Analysis of Adverse Drug Reactions with Carbamazepine and Oxcarbazepine at a Tertiary Care Hospital

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Purpose: To describe adverse drug reactions (ADRs) to carbamazepine (CBZ) and oxcarbazepine (OXC), including severe cutaneous ADRs, at a tertiary care hospital over a 10-year period.

Materials and Methods: The frequency and clinical features of ADRs caused by CBZ and OXC were analyzed using the pharmacovigilance database and spontaneous ADR reporting data of Yonsei University Severance Hospital & Dental Hospital (Seoul, Korea) from January 1, 2010 to January 31, 2020.

Results: Among 10419 cases prescribed CBZ and OXC, 204 ADR cases were reported. The incidences of ADRs were 1.8% and 2.2% for CBZ and OXC respectively, with no significant difference (p=0.169). The most common clinical presentations were skin disorders. Female patients had relatively more frequent ADRs than male patients. Although mild skin ADRs were more frequent with OXC, nervous system disorders, general disorders, and hepatobiliary disorders occurred more often with CBZ. There were six reports of severe cutaneous adverse reactions to CBZ, while OXC had none. Both CBZ and OXC caused ADRs at daily doses lower than the recommended initial dose.

Conclusion: Due to lower incidence of severe ADRs with OXC than CBZ, we suggest OXC as a first-line prescription.

Key Words: Carbamazepine, oxcarbazepine, drug related adverse reactions, anticonvulsants
number of seizures, increased alertness and concentration, and disappearance of allergic skin reactions associated with CBZ. OXC is known to exhibit anti-epileptic activity comparable with CBZ when a 50% higher dose is applied. Despite the higher dose, the incidence and severity of adverse reactions are reportedly lower than those with CBZ.

CBZ and OXC can cause similar adverse reactions, such as skin rash, central nervous system disorders, and digestive system disorders. They are also known to be causative drugs for severe cutaneous adverse reactions (SCARs), such as erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). Based on the individual case safety reports of SCARs in the Korean population from 1988 to 2013, CBZ is known to be the second most common causative drug for SCARs, including SJS, TEN, and DRESS.

This study aimed to examine the frequency and clinical features of ADR caused by CBZ and OXC using the spontaneous ADR reporting database of Yonsei University Severance Hospital & Dental Hospital.

**MATERIALS AND METHODS**

Using the pharmacovigilance database and spontaneous ADR reporting data of Yonsei University Severance Hospital & Dental Hospital (Seoul, Korea) from January 1, 2010 to January 31, 2020, we selected the data and reports of patients with spontaneous reports of ADR associated with CBZ and OXC. The subjects were of ages 15 and over, and their diagnoses were classified. The clinical features of ADR reports were classified using the preferred terms of System Organ Class published by MedDRA®, Medical Dictionary for Drug Regulatory Activities, a standardized dictionary of medical terminology, developed under the auspices of the International Conference of Harmonisation (MedDRA MSSO, Brussels, Belgium): “Skin disorders,” “Nervous system disorders,” “Gastrointestinal disorders,” “Blood and lymphatic system disorders,” “General disorders and administration site conditions,” and “Hepatobiliary disorders.”

Symptoms of skin disorders included rash, urticaria, erythema, and symptoms of fatal cutaneous reaction (e.g., EM, SJS, TEN, and DRESS). Symptoms of nervous system disorders included sleepiness, dizziness, memory impairment, headache, and tremor. Indigestion and vomiting were classified as gastrointestinal disorders. General disorders showed fever and weakness.

With the obtained data and reports, we analyzed the ADR incidences for each drug in connection with the reported daily dose. For CBZ, we also compared the stated ADR daily dose of immediate-release (IR) and controlled-release (CR) formulations.

This study protocol was approved by the Institutional Review Board of Yonsei University Dental Hospital (IRB No. 2-2020-0017).

**Statistical analyses**

From obtained reports, we calculated incidences according to the clinical features of ADRs for CBZ and OXC. The data were analyzed using Statistical Software for Social Sciences version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics and chi-square tests were used. Statistical significance was considered at p<0.1.

**RESULTS**

There were 9312 patients who have been prescribed either CBZ or OXC among a total of 10419 cases, of which 5094 (48.9%) were male and 5325 (51.1%) were female; the remaining 1107 were prescribed both. The age of the subjects ranged from 15 to 97, with a mean age of 46.6 years. The diagnoses of the patients were classified as “neuropathic pain,” “episodic neurologic symptoms,” “bipolar disorders,” or others (Table 1).

