Drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in children: 20 years study in a tertiary care hospital

Leelawadee Techasatian, Sunee Panombualert, Rattapon Uppala, Charoon Jetsrisuparb
Khon Kaen, Thailand

Background: **Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe life-threatening skin conditions. The most common cause of these manifestations is medications. Beside discontinued of the culprit drug, systemic corticosteroids were used as a primary treatment option among pediatric population. This study aimed to explore causative drugs (drug group/latent period), treaments, complications, and treatment outcome (morbidity, mortality, length of hospital stay) of SJS and TEN in children.**

Methods: **A retrospective chart was reviewed during the period of 1992 to 2012 at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand. SJS and TEN were clinically diagnosed and confirmed by pediatric dermatologists. Other possible causes other than drug-induced SJS and TEN were excluded.**

Results: **A total of 30 patients was recorded, including 24 (80%) SJS patients and 6 (20%) TEN patients. The mean age was 6.9 years (SD 4.4). Male to female ratio was 1.5:1. Antiepileptic drug group was the most common causative drug (*n*=18, 60%), followed by antibiotic drug group (*n*=8, 26.6%), and others (*n*=4, 13.3%) which included nonsteroidal antiinflammtory drugs (NSAIDs) and chemotherapy drugs. Systemic corticosteroids were used in 29 patients (96.6%). Intravenous immunoglobulin was used in one TEN patient (3.3%). There was a medium correlation between time to treatment (systemic corticosteroids) and the length of hospital stay (Spearman correlation coefficient=0.63, *P*=0.005). Two TEN patients (6.6%) died.**

Conclusions: **Carbamazepine was the most common causative drug of SJS and TEN in our study. The severity of skin detachment is not correlated to severity of ocular findings. However, the persistent of ocular complications up to one year is suggested for promptly appropriate ocular treatment in all SJS and TEN patients. Our data suggested that early administration of systemic corticosteroid may reduce the length of hospital stay and should be considered for the treatment of pediatric drug-induced SJS and TEN.**

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Original article

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe life-threatening skin conditions with high morbidity and mortality rate. The clinical manifestations are the combinations of typical skin finding (i.e. target-like lesion) or denuded/detachment of the skin with at least 2 or more mucosal involved. Less than 10% of the skin involved is defined as SJS, while more than 30% is defined as TEN. The term SJS-TEN overlap is used if 10%-30% of skin is involved.

The etiology of SJS and TEN is unclear; however, many studies have shown the similar causative agents as the result of a hypersensitivity reaction to many types of drugs such as antiepileptic drugs, antibiotics, chemotherapy, and nonsteroidal antiinflammtory drugs (NSAIDs).[1] Infection has also been described as the cause of SJS and TEN. Various pathogen can cause this manifestation, especially *Mycoplasma pneumonia* among pediatric population.[2] Some vaccines[3] and unknown causes have also been documented.

Author Affiliations: Pediatric Department, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand (Techasatian L, Panombualert S, Uppala R, Jetsrisuparb C)

Corresponding Author: Leelawadee Techasatian, MD, Division of Dermatology, Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand (Tel: 66-43-36-3012-3; Fax: 66-43-348382; Email: drleelawadee@gmail.com)

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Because of its rareness and critical condition, the treatment records for this condition are very limited especially in pediatric group. Withdrawal of the suspected drug in combination with good nursing and supportive care to prevent complication has been proven to decrease morbidity and mortality.[4]

Some medications that have been used and proved to have some benefits in the treatment of SJS and TEN. These include systemic corticosteroids, intravenous immunoglobulin (IVIG),[5] tumor necrosis factor-α (TNF-α) inhibitors, cyclosporine,[6] cyclophosphamide, plasmapheresis,[7] and hemodialysis.[8]

The use of systemic corticosteroids remains controversy since some infections can cause SJS and TEN as well. As of this circumstance, the use of systemic corticosteroids may increase mortality in sepsis.[9-11]

There are various complications found in SJS and TEN patients. Among the overall complications, secondary skin infection is the most common finding. Due to epidermal detachment, bacterial infection is inevitable. Other complications such as pneumonia, hepatitis, and septicemia occur more frequently in critically ailing patients. Together, these complications are the leading cause of patients' morbidities and mortalities.

Mucosal complications in ocular area are commonly found in both SJS and TEN patients. These findings can be presented as mild as dry eyes to severe as blindness. To date, early detection with prompt appropriate intervention in all SJS and TEN patients[12] is suggested as the standard treatment to prevent ocular complications.

It is well accepted that SJS has less mortality than TEN in both adult and pediatric population.[1,8,13,14] Long term complications are various and mainly focused to the area of mucosal involvement during acute phase, such as esophageal and/or urinary tract constriction, symblepharon, severe dry eyes, as well as post inflammatory hypo-hyperpigmentation of skin and scar.[8]

This report aimed to explore the causative drugs, treaments, complications, and treatment outcome of drug-induced SJS and TEN in children.

