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Adverse Skin Reactions with Antiepileptic Drugs Using Korea Adverse Event Reporting System Database, 2008–2017

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ABSTRACT

Background: Severe and life-threatening drug eruptions include drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). One class of medications that has been highly associated with such drug eruptions is antiepileptic drugs (AEDs). We attempt to investigate drug eruptions associated with AEDs as a class, as well as with individual AEDs, in Korea.
Methods: We used the Korea Institute of Drug Safety and Risk Management - Korea Adverse Event Reporting System (KIDS-KAERS) database, a nationwide database of adverse events reports, between January 2008 and December 2017 to investigate the reporting count of all drug eruptions and calculated the ratio of DRESS/SJS/TEN reports for each AED.
Results: Among a total of 2,942 reports, most were of rash/urticaria (2,702, 91.8%), followed by those of DRESS (109, 3.7%), SJS (106, 3.6%), and TEN (25, 0.85%). The common causative AEDs were lamotrigine (699, 23.8%), valproic acid (677, 23%), carbamazepine (512, 17.4%), oxcarbazepine (320, 10.9%), levetiracetam (181, 6.2%), and phenytoin (158, 5.4%). In limited to severe drug eruptions (DRESS, SJS, and TEN; total 241 reports), the causative AEDs were carbamazepine (117, 48.8%), lamotrigine (57, 23.8%), valproic acid (20, 8.3%), phenytoin (15, 6.3%), and oxcarbazepine (10, 4.2%). When comparing aromatic AED with non-aromatic AED, aromatic AEDs were more likely to be associated with severe drug eruption (aromatic AEDs: 204/1,793 versus non-aromatic AEDs: 37/1,149; OR, 3.86; 95% CI, 2.7–5.5). Death was reported in 7 cases; DRESS was the most commonly reported adverse event (n = 5), and lamotrigine was the most common causative AED (n = 5).
Conclusion: Although most cutaneous drug eruptions in this study were rash or urticaria, approximately 8% of reports were of severe or life-threatening adverse drug reactions, such as SJS, TEN, or DRESS. When hypersensitivity skin reactions occurred, aromatic AEDs were associated with 4 fold the risk of SJS/TEN/DRESS compared with non-aromatic AEDs. Our findings further emphasize that high risk AEDs should be prescribed under careful monitoring, and early detection and prompt interventions are needed to prevent severe complications.

Keywords: Antiepileptic Drugs; Adverse Skin Reactions; Pharmacovigilance; KIDS-KAERS

Supervision: Kim DW. Validation: Kim HK. Writing - original draft: Kim HK. Writing - review & editing: Kim HK, Kim DW.

INTRODUCTION

Epilepsy is one of the most common neurologic disorders, with a global prevalence of almost 50–60 million people and an annual incidence of 50 per 100,000 persons per year in developed countries.[1,2] Antiepileptic drug (AED) treatment is the most important means of preventing seizures, and two-thirds of patients with epilepsy become seizure free with appropriate pharmacotherapy.[3] However, more than 25% of patients discontinue treatment because of adverse effects of the initial AED chosen, and up to one-third are refractory to multiple AEDs; such cases may potentially lead to recurrent adverse drug reactions (ADRs) and drug interactions.[4]

Adverse skin reactions (ASRs) to drugs occur in up to 8% of the global population and in 2%–3% of hospitalized patients. They occur in 3% of individuals who receive AEDs and are the most common reason for withdrawal of the drugs.[5] ASRs are usually mild, appearing in the form of a diffuse, erythematous, maculopapular, pruritic rash or urticaria. However, occasionally they may be severe when occurring as part of the syndromes of erythema multiforme, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). These require immediate AED discontinuation to prevent a fatal outcome.[6,7]

The importance of post-marketing surveillance is emphasized because ADRs cannot be fully detected during the premarketing developing process.[8] Current trends in pharmacovigilance systems are veering towards patient involvement in the spontaneous reporting of ADRs.[9] Several studies for ADRs of AEDs using spontaneous reporting systems have been conducted in other countries, but there are no such studies in Korea.[2,10-12] The aim of our study was to assess the association between ASRs, including SJS, TEN, and DRESS, and AEDs using the Korea Institute of Drug Safety and Risk Management-Korea Adverse Event Reporting System (KIDS-KAERS) database.

