ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 12, 2024

Online - 2455-3891
Print - 0974-2441

Research Article

COMPARATIVE ANALYSIS OF STEVENS-JOHNSON SYNDROME INCIDENCE AMONG SEIZURE PATIENTS ON DIFFERENT ANTIEPILEPTIC DRUGS

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Received: 10 October 2024, Revised and Accepted: 22 November 2024

ABSTRACT

Objectives: Steven-Johnson syndrome (SJS) is a severe, immune-mediated hypersensitivity reaction which is often triggered by medications, notably antiepileptic drugs (AEDs). AEDs such as phenytoin, carbamazepine, and sodium valproate are reported to be commonly offending drugs, particularly in individuals with genetic factors such as HLA-B*1502. A retrospective analysis of 1000 seizure patients revealed variability in SJS incidence among AEDs, highlighting levetiracetam as relatively safer but not risk-free. Early detection and tailored treatment can improve outcomes and mitigate risks.

Methods: This retrospective study (2019–2024) at a tertiary care center examined the incidence of SJS in epilepsy patients aged ≥18 years treated with phenytoin, carbamazepine, sodium valproate, or levetiracetam for ≥6 months. Using electronic health records, patient demographics, AED patterns, and genetic predispositions (HLA-B*1502 allele) were analyzed. The study identified SJS rates and potential risk factors. For statistical analysis, $p<0.05$ was taken as significant.

Results: An overall SJS incidence of 3.0%. Phenytoin (4.8%) and carbamazepine (3.6%) had significantly higher SJS rates than sodium valproate (2.4%) and levetiracetam (1.2%) ($p<0.01$). HLA-B*1502 allele strongly correlated with SJS, especially for phenytoin and carbamazepine. Age and comorbidities were not statistically significant risk factors. Genetic predisposition was the primary determinant of SJS risk, emphasizing personalized treatment strategies.

Conclusion: There was a higher risk of SJS with phenytoin and carbamazepine compared to sodium valproate and levetiracetam, with levetiracetam being the safest option. Genetic screening for HLA-B*1502 in at-risk populations is essential to prevent SJS.

Keywords: Stevens-Johnson syndrome, Antiepileptic drugs, HLA-B*1502 allele, Drug hypersensitivity.

 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i12.53471. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Steven-Johnson Syndrome (SJS) is a rare, life-threatening type of hypersensitivity reaction characterized by severe skin and mucous membrane involvement, usually due to certain medications [1]. The clinical manifestations begin with flu-like symptoms, painful blistering rashes, and widespread epidermal detachment. In the absence of appropriate management, SJS can progress into potentially life-threatening complications such as sepsis and organ failure [2]. The condition is immune-mediated, with many cases involving genetic factors. Carriers of specific alleles, such as HLA-B*1502, are more susceptible to the adverse reactions of some drugs [3]. The key to better outcomes lies in the early detection and withdrawal of the offending drug, along with prevention among those populations at higher risk.

Antiepileptic drugs (AEDs) are among the well-recognized causes of SJS, with phenytoin, carbamazepine, and sodium valproate being the most commonly implicated drugs in the condition. Genetic predisposition, such as the HLA-B*1502 allele, significantly influences the risk with phenytoin and carbamazepine in some ethnic populations [4]. Levetiracetam, a newer AED, has been considered safer about a lower incidence of SJS, although not entirely risk-free [5]. The variability in the reported incidences of SJS across these AEDs forms a basis for treatment individualization [6]. We retrospectively compared the incidence rates of SJS in seizure patients treated with these four AEDs in a tertiary care setting. Analyzing 1000 cases provided insight into each drug's relative risks in seizure patients.

METHODS

This retrospective observational study was conducted in a tertiary care center from 2019 to 2024. The study used cohort data to approximate the rate of SJS in patients with epilepsy on one of the four prevalent AEDs, including phenytoin, carbamazepine, sodium valproate, and levetiracetam. A retrospective study design was preferred to include a thorough review of pre-existing medical records, and it gave quite a detailed record of the patient's history: their medication schedules, demographic characteristics, and potential side effects. This is useful in the investigation of time trends and the association of AED usage with SJS incidence over a sufficiently long period for clinically informing the safety profiles of these drugs.

The patients were aged 18 years and above with a diagnosis of epilepsy who had at least 6 months of one of the four AED treatments comprising phenytoin, carbamazepine, sodium valproate, and levetiracetam. The diagnosis of epilepsy should have neurological documentation, and the subject should have followed the next consecutive course of the particular AED during the period under consideration. Only patients with a well-defined and documented history of epilepsy were included to ensure the consistency of data. Patients with other known skin disorders, prior hypersensitivity reactions, or non-epileptic seizure conditions were excluded from the study. This was done to eliminate potential confounders that could skew the results, such as pre-existing dermatological conditions or adverse reactions unrelated to the AEDs.

