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Full Length Research Paper

Antiepileptic Drugs-induced Stevens-Johnson syndrome: systematic review of descriptive studies

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Abstract

Purpose
Stevens-Johnson on syndrome (SJS) adverse reactions to antiepileptic drug (AED), are not common but can result in significant morbidity and mortality. Major culprit drugs, clinical characteristics, and clinical course and outcomes of AED-induced SJS were investigated.

Methods
A comprehensive search of data sources collected from PubMed, Medline, Cochrane Library was performed. All published papers, studies, systematic reviews were evaluated. Any literature that was written in any language other than English was excluded. A total of 161 patients with AED-induced SCARs were analyzed from the extracted papers. The causative AEDs, clinical characteristics, organ involvements, details of treatment, and outcomes were investigated. Different AEDs-induced SJS were compared to each other according to the clinical and laboratory parameters. Risk factors for prolonged hospitalization in AED-induced SJS were discussed.

Results
Carbamazepine and lamotrigine were the most common culprit drugs causing SCARs. Valproic acid and levetiracetam also emerged as the major causative agents. The disease duration and hospital stay in carbamazepine-induced SJS were shorter than those in other AEDs ($P< 0.05$, respectively). Carbamazepine, the most common culprit drug for SJS, was associated with a favorable outcome related to prolonged hospitalization in SJS (odds ratio, 0.12; 95% confidence interval, 0.02-0.63, $P= 0.12$).

Conclusion
Valproic acid and levetiracetam (Keppra®) were the significant emerging AEDs causing SJS in addition to the well-known offending AEDs such as carbamazepine and lamotrigine. Carbamazepine was associated with reduced hospitalization, but thrombocytopenia was a risk factor for prolonged hospitalization. It is suggested that the clinical characteristics and courses of AED-induced SJS might differ according to the individual AEDs.

Keywords: *Antiepileptic drugs, Stevens-Johnson syndrome, Adverse Drug Reactions, SCAR, AEDs induced-SJS.*

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INTRODUCTION

Antiepileptic drugs (AEDs) exhibit various adverse drug reactions (ADRs) which impairs the health-related quality of life in epileptic patients.[i] The majority of these ADRs are acute and dependent on the properties of the pharmacology of the drugs. The development of ADRs usually starts to progress after the initiation of a drug or during dose escalation and mostly decrease by time, after dose reduction or drug withdrawal. On the other hand, unpredictable and idiosyncratic reactions may occur in 3%–10% of the patients treated with AEDs, which can erupt to serious and life-threatening severe cutaneous adverse drug reactions (SCARs), such as Stevens-Johnson syndrome (SJS) which usually occur within the first few weeks of treatment and could be reversed after drug discontinuation. The risk of morbidity and mortality is in proportion with delayed recognition and intervention. Most SJS cases are caused by aromatic AEDs, such as phenytoin, carbamazepine, phenobarbital, oxcarbazepine, levetiracetam (keppra®).

Recent studies have reported that lamotrigine (LTG) which is different in structure from other aromatic AEDs, has also caused SJS.

ADRs to AEDs are the leading factors of treatment failure and the suffering of patients with epilepsy. Although non-serious drug eruptions are relatively frequent with AEDs, the incidence of SJS with AEDs is known to be 1–10 in 10,000 patients. Despite a low incidence rate, the mortality rate of SJS is 10%–40%.

Although several published reports are describing the clinical characteristics, causative agents, and risk factors of AED-induced SJS,[ii] there have been quite a few reports to date describing the relation of AEDs with the occurrence of SJS. The variation in the incidence and risk factors of SJS among different ethnic populations across their genetic constitutions has been reported.[iii]

In this study, we investigated the major AEDs, clinical characteristics, and clinical courses and outcomes of AED-induced SJS.

MATERIALS AND METHODS

Data collection and study subjects

Studies reporting SJS cases in the period between 2010 and 2019 were investigated. Offending drugs and causal relationships between the drugs and the reactions in each case were evaluated.

