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Original Article

Pharmacology Section

Antecedent Drug Exposure Aetiology and Management Protocols in Steven-Johnson Syndrome and Toxic Epidermal Necrolysis, A Hospital Based Prospective Study

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ABSTRACT

Aim: The study sought to identify the magnitude and characteristic of severe cutaneous adverse reactions (SCAR's) like Steven–Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

Materials and Methods: A prospective study was conducted by the Department of Pharmacology in association with Department of Dermatology in SMHS hospital. The study was carried out from June 2013-June 2015 on hospitalized cases of cutaneous adverse drug reaction reporting in hospital. The SCAR's were reported in a structured questionnaire based on adverse drug reaction (ADR) reporting form provided by the Central Drug Standard Control Organization (CDSCO) Ministry of Health and Family welfare, Government of India. The SCAR's were analysed for their characteristics, causality, severity and prognosis. Causality assessment was done by using a validated ADR probability scale of Naranjo as well as WHO Uppsala Monitoring Center (WHO-UMC) system for standardized case causality assessment. The management protocol were analysed for their clinical outcome through a proper follow up period.

Results: A total of 52 hospitalized cases of cutaneous adverse drug reactions were reported during the study period. We identified a total of 15 cases (28%) of SCAR's involving 9(17%) of SJS and 6 (12%) of TEN. SJS was seen in 2(22%) males and 7(78%) females. TEN was seen in all females (100%) and in no male. Drugs implicated in causing these life threatening reactions were identified as anticonvulsant agents like carbamazepine (CBZ), phenytoin (PHT) and Lamotrigine (LTG), oxicam NSAID, Sulfasalazine and levofloxacin. Despite higher reported mortality rates in SJS and TEN all patients survived with 2 patients surviving TEN suffered from long term opthalmological sequelae of the disease.

Conclusion: Present study suggest that drug induced cutaneous eruptions are common ranging from common nuisance rashes to rare life threatening diseases like SJS and TEN, SJS/TEN typically occur 1-3 weeks after initiation of therapy. Aromatic AED's, LTG, oxicam NSAID's, sulfasalazine and levofloxacin have a tremendous potential to trigger SCARS's. To ensure safe use of pharmaceutical agents and better treatment outcomes post marketing voluntary reporting of severe rare and unusual reactions remains inevitable.

Keywords: Anticonvulsants, Oxicam NSAIDs, Severe cutaneous adverse reactions (SCAR's)

INTRODUCTION

Adverse drug reactions (ADRs) are the inevitable consequence of pharmacotherapy. Cutaneous manifestations are among the most frequent adverse reaction to drugs [1]. Several multicentric trails have established that acute cutaneous reaction to drugs affected 3% of hospital inpatients. Reactions usually occur a few days to 4 weeks after initiation of therapy [2]. SJS and TEN are two rare acute life threatening SCAR's characterized by mucocutaneous tenderness, erythema, and extensive exfoliation and detachment of epidermis. SJS is characterized by <10% of body surface area of epidermal detachment, SJS-TEN overlap by 10-30% and TEN by >30%. SJS and TEN have an annual incidence of 1.2-6 and 0.4-1.2 per million people's respectively. Both effect women more frequently than men with a ratio of 1.5:1 and the incidence increases with age [3-6]. The average mortality rate is 1-5% for SJS and 25-35% for TEN. Elderly, immunocomprised and those on radiotherapy are at higher risk. Around 100 drugs have been identified as causal agents of SJS/TEN [3,4,7-12]. Most frequently implicated drugs are sulphonamides, antibiotics, oxicam NSAID's, quinolones, AED's and allopurinol [13].

In view of the above facts a prospective study was undertaken with an objective to estimate risk of SJS and TEN associated with use of specific drugs in patients of North Indian ethnic background. Moreover, since the treatment protocols are not well established with clear- cut outcome the patients were therefore, followed up to recognize the outcome and asses the development of complication sequelae which could be delayed but debilitating.

MATERIALS AND METHODS

The study was carried out by the Department of Pharmacology and Dermatology in SMHS, Government Medical College, Srinagar, India. A prospective study was conducted between June 2013-June 2015 which included patients who were admitted to the hospital with a diagnosis of various patterns of cutaneous adverse drug reaction (CADR's). These also included SJS/TEN patients as an important group because of their rarity of occurrence. The study received an approval from college ethical committee.

