



Adverse Cutaneous Drug Reactions Associated with Old- and New-Generation Antiepileptic Drugs Using the Japanese Pharmacovigilance Database

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Abstract

Background and Objective Adverse cutaneous drug reactions associated with antiepileptic drugs (AEDs) are a serious problem in the clinical setting. New-generation AEDs have been reported to be better tolerated than old-generation forms; however, information about the risks of adverse cutaneous drug reactions to new-generation AEDs is limited.

Objective The purpose of this study was to clarify the association of AEDs with adverse cutaneous drug reactions using a spontaneous reporting database.

Methods We performed a retrospective pharmacovigilance disproportionality analysis using the Japanese Adverse Drug Event Report (JADER) database. Adverse event reports submitted to the Pharmaceuticals and Medical Devices Agency between April 2004 and January 2017 were analyzed. Based on reports of all adverse events, we obtained 4805 reports of adverse cutaneous drug reactions associated with AEDs, and calculated the reporting odds ratio (ROR) and 95% confidence interval (CI) for drug rash, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

Results Individual AEDs had variable signals for drug rash, SJS, and TEN. The strongest signals were detected for drug rash caused by lamotrigine (ROR 9.18, 95% CI 8.65–9.74), SJS caused by zonisamide (ROR 9.85, 95% CI 8.23–11.78), and TEN caused by phenobarbital (ROR 14.08, 95% CI 11.28–17.57).

Conclusion There are clear differences in the risk of cutaneous reactions among AEDs, and further studies are needed to confirm these findings.

Key Points

It is well known that old-generation antiepileptic drugs (AEDs) induce adverse cutaneous drug reactions, but information about the risks of new-generation AEDs is limited.

Spontaneously reported adverse drug event in the Japanese national pharmacovigilance database revealed that there is a wide-ranging strength of association between old- and new-generation AEDs with adverse cutaneous drug reactions.

1 Introduction

Epilepsy is one of the most common neurologic disorders, with a global prevalence of almost 60 million people [1] and an annual incidence of 50 per 100,000 persons [2]. For definitely diagnosed epilepsy patients, long-term treatment with antiepileptic drugs (AEDs) is needed; however, adverse events often result in the early discontinuation of treatment in up to 25% of patients, interfere with the ability to realize fully effective doses, and lower the rate of treatment adherence [3, 4]. Of these, an adverse cutaneous drug reaction is one of the most frequently observed disorders in patients treated with AEDs, and is often responsible for treatment failure and poor quality of life [5]. For example, in a randomized trial involving patients with de novo diagnosed epilepsy, 5.5% of 291 patients receiving carbamazepine, an old-generation AED, developed skin rashes. Furthermore, 9 of the 291 patients discontinued carbamazepine because of skin rash during the treatment period [6]. Serious reactions such as Stevens–Johnson syndrome (SJS) or toxic epidermal

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necrolysis (TEN) are rare but may be life-threatening. The EuroSCAR study revealed that three of the top seven medications associated with SJS or TEN were AEDs, i.e. carbamazepine, phenobarbital, and phenytoin [7].

During the past 20 years, marked progress has been made in the development of new-generation AEDs, such as gabapentin, topiramate, lamotrigine, and levetiracetam, with unique pharmacologic properties as well as an improved safety and tolerability profile [8, 9]; however, adverse cutaneous drug reactions associated with new-generation AEDs have not been fully evaluated in real-world clinical practice.

Recently, spontaneous reporting systems have been used as a crucial method of postmarketing drug safety surveillance for the detection of adverse drug events [10, 11]. The Japanese Adverse Drug Event Report (JADER) database is a large published database managed by the Pharmaceuticals and Medical Devices Agency (PMDA) for pharmacovigilance activities [12–15]. The objective of this study was to assess adverse cutaneous drug reactions classified as old- and new-generation AEDs using the JADER database.

2 Methods

We used the PMDA JADER database as a spontaneous reporting database [16, 17]. This database is freely obtainable from the website of the PMDA, and we hence accessed the dataset to which adverse event reports were submitted between April 2004 and January 2017. The data structure of JADER consists of four datasets: patient demographic information (DEMO), drug information (DRUG), adverse events (REAC), and medical history. Duplicated data, as a result of the same case report being received from different sources, were removed from each table [18]. Physicians represented the most frequent source of reports, while other sources included pharmacists, other healthcare professionals, and patients.

