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

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

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감사의 글

어느덧 전문의 수련과정이 끝나고, 대학원 과정을 마무리 지어감에 따라 연세대학교치과병원 구강내과학교실에서의 인연이 한 번의 끝맺음을 향해가고 있습니다. 대학원 학위 과정을 마무리하면서 그 동안 도움을 주신 모든 분들께 감사의 마음을 전하고자 합니다.

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항상 저를 지지하고 격려해주시는 부모님과 오랜 기간 공부하느라 고생하고 있는 소중한 동생 주은이에게도 감사한 마음을 전합니다. 가족이라는 든든한 버팀목이 있었기에 결실을 맺을 수 있었습니다.

본 학위 과정을 통해 얻은 지식과 지혜로 더욱 발전하여 연세대학교치과병원 구강내과학교실과의 인연을 더 빛낼 수 있는 사람이 되도록 앞으로도 정진하고 노력하겠습니다.

2021년 12월

저자 이정은 드림

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Adverse drug reactions (ADRs) of carbamazepine (CBZ) and oxcarbazepine (OXC), including severe cutaneous adverse reactions (SCARs) have been constantly reported.

The aim of this study is to examine the frequency and clinical features of the ADR caused by CBZ and OXC using the pharmacovigilance database and spontaneous ADR reporting data of tertiary care hospital.

Among 10419 cases of prescribing CBZ and OXC, 204 ADR cases were reported. The incidence

of ADR was 1.8% and 2.2% for CBZ and OXC, with no significant difference (p=0.169). The most common clinical feature of ADR was skin and subcutaneous tissue disorders. Female patients had relatively more frequent ADR occurrence compared to the male patients(p<0.001). Although mild skin ADRs were more frequent in OXC, nervous system disorders, general disorders and hepatobiliary disorders occurred more often by CBZ. There were 6 reports of severe skin reaction by CBZ, while OXC had none. For CBZ, immediate-release (IR) formulation was reported to cause ADR at 200 mg/day and 400 mg/day, while controlled-release (CR) formulation mostly caused ADR at a dose of 400 mg/day. OXC was reported to cause ADR at both 300 mg/day and 600 mg/day.

Based on this limited study, we suggest the possibility of considering OXC a firstline prescription of anti-epileptic drugs due to lower incidence of severe ADRs compared to CBZ. Furthermore given the helpfulness of the ADR reporting system for both clinicians and patients, we should make an effort to reduce under-reporting of ADR.

Keywords: carbamazepine, oxcarbazepine, drug-related side effects and adverse reactions, antiepileptic drugs

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Ⅰ. INTRODUCTION

Since Phenytoin (diphenylhydantoin, Dilantin) was introduced as a major anticonvulsant in the 1930s, various antiepileptic drugs (AEDs) have been used to prevent epileptic seizures. They are also beneficial in diverse non-epileptic conditions and are commonly used in the treatment of neuropathic pain, bipolar affective disorder and migraine headache. AEDs can also be useful for treating essential tremor, myotonia, dystonia, anxiety disorders, schizophrenia, restless legs

syndrome, social phobia, post-traumatic stress syndrome, and alcohol dependence and withdrawal (Stefan and Feuerstein, 2007).

AEDs act on diverse molecular targets to selectively modify the excitability of neurons so that seizure-related firing can be blocked without disturbing non-epileptic activity which subserves normal signals between neurons. Voltage-dependent ion channels are the molecular targets of a number of chemically different anticonvulsant drugs. These ion channels include sodium, calcium and potassium channels. Anticonvulsant drugs inhibit or enhance ionic currents through the channels, but the precise way in which these result in protection against seizures is not completely understood for all drugs. The gating of brain sodium channels is modulated predominantly or partly by phenytoin, carbamazepine (CBZ), lamotrigine, oxcarbazepine (OXC) and, halfway, by zonisamide through blocking high frequency repetitive spike firing. The rate and extent to which these (and further) drugs block sodium channels differ (Rogawski and Löscher, 2004).

Carbamazepine (CBZ) was first synthesized by Walter Schindler in 1953 and Blom saw its potential in the treatment of trigeminal neuralgia in 1962 (Blom, 1962). Since the US Food and Drug Administration (FDA) approved CBZ tablets for epilepsy and trigeminal neuralgia more than 50 years ago, CBZ has become one of the most widely used as first drug of choice to treat seizure disorders and neuropathic pain. It is also used for a second-line treatment as bipolar disorder (Ghaemi, et al., 2003; Hirschfeld, et al., 2010). CBZ is predominantly metabolized in the liver. At least 30 different metabolites have been identified, including carbamazepine-10,11-epoxide (Lertratanangkoon and Horning, 1982). The metabolites of CBZ not only contribute to anti-convulsant and anti-neuralgic properties, but are also related to neurotoxic adverse reactions. Notably, the main metabolite carbamazepine-10,11-epoxide is known to cause HLA-B*1502 CBZ hypersensitivity (Simper, et al., 2018). The various types of adverse drug reaction (ADR) of CBZ were first reported not long after the approval of the drug (Gayford and Redpath, 1969). A fair

amount of severe skin reactions of CBZ as well as mild symptoms of ADR have been reported (Kim, et al., 2020).