METHODS

Database, study drugs and ADRs

We reviewed adverse-event reports from the KIDS-KAERS database between January 2008 and December 2017. This adverse event reporting system was first launched in 1988 by the Korea Food and Drug Administration and has collected nationwide spontaneous ADR reports since then. In 2012, the pharmacovigilance activities were transferred to KIDS, which developed KIDS-KAERS database. Suspected drug and adverse event information are reported to KIDS in a form named 'Individual Case Safety Reports (ICSR)' using voluntary reporting system by health care workers (doctor, pharmacist or nurse) or general public. Reports are collected via call center, paper forms, the telephone, FAX, e-mail or website. All information received is stored within KIDS-KAERS database as an ICSR. KIDS detects and evaluates signals from cumulated data to generate and provide drug safety information. KAERS database includes adverse event information, drug information, patient and reporter information, and assessment information.

We included 22 AEDs available in Korea with an FDA indication for epilepsy or seizures and classified the drugs into aromatic and non-aromatic AEDs (**Table 1**).[13,14] ADRs were coded according to the Preferred Terms (PTs) among World Health Organization Adverse Reaction

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Table 1. AEDs evaluated in this study

AEDs (Generic names)	
Carbamazepine[a]	Oxcarbazepine[a]
Clobazam	Perampanel
Clonazepam	Phenobarbital[a]
Diazepam	Phenytoin[a]
Ethosuximide	Pregabalin
Fosphenytoin[a,b]	Primidone[a]
Gabapentin	Rufinamide[a]
Lacosamide[a,c]	Topiramate
Lamotrigine[a]	Valproic acid/Divalproex sodium
Levetiracetam	Vigabatrin
Lorazepam	Zonisamide[a]

AED = antiepileptic drug.
[a]Aromatic antiepileptic drugs; [b]Fosphenytoin is a prodrug of phenytoin (only intravenous formulation); [c]Lacosamide was launched after 2017 in Korea.

Terminology (WHO-ART).[15,16] We conducted searches of the WHO-ART PTs "Rash (0027)," "Urticaria (0044)," "SJS (0042)," "TEN (0014)," and "DRESS (2309)."

The WHO-Uppsala Monitoring Centre (WHO-UMC) causality assessment system categorizes the evaluation of ADRs into six groups: certain, probable, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable.[15,17] We included cases where the level of causality category was equal to or above "possible" ("certain," "probable," and "possible"). We excluded cases where there was no information on the causality category or where two or more drugs had the same level of causality category.

Statistical analysis

We investigated the reporting count of ASRs for 22 AEDs and calculated the ratio of severe ASRs (DRESS/SJS/TEN) to all ASRs for each AED. Comparisons were made between aromatic AEDs and non-aromatic AEDs for the ratio of DRESS/SJS/TEN to all ASRs using χ^2 tests (with 2 × 2 cross tabulation).

Ethics statement

The Institutional Review Board of the National Medical Center of Korea reviewed and approved the study protocol (Approval No. H-1905-102-003). The need for informed consent was waived by the board.

RESULTS

During the study period, a total of 2,942 ASRs caused by AEDs were reported; the demographics of these reports are presented in **Table 2**. Among the 2,942 reports, 1,450 (49.3%) were of men and 1,456 (49.5%) were of women. Adults (18 years < aged < 65 years; 1,750; 59.5%) were most commonly affected, followed by the elderly (aged ≥ 65 years; 556; 18.9%). The most frequent report source by person was nurses (1,249; 42.5%), followed by doctors (1,000; 34%).