Methods

We retrospectively reviewed the medical records of SJS and TEN patients aged less than 15 years old who were admitted to Srinagarind Hospital, the tertiary center at Faculty of Medicine, Khon Kaen University, Thailand between 1992 and 2012. The diagnosis of SJS and TEN were confirmed by pediatric dermatologists. The study was approved by the institutional review board (# HE571361).

Statistical analysis was performed using STATA software, version 10. Descriptive statistical methods (mean, standard deviation, median, and frequency) were applied to analyze the demographic data. Comparisons of categorical variables among groups were performed using chi-square or Fisher's exact test. The continuous variables (latent period, length of hospitalization) were compared using one-way ANOVA with multiple comparisons. Spearman correlation was used to explore the correlation between time to systemic corticosteroids treatment and the length of hospital stay. Values of $P<0.05$ were considered to indicate statistical significance.

Results

Demographic data

A total of 30 patients were recorded, including 24 (80%) SJS patients and 6 (20%) TEN patients. The age range was from 1-year-old to 14-year-old with a median age of 7 years. The mean age was 6.9 years (SD 4.4). Male to female ratio was 1.5:1. All Asian ethnic background were reported in our study. Among the causative drug, antiepileptic drug group was the most common cause (n=18, 60%), followed by antibiotic drug group (n=8, 26.6%) and others (n=4, 13.3%) which included nonsteroidal antiinflammtory drugs (NSAIDs), paracetamol, and chemotherapy drugs. As for antiepileptic drug group, carbamazepine was the most common drug found in this study (n=8, 26.6%). Phenytoin, phenobarbital and levetiracetam were found in 7 (23.3%), 2 (6.6%), and 1 (3.3%) cases, respectively. Antibiotic drug group included erythromycin, cefotaxime, trimethoprim-sulfamethoxasone, cloxacillin, and amoxycillin. Subgroup analysis was performed, and we did not find any difference in the type of culprit drug between SJS and TEN patients (P=0.820) (Table 1).

Table 1. Comparison of culprit drug between SJS and TEN

Culprit drugs	Total (n=30), n (%)	SJS (n=24)	TEN (n=6)
Antiepileptics (n=18, 60%)	18 (60.0)	15	3
Carbamazepine	8 (26.6)	7	1
Phenobarbital	7 (23.3)	5	2
Phenytoin	2 (6.6)	2	0
Levetiracetam	1 (3.3)	1	0
Antibiotics (n=8, 26.6%)	8 (26.6)	5	2
Erythromycin	3 (10.0)	2	0
Trimethoprim-sulfamethoxasone	2 (6.6)	2	0
Cefotaxime	1 (3.3)	0	1
Cloxacillin	1 (3.3)	0	1
Amoxicillin	1 (3.3)	1	0
Others (n=4, 13.3%)	4 (13.3)	3	1
Aspirin	1 (3.3)	1	0
Brufen	1 (3.3)	1	0
Methotrexate	1 (3.3)	0	1
Paracetamol	1 (3.3)	1	0

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

HLA-B*1502 genotyping was performed in 3 SJS patients who received carbamazepine. As expected, all 3 patients were positive for HLA-B*1502 allele. We did not have genotyping results for the other 5 patients who received carbamazepine due to the fact that the genotyping testing just became available during this decade in our institute. It is noteworthy that this genetic test is not considered a routine test in Thailand due to its cost and also not readily available in all hospitals.

Latent period which referred as the beginning of drug exposed to the time of diagnosis ranged from 1 to 31 days. The mean latent period was 10.7 days (SD 8.3 days), with median duration of 10 days. Antiepileptic drug group had a longest latent period compared to antibiotic group and others. The median difference was 11 days [P<0.01, 95% confidence interval (CI) 8-16].

Treatments

All patients received standard in-patient cares which included sterile wound care, intravenous fluid replacement, adequate analgesic drug, as well as adequate nutritional supports. Twenty-eight patients were admitted in the regular pediatrics ward. Two of them were admitted in Intensive Care Units since severe degrees of skin detachment were presented and intensive monitoring were needed. The use of sterile gauze with normal saline and vaseline gauze were routinely used in the area of skin detachment. Topical antibiotics were used in combination of vaseline gauze on the area with the sign of secondary bacterial skin infection. Discharge from wound was sent for bacterial culture as monitoring of skin infection.

Pain during wound dressing was controlled by intravenous analgesic drug included fentanyl, ketamine and morphine prior started dressing processes. Four cases were received patient-controlled analgesia.