Oxcarbazepine (OXC), the keto-analogue of CBZ, has been developed to avoid metabolites causing side effects. It is mainly metabolized into 10-hydroxy-10,11-dihydrocarbamazepine, a therapeutically active metabolite (Breton, et al., 2005). Compared to CBZ in a randomized double-blind crossover trial, OXC showed reduction of the total number of seizures, increased alertness and concentration, and disappearance of an allergic skin reaction with CBZ (Houtkooper, et al., 1987). OXC is known to have efficacy in anti-epileptic activity comparable with CBZ when a 50% higher dose is applied. Despite the higher dose, the incidence and severity of adverse reaction were lower than with CBZ (Dam, et al., 1989).

Adverse effects are a leading cause of treatment failure with AEDs. Not only do they result in early treatment discontinuation in up to 25% of patients, but also they preclude attainment of fully effective doses and have a negative effect on patient adherence. Further-more, adverse effects of antiepileptic drugs are a major source of disability, morbidity, and mortality and a substantial burden on use and costs of health care. WHO defines an adverse drug effect as “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”. Although adverse effects have been recorded since the dawn of antiepileptic drug treatment, only in recent years has substantial effort been made to define, quantify, and address their clinical relevance (Perucca and Gilliam, 2012).

CBZ and OXC show similar adverse reactions such as skin rash, central nervous system disorders, and digestive system disorders. They are also known as 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) (Kim, et al., 2020; Yang, et al., 2011). 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 (Kang, et al., 2019).

Pharmacovigilance system for ADR monitoring in Republic of Korea has been updated since 1988, and Ministry of Food and Drug Safety designated 3 tertiary care hospitals including Yonsei University Severance Hospital as regional pharmacovigilance center for spontaneous ADR reporting in 2006. The number of spontaneous reporting cases has increased dramatically as the accumulated number of ADR reporting cases reached 165,430 in 2011, making the pharmacovigilance data of Korea sufficient to join the ranks of other advanced countries (Chung, et al., 2012).

As a major tertiary care hospital in Korea, Yonsei University Severance Hospital & Dental Hospital follows the national pharmacovigilance system for spontaneous ADR reporting. It allows practitioners to classify 13 different aspects of ADR with detailed description of the symptoms.

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

Ⅱ. SUBJECTS AND METHODS

1. Analysis of Baseline Characteristics of the Patients

The data for this retrospective study was collected using the pharmacovigilance database and spontaneous ADR reporting data of Yonsei University Severance Hospital & Dental Hospital (Seoul, Korea) from 01/01/2010 to 31/01/2020, we selected the data and reports of patients with spontaneous reports of ADR associated with CBZ (CARMAZEPINE®, CARMAZEPINE CR®) and OXC (TRILEPTAL®, OXAZEPINE®).

9312 cases from a total of 10419 patients were reported to have been prescribed either CBZ or OXC; the remaining 1107 had reportedly been prescribed both. The age of the subjects ranged from 15 to 97, with the mean age of 46.6. 5094 (48.9%) of them were men, and 5325 (51.1%) of them were women. The diagnoses of the patients were classified into “neuropathic pain,” “episodic neurologic symptoms,” “bipolar disorders,” and “others” including cancer, Moyamoya disease, head injury and Meniere disease (Table 1).

The drugs were prescribed evenly to most of the age groups except for the age group of 15 to 19. Since OXC is known to be more effective for seizure disorders in children and adolescents (Donati, et al., 2007).

Investigation procedures were approved by Yonsei University Dental Hospital Institutional Review Board (Approval number 2-2020-0017).

Table 1. Baseline Characteristics of the Patients.

	CBZ, n (%)	OXC, n (%)	Total, n (%)
Sex			
Male	3040 (29.2)	2054 (19.7)	5094 (48.9)
Female	3368 (32.3)	1957 (18.8)	5325 (51.1)
Age			
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	2959 (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 (%).

2. Materials and Methods

The clinical features of ADR reports were classified using the preferred terms of System Organ Class (SOC) 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 and subcutaneous tissue disorders,” “Nervous system disorders,” “Gastrointestinal disorders,” “Blood and lymphatic system disorders,” “General disorders and administration site conditions,” and “Hepatobiliary disorders.”

Skin and subcutaneous tissue disorders include rash, urticaria, erythema, and symptoms of fatal cutaneous reaction (e.g. EM, SJS, TEN, DRESS). Nervous system disorders include sleepiness, dizziness, memory impairment, headache, and tremor. Indigestion and vomiting were classified as gastrointestinal disorders. General disorders show fever and weakness.