The DEMO table was then linked to the REAC and DRUG tables using the ID number. In total, 5,195,890 reports were obtained after combining the three tables. In each case, the contribution of the medication to adverse events was classified into three categories: ‘suspected medicine’, ‘concomitant medicine’, and ‘interaction’. A ‘suspected medicine’ is defined as a pharmaceutical product suspected to cause an adverse event, and when the reporter suspects an interaction, he/she reports it as an ‘interaction’. A ‘concomitant medicine’ is defined as another pharmaceutical product used at the time of the adverse reaction. In signal detection analysis, the masking effect is defined as the condition whereby a given drug–event pair might be hidden by the presence of another product [19]. We only extracted cases that were classified as ‘suspected medicine’; the total number of reports used was 1,984,122.

We then analyzed reports of suspected drugs and adverse events, which we selected as ‘drug rash’, ‘Stevens–Johnson syndrome’ (SJS), and ‘toxic epidermal necrolysis’ (TEN) in the ‘Preferred Term’ (PT) coded in the Medical Dictionary for Regulatory Activities (MedDRA) [version 20.1]. We compiled a cross-tabulation table based on two classifications: the presence or absence of the adverse event, and the presence or absence of the suspected medicine. Next, we calculated the reporting odds ratio (ROR), which is the rate of reporting a specific adverse event caused by a particular drug divided by the rate of the same adverse event caused by all other drugs present in the database. In addition, the ROR was frequently used with the spontaneous reporting database as an index of the relative risk of drug-associated adverse events. A signal was considered to be present when the lower limit of the 95% confidence interval (CI) of the ROR was > 1 .

In this study, carbamazepine, clonazepam, clobazam, diazepam, ethosuximide, phenobarbital, phenytoin, primidone, and valproic acid were classified as old-generation AEDs, while gabapentin, lacosamide, lamotrigine, levetiracetam, perampanel, rufinamide, stiripentol, topiramate, vigabatrin, and zonisamide were classified as new-generation AEDs (electronic supplementary Table 1), on the basis of previous studies [20–22].

In this database, age, height, and weight information are reported as decades, centimeters, and kilograms, respectively. However, because these data are not continuous variables, we could not conduct multiple analyses using the data. All analyses were performed using JMP Pro 12 (SAS Institute Inc., Cary, NC, USA).

3 Results

Among the total 1,984,122 reports of all adverse events, the total number of reported adverse cutaneous reactions associated with AEDs was 4805 (drug rash: 2471 reports; SJS: 1705 reports; TEN: 629 reports) (see Table 1 for the annual number of reports during 2004–2016). The number of reports of adverse cutaneous drug reactions showed a marginal change. Of note, the annual reports of drug rash and SJS caused by new-generation AEDs exceeded those caused by old-generation AEDs, after 2011.

Table 2 presents the ROR values for drug rash, SJS, and TEN induced by AEDs. Signals for drug rash, SJS, and TEN with both old- and new-generation AEDs were detected. As for drug rash, signals were detected for carbamazepine, diazepam, phenobarbital, phenytoin, valproic acid, gabapentin, lamotrigine, levetiracetam, and zonisamide, and signal scores suggested a stronger association for lamotrigine (ROR 9.18, 95% CI 8.65–9.74). With respect to SJS, although signals were detected for carbamazepine,

clonazepam, diazepam, ethosuximide, phenobarbital, phenytoin, valproic acid, lamotrigine, levetiracetam, and zonisamide, the association with zonisamide (ROR 9.85, 95% CI 8.23–11.78) was noteworthy. In the case of TEN, signals for eight AEDs (carbamazepine, ethosuximide, phenobarbital, phenytoin, valproate acid, gabapentin, lamotrigine, and zonisamide) were detected. The scores for TEN were highest for phenobarbital (ROR 14.08, 95% CI 11.28–17.57).

4 Discussion

In a large, nationwide study of pharmacovigilance data, comprehensive information on adverse drug events was accumulated, and thus the study was suitable for the evaluation of rare but very serious adverse drug event signals. We found a potential association of old- and new-generation AEDs with adverse cutaneous drug reactions using a retrospective disproportionality analysis.

In our results, the annual number of reports in the early years on each adverse cutaneous drug reaction caused by old-generation AEDs was higher than those caused by new-generation AEDs; however, most of the new-generation AEDs were launched after 2008 in Japan, therefore the annual reports on these AEDs exceeded those of old-generation AEDs after around 2011. In our results, the most frequent cause of adverse cutaneous drug reactions among the new-generation AEDs was lamotrigine. In 2012, the PMDA issued an alert regarding the proper use of lamotrigine, which was first approved for epileptic patients in 2008, emphasizing compliance with the dosage and administration protocol and ensuring the early detection of serious

lamotrigine-induced adverse cutaneous drug reactions (http://www.info.pmda.go.jp/iyaku/_info/tekisei/_pmda_06.pdf). After this alert, reports of drug rash caused by new-generation AEDs slightly decreased, but reports of SJS and TEN showed marginal changes.