Data were collected by thoroughly reviewing medical records at the tertiary care center. Patient demographic information (age, sex, and

race) was abstracted from electronic health records. Further details on seizure type (focal or generalized), epilepsy duration, and the AED treatment pattern, including dosage and duration of the treatment with the drug, were also abstracted. Particular emphasis was placed on the documentation of reported skin reactions, including the onset and clinical manifestations of SJS, as confirmed by dermatological and clinical examination. Furthermore, noted was the estimated timing of SJS development about the start of AED therapy to derive any association with drug exposure.

The primary outcome measure in this study was the incidence of SJS associated with each of the four AEDs under the study, namely, phenytoin, carbamazepine, sodium valproate, and levetiracetam. The number of SJS cases measured the incidence compared with the total number of exposed patients in each drug group. Secondary outcomes included the identification of possible risk factors toward the development of SJS, including patient age and genetic factors, such as the carrier state of the HLA-B*1502 allele, also considering comorbidities such as HIV status or other immune-related diseases since these may affect the host's susceptibility to skin reactions. Instead, this was meant to gain more insights into the roles of these factors in producing AED users with SJS.

Descriptive statistics were used to summarize demographic data on age, sex, race, and characteristics of AED usage. The Chi-square test was used to test whether the distribution of skin reactions in the four AED groups differs significantly in comparing the incidence of SJS among the four drugs [6]. Furthermore, to study the genetic predisposing factors, the data of gene typing HLA-B*1502 allele for the groups receiving phenytoin and carbamazepine were added to investigate the importance of genetic factors in SJS genesis. This enabled the probable pharmacogenomic effect to be estimated to the risk of severe cutaneous adverse reactions regarding these drugs. In all the tests, the estimation of the level of significance was set at 0.05.

Inclusion criteria

The following criteria were included in the study:

- Confirmed diagnosis of epilepsy by a neurologist
- Age 18 years and above
- Patients who have received at least 6 months of treatment with any of the following AEDs: Phenytoin, carbamazepine, sodium valproate, or levetiracetam
- Availability of complete clinical data for review and assessment
- Patients are willing to provide informed consent for participation in the study.

Exclusion criteria

The following criteria were excluded from the study:

- History of SJS or other severe hypersensitivity reactions before starting AEDs
- Pregnant or lactating women
- Patients with severe concomitant diseases (e.g., autoimmune disorders, advanced malignancies, or organ failure) that could confound the analysis
- Patients on combination therapy with more than one AED
- Patients with known non-compliance to prescribed AED therapy
- Recent use of other medications or treatments known to increase the risk of SJS (e.g., sulfa drugs and allopurinol)
- Patients with insufficient clinical or laboratory data to confirm a diagnosis of SJS or assess risk factors.

RESULTS

A total of 1000 patients diagnosed with epilepsy were included in the study, with a mean age of 45 years (range 18–75 years). Of the study population, 58% were male, and 42% were female. There was a male preponderance in the studied cases, with M: F ratio being 1:0.92 (Fig. 1).

Comorbid conditions were common, with 32% of patients having one or more chronic illnesses, such as hypertension (22%), diabetes (8.4%), cardiovascular diseases (9%), and asthma (3.2%). A total of

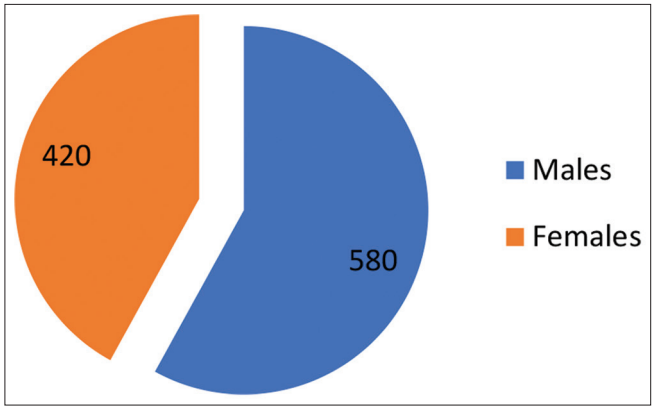

Fig. 1: Gender distribution of studied cases

150 (15%) answered that they had been diagnosed with HIV or any other immunocompromising illness that might be the cause of severe skin reactions (Fig. 2).

The cohort was distributed across four AED groups: 250 patients on each of the AEDs, namely, phenytoin, carbamazepine, sodium valproate, and levetiracetam. All patients had been on their particular AED treatments before the study period for not <6 months (Table 1).