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

3. Statistical Analysis

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

Ⅲ. RESULTS

The spontaneous ADR reporting system showed 204 ADR cases from 195 patients. 107 patients reported ADR for CBZ only, 79 patients for OXC only, and nine reported ADR for both drugs. 153 patients (75.0%) complained of only one clinical feature of ADR, while 39 patients (19.1%) and 11 patients (5.4%) showed 2 and 3 features of ADR, respectively. Only 1 patient (0.5%) presented 4 features of ADR. There was no statistically significant difference in ADR incidence for CBZ and OXC (CBZ: 1.8%, OXC: 2.2%, p=0.169). Age did not correlate with the ADR incidence (p=0.495). Otherwise, women showed a higher ADR rate for both drugs (p<0.001) (Table 2). Both CBZ (p=0.511) and OXC (p=0.465) showed no significant difference in ADR incidence by age. As both drugs had higher incidence of ADRs in female, CBZ (p<0.001) showed higher significance of sex difference compared to OXC (p=0.002) (Table 3).

The number of prescription for CBZ and OXC with the ADR incidence has been presented in Figure 1. The broken line graphs show the total amount of prescriptions for each drug, which indicates the number of prescriptions for CBZ was higher in most of the years compared to which of OXC. The bar graphs represent the ADR incidence of the drugs, which indicates OXC had a bit higher ADR incidence except in year 2017.

Table 2. Comparison of the Number of Patients with or without ADR.

	ADR, n (%)		Total, n (%)	*p* value
	Yes	No		
Drug				0.169
CBZ	116 (1.8)	6292 (98.2)	6408 (100)	
OXC	88 (2.2)	3923 (97.8)	4011 (100)	
Age				0.495
15-19	13 (1.4)	897 (98.6)	910 (100)	
20-29	37 (2.4)	1481 (97.6)	1518 (100)	
30-39	26 (1.6)	1574 (98.4)	1600 (100)	
40-49	35 (2.1)	1637 (97.9)	1672 (100)	
50-59	34 (1.9)	1758 (98.1)	1792 (100)	
60-69	35 (2.3)	1509 (97.7)	1544 (100)	
70 and over	24 (1.7)	1359 (98.3)	1383 (100)	
Sex				**<0.001**
Male	63 (1.2)	5030 (98.8)	5093 (100)	
Female	141 (2.6)	5185 (97.4)	5326 (100)	
Total	204 (2.0)	10215 (98.0)	10419 (100)	

ADR, adverse drug reaction; CBZ, carbamazepine; OXC, oxcarbazepine.

Data are presented as n (%).

Table 3. Comparison of the number of ADRs of each drug by age and sex.

	CBZ, n (%)	*p* value	OXC, n (%)	*p* value	Total, n (%)
Age		0.511		0.465	
15-19	2 (1.7)		11 (12.5)		13 (1.4)
20-29	16 (13.8)		21 (23.9)		37 (2.4)
30-39	12 (10.3)		14 (15.9)		26 (1.6)
40-49	23 (19.8)		12 (13.6)		35 (2.1)
50-59	22 (19.0)		12 (13.6)		34 (1.9)
60-69	22 (19.0)		13 (14.8)		35 (2.3)
70 and over	19 (16.4)		5 (5.7)		24 (1.7)
Sex		**<0.001**		**0.002**	
Male	32 (27.6)		31 (35.2)		63 (1.2)
Female	84 (72.4)		57 (64.8)		141 (2.6)
Total	116		88		204 (2.0)

ADR, adverse drug reaction; CBZ, carbamazepine; OXC, oxcarbazepine.

Data are presented as n (%).

