics. There have been reports in the past regarding the association of HLA-B*1502 with the genetic sensitivity of the Oxcarbazepine-induced skin reactions.\textsuperscript{[9,10]} Sometimes two drugs are prescribed simultaneously to the patient, one being a CYP3A inhibitor and Oxcarbazepine being a CYP3A4/5 inducer, thereby increasing the serum concentration of the drug in the body.\textsuperscript{[11]} There have been reports of skin toxicity dependent on normal doses, as happened in Case 2 [Table 1]. However, in Cases 1 and 3, the patient was prescribed Tab. Oxcarbazepine and Tab. Sodium Valproate which may have some association leading to an increased risk of cutaneous ADRs, for which scanty reports are available. Dechallenge was done in all three cases and based on the history and clinical presentation; it is highly likely that skin reactions in all the three cases were due to Tab. Oxcarbazepine. The reactions occurred shortly after the initiation of Tab. Oxcarbazepine, which improved after the discontinuation of the medication. Therefore, based on the temporal relationship, clinical presentation, and response to treatment, Tab. Oxcarbazepine is the most probable cause of the skin reactions. According to the WHO-UMC causality assessment,\textsuperscript{[11]} there is a probabilistic cause in all the cases.

### Table 1: Comparative evaluation of similar studies

<table>
<thead>
<tr>
<th>Reporter details</th>
<th>Study</th>
<th>Inferences</th>
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</thead>
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<td>Prospective study</td>
<td>HLA-B*1502 has association with Oxcarbazepine induced maculopapular eruption in the Han population of China</td>
</tr>
<tr>
<td>He et al.,\textsuperscript{[10]}</td>
<td>Prospective study</td>
<td>HLA-B*1502 has association with Oxcarbazepine induced maculopapular eruption in the Han population of China</td>
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<td>Wang et al.,\textsuperscript{[12]}</td>
<td>Retrospective study</td>
<td>8.92% of skin adverse reactions among AEDs are due to Oxcarbazepine</td>
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<td>Keshri\textsuperscript{[13]}</td>
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<td>Oxcarbazepine 300 mg/day is associated with Toxic epidermal necrolysis with high leucocyte count and high C-reactive protein count</td>
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<td>Trivedi et al.,\textsuperscript{[4]}</td>
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<td>Sharma et al.,\textsuperscript{[3]}</td>
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<td>Oxcarbazepine 600 mg/day has association with Stevens-Johnson syndrome, high leucocyte count and high C-reactive protein count</td>
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</table>

### CONCLUSION

A registry should be prepared of all patients presenting with the skin reactions after taking Oxcarbazepine. This will give us a fair idea regarding the association of adverse drug reaction with Oxcarbazepine. It will guide the physicians towards judicious use of Oxcarbazepine in the future. To start with a low dose of the medication and gradually increase it over a period, it will help the body to adjust to the medication and can reduce the likelihood of developing serious rashes.

### REFERENCES


**Source of Support:** Nil, **Conflicts of Interest:** None declared.