The diagnosis of SJS was based on the diagnostic criteria proposed by the RegiSCAR study group.[iv] SJS is characterized by blisters or widespread exanthema with skin detachment affecting < 10% of the body surface area (BSA). In all cases, causality evaluation using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment system was performed, and 'certain,' 'probable,' and 'possible' cases were recruited. A total of 745 SCAR cases were collected including 384 cases of SJS. The main causative AED of SJS was attributed to carbamazepine (9.3%). A total of 161 patients with AED-induced SCARs were enrolled, which contributed to 21.6% of all SCARs cases. The obtained information was gathered from the included patients treated with AEDs including CBZ, PHT, LTG, PHB, valproic acid (VPA), fosphenytoin, levetiracetam (LEV), zonisamide, and oxcarbazepine (OXC). The names of the offending AEDs, clinical manifestations, hospital courses, time intervals from the onset of

symptoms to the day of resolve/discharge (disease duration), time intervals from the drug exposure to the onset of symptoms (latent period), organ involvements, laboratory data, complications, and outcomes were all analyzed.

Statistical analyses

The data are represented in the form of mean ± standard deviation (SD) if normally distributed, or the median and range if otherwise. The variation in the characteristics of the study participants was compared with the χ^2 test or Fisher's exact test for the categorical variables, and analysis of variance with Scheffé's POST-HOC test or Kruskal-Wallis test with Dunn's POST-HOC test for the continuous variables, as applicable. Normality tests were performed for the distribution of data using Shapiro-Wilk's test. Univariate and multivariate logistic regression analyses to identify prognostic factors were performed which were independently associated with prolonged hospitalizations. A multivariate model using a backward elimination method was created, and the probability was set at 0.05 for exclusion. Odds ratio (OR) with 95% confidence interval (CI) were calculated for prognostic factors corelated with prolonged hospitalizations. All statistical analyses were performed with SPSS version 24.0 and a P value of < 0.05 was considered statistically significant.