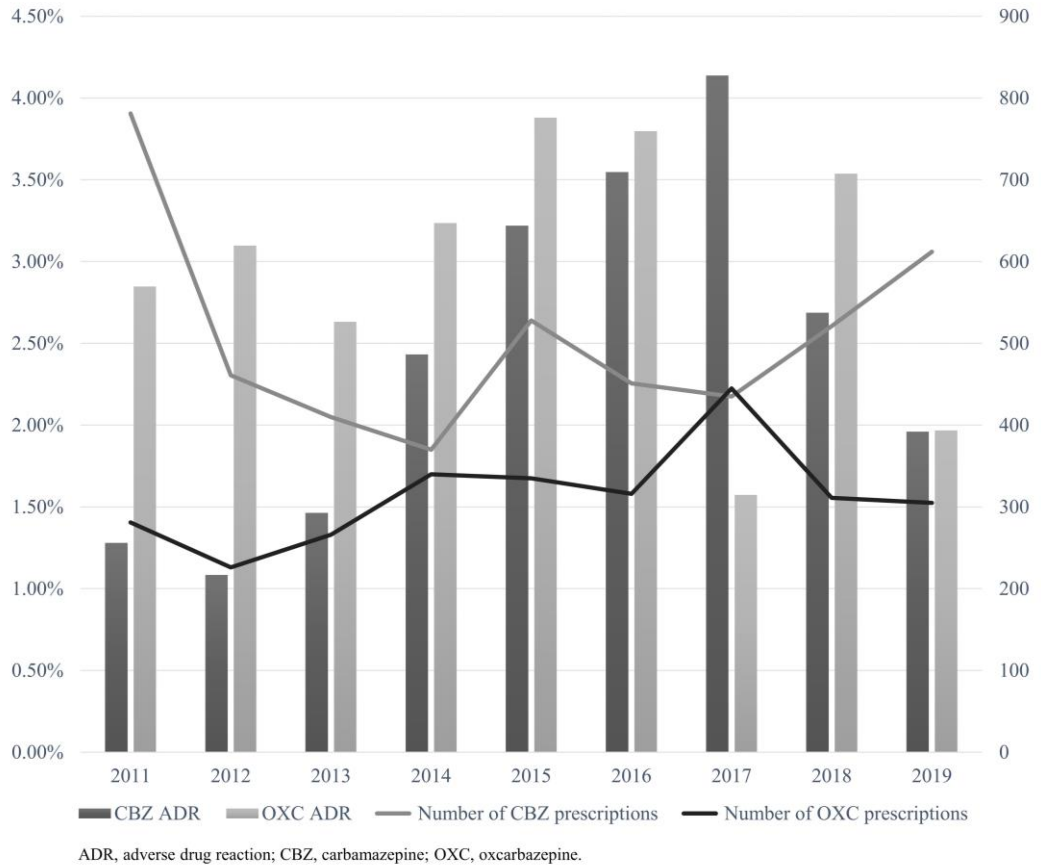


Figure 1. The number of prescriptions and ADR incidences of CBZ and OXC by year.

The most common type of ADR associated with the drugs consisted of mild skin and subcutaneous tissue disorders, followed by nervous system disorders (Table 4). CBZ caused more ADR related to the nervous system (p=0.087), general (p=0.077), and hepatobiliary (p=0.091) disorders than did OXC (Figure 2), while OXC was linked to a higher incidence rate of mild skin and subcutaneous tissue disorders (p=0.013) (Figure 3).

Table 4. Clinical features of ADR by drug.

	Clinical features of ADR, n (%, incidence)								Patient demographic, n (%)
	Skin and SCT		Nervous system	Gastro-intestinal	Blood and lymphatic system	General disorders	Hepato-biliary	Others	
	Mild	Severe†							
Drug									
CBZ	**59 (0.92)**	**6 (0.09)**	**42 (0.66)**	11 (0.17)	10 (0.16)	**14 (0.22)**	**8 (0.12)**	17 (0.27)	6408 (100)
OXC	**58 (1.45)**	**0 (0.00)**	**16 (0.40)**	6 (0.15)	9 (0.22)	**3 (0.07)**	**1 (0.02)**	8 (0.20)	4011 (100)
p value	**0.013****	**0.053***	**0.087***	0.785	0.427	**0.077***	**0.091***	0.503	
Total	117 (1.12)	6 (0.06)	58 (0.56)	17 (0.16)	19 (0.18)	16 (0.15)	9 (0.09)	25 (0.24)	10419 (100)

SCT, subcutaneous tissue; CBZ, carbamazepine; OXC, oxcarbazepine

†Severe skin and SCT disorders include erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms

**p<0.05

*p<0.1

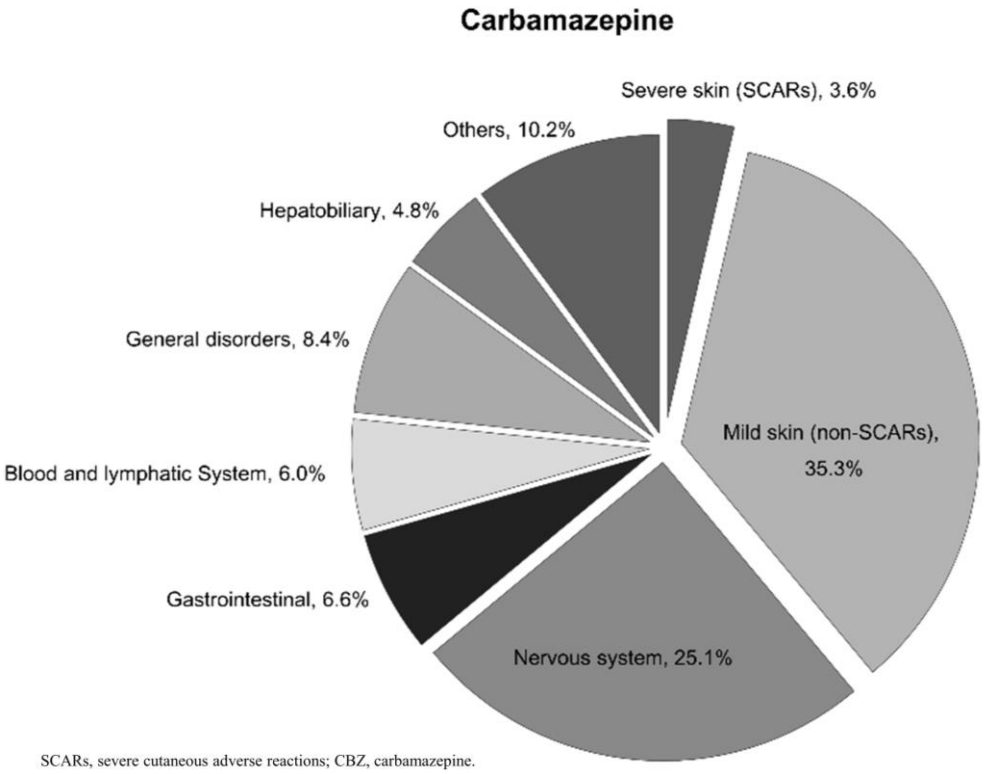


Figure 2. The ratio of clinical features of ADRs to CBZ.

