Research Article

Comparative evaluation of antimicrobial and anticonvulsant induced cases of Steven Johnson syndrome and toxic epidermal necrolysis

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ABSTRACT

Background: Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) constitute a spectrum of severe, potentially life threatening, mucocutaneous adverse drug reactions. Antimicrobial agents and anticonvulsants are the most commonly implicated drugs. This study was aimed to compare and analyse the differences in the incubation period, clinical presentation and outcome in patients of SJS/TEN caused by the antimicrobials and anticonvulsants.

Materials and Methods: Patients of SJS, TEN and SJS/TEN overlap admitted in the dermatology ward of our hospital, in whom an antimicrobial agent or an anticonvulsant were found to be probable causative agent by Naranjo score were assigned to Group A and B respectively. Inpatient records of the selected patients were studied to compare the differences.

Results: Total of forty patients (twenty each of Group A and B) were included in the study. Fluoroquinolones followed by chloroquine were the most commonly implicated antimicrobials. The anticonvulsants most commonly implicated were phenytoin followed by carbamazepine. Incubation period in the antimicrobial group was significantly shorter [Group A (7.32 ± 5.4 days) vs Group B (28.58 ± 19.35 days)] with p value < 0.001. The duration of stay, in the dermatology ward, was significantly longer (p value< 0.05) in the cases of TEN caused by antimicrobials (20.1 ± 7.49 days) as compared to those caused by anticonvulsants (14.5 ± 5.36 days). Three patients in Group A and one patient in Group B expired.

Conclusion: A shorter incubation period and a higher morbidity and mortality were seen in the antimicrobial induced cases as compared to the anticonvulsant group.

Key words: Steven Johnson syndrome, toxic epidermal necrolysis, antimicrobials, anticonvulsants.

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INTRODUCTION

Cutaneous drug eruptions are one of the most frequent manifestations of adverse drug reactions, seen in 2-3% of hospitalised patients.[1,2] They can have a myriad of presentations, varying from mild rashes to severe life threatening desquamation of skin. Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute, life threatening mucocutaneous reactions, with drugs accounting for 77-95% of the total cases.[3,4] Due to similarities in clinical presentation, drug causality and mechanism, SJS and TEN are now considered as severity variants of the same process, which differ only in the extent of body surface area involvement (< 10% for SJS; 10-30% for SJS/TEN overlap and more than 30% in TEN).[5]

Although more than 250 drugs have been

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suggested as possible "culprit drugs", antimicrobials and anticonvulsants are the two most common groups of drugs causing these dramatic and potentially life threatening reactions.[6] According to a recent review of Indian studies on SJS and TEN, antimicrobials and anticonvulsants were found to account for 37.27% and 35.73% of the total cases, respectively.[6]

Clinically, we have been observing significant differences in the incubation period and outcome of antimicrobial and anticonvulsant induced SJS/TEN. Moreover, a recent study has documented increased mortality in cases of SJS/ TEN caused by ofloxacin as compared to those caused by antiepileptics.[7] Due to a paucity of studies in this regard, the present study was undertaken to compare and analyse the differences in the incubation period, clinical presentation and outcome in patients of SJS/TEN caused by the two groups of drugs.

MATERIALS AND METHODS

Study setting

A retrospective study was conducted from the inpatient records, admitted in the dermatology ward of Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences hospital, Rohtak, Haryana, India. The protocol was approved by the Institutional review committee.

Patients and data collection

Data was collected from patients' medical records from 2008 to 2013 with biopsy proven cases of SJS, TEN and SJS/TEN overlap. Classification into SJS, TEN and SJS/TEN overlap was done using the Bastuji's criteria.[5] Patients in whom there was definitive history of intake of antimicrobial agent or anticonvulsant drug prior to onset of the eruption were assigned to Group A and B respectively. As a rechallenge testis unethical due to the severe, life threatening nature of the reaction; Naranjo score [8] was applied to assess the probability of the suspected drug to cause the reaction. Only those patients with Naranjo score 5 or more were included in the study. Patients with history of taking multiple drugs prior to the reaction, those who had left against medical advice, HIV positive patients and those with autoimmune diseases were excluded from the study.

SCORTEN (SCORe of Toxic Epidermal Necrolysis), a specific severity-of illness score to determine prognosis for cases of TEN, was applied for all patients of TEN. Seven independent factors were evaluated and the predicted mortality determined by the total score.[9]

All the patients were managed under aseptic conditions, with adequate fluid and electrolyte replacement, short tapering dose of steroids and prophylactic antibiotics. The epidemiological parameters, time interval from drug ingestion to onset of rash, presence / absence of prodromal symptoms, clinical presentation, SCORTEN, duration of hospital stay, complications and outcome were studied from the case records of the selected patients to evaluate and compare the findings in the two groups.