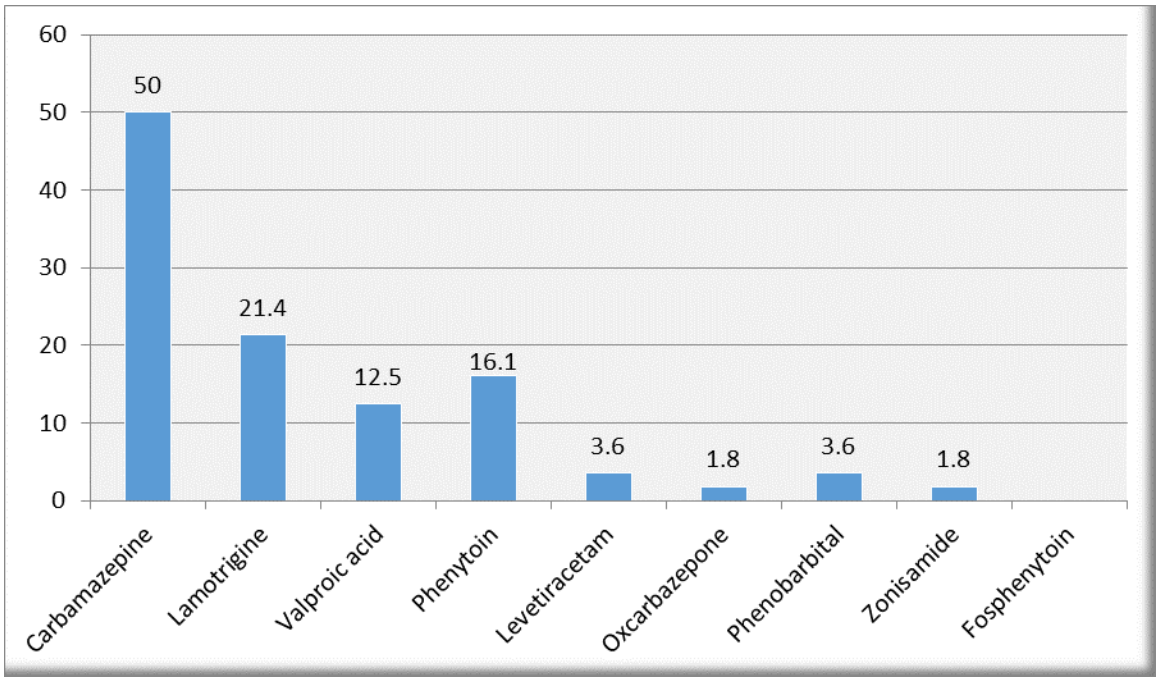
RESULTS

Demographic data

A total number of 56 patients had SJS (34.87%) among 161 patients with ADE-induced SCARs. There were insignificant differences in the age of onset and sex. The latent period was about 29.6 ± 33.2 days and the median duration of the disease was 23.7 days. Further information regarding past exposure to drugs was investigated. It was found that 4 people had been taking the same AEDs as the causative drug of SJS including 3 for carbamazepine, 1 for levetiracetam (kepra®), excluding one with inaccurate information. Additionally, high malignancy rates were reported in SJS (14.3%). Among a total of 15 patients with malignancy, six patients had a brain tumor, and one patient had brain metastasis due to lung cancer. They took AEDs for seizure prevention. The rest of the patients were prescribed AEDs for, seizure control (n = 2), pain control (n = 4) and spasm control (n = 1). One patient was unable to determine the reason.

Offending drugs for AED-induced SCARs

In all the cases of SJS, CBZ was the most common offending drug, followed by LTG, PHT, VPA, and LEV. In the 56 cases of SJS, 28 (50%) were caused by CBZ, followed by LTG (21.4%), PHT (16.1%), VPA (12.5%), and LEV (3.6%).



Clinical manifestations and laboratory findings of AED-induced SCARs

The clinical features and laboratory findings of the reviewed patients in literature are summarized in Table 1. Fever at presentation was found in 53.7% in SJS patients. The majority of the patients had different types of cutaneous complications. Skin detachment occurred in 26.8% of the patients. Laboratory findings, the proportion of leukocytosis, atypical lymphocytosis, hepatic involvement, and renal involvement were high.

Table 1

Characteristics	SJS
Fever	29/54 (53.7%)
Duration (day) (min–max)	5.1 ± 5.1 (1–20)
Cutaneous involvement	
Erythema	54/56 (96.4)
Targetoid lesion	9/56 (16.1)
Detachment	15/56 (26.8%)
Vesicle/bullae	19/56 (33.9)
Nikolsky's sign	9/24 (37.5)
Mucosal involvement	49/53 (92.5)
Leukocytosis	15/24 (62.5)
Peak leukocytosis	12,861 ± 7,207 (2,029–32,000)
Atypical lymphocytosis	3/12 (25.0)
Eosinophilia	19/37 (51.4)
Peak eosinophil count	980 ± 1,402 (49–6,009)
Thrombocytopenia	5/32 (15.6)
Lymphadenopathy	1/24 (4.2)
Hepatic involvement	30/44 (68.2)
Peak ALT (IU/L)	186.7 ± 238.9 (7–1,175)
Renal involvement	5/25 (20.0)
Peak Scr (mg/dL)	1.0 ± 0.8 (0.3–4.5)

Most of the patients had fully recovered, however, twelve patients suffered from sequelae. The overall mortality rate was estimated to be 3.8%. Regarding the causative drug for mortality, VPA was the most common drug causing death (3 out of 6 deaths), followed by PHB, CBZ, and LTG (1 death each).

Comparison between the clinical course and outcomes of SCARs according to the culprit drugs

The differences in the clinical characteristics and outcomes against major culprit drugs were evaluated, including CBZ, LTG, VPA, PHT, and LTV. Patients suffering from SJS, the latent period and disease duration were shorter with CBZ than with the other AEDs. The length of drug administration in SJS was remarkably shorter with CBZ than with VPA (P= 0.047, POST HOC analysis).