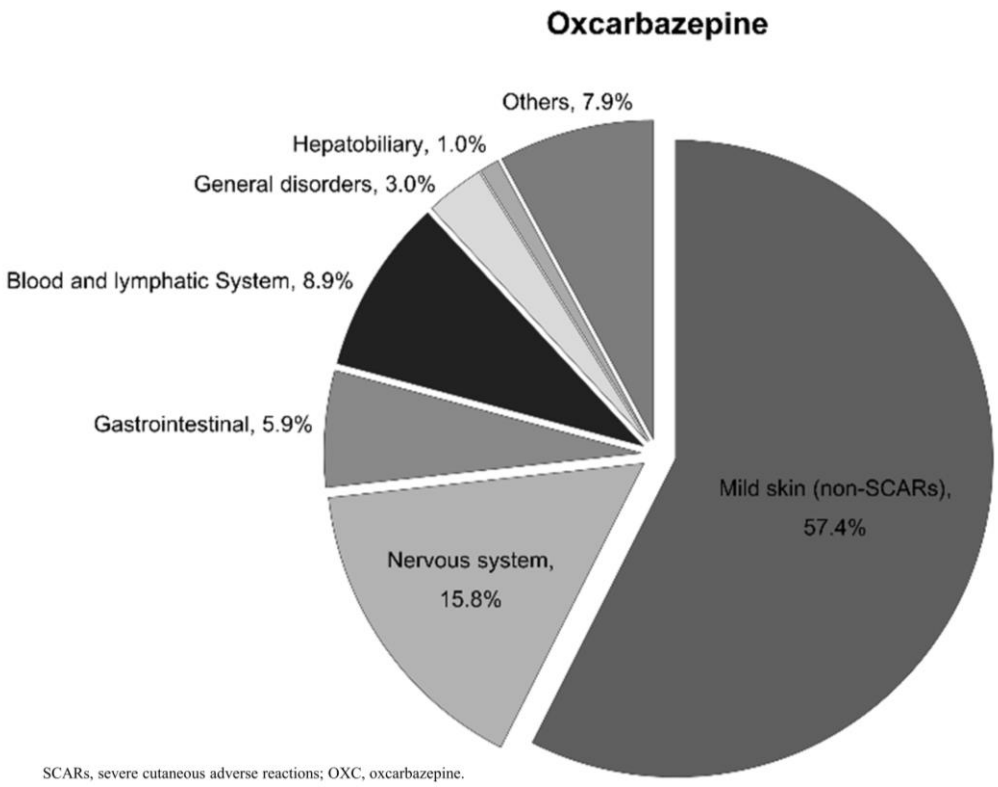


Figure 3. The ratio of clinical features of ADRs to OXC.

Six patients reported severe skin and subcutaneous symptoms including EM, SJS, TEN and DRESS by CBZ (Table 5). 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, and were then diagnosed as EM (F/70), SJS (F/74, F/37), TEN (F/44), and DRESS (M/72). One patient diagnosed with SJS (F/67), was switched from CBZ to OXC after the severe skin rash, but without relief of symptoms. They were referred to the Departments of Allergy and Immunology and of Dermatology and Infectious Diseases. After supportive care, all six experienced relief of symptoms. There was no report of severe skin reaction directly by OXC.

Table 5. Summary of 6 reported cases of SCARs by CBZ.

Case Number	Gender	Age	Medication	Daily dose (mg/day)	Days of doses taken	SCAR	Days of supportive care
1	F	70	Carmazepine®	400	7days	EM	30days
2	F	74	Carmazepine®	400	3days	SJS	7days
3	F	37	Carmazepine CR®	400	24days	SJS	29days
4	F	44	Carmazepine®	200	30days	TEN	34days
5	M	74	Carmazepine®	400	31days	DRESS	25days
6	F	67	Carmazepine®	600	22days	SJS	9days