Total parenteral nutrition was used in two TEN patients. Both of them had severe mucosal involvement and oral intake was limited. Systemic corticosteroids were used in 29 patients (96.6%). The routes of administrations were various, including intravenous methylprednisolone/hydrocortisone and oral prednisolone. IVIG was used in 1 TEN patient (3.3%) in our study.

Time to treatment was referred as the period from diagnostic date to the date when treating medication was started. The mean duration of time to treatment in our study was 7.2 days (SD 1.4 days). Medium correlation was found between time to treatment (systemic corticosteroids) and the length of hospital stay (Spearman correlation coefficient=0.63, P=0.005) (Fig.).

Majority of the cases were taken care by ophthalmologist within the first day of admission. Routine eyes discharge removal was performed every single day by ophthalmologist. Topical medications were applied direct to the eyes which included sterile eye lubricant, sterile eye drop and corticosteroid eye drop.

Complications and outcomes

Acute complications during hospital stay included ocular complication, pneumonia, septicemia, and secondary skin infection. Table 2 illustrates that TEN patients were prone to have more frequent and severe complications when compared to SJS patients. However, the severe ocular involvements such as corneal ulcerations were found equally in both SJS and TEN. The ocular findings during acute phase in our study were severe dry eyes (n=3, 10%), cornea ulcerations (n=2, 6.7%), and symblepharon (n=1, 3.3%).

Mean length of hospital stay was 14.0 days (SD 11.6 days) . It was 12.3 days (SD 10.4 days) in SJS patients and 20.6 days (SD 13.1 days) in TEN patients. Our data indicated that a significant longer duration of hospital stay was found in the patients with complications than those without complications. The mean difference was 10.5 days (P<0.01, 95% CI 2.5-18.4).

The complications included pneumonia, septicemia,

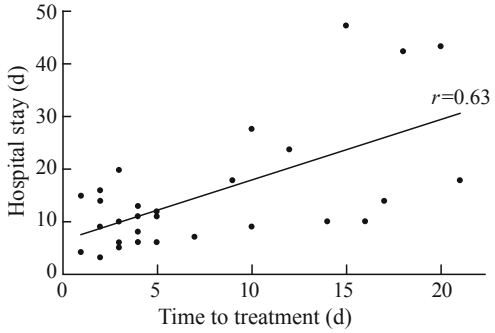

Fig. Spearman correlation between time to systemic corticosteroids treatment and the length of hospital stay.

Table 2. Acute complications in patients with SJS and TEN

Acute complications	n (%)	SJS (n=24)	TEN (n=6)
Ocular involvement	6 (20.0)	3	3
Pneumonia	2 (6.6)	0	2
Septicemia	6 (20.0)	1	5
Secondary skin infection	5 (16.6)	1	4

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

Table 3. Mean difference of hospital stay between the patients with or without individual complications

Complications	Mean difference of hospital stay (d)	P-value	95% confidence interval
Ocular involvement	3.3	0.57	-15.1-8.5
Pneumonia	15.14	0.03	1.5-28.7
Septicemia	13.08	0.01	3.1-22.9
Secondary skin infection	11.48	0.04	4.0-22.0

Table 4. Outcome at 1-year follow-up in patients with SJS and TEN.

Outcome at 1 year follow-up	Total (*n*=30)	SJS (*n*=24)	TEN (*n*=6)
Complete recovery	24	21	3
Complications	4	3	1
Dry eyes	2	2	0
Symblebpharon	1	1	0
Corneal pannus	1	0	1
Dead	2	0	2

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

secondary skin infection and ocular complication. Each complication was then evaluated for the length of hospital stay by using multivariated analysis. We found significant longer duration of hospital stay when the patients had pneumonia, septicemia and secondary skin infection. Ocular complication did not indicate prolonged hospital stay in our study (Table 3).

The follow-up rate was 100% and 60% at the first and second year, respectively. Twenty-four cases (80%) resulted in complete recovery with no long-term complications. However, ocular complications such as symblepharon, corneal pannus, and dry eyes were still persisted at 1-year follow-up. These complications were found in 4 cases (13.3%). Two TEN patients (6.6%) died (Table 4).

Discussion

Our study showed the data of drug-induced SJS and TEN in children population during the past 20 years at Srinagarind hospital, Faculty of Medicine, Khon Kaen University, the tertiary care medical school institute in the north east of Thailand. It has been reported previously that the prevalence of SJS was higher than TEN. Male gender is slightly more susceptible to SJS than female, with a ratio of 1.5:1. These findings showed the same pattern in all previous studies in both adults and pediatric population.[3,6,13-16]

The main culprit drugs in this study were antiepileptic and antibiotics drug groups. Both are the two common causative drug groups among children and adults population.[4,14,17] Carbamazepine was the most prevalence cause which was in accordance with other previous studies.[4,14,17,18]