Clinical course and outcomes in SJS/TEN according to the major causative drugs

Characteristics	Carbamazepine (n = 35)	Lamotrigine (n = 16)	Valproic acid (n = 9)	Phenytoin (n = 10)	Levetiracetam (n = 3)	*P* value
Age (yr)	54 (15–81)	56 (15–69)	56 (15–70)	68 (2–84)	48 (37–83)	0.587
Female	17 (48.6)	9 (56.3)	6 (66.7)	5 (50.0)	1 (33.3)	0.836
Latent period (day)	14 (0–151)	28 (3–182)	27 (0–182)	31 (19–91)	41 (22–47)	0.039*
Disease duration (day)	18 (4–91)	23 (12–91)	19 (6–91)	27 (16–35)	27 (27–31)	0.038*
Admission duration (day)	14 (0–88)	20 (0–103)	42 (8–103)	21 (6–31)	17 (13–28)	0.035†
Intensive care unit care	1 (2.9)	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0.435
Clinical outcome						
Recovery	31 (88.6)	12 (80.0)	4 (44.4)	8 (80.0)	3 (100.0)	0.065
Sequelae	4 (11.4)	2 (13.3)	2 (22.2)	2 (20.0)	0 (0.0)	0.827
Skin	3 (75.0)	2 (100.0)	1 (50.0)	2 (100.0)	-	1.000
Eye	2 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	-	0.600
Death	0 (0.0)	1 (6.7)	3 (33.3)	0 (0.0)	0 (0.0)	0.010

Prognostic factors of AED-induced SCAR

The risk factors were evaluated for prolonged hospitalization (more than 3 weeks). Fever and use of VPA were significantly accompanied by prolonged hospitalization. Leukocytosis and infections were demonstrated as poor prognostic factors. In the multivariate analysis, CBZ was found to be negatively related to prolonged hospitalization in SJS (OR, 0.08; 95% CI, 0.01–0.78; P = 0.03).

Risk factor analysis for prolonged hospitalization in SCARs (SJS)

Variable			**Multivariate analysis**	
			OR (95% CI)	***P* value**
SJS				
	Carbamazepine			
		Yes	0.08 (0.01–0.78)	0.030
		No	1.00	

DISCUSSION

It was found that CBZ, LTG, VPA, LEV and PHT were the most common causing culprit drugs to SJS and the estimated mortality rates were 3.6%. Despite the fact that CBZ was the most common causative agent to SJS, It had a good prognostic factor for prolonged hospitalization.

SJS is T cell-mediated delayed hypersensitivity reactions[v]. The clinical manifestations of SJS typically occur 1–4 weeks after the initiation of therapy[vi]. In a recent study, the mean latent period in AED-induced SJS was reported to be around 31 days (ranging from 0 to182 days), which is equivilant to other previous studies[vii]. Hence, it is necessary to closely monitor the laboratory reports and clinical symptoms for at least one month after AEDs initiation because early diagnosis and withdrawal of the culprit drug are crucial to improve the results of drug hypersensitivity reactions, particulary SJS.

This study search result estimate that more than 50% of SJS patients had eosinophilia. A total number of 25% of patients with SJS had atypical lymphocytosis. Moreover, a considerable number of SJS patients also had hepatic and renal involvement. Also, around 26% of the SJS patients had mucosal involvement. Therefore, further studies are required to investigate the frequency of patients manifesting the common clinical features of the disease.

Aromatic AEDs, including CBZ, PHT, LTG, and PHB, are classified as high-risk drugs for ADRs and are also the main offenders causing SJS[viii]. In the present study, LTG and CBZ were the most common offending drugs that cause SJS. This is similar to the previous studies in which aromatic AEDs such as CBZ, PHT, LTG, and PHB are classified as high-risk drugs for ADRs and the primary offenders that lead to SJS.[ix] However, it was found in some recent literature that VPA and LEV were the most commonly AEDs causing SJS[x]. Hypersensitivity reactions have been rarely observed in patients taking non-aromatic AEDs, such as VPA, LEV, and vigabatrin. It has been reported that the incidence of LTG-induced hypersensitivity was increased when VPA and/or other AEDs are administered concurrently. In this study, a total of 13 (8%) patients were treated with different AEDs as combination therapies. Among them, VPA was the most commonly used drug, accounting for 69% (9/13) in the combination regimen (5 with LTG, 2 with PHT, 1 with LEV, and 1 with PTB). It should be, however, noted that there was a considerable number of SJS caused by VPA monotherapy.