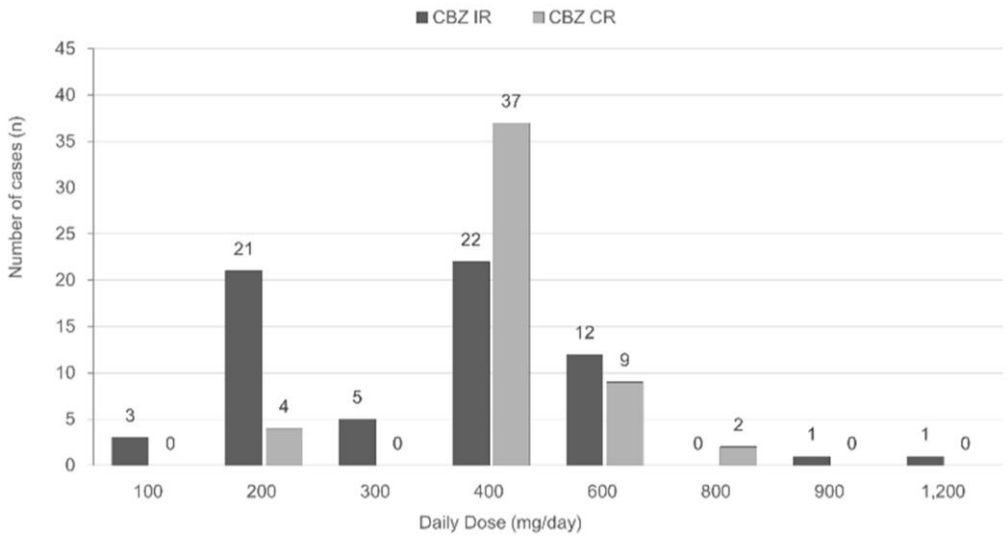
SCARs, severe cutaneous adverse reactions; CBZ, carbamazepine; CR, controlled-release; EM, erythema multiforme; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug reaction with eosinophilia and systemic symptoms

In case number 2, the patient had a previous history of SJS from other hospital using CBZ to treat trigeminal neuralgia, 6 years before the visit. Gabapentin (NEURONTIN®) was the first drug choice for the patient, but she needed to change the medication due to lack of efficacy. This case shows the previous history of SCAR should be considered, as the occasion can be repeated.

In case number 4, HLA typing test was performed after the SCAR eruption. The result showed that the patient had B*15:01(B62), B*15:11(B75) genes, which are known to be related to SCARs of Asians.

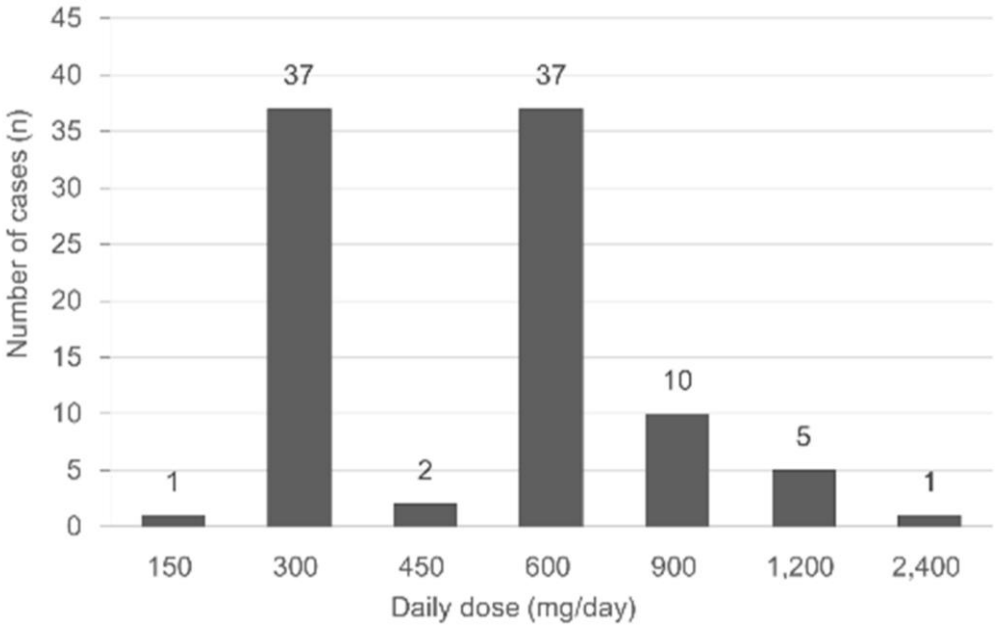
In case number 6, the first drug of choice to treat trigeminal neuralgia for the patient was CBZ. After the eruption of urticaria due to CBZ, the doctor changed the medication into OXC. The change of drug did not worsen the symptoms nor improved them. This case indicates that eradication of the causative drugs including those with similar pharmacological effects is significant for the relief of SCAR symptoms.

The daily doses of the ADR reported drugs were also analyzed. For CBZ, the IR formulation was reported to cause ADR at 200 mg/day and 400 mg/day, while the CR formulation mostly caused ADR at 400mg /day (Figure 4). Since the CR formulation cannot be halved, there was no report of ADRs in daily dose of 100mg, 300mg and 900mg of CBZ CR. OXC was reported to cause ADR at both 300 mg/day and 600 mg/day (Figure 5). Both drugs showed ADR cases below the recommended daily dose, which are 400mg/day for CBZ and 600mg/day for OXC.



ADR, adverse drug reaction; CBZ, carbamazepine; IR, immediate-release; CR, controlled-release.

Figure 4. The number of ADR cases and daily dose of CBZ at the occurrence of ADR.



ADR, adverse drug reaction; OXC, oxcarbazepine.

Figure 5. The number of ADR cases and daily dose of OXC at the occurrence of ADR.