Among the 1000 patients, 30 cases of SJS were identified, yielding an overall incidence rate of 3.0%. Among all the AEDs, phenytoin was found to have the highest incidence, and the total of SJS was 12 (4.8%), followed by carbamazepine with cases 9 (3.6%). Phenytoin was surprisingly linked with SJS in Asian patients, eight of the 12 being of Asian origin. For five of these patients, there was molecular data on HLA-B*1502, which was positive, making a strong genetic connection between SJS in this population even more certain. Carbamazepine showed a higher rate in Asian patients (five out of nine), out of whom four were positive for HLA B*1502. However, sodium valproate had a comparatively lower frequency of SJS, 6 cases (2.4%), and the drug with the least reported SJS was levetiracetam, 3 cases (1.2%) (Fig. 3).

A Chi-square test was used to compare the incidence of SJS across the four AED groups. The results showed a statistically significant difference in the incidence rates of SJS between the AEDs ($p<0.01$). Phenytoin and carbamazepine had significantly higher SJS rates than sodium valproate and levetiracetam. In addition, the risk of developing SJS was evaluated, exhibiting a nearly four-fold increased risk among patients on phenytoin and carbamazepine rather than sodium valproate or levetiracetam. Additional Chi-square test performed showed that phenytoin was statistically more likely to cause SJS than levetiracetam ($p<0.05$), and that carbamazepine was statistically more likely to cause SJS than sodium valproate ($p<0.05$) (Table 2).

In this cohort, several factors influenced the risk of developing SJS. The age factor was not considered necessary, for it was deduced that there is no substantial variation in the risk of getting SJS for patients between 18 and 60. However, the overall presence of the HLA-B*1502 allele was significantly linked with high-risk SJS, especially in patients taking phenytoin and carbamazepine. Of the 21 patients positive for the HLA-B*1502 allele, 9 (42.9%) developed SJS, with seven cases occurring in the phenytoin and carbamazepine groups. Comorbidities such as diabetes, cardiovascular diseases, and HIV did not have a statistically significant relation with the development of SJS. However, patients with multiple comorbidities were more prone to other AED treatment side effects such as hepatotoxicity. Genetic predisposition, particularly in Asian patients, became the highest risk factor for SJS development, especially in those treated with phenytoin and carbamazepine.

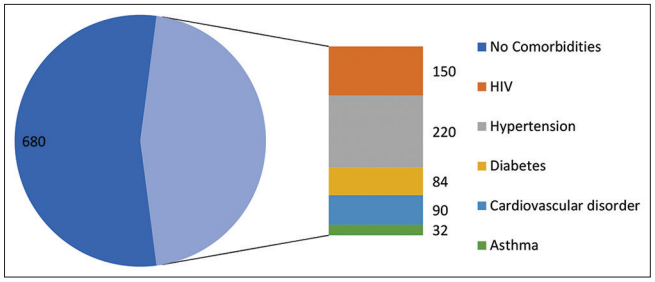

Fig. 2: Comorbidities in studied cases. *Some patients had more than one comorbidity

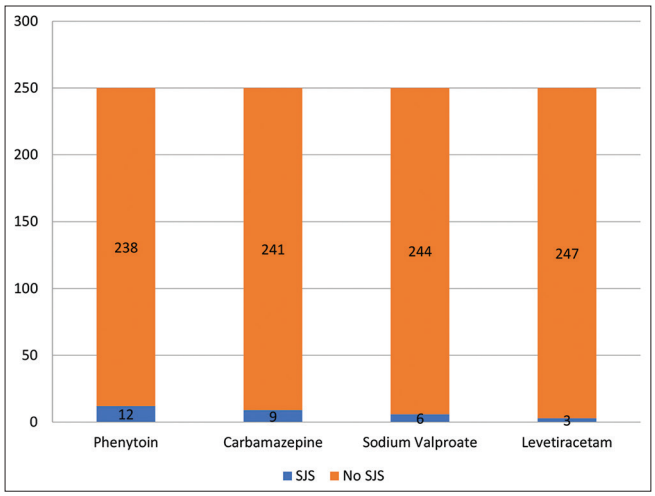

Fig. 3: Comparison of patients based on incidence of Steven-Johnson syndrome

Table 1: Distribution of patients based on antiepileptic drug they received

AED group	Number of patients	Percentage
Phenytoin	250	25
Carbamazepine	250	25
Sodium Valproate	250	25
Levetiracetam	250	25
Total	1000	100