Statistical Analysis

Data was analyzed using SPSS 2.0 software and the p value < 0.05 was considered as statistically significant. The incubation period and duration of stay among the two groups were compared using unpaired student's t - test. Chi square test was applied to compare the mortality .

RESULTS

Total of forty patients were included in the study, twenty each in Group A and Group B. Group A consisted of 3 cases of SJS, 6 of SJS/TEN overlap and 11 of TEN caused by antimicrobials while Group B comprised 2 cases of SJS, 6 of SJS/TEN overlap and 12 of TEN caused by anticonvulsants. Average age in

both the groups was about 24 years with male: female ratio of 1.71 and 1.37 in Group A and B respectively. Fluoroquinolones followed by chloroquine were the most commonly implicated antimicrobials in Group A.

In group B, phenytoin followed by carbamazepine was the most common culprit drug. The causative antimicrobials in Group A and anticonvulsants in Group B with number of cases caused by each drug in decreasing order are summarised in [Table 1].

Table 1: Implicated drugs in the antimicrobial and anticonvulsant group

Implicated antimicrobials	Number of cases in which implicated
Fluoroquinolones (Ofloxacin, Ciprofloxacin)	6
Chloroquine	5
Cephalosporins (Cefotaxime, Ceftazidime)	4
Amoxicillin	2
Cotimoxazole	1
Sulphamethoxole – pyrimethamine	1
Chloramphenicol	1
Implicated anticonvulsants	**Number of cases in which implicated**
Phenytoin	11
Carbamazepine	5
Phenobarbitone	2
Lamotrigine	2

Incubation period (the time from initiation of drug to onset of rash) was found to be significantly higher in Group B (28.6 days) as compared to Group A (7.3 days). The difference was found to be statistically significant with p value < 0.001.

History of prodromal period in the form of fever, headache and burning sensation could be elicited in fifteen patients of Group A and twelve patients of Group B. The clinical symptoms were similar in both the groups with almost equal number of patients having oral and genital mucosal involvement in both the groups. However, the average SCORTEN was much higher in Group A (2.2) as compared to Group B (1.7). The average duration of stay was also much higher in the patients of TEN in Group A as compared to Group B, though the duration was similar for patients of SJS and SJS/TEN overlap. Unpaired student's t test showed statistically significant increase ($p < 0.05$) in duration of stay of TEN patients of Group A and Group B.

Three patients in Group A and one patient in Group B expired. Chi square test was applied to compare the mortality in the two groups. The difference was not found to be statistically significant ($\chi = 1.721$, degree of freedom =1, $p = 0.19$). The differences between the two groups are summarised in [Table 2]

Table 2: Subjects with history of intake of antimicrobial agent (group A) and anticonvulsant drugs (group B)

	Group A	Group B
Total no. of cases	20	20
SJS	3	2
SJS/TEN overlap	6	6
TEN	11	12
Average incubation period (in days)	7.3 ± 5.4	28.6 ± 19.4*
No. of patients giving history of prdrome	15 (75%)	12 (60%)
Average duration of stay (in days)		
SJS	9.33	7.5
SJS/TEN overlap	11.4	10.5
TEN	20.1 ± 7.5	14.5 ± 5.4†
Average SCORTEN		
On admission	2.3	1.66
At 48 hours	2.3	1.58
Total number of deaths		
SJS	0	0
SJS/TEN overlap	0	0
TEN	3	1
Mortality (percentage)		
SJS	0	0
SJS/TEN overlap	0	0
TEN	27.2%	8.3%

SJS = Steven Johnson syndrome, TEN = Toxic Epidermal Necrolysis. *P < 0.001 vs. group A, †P < 0.05 vs. group A.

DISCUSSION

Epidermal cell apoptosis, leading to formation of subepidermal blisters and sloughing of epidermis, is the hallmark of SJS and TEN. Apoptosis may be mediated through keratinocyte Fas-Fas L interaction or through drug specific cytotoxic T-cells via the perforin-granzyme B pathway.[10] In antimicrobials like cotrimoxazole, the drug itself acts as hapten for stimulation of T cell cytotoxicity.[11]

On the contrary, in carbamazepine - induced TEN, lymphocytes were found to be more susceptible to cytotoxic killing by liver microsome-induced carbamazepine intermediates than by the parent drug [12] . It is probable that a similar toxic metabolite mediated mechanism is responsible for the causation of TEN in other aromatic amine anticonvulsants, such as phenytoin, oxcarbazepine and lamotrigine. The fact that several studies in the Chinese, Thai and Indian populations have shown a strong association between HLA-B*1502 and SJS/ TEN induced by aromatic anticonvulsants such as carbamazepine (CBZ), phenytoin, lamotrigine and oxcarbazepine,[13-16] further lends support to this hypothesis.