Ⅳ. DISCUSSION

Prior to 1993, the choice of an anticonvulsant medication was limited to phenobarbital, primidone, phenytoin, carbamazepine, and valproate. Although these “traditional” anticonvulsants have the advantage of familiarity as well as proven efficacy, many patients are left with refractory seizures as well as intolerable adverse effects. Since 1993, 8 new medications (felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine and zonisamide) have been approved by the US FDA, expanding treatment options (LaRoche and Helmers, 2004). The newer AEDs offer the potential advantages of fewer drug interactions, unique mechanisms of action, and a broader spectrum of activity. With more options, however, comes the challenge of determining what role the new AEDs play in optimizing treatment in addition to understanding important adverse effects and drug interactions of these increasingly prescribed medications.

In this study, we chose subjects over 15, since CBZ is more rapidly metabolized to carbamazepine-10,11-epoxide in children below age 15 (Korinthenberg, et al., 1994). On the other hand, 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.

Gender differences in ADR have been reported mainly in gastrointestinal disorders (Yu, et al., 2015). Women commonly present more gastrointestinal and cutaneous allergic reactions. In males, electrolyte disturbances are known to be more frequent (Domecq, et al., 1980). Women generally have a lower lean body mass, reduced hepatic clearance, and differences in the activity of cytochrome P450 (CYP) enzymes. Women also metabolize drugs at different rates compared with men (Rademaker, 2001). There are also factors such as females having higher rates of consultation

and complaint as well as better compliance with drugs (Montastruc, et al., 2002).

The results showed no significant difference in overall ADR incidence between CBZ and OXC. However, nervous system disorders, general disorders and hepatobiliary disorders occurred mostly by 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 currents 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 (MHD), 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 (Schmidt and Elger, 2004).

The fact that there was no report of severe skin reaction directly by OXC while CBZ had six cases is noticable. Fortunately, all patients with severe skin ADR by CBZ in this study were well-cared for with a proper referral. Management should begin with the withdrawal of the suspected drug as earlier withdrawal of drugs with a short elimination half-life is associated with better survival of patients with severe drug eruptions. In the one case of the SJS patient, changing the drug right after the occurrence of 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 (Roujeau, 1999). The prompt decision of the clinician is necessary for a favorable prognosis.

CBZ can be prescribed with National Health Service (NHS) in Korea for the first choice of drug for neuropathic pain or cancer patients. OXC has no indication for NHS prescription, which aggravates the financial burden for patients compared to those who are prescribed to take CBZ. Accordingly, the clinicians in Korea usually prescribe OXC only for the cases in which CBZ shows lack of efficacy or the unsustainable ADRs.

Considering the fact that OXC has shown no significant difference in drug efficacy as well as the

lower incidence of serious ADRs, the need for discussion to change the first drug of choice of NHS prescription for neuropathic pain into OXC can be raised.

According to the ADR reports, there was a difference in daily dose between IR and CR tablets of CBZ. For CBZ CR, most of the ADR cases were reported at 400 mg/day while CBZ IR had a similar number of reports at 200 mg/day. OXC showed ADR occurrences at a dose of 300 mg and 600 mg/day. This might arise from the drug use instructions. The CBZ medications we use in Yonsei University Severance Hospital & Dental Hospital consist of 200 mg and 400 mg tablets of CBZ IR formulation and 200 mg tablets of CBZ CR formulation. For OXC, 300 mg and 600 mg OXC IR formulations were 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 (McDevitt, et al., 1998; Quinzler, et al., 2006; Verrue, et al., 2011), 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 the lower dose to prevent possible ADR events. Also the dosage titration can be the contributing factor for ADR incidence. In the case when the daily dose of the medication should be increased, ADR incidence can be reduced with the use of slow titration (Chopra and de Leon, 2016). Titration from the lower daily dose should be considered and the succeeding studies showing the associations of titration and lower initial dose of the medication with ADRs are recommended.

This study was based on spontaneous reports of clinicians prescribing the drugs. Over the years, advances in clinical trial methodology, drug surveillance systems, and understanding of pathophysiological mechanisms have permitted better characterization of the adverse effect profile of individual AEDs. In parallel, new knowledge has been acquired on risk factors for specific adverse effects and on strategies not only to minimize toxic effects, but also to improve their early detection and management. Doctors are increasingly aware of the importance of adverse effects as

a determinant of health-related quality of life. However, spontaneous reporting systems have their limitations, including that they are affected by under-reporting (Thiessard, et al., 2005). Considering the purpose of the system, most reports were intended to indicate that the doctor had to change or withdraw the medication due to ADR symptoms. As the medical records are getting digitalized, clinicians can use the previously settled system to fill out a lot of information compared to the paper records. For instance, if the basic prescription records allow doctors to easily choose the reason in case of a change or withdrawal of the medication, the number of spontaneous ADR reports can be highly increased. Also, we should keep in mind that the ADR incidence might not include mild symptoms that the patient could endure during treatment. In some cases, patients might not recognize the ADR symptoms before objective examinations. Hypernatremia and bone marrow depression are the examples of ADRs that can only be identified through laboratory tests. Asking patients about the condition or performing medical examinations to check the mild or hidden ADR symptoms of the prescribed medications can be helpful. Nationwide improvement of digitalized medical recording system including pharmacovigilance data is recommended to solve the under-reporting problem in the further study.