The spontaneous ADR reporting system contained records of 204 ADR cases in 195 patients. There were 107 patients who experienced ADRs for CBZ only, 79 patients for OXC only, and nine for patients taking both drugs. 153 patients (75.0%) were reported to have one ADR clinical feature, while 39 patients (19.1%) and 11 patients (5.4%) had two and three ADR clinical features, respectively. Only 1 patient (0.5%) presented with four ADR clinical features. There was no statistically significant difference in ADR incidence for CBZ and OXC (CBZ: 1.8%, OXC: 2.2%, p=0.169). ADR incidence did not correlate with age (p=0.495). Female, however, showed higher ADR rates for both drugs (p<0.001) (Table 2).

The most common types of ADRs associated with the drugs

| Table 1. Baseline Characteristics of the Patients |
|-----------------------------------------------|
| Sex                                           |
| Male                                         | 3040 (29.2) | 2054 (19.7) | 5094 (48.9) |
| Female                                       | 3368 (32.3) | 1957 (18.8) | 5325 (51.1) |
| Age (yr)                                      |
| 15–19                                        | 280 (2.7)   | 630 (6.0)   | 910 (8.7)   |
| 20–29                                        | 873 (8.4)   | 645 (6.2)   | 1518 (14.6) |
| 30–39                                        | 966 (9.3)   | 634 (6.1)   | 1600 (15.4) |
| 40–49                                        | 1030 (9.9)  | 642 (6.2)   | 1672 (16.0) |
| 50–59                                        | 1180 (11.3) | 612 (5.9)   | 1792 (17.2) |
| 60–69                                        | 1038 (10.0) | 506 (4.9)   | 1544 (14.8) |
| 70 and over                                   | 1041 (10.0) | 342 (3.3)   | 1383 (13.3) |
| Diagnosis                                     |
| Neuropathic pain                              | 2582 (24.8) | 886 (8.5)   | 3468 (33.3) |
| Episodic neurologic symptoms                  | 2953 (28.4) | 2964 (28.5) | 5923 (56.8) |
| Bipolar disorders                             | 410 (3.9)   | 44 (0.4)    | 454 (4.4)   |
| Others                                        | 457 (4.4)   | 117 (1.1)   | 574 (5.5)   |
| Total                                         | 6408 (61.5) | 4011 (38.5) | 10419 (100) |

CBZ, carbamazepine; OXC, oxcarbazepine. Data are presented as n (%).
were mild skin disorders (non-SCAR), followed by nervous system disorders (Table 3). CBZ caused more ADRs related to the nervous system ($p=0.087$) and general ($p=0.077$) and hepatobiliary ($p=0.091$) disorders than did OXC (Fig. 1A). OXC was associated with a higher incidence of mild skin disorders ($p=0.013$) (Fig. 1B). Six patients reported SCARs, including EM, SJS, TEN, and DRESS, by CBZ. The symptoms started with skin rash and urticaria 14–30 days after taking the drug. Five of them had discontinued the drug right after the symptoms appeared. They were referred to the Departments of Allergy and Immunology and of Dermatology and Infectious Diseases and diagnosed with EM (F/70), SJS (F/74, F/37, F/67), TEN (F/44), and DRESS (M/74). After supportive care, all six experienced relief of symptoms. There were no reports of SCARs due to OXC.

The daily doses of the drugs, compared to the initial daily dose in patients without ADRs, were analyzed. At daily doses lower than the recommended initial dose (400 mg/day for CBZ IR and CR formulation, 600 mg/day for OXC), all drugs were found to cause ADRs (Fig. 2).

### DISCUSSION

OXC is indicated in both monotherapy and adjunctive therapy for the treatment of partial seizures with or without secondary generalization in adults and children above 4 years (USA) or 6 years (Europe) of age. However, in this study, we chose subjects older than 15 years, since CBZ is more rapidly metabolized to carbamazepine-10,11-epoxide in children below age 15. Thus, over the age of 15 years, the result of our study showed no significant relationship between age and ADR incidence.