Although there are many lacunae in our current understanding of the initial and intermediate pathways leading to keratinocyte apoptosis, it is reasonable to expect differences in the incubation period, severity of illness and outcome of patients of antimicrobial and anticonvulsant induced SJS/TEN based on the above difference in pathomechanism. A thorough search of current literature failed to show any previous studies comparing SJS/ TEN caused by the two groups of drugs. Hence, our study is an endeavour to highlight the differences in presentation and outcome in antimicrobial and anticonvulsant induced cases.

In our study, both the groups shared a similar age and sex distribution and were comparable with respect to other epidemiological parameters. Patients on antiretroviral therapy and antitubercular therapy were excluded from the study as it is difficult to implicate any single causative drug.

Implicated drugs in the groups

Fluoroquinolones (ciprofloxacin and ofoxacin) were the most commonly implicated antimicrobials. This is consistent with other studies. The next most common antimicrobial to be involved was found to be chloroquine, which is not commonly cited as an implicated drug in previous literature. Only a single case has been reported in the recent review of Indian literature.[6]

Phenytoin and carbamazepine were the most common anticonvulsants to be involved, which is also consistent with other studies.[17] Anticonvulsants account for roughly 35 % of the total cases of drug induced SJS/TEN.[6] The recent identification of strong association of HLA- B*1502 with carbamazepine and other aromatic arene anticonvulsants[13-16] has ushered a new era of pharmacogenomics where we can hope to prevent adverse drug reactions in a majority of these patients by testing for the above HLA associations prior to starting these drugs.

Incubation period

There was significant difference in the incubation period in the two groups, with incubation period for SJS/TEN induced by antimicrobials significantly lower. Similar findings were reported in a recent study in Singapore where antibiotics were found to have the shortest interval between ingestion time and onset of symptoms {fluoroquinolones (2 days); beta-lactams (4 days) vs CBZ (15 days)}.[18] The possible explanation for this finding could be that antiepileptic drugs are metabolized to toxic substances that are subsequently detoxified in most individuals. It is postulated that in some individuals, due to a genetic defect, the metabolites may bind to the proteins and trigger an immune response that leads to the cutaneous reactions of SJS.[19]

The HLA associations with SJS/ TEN caused by aromatic anticonvulsants, as cited above, further point to a toxic metabolite mediated mechanism, which probably accounts for the longer incubation period. Thus, it is no surprise that the patient often does not relate the anticonvulsant to the skin rash as he/ she would have already been taking the drug uneventfully for many days. Among the medical practitioners also, it is a common practice to implicate the most recently introduced drug as the causal agent. As antiepileptics are commonly implicated drugs for SJS/TEN, it is important not to ignore this drug history, even if the patient has been on antiepileptics for many days.

Severity of illness and outcome in the TEN patients

The duration of stay (a proxy marker for time of recovery) was found to be significantly longer in the TEN cases caused by antimicrobials (Group A). SCORTEN, a specific severity-of illness score to determine prognosis for cases of TEN, was also found to be higher in Group A. Naveen KN et al, in a recent study, have observed that SJS-TEN induced by ofloxacin was associated with a longer duration of stay and higher morbidity and mortality as compared to anticonvulsants.[7]

Mortality in Group A was also much higher than in Group B. The major cause of mortality (seen in all three patients) in Group A was septicaemia. Since these patients were taking antimicrobials in the first place due to an underlying focus of infection, it is probable that immune suppression associated with SJS/TEN led to systemic dissemination and septicaemia. This could probably also explain the longer recovery period and higher SCORTEN in Group A. Although asepsis forms an essential element in the management of any case of SJS/ TEN, its importance is further highlighted in the antimicrobial induced cases.

Our study has brought out important statistically significant differences in the antimicrobial and anticonvulsant induced cases of SJS/TEN. However, there were some limitations. Since the study has been conducted at a single centre, we could only compare twenty patients of each group. Larger, multicenter studies are required to confirm our observations. Cases of SJS are relatively less as the data has been taken from the inpatient records. It is likely that stable patients of SJS, who were accepting well orally and did not have any systemic features of secondary infection, were treated on OPD basis.

In conclusion, we have observed a statistically significant shorter incubation period, longer recovery time and greater mortality in the antimicrobial induced cases of SJS/ TEN.

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