Among the total 2,942 reports, most were of rash/urticaria (2,702; 91.8%), followed by those of DRESS (109; 3.7%), SJS (106; 3.6%), and TEN (25; 0.85%) (**Table 3**). The common causative AEDs were lamotrigine (699; 23.8%), valproic acid (677; 23%), carbamazepine (512; 17.4%), oxcarbazepine (320; 10.9%), levetiracetam (181; 6.2%), and phenytoin (158; 5.4%).

Table 2. Demographics and reporters of adverse skin reactions reports of antiepileptic drugs

Parameters	No. of reports	%
Gender		
Men	1,450	49.3
Women	1,456	49.5
Unknown	36	1.2
Age group, yr		
Infant, < 1	33	1.1
Child/adolescent, 1 to 18	459	15.6
Adult, 19 to 64	1,750	59.5
Elderly, ≥ 65	556	18.9
Unknown	144	4.9
Report source by person		
Doctor	1,000	34.0
Pharmacist	277	9.4
Nurse	1,249	42.5
Customer	25	0.85
Others/unknown	391	13.3
Total	2,942	

Table 3. Adverse skin reactions related to AEDs

All AEDs	Total	Rash/urticaria	SJS	TEN	DRESS
	2,942	2,702 (91.8%)	106 (3.6%)	25 (0.85%)	109 (3.7%)
Carbamazepine[a]	512	395	48	9	60
Clobazam	6	6	0	0	0
Clonazepam	25	25	0	0	0
Diazepam	24	23	0	0	1
Ethosuximide	4	4	0	0	0
Fosphenytoin[a]	27	27	0	0	0
Gabapentin	83	81	2	0	0
Lacosamide[a]	6	6	0	0	0
Lamotrigine[a]	699	642	34	11	12
Levetiracetam	181	172	2	1	6
Lorazepam	22	20	0	0	2
Oxcarbazepine[a]	320	310	2	0	8
Perampanel	1	1	0	0	0
Phenobarbital[a]	47	44	0	0	3
Phenytoin[a]	158	143	10	0	5
Pregabalin	58	56	1	0	1
Primidone[a]	2	2	0	0	0
Rufinamide[a]	1	1	0	0	0
Topiramate	64	63	0	0	1
Valproic acid	677	657	6	3	11
Vigabatrin	4	4	0	0	0
Zonisamide[a]	21	19	1	1	0

AED = antiepileptic drug, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, DRESS = drug reaction with eosinophilia and systemic symptoms.
[a]Aromatic AEDs.

Limited to severe ASRs (DRESS, SJS, and TEN; total 241 reports), the common causative AEDs were carbamazepine (117; 48.8%), lamotrigine (57; 23.8%), valproic acid (20; 8.3%), phenytoin (15; 6.3%), and oxcarbazepine (10; 4.2%). When comparing aromatic AEDs with non-aromatic AEDs, aromatic AEDs were more likely to be associated with severe ASRs (aromatic AEDs: 204/1,793 vs. non-aromatic AEDs: 37/1,149; odds ratio [OR], 3.86; 95% confidence interval [CI], 2.7–5.5) (**Table 4**).

We summarized the WHO-UMC causality categories for AEDs that had more than 30 reported ASRs (**Table 5**). "Probable/likely" and "possible" were similar for most drugs, but

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Table 4. Aromatic AEDs and non-aromatic AEDs for severe adverse skin reactions

Variables	Total	Rash/urticaria	SJS/TEN/DRESS	OR (95% CI)	*P* value
Aromatic AEDs	1,793	1,589	204	3.86 (2.7–5.5)	< 0.001
Non-aromatic AEDs	1,149	1,112	37	-	-

AED = antiepileptic drug, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, DRESS = drug reaction with eosinophilia and systemic symptoms, OR = odds ratio, CI = confidence interval.