Because of the highest prevalence of carbamazepine induced SJS and TEN in many studies and the recent evidence showed a strong correlation between carbamazepine-induced SJS and HLA-B*1502 genotyping in a Han Chinese population.[19] As a result, the US Food and Drug Administration has recommended genotyping screening in all Asian patients for HLA-B*1502 before starting carbamazepine treatment.[20] However, this universal screening does not apply to Thai population yet because the prevalence of carbamazepine-induced SJS and TEN in the Thai population and the positive predictive value (PPV) which are the major factors that influence the cost-effectiveness of HLA-B*1502 screening are still lacking.[21] Nevertheless, with our institutional support, we were able to screen few of the patients who underwent carbamazepine treatment only. Our study clearly showed positive HLA-B*1502 in all 3 SJS cases whom were tested for this genotyping. We strongly believed that more data on the prevalence carbamazepine-induced SJS and TEN in the Thai population would enhance the universalizability of the genotype testing in the future.

One of the interesting findings in our study was the difference in latent period between drug groups. Our data showed significantly longer duration in the patient who were exposed to antiepileptic drug when compared to others. This latent period could serve as a meaningful prediction of the suspected culprit drug when the patients were exposed to multiple drugs during the same period of time.

A severity-of-illness score for toxic epidermal necrolysis (SCORTEN) is a clinically predictive score used to evaluate the risk of mortality in TEN patients. It was first proposed by Bastuji-Garin et al[22] in August, 2000. This score is based on 7 prognostic factors: age, malignancy, surface area involved, heart rate, serum urea, bicarbonate, and glucose. The calculation of these factors within 24 hours after admission, SCORTEN, has been shown to be very precise to assess the risk of mortality. However, the use of this method in the pediatric population had not been fully validated. Thus, it was not used in our institute during the period of our study.

Treatment of SJS and TEN requires prompt diagnosis with immediate discontinuation of the causative drug. In addition, it has been previously reported that the early withdrawal from the causative drug was correlated with the better prognosis outcome. Optimal supportive therapy is still of the most importance in the treatment of patients with SJS and TEN. Because of the rareness of the disease, randomized controlled trials comparing medical therapies for SJS and TEN are rare. The majority of medical treatments used in our study was systemic corticosteroids which correlated with the most prevalent treatment options in SJS and TEN in Thai children.[14] Some studies from Asian countries showed no benefit in treating SJS and TEN with this medication.[23] However, our study illustrated some benefits in shorting hospitalization when early administration of systemic corticosteroids (Spearman correlation, r=0.63). This finding is similar to some previous studies in both adults and pediatric population.[14,17,24] One of the reasons which influenced this finding in our study was the fact that we focused on drug-induced SJS and TEN only, other possible

causes such as infections which systemic corticosteroids may increase the chance of sepsis were excluded. Here, we suggested early administration of systemic corticosteroids especially in pediatric drug-induced SJS and TEN.

Acute complications during hospitalization in our study included systemic septicemia, pneumonia, ocular complications and secondary skin infections. Our data clearly demonstrated that having complications contributed to significant longer duration of hospital stay. However, when applied multivariated analysis on each complication, having only ocular complication did not indicate prolonged hospitalization in our study.

TEN patients were noteworthy to have more frequent and more severe complications when compared to SJS patients. However, this finding is not applied to the ocular complications. Severe ocular complications such as corneal ulcerations were found equally in both SJS and TEN. Our result is correlated to previous study from Yip et al,[12] who found that diagnosis of TEN did not indicate more severe eyes complications.

Complete recovery was found in 80% of the patients at 1-year follow-up in our institute. The other 20% had long-term ocular complications which included symblepharon, corneal pannus, and dry eyes. These findings will enhance our standard of practice to focus more in the ocular care. We firmly believe that early action with the good eyes care may prevent long-term ocular complication.

Moreover, our study showed a mortality rate of 6.6% (n=2). Both of them were diagnosed with TEN and severe sepsis during hospitalization. We found no mortality rate in SJS patients due to the fact that TEN patients were prone to have unfavorable outcome compared to SJS patients.

In conclusion, carbamazepine was the most common causative drug of SJS and TEN in our study. Antiepileptic drug group showed longer latent period when compared to other drug groups. Additionally, the severity of skin detachment is not correlated to severity of ocular findings. The persistent of ocular complications that last up to one year suggested prompt eyes examination with appropriate treatment in all SJS and TEN patients. Our data suggested that early administration of systemic corticosteroid in drug-induced SJS and TEN may reduce the length of hospital stay and should be considered for the treatment of pediatric drug-induced SJS and TEN.

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Contributors: Techasatian L wrote the main body of the manuscript, contributed the study concepts and performed the manuscript review. Panombaulert S and Uppala R performed the literature reseach. Jetsrisuparb contributed to the manuscript review.

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