Table 2: Statistical comparison of SJS incidence

AED comparison	p-value
Phenytoin versus Levetiracetam	<0.05*
Carbamazepine versus Sodium Valproate	<0.05*
Phenytoin versus Carbamazepine	<0.01*
Sodium Valproate versus Levetiracetam	<0.05*

*Significant

DISCUSSION

In our study, the rank order of incidence was as follows: Phenytoin with 4.8%, followed by carbamazepine with 3.6%. These results go in agreement with previous studies that have identified these drugs as having a high risk for severe cutaneous adverse reactions, especially in genetically predisposed individuals. It carried the HLA-B*1502 allele, a known risk factor in five of the 12 SJS phenytoin users. Genetic predisposition is a significant risk factor, with most cases occurring among Asians [7]. In contrast, a low incidence was reported for levetiracetam and sodium valproate, at 1.2% and 2.4%, respectively, demonstrating favorable safety. This suggests that the latter drugs may be safer and a good alternative, particularly among patients at high risk for hypersensitivity reactions. Levetiracetam's safety profile has also been reported by authors such as Harden [8] and French *et al*. [9].

Considering the pharmacodynamics and metabolic pathways of the AEDs explains these observed differences in the risk of SJS. Phenytoin and carbamazepine are metabolized through the liver into metabolites with the potential for initiating the immune responses associated with SJS [10]. The HLA-B*1502 allele is at increased risk of SJS because it influences how the immune system processes the metabolites of each drug. In contrast, the metabolic pathway for sodium valproate is less reactive and does not increase the risk of immune-mediated skin reactions. Levetiracetam acts through a different mechanism of action, modulating the SV2A protein, which does not induce an immune response; therefore, its incidence of SJS is much lower [11]. This makes levetiracetam safer, especially for those patients with a history of drug hypersensitivity or those at risk genetically.

These findings also emphasize the application of pharmacogenetic testing in clinical settings, especially in regions characterized by high prevalence of the HLA-B*1502 allele, including Asia. Pre-prescription genetic screening has the potential to reduce cases of SJS caused by high-risk AEDs such as phenytoin and carbamazepine, as illustrated in the studies by Puri *et al*. [12] and Pannu *et al*. [13]. Moreover, the recent development of safer alternatives, such as levetiracetam, reflects the move toward personalized therapy to reduce adverse reactions. Future studies should be designed as large-scale prospective studies to confirm the above findings and assess cost-effectiveness related to routine genetic screening [14]. The pharmacogenomic basis of SJS in other ethnic populations could be further investigated to extend the knowledge of genetic predisposition and thus facilitate global efforts toward optimizing AED prescribing practices [15].

Several limitations should be considered; first, the study's retrospective nature means we can only establish associations, not causality, between AED use and SJS. Prospective studies are needed to confirm these findings. Second, not all patients were screened for the HLA-B*1502 allele, which limits our understanding of how genetic predispositions contribute to SJS [16]. Genetic factors are essential in developing SJS, but their contribution cannot be entirely ascertained due to a lack of comprehensive screening [17]. Finally, the study was conducted at a single tertiary care center, with possible bias in patient selection. A multicentric study with a broader patient population would improve the external validity of the findings.

The results of the present study have significant clinical relevance. The association of the HLA-B*1502 allele with SJS in users of phenytoin and carbamazepine underlines the need for genetic screening before starting those AEDs, more so in Asian patients [18]. This would help the clinician correctly identify at-risk patients and offer them much safer alternatives such as levetiracetam or sodium valproate. Similarly, patients on phenytoin and carbamazepine should also be closely monitored, especially in the initial days of treatment, for the initial manifestation of SJS [19]. The development of symptoms calls for early intervention. Further, Levetiracetam is less likely to cause hypersensitivity reactions; therefore, it may be considered for use as a first-line AED in patients with known drug hypersensitivity or genetic predisposition to SJS [20].

Ultimately, the study explains the risk of SJS with the drugs phenytoin and carbamazepine, with the support of genetic screening for high-risk patients. This also suggests the drugs levetiracetam and sodium valproate as being safer options among the AEDs for cases that have a high potential of adverse cutaneous reactions. These would be very helpful for clinicians in deciding on the appropriateness of AED with the least risks.

CONCLUSION

This study highlights the higher risk of SJS with phenytoin and carbamazepine as compared to sodium valproate and levetiracetam.

Levetiracetam is a safer choice for patients with drug hypersensitivity, whereas sodium valproate shows lower SJS incidence. The higher incidence of SJS in genetically susceptible individuals emphasizes the need for genetic screening for HLA-B*1502 in at-risk populations. Large-scale, multicenter studies are needed to further explore genetic and environmental factors to optimize AED safety and patient care.

CONFLICT OF INTEREST

None.

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