Table 5. Causality categories for each antiepileptic drug (more than 30 reports)

Variables	Total	Certain	Probable/likely	Possible
Carbamazepine	512	28	237	247
Gabapentin	83	2	30	51
Lamotrigine	699	31	400	268
Levetiracetam	181	3	94	84
Oxcarbazepine	320	9	177	134
Phenobarbital	47	1	20	26
Phenytoin	158	4	76	78
Topiramate	64	4	31	29
Valproic acid	677	2	233	442

"possible" was markedly more common than "probable/likely" for valproic acid. Death was reported in 7 cases; DRESS was the most commonly reported adverse event (n = 5), and lamotrigine was the most common causative AED (n = 5) (**Table 6**).

DISCUSSION

In this study, we investigated hypersensitivity skin reactions to AEDs using pharmacovigilance data in Korea. In large, accessible, nationwide drug safety databases, comprehensive information on adverse drug events had been collated, and thus the study design was suitable for the evaluation of rare but very serious adverse drug events.[2]

In the present study, we identified that most ASRs associated with AEDs are benign rash or urticaria (91.8%), but severe or fatal skin reactions were not rare, occurring in up to approximately 8% of cases. The common causative AEDs were lamotrigine, valproic acid, carbamazepine, oxcarbazepine, levetiracetam, and phenytoin. In case of AED-related ASRs, aromatic AEDs were found to be associated more frequently with severe or fatal skin reactions than non-aromatic AEDs, with an OR of 3.86. The results of the present study are similar to the results of earlier studies except that there were few reports related to zonisamide (21; 0.7%) in the present study[2,18] A recent study on severe cutaneous adverse reactions to AEDs in Korean hospitalized patients showed similar results.[19]

Table 6. Mortality cases from adverse drug reactions of AEDs[a]

AED	Gender	Age, yr	Adverse drug reactions
Lamotrigine	Man	20	DRESS
Lamotrigine	Woman	21	DRESS
Lamotrigine[a]	Man	52	Rash
Lamotrigine	Man	33	SJS
Levetiracetam	Woman	Unknown	DRESS
Phenytoin	Woman	28	DRESS
Valproic acid	Man	58	DRESS

AED = antiepileptic drug, DRESS = drug reaction with eosinophilia and systemic symptoms, SJS = Stevens-Johnson syndrome.
[a]Rash was not direct cause of death, and patient died from drug-induced hepatitis.

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The modified version of the WHO classification distinguishes the toxic and adverse effects of AEDs into five types: acute, related to the pharmacological properties of the drug (type A); idiosyncratic (type B); chronic (type C); delayed (type D); and secondary to drug interactions (type E).[20] Skin rashes and severe mucocutaneous reactions (DRESS, SJS, and TEN) belong to type B adverse effects. They are related to individual vulnerability (immunological, genetic, or other mechanism) and are unpredictable, with high morbidity and mortality rates.[20] ASRs are the most common idiosyncratic reactions to AEDs and occur in 5%–15% of individuals who receive AEDs.[6] In a meta-analysis of Chinese patients, AEDs were found to be the second most common causative drugs associated with severe ASRs.[21] Carbamazepine was also reported as the second causative drug of severe cutaneous adverse reactions in Korea.[19] Moreover, in relief system for ADRs, AEDs are one of the most common causative drugs; in 2018, all 18 reports related to AEDs were due to severe ASRs (SJS, TEN, and DRESS).[22,23]

Many investigations of genomic contributions that modulate the risk of developing AED-induced hypersensitivity reactions have revealed significant associations with genes encoding the human leukocyte antigen (HLA) alleles.[24] Pharmacogenomics studies have identified a striking association between the HLA-B*15:02 allele and carbamazepine-induced SJS/TEN in the Han Chinese population.[25] The frequency of the HLA-B*15:02 allele is substantially lower among European Caucasians (about 0.001%) and higher in Asian populations (1.6%–11%).[26] In addition to HLA-B*15:02, the association between several other HLA types (HLA-A*31:01, HLA-B*15:11, and HLA-A*24:02) and AED-induced ASRs has also been reported in Korean populations.[24]