LEV (Keppra®) is a new-generation AED having a chemical structure that differs from the conventional AEDs[xi], and its usage has rapidly increased in recent years. There were many cases of LEV-induced hypersensitivity reactions that have been reported, despite that it is generally well tolerated. In this study, a total of 12 (7.5%) LEV-induced SJS has been reported. It might be explained by the fact that non-aromatic AED-induced SJS might be accompanied by some specific HLA genotypes in the patients like with CBZ[xii]. Hence, LEV-induced SJS (Keppra®) requires continuous monitoring and studying.

The mortality rate of SJS has been reported to be 10%.[xiii] Recently, in the United States, the mean adjusted mortality rates were found to be 4.8% for SJS.[xiv] Similarly, a recent study using has shown that the in-patient mortality was 15.7% in SJS.[xv] But the current review data showed that the mortality rate in SJS was 3.6%.

Unfortunately, up till now, there are no established therapies for SJS. The previous results from a RegiSCAR cohort could not confirm the beneficial effects of systemic corticosteroids on reducing mortality in SJS.[xvi] A recent meta-analysis, however, showed that corticosteroids and cyclosporine were associated with a decreased mortality rate as compared to a supportive treatment in SJS.[xvii] In the present systematic review, the majority of studied papers demonstrated patients were treated with systemic corticosteroids, and a total of 13.2% of patients were treated with IVIG. Although a randomized controlled trial is lacking and there is much controversy regarding the benefits of IVIG, our conclusions and results suggest that IVIG or the combination of corticosteroids and IVIG may decrease the mortality rate in SJS.

In this review, VPA was detected as the third most AED causing SJS, and all deaths were associated with VPA monotherapy. In addition, VPA was accompanied by prolonged hospitalization, suggesting that VPA could be related to more severe disease and poorer results. An interesting thing is that the latent period, disease duration, and hospitalization with CBZ were shorter than in other drugs demonstrating a better prognosis. The progress and prognosis of SJS differed according to each AED, and therefore further studies are required to elucidate these outcomes.

SJS prognostic factors are not well established. Uptill now, in addition to the SCORe of Toxic Epidermal Necrosis (SCORTEN), numerous laboratory parameters such as hypernatremia, serum lactate dehydrogenase, and thrombocytopenia are suggested to be prognostic factors in SJS.[xviii] This is also included in the diagnostic criteria presented by ResiSCARs (European registration of SCARs).[xix] Significantly, the risk of prolonged hospitalization that exceeds 3 weeks was reduced in CBZ-induced SJS in the present study. The mean period of hospitalization in CBZ-induced SJS was 15.6 days, which were around 4 days shorter than the mean period of hospitalization 20.2 days. To date, CBZ has been considered as a critical risk factor for SCARs.[xx] In a retrospective study using health insurance data that was found in the literature for elderly patients, CBZ was reported to increase the incidence of SJS by about ten times.[xxi] It is a remarkable outcome that CBZ is not a positive risk factor for the length of hospitalization. This can be illustrated by the fact that 1) CBZ is known to cause SJS well, therefore clinicians are alert in detecting it early and promptly stop the medication, and 2) Of course, the severity of CBZ-induced SJS might be less severe than SJS by other AEDs.

There are several limitations to the present study. There were limited data with missing values in some literature studies. Notably, we could not analyze the SCORTEN score and HHV-6 reactivation in this study. Because the majority of patients reviewed in literature studies were treated in various departments, they have not been adequately assessed and tested in the beginning. Secondly, there were also the possibilities of selection bias and wrong identification of the offending drug. Despite a thorough check, we could not obtain the detailed history of pre-existing diseases and co-medications used in the patients included. Thirdly, we could not verify the SJS incidences because hospitals that have prescribed causative drugs are different from those that enrolled in the study. Also, there might be AED-induced SJS patients present in literature papers missing from this study.

In conclusion, this systematic review investigated the prognostic factors as well as clinical characteristics common causative drugs and clinical courses. CBZ and LTG are the most common culprit drugs in SJS, and VPA and LEV (Keppra®) have emerged as the major causative agents. VPA was associated with a higher mortality rate. CBZ was correlated negatively with prolonged hospitalization in SJS. Further studies will be needed with a more substantial cohort of AED-induced SJS to clarify drug-specific characteristics and prognoses.

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