Gender differences in ADRs have been reported mainly for gastrointestinal disorders. In males, electrolyte disturbances are known to be more frequent, while female commonly present with more gastrointestinal and cutaneous allergic reactions. Female generally have a lower lean body mass, reduced hepatic clearance, and lower activity of cytochrome P450 (CYP) enzymes; thereby, female tend to metabolize drugs at lower rates than male. Female also show higher rates of consultation and complaints, as well as better compliance with drugs. Our results revealed no significant differences in overall ADR incidences between CBZ and OXC. However, nervous system disorders, general disorders, and hepatobiliary disorders occurred mostly with CBZ. Since OXC was developed by altering the structure of CBZ with the intent to avoid metabolites causing side effects, the mechanism of action of OXC mainly involves blockade of sodium channels, but differs from CBZ by modulating different types of calcium channels. In contrast to CBZ, which is oxidized by the cytochrome P-450 system, OXC undergoes reductive metabolism at its keto moiety to form the monohydroxy derivative, which is glucuronidated and excreted in the urine. The involvement of the hepatic cytochrome P-450 dependent enzymes in the metabolism of OXC is minimal.

The fact that there was no report of SCAR directly for OXC, while CBZ had six cases, is notable. Fortunately, all patients with SCARs to CBZ received treatment after proper specialist care.
referral. Management should begin with the withdrawal of the suspected drug, as early withdrawal of drugs with a short elimination half-life is associated with better outcomes of patients with severe drug eruptions. In the one case of the SJS patient, changing the drug right after the occurrence of the severe ADR did not eradicate the symptoms. In cases of acute skin failure, patient management must be undertaken in specialized intensive care units or in burn units. The prompt decision of the clinician is necessary for a favorable prognosis.

According to the ADR reports in this study, there was a difference in daily doses between IR and CR tablets of CBZ in relation to ADRs. For CBZ CR, most of the ADR cases were reported at 400 mg/day, while CBZ IR had a number of reports at 100, 200, and 300 mg/day. OXC mainly showed ADRs at a dose of 150, 300, and 600 mg/day. This might arise as a result of use instructions provided to patients at Yonsei University Severance Hospital & Dental Hospital. The CBZ medications we use consist of 200 mg tablets of CBZ CR formulation and 200 mg and 400 mg tablets of CBZ IR formulation. For OXC, 300 mg and 600 mg OXC IR formulations are available. The recommended initial doses of CBZ and OXC are 200 mg twice daily (400 mg/day) and 300 mg twice daily (600 mg/day), respectively. Although the accuracy of tablet splitting is controversial, IR formulation can be halved, while CR formulation is not recommended to be modified. Since the halved CBZ IR and OXC already showed a considerable number of ADR reports, we recommend starting from a lower dose to prevent possible ADR events. Also, clinicians should consider administering half-dose tablets of CBZ and OXC.

This study was based on spontaneous reports of clinicians prescribing the drugs. All spontaneous reporting systems are affected by under-reporting. Considering the purpose of the system, most reports were intended to document that the doctor had to change or withdraw the medication due to ADR symptoms. We should keep in mind that the incidence might not include mild symptoms that the patient could endure during treatment.

As CBZ and OXC are commonly used in clinics, clinicians should be aware of the likelihood of ADRs with respect to these drugs. Although OXC had more reports of mild skin reactions, SCARs only occurred with CBZ. Furthermore, other types of ADRs, such as nervous system disorders, general disorders, and hepatobiliary disorders, showed higher incidences with CBZ. OXC has been proven to have anti-epileptic efficacy comparable with CBZ and also has FDA approved indications for children. Based on this limited study, we recommend OXC as a first-line prescription of anti-epileptic drugs. Given the significant number of ADR reports at daily doses below the recom-
mendment, initial doses of CBZ and OXC should be set even lower. Even in cases of severe ADRs, fast and proper management by clinicians can prevent serious outcomes.

**AUTHOR CONTRIBUTIONS**

Conceptualization: Alec Hyungtack Kim and Seong Taek Kim. Data curation: Jung Eun Lee and Soo Hyun Kim. Formal analysis: Jung Eun Lee. Funding acquisition: Seong Taek Kim. Investigation: Jung Eun Lee and Soo Hyun Kim. Methodology: Jung Eun Lee. Project administration: Jung Eun Lee. Resources: Soo Hyun Kim. Software: Jung Eun Lee and Kang Ryul Min. Supervision: Alec Hyungtack Kim and Seong Taek Kim. Validation: Seong Taek Kim. Visualization: Jung Eun Lee and Seong Taek Kim. Writing—original draft: Jung Eun Lee. Writing—review & editing: Kang Ryul Min, Alec Hyungtack Kim, and Lee and Seong Taek Kim. Writing—review & editing: Kang Ryul Min, Alec Hyungtack Kim, and Seong Taek Kim. Approval of final manuscript: all authors.

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