In this study, a total of six AEDs (lamotrigine, valproic acid, carbamazepine, oxcarbazepine, levetiracetam, and phenytoin) had reports of more than 100 ASRs, and among them, four AEDs are aromatic AEDs, which contain an aromatic ring in their chemical structure. In addition, the risk of severe ASRs was significantly higher with aromatic AED use than with that of non-aromatic AEDs. These results are similar to those of previous studies.[12,16,27,28] One of the main hypotheses explaining this observation is that AEDs containing an aromatic ring in their chemical structure can form an arene-oxide intermediate.[13,28] This chemically reactive product may become immunogenic through interactions with proteins or cellular macromolecules in accordance with the hapten hypothesis, suggesting that this structural commonality between AEDs may be responsible for hypersensitivity reactions.[13] Another argument supporting this hapten hypothesis is the rate of cross sensitivity that has been reported among patients using aromatic AEDs, which has been reported to be as high as 80%–87%.[28] Identification of genetic polymorphisms that predispose to AED-induced skin reactions and the subsequent avoidance of AED treatment could help to prevent life-threatening events.[28]

Our results showed that valproic acid (a non-aromatic AED) was the second most commonly reported drug (677; 23%). This finding is different from that of previous retrospective studies of epilepsy patients but similar to that of a pharmacovigilance study using spontaneous reporting.[2,7,16] Valproic acid was the most frequently prescribed AED in Korea based on the 2007 databases of National Health Insurance.[29]

Valproic acid is an FDA-approved drug to treat manic or mixed episodes associated with bipolar disorder, and migraine as well as seizure. It is also used for treating neuropathic pain, fibromyalgia, and behavioral symptoms in dementia.[30,31] As the pharmacovigilance study includes not only epilepsy but also other diseases, it is likely that the frequency of adverse

events is relatively high. In addition, considering that it was relatively common for valproic acid to belong to the "possible" causality category, the possibility of an exaggerated number of ASRs for it cannot be excluded.

In case of zonisamide, the number of reports was low in contrast to that in previous studies.[2,7,16] In Korea, zonisamide is available only as a single original drug, and although it seems that the low number of prescriptions is one of the reasons for low adverse event reports, further investigation is needed to confirm this.

Several serious limitations of our study should be noted. First, we were unable to calculate the reporting ORs due to the data characteristics of single category adverse events. We were also unable to calculate the true incidence rates due to the lack of total number of patients receiving the drugs of interest.[2] Second, adverse event reports of this study might have been underreported because the KIDS-KD is a spontaneous adverse event reporting system.[8] Especially, a reporting bias can be influenced by severity of adverse events. The chance of reporting would be higher in patients with serious skin reactions such as SJS, TEN and DRESS, and lower in patients with simple rash or urticaria. Therefore, the proportion of serious skin reactions (241/2,942 in this study) might have been over-estimated or exaggerated. In addition, this voluntary reporting database nature results in several limitations such as a lack of central quality control by expert panels and many missing or lacking clinical data (e.g., age, gender, indications, etc.).[3] As ADR reports in the KIDS-KAERS were anonymized, additional information could not be assessed.[32]

The present study found that various AEDs are associated with cutaneous ADRs. Although most cutaneous drug reactions were benign, certain AEDs were associated with a higher risk of severe cutaneous drug reactions such as SJS, TEN, or DRESS. Our findings support previous evidence that the presence of an aromatic ring as a common feature in chemical structures of AEDs partly explains AED-associated cutaneous drug reactions. High risk AEDs should be prescribed under careful monitoring, and early detection and prompt intervention are needed to prevent severe complications.

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