Despite these considerations, the future looks promising. Pharmacoepidemiological resources are being used increasingly to identify the individual profiles of patients at increased risk of specific adverse effects. Successes in pharmacogenetics are fuelling research into biomarkers of different aspects of toxic effects of AEDs.

The HLA typing is an example of efforts to study pharmacogenetic factors. Since Chung et al. first identified the association of HLA-B*1502 and SJS/TEN in Han Chinese (Chung, et al., 2004), there has been research trying to find an association between the HLA genotypes and severe, CBZ-induced ADR in Koreans (Kim, et al., 2011). They reported that HLA-B*1502 was present in all 44 (100%) CBZ-SJS/TEN patients, but in only 3% of CBZ-tolerant controls, and in 8.6% of the normal

population, suggesting that the HLA-B*1502 allele has 100% sensitivity and 97% specificity for testing for CBZ induced SJS and TEN. This study led the US FDA to recommend screening for the HLA-B*1502 allele in Asians before initiating CBZ therapy (Ferrell and McLeod, 2008). As HLA typing test is not performed commonly to the patients nowadays, still the database of gene typing in Korea is insufficient. SCARs can cause serious results in elderly patients, so even a little chance to reduce severe ADRs is important, especially for the drugs that are commonly prescribed to senior patients. To prevent the severe cutaneous ADR of patients taking CBZ or OXC, routine genetic screening should also be considered.

Ⅴ. CONCLUSION

As CBZ and OXC are commonly used in clinics, clinicians should be aware of the likelihood of ADR with respect to certain drugs. Although OXC had more reports of mild skin reactions, severe skin ADRs only occurred by CBZ and other types of ADRs such as nervous system disorders, general disorders and hepatobiliary disorders had higher incidence with CBZ. OXC has been proved to have anti-epileptic efficacy comparable with CBZ and also has US FDA approved indications for children. Based on this limited study, we suggest the possibility of considering OXC a firstline prescription of anti-epileptic drugs. Given the significant number of ADR reports at daily doses below the recommendation, initial doses of CBZ and OXC should be set lower. Even in cases of severe ADR, the fast and proper decision of the clinician can make a good prognosis. Spontaneous ADR reporting systems can help both clinicians and patients, and we must make an effort to reduce under-reporting.

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ABSTRACT (in Korean)

삼차진료기관에서 카바마제핀과 옥스카바제핀의 약물유해반응 분석

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목적: 연세의료원과 연세대학교치과병원의 약물 부작용 보고 시스템을 통해 카바마제핀과 옥스카바제핀의 부작용 보고 사례를 분석하여 그 빈도와 임상 양상을 비교하고자 하였다.

대상 및 방법: 2010 년 1 월 1 일부터 2020 년 1 월 31 일까지 연세의료원과 연세대학교치과병원에 내원하여 항전간제(CBZ, OXC)를 처방 받아 복용한 환자 중 의약품부작용보고 시스템에 의해 해당 약물에 대한 부작용 보고된 환자를 대상으로 처방 받은 약물의 종류와 용량, 보고된 부작용의 종류 등에 대한 통계적 연구를 진행하였다.

결과: CBZ 또는 OXC 를 처방받은 총 9312 명의 환자에게서 204 건의 부작용 사례가 보고되었다. 환자 연령에 따른 유의할만한 차이는 없었으나, 성별에 따라서는 여성에게서 더 많은 부작용 사례가 보고되었다(p<0.001). 두 약물 모두에서 가장 많은 부작용 양상은 경증 피부반응이었으며, OXC 에 비해 CBZ 약물에서 신경계 부작용, 전신 반응, 간담췌 부작용이 더 빈번하게 나타났다. Severe Cutaneous Adverse Reaction(SCAR) 사례의 경우, OXC 복용 환자에게서는 보고되지 않았으나, CBZ 복용 환자에서는 6 건이 보고되었다.

고찰: 부작용 발생 용량에 대한 분석에서, 두 약물 모두 권장 일일 복용량(CBZ 400mg/day, OXC 600mg/day)보다 적은 초기 용량에서도 부작용 발생 사례가 보고되었다.

결론: 약물 복용으로 인해 발생한 SCAR 사례의 경우, 원인 약물을 즉시 중단하는 것이 중요하며 증상 개선을 위한 빠른 전원이 필수적이다. CBZ에 비해 OXC는 부작용의 양상이 보다 경미하고, SCAR의 발생 빈도가 적기 때문에 1차 선택 약물로서 효용성이 있을 것으로 생각된다. 두 약물 모두 권장 용량보다 낮은 용량에서도 부작용 사례가 보고되었기 때문에 보다 낮은 초기 용량에서 점진적으로 증량하여 복용하는 것이 필요하다.

핵심어: 카바마제핀, 옥스카바제핀, 약물유해반응, 항경련제