Our findings revealed real-world trends of reported adverse events that are inconsistent with findings from clinical trials and other published retrospective studies that investigated the association between AED use and drug rash. For example, in a retrospective study of 663 patients, Alvestad et al. found that rash frequently occurred with carbamazepine (11%) rather than lamotrigine (8%) [23]. In addition, the SANAD study revealed that the rate of allergic rash development was higher in patients taking carbamazepine (intention-to-treat: 38/378; per protocol: 32/378) than in those with lamotrigine (intention-to-treat: 17/378; per protocol: 15/378), in a randomized controlled trial involving 1721 patients [24]. However, in this study, we found that signals for drug rash were detected with four new-generation AEDs, i.e., gabapentin, lamotrigine, levetiracetam, and zonisamide (Table 2). Of note, the signal score was higher for lamotrigine than carbamazepine. In a prospective, observational study of 654 adult patients, Zeng et al. found that the frequency of skin rash was higher with lamotrigine (14.1%) than carbamazepine (8.8%) [25], and, for this reason, further studies are required.

SJS/TEN is a rare but potentially fatal complication of treatment with antiepileptic medication, characterized by acutely developing purplish rashes and blisters that affect both the skin and mucous membranes. Common offenders include carbamazepine, phenytoin, and phenobarbital among old-generation AEDs [26–28], and lamotrigine among new-generation AEDs. Interestingly, our results

Table 1 Annual reports of drug rash, SJS, and TEN induced by all drugs and AEDs from 2004 to 2016

	Year													Total
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	
Number of reports of drug rash														
All drugs	817	805	818	802	856	760	964	1320	2361	1369	1622	1481	1078	15,053
Old-generation AEDs	52	66	55	56	105	78	91	91	105	103	114	72	56	1044
New-generation AEDs	9	4	2	6	15	39	72	268	220	204	260	204	124	1427
Number of reports of SJS														
All drugs	695	744	843	826	711	836	796	734	1006	770	938	843	692	10,434
Old-generation AEDs	55	47	40	69	64	88	56	55	71	60	66	62	45	778
New-generation AEDs	14	12	5	1	22	39	43	135	153	130	174	110	89	927
Number of reports of TEN														
All drugs	349	587	411	652	959	454	766	490	554	510	691	478	345	7246
Old-generation AEDs	26	23	26	24	56	34	31	32	39	28	26	21	4	370
New-generation AEDs	2	1	2	6	11	13	14	35	33	42	44	40	16	259

AEDs antiepileptic drugs, SJS Stevens–Johnson syndrome, TEN toxic epidermal necrolysis

Table 2 Signal detection for drug rash, SJS, and TEN induced by AEDs

	Drug rash			SJS			TEN		
	<i>N</i>	ROR	95% CI	<i>N</i>	ROR	95% CI	<i>N</i>	ROR	95% CI
Old-generation AEDs									
All old-generation AEDs	1044	5.35	5.02–5.70	778	5.74	5.33–6.18	370	3.78	3.40–4.20
Carbamazepine	688	8.18	7.56–8.85	429	7.18	6.51–7.92	99	2.26	1.85–2.76
Clobazam	8	1.32	0.66–2.65	7	1.67	0.79–3.51	1	0.34	0.05–2.42
Clonazepam	15	1.13	0.68–1.87	30	3.29	2.29–4.72	8	1.25	0.62–2.50
Diazepam	21	1.95	1.27–3.00	13	1.74	1.01–3.00	4	0.77	0.29–2.04
Ethosuximide	2	3.11	0.77–12.66	3	6.84	2.16–21.64	2	6.50	1.60–26.41
Phenobarbital	62	4.94	3.83–6.37	69	8.00	6.29–10.19	83	14.08	11.28–17.57
Phenytoin	116	5.76	4.78–6.95	111	7.99	6.60–9.67	56	5.68	4.35–7.40
Primidone	1	4.51	0.61–33.12	1	6.52	0.89–47.89	0	–	–
Valproic acid	131	2.38	2.00–2.83	115	3.02	2.51–3.64	117	4.46	3.71–5.36
New-generation AEDs									
All new-generation AEDs	1427	6.87	6.50–7.27	927	6.31	5.89–6.75	259	2.35	2.07–2.66
Gabapentin	18	2.53	1.58–4.03	7	1.40	0.67–2.95	8	2.32	1.15–4.65
Lacosamide	0	–	–	0	–	–	0	–	–
Lamotrigine	1262	9.18	8.65–9.74	749	7.57	7.02–8.17	169	2.28	1.95–2.65
Levetiracetam	52	1.87	1.42–2.46	33	1.71	1.21–2.41	17	1.26	0.78–2.04
Perampanel	0	–	–	0	–	–	0	–	–
Rufinamide	6	1.34	0.6–2.99	0	–	–	0	–	–
Stiripentol	4	0.63	0.24–1.68	0	–	–	0	–	–
Topiramate	7	0.62	0.29–1.30	11	1.41	0.78–2.55	0	–	–
Vigabatrin	0	–	–	0	–	–	0	–	–
Zonisamide	78	4.07	3.25–5.11	127	9.85	8.23–11.78	65	7.07	5.52–9.05

AEDs antiepileptic drugs, CI confidence interval, ROR reporting odds ratio, SJS Stevens–Johnson syndrome, TEN toxic epidermal necrolysis

revealed high signal scores of zonisamide for SJS (ROR 9.85, 95% CI 8.23–11.78) and TEN (ROR 7.07, 95% CI 5.52–9.05), in addition to known offenders such as carbamazepine, phenobarbital, phenytoin, and lamotrigine (Table 2). The results for zonisamide are inconsistent with one postmarketing surveillance study of 1948 patients in Korea, which reported rare instances of SJS/TEN induced by zonisamide (one case of SJS) [29]. The incidence of serious and life-threatening adverse events due to zonisamide needs to be further investigated.

The mechanisms by which AEDs might contribute to adverse cutaneous drug reactions may involve their chemical structure containing an aromatic ring, which can form an arene oxide intermediate [30]. These metabolites bind to cellular macromolecules, causing cell necrosis or a secondary immunological response [31]. Some AEDs contain an aromatic ring in their structure, such as carbamazepine, lamotrigine, phenytoin, phenobarbital, and zonisamide; however, lamotrigine has an aromatic ring in its chemical structure but is not involved in this mechanism. Lamotrigine is not involved in the pathway producing reactive metabolites such as toxicant arene oxides [32], but is involved in

the pathway causing reactions to allergens [33]; however, the precise mechanism remains unknown.

This pharmacovigilance study using the JADER database has several limitations. First, as in all pharmacovigilance studies, we were unable to calculate the true incidence rates, notably due to (1) the lack of total number of patients receiving the drugs of interest; and (2) underreporting. Adverse events that are well-known to be due to certain drugs are less likely to be reported. Second, ROR does not provide a robust indication of the signal strength. In spontaneous reporting systems such as JADER, control populations are not included, therefore the ROR is different from the ‘odds ratio’ that is commonly used in epidemiological studies. In real terms, the ROR indicates an increased risk of adverse event reporting, and not the risk of an adverse event itself. Finally, the present method did not provide us with detailed clinical information on the patients [34], such as genetic factors like HLA-A*02:07 allele involvement in the development of SJS caused by AEDs.

5 Conclusion

There is a diverse strength of association between old- and new-generation AEDs with serious cutaneous adverse events, and physicians should be alerted in order to take precautions against these associated cutaneous adverse reactions, and therefore potentially avoiding them.

Author Contributions KH, AI, and SO conceived and designed the study; KH, AI, SO, IN, TW, and KI analyzed the data and drafted the manuscript. All authors have read and approved the final manuscript submitted for publication.

Compliance with Ethical Standards

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Conflict of interest Keiko Hosohata, Ayaka Inada, Saki Oyama, Iku Niinomi, Tomohito Wakabayashi and Kazunori Iwanaga report no conflicts of interest related to this work.

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Table S1 List of new-generation AEDs in this study

AED drug	Brand name drug	Year of introduction in Japan
Gabapentin	GABAPEN ^{○,R}	2006
Lacosamide	VIMPAT ^{○,R}	2016
Lamotrigine	Lamictal ^{○,R}	2008
Levetiracetam	E Keppra ^{○,R}	2010
Perampanel	Fycompa ^{○,R}	2016
Rufinamide	Inovelon ^{○,R}	2013
Stiripentol	DIACOMIT ^{○,R}	2012
Topiramate	TOPINA ^{○,R}	2014
Vigabatrin	Sabril ^{○,R}	2016
Zonisamide	EXCEGRAN ^{○,R}	1989

AED, antiepileptic drug