Data collection and drug enquiry: After obtaining informed consent a structured questionnaire was used to interview the patients clinically diagnosed as SJS/TEN with a definite antecedent drug history. The questionnaire included the contents based on suspected ADR reporting form provided by CDSCO, Ministry of Health and Family Welfare, Government of India. It was used to gather information on patients preceding hospitalization. The drug history included brand/generic name of drug, manufacturer, batch no, expiry date, timing of use, dose, indications, plasma

concentration of drug if available for low therapeutic range drugs, previous exposure and previous ADR if any. For seriously ill patients and children to be interviewed patient medical record and family members provided the information. In addition clinical examination and laboratory parameters were also recorded in questionnaire. Causality assessment was performed using a Naranjo scored algorithm [14]. This method incorporates ten questions or criteria related to the ADR. Every question is provided with a particular score based on the presence or absence of those criteria. These criteria are: (i) Previous reports; (ii) Event after drug was administered; (iii) Event abate on drug removal; (iv) Reaction appeared when the drug was administered; (v) Other non-drug causes for the adverse event; (vi) Was a toxic serum concentration noted; (vii) Reaction more severe with increased dose or less severe with decreased dose; (viii) Did the reaction appear when a placebo was given; (ix) Does patient have a history of similar reaction with drug or drug class; (x) ADR confirmed objectively.

Based on the scoring the probability that the adverse event was caused by the drug was classified as definite (score ≥9), probable (5-8), possible (1-4) or doubtful (≤0).

Moreover, a highly dependable WHO-UMC system [15] for case causality assessment has also been applied to reinforce the reliability of the study. The various causality categories based on assessment criteria are certain, probable/likely, possible, unlikely conditioned/ unclassified and unassessable/unclassifiable. The rationale for combining two tools is to overcome limitations associated with individual methods. In our study all patients of SJS/TEN were evaluated for severity and prognosis by using SCORTEN prognostic scoring system [16,17] that has been developed to correlate mortality with selected parameters [Table/Fig-1]. The management protocol would involve prompt identification and withdrawal of culprit drug (s) followed by vigorous supportive care. The drug therapy included systemic steroids in form of i.v. Dexamethasone or Hydrocortisone on short-term basis.

RESULTS

A total of 52 patients were identified as CADR's of which 15 cases (28%) were SCAR's of these 9 (17%) cases were diagnosed as SJS and 6 (12%) cases as TEN. SJS was seen in 2 (22%) males and 7 (78%) females while as TEN was diagnosed in females only.

The study revealed that these events were associated more commonly with short term therapy with agents like lamotrigine, carbamazepine, valproic acid and phenytoin. The other drugs associated were levofloxacin, oxicam NSAID's and Ibuprofen. The study revealed that almost all cases of SJS/TEN develop within two months of use of aromatic anticonvulsant and within 3 week of lamotrigine use. All the hospitalized patients of SJS/TEN survived following discharge from the hospital.

Among patients of TEN, 2 patients continued to suffer from ocular complications (like chronic inflammation, fibrosis entropion, trichiasis and symblepheron) and persistent mucosal lesions. Another patient of levofloxacin induced TEN was complicated with sepsis.

SJS patients did not leave any sequelae following discharge from hospital. On the basis of Naranjo algorithm SJS patients were classified as: 2 as possible; 5 as probable; and 2 as definite and TEN patients were classified as 1 as possible 2 as probable and 3 as definite.

A detailed overview of the SJS/TEN patients in the form of age, sex, drug therapy, and dose, indicator of use, onset of reaction, concomitant drug therapy and cutaneous manifestations is shown in [Table/Fig-2].

Prognostic factors	Points
Age >40 years	1
Presence of Malignancy/ Haematological malignancy	1
Epidermal Detachment >30%	1
Heart rate >120/min	1
Bicarbonate < 20mmol/L	1
Urea > 10mmol/L	1
Glycaemia >14mmol/L	1
SCORTEN	**Probability of death(%)**
0-1	3
2	12
3	35
4	58
≥5	90

[Table/Fig-1]: SCORTEN: A Prognostic scoring system for patients with epidermal necrolysis

DISCUSSION

The results in [Table/Fig-2] suggest that in a series of cases short term use of AED's act as a culprit in 56% of SJS/TEN patients followed by NSAID's use. The study revealed a mean age of 37 years in SJS/TEN patients. Aromatic anticonvulsants, lamotrigine, NSAID's, sulfasalazine and quinolones are among the high risk medications most frequently associated with SJS/TEN [5,11,18,19]. Lamotrigine a phenyltriazine is a new anticonvulsant and has shown its efficacy for prophylaxis of depression in bipolar disorders. Our study reveals 2 cases of SJS and 2 cases of TEN which are associated with LTG use and reaction occurs within 3 weeks after the initiation of therapy. This is in conformity with other studies where LTG has strong association with SJS/TEN. In two cases of our study valproate is a concomitant drug with LTG. Its concomitant use with LTG significantly increases the risk for development of adverse cutaneous reaction. [20]. Valproate increases plasma levels of LTG by inhibiting its metabolism [21,22]. Moreover, there have been several case reports on the short term use of LTG in association of SJS and TEN [23-28].

Other drugs including aromatic AED's show an onset of reaction within 1-2 months. The results are obviously showing predilection for female gender. Despite, no evidence based medicine standards of acceptance; present study reveals that all the patients responded well to short-term administration of systemic corticosteroids without any mortality. In patients, where AED therapy were offending agents the drugs were withdrawn immediately as a measure for prevention of drug reaction and were switched to Levetiracetam and Clobazam to maintain seizure free remission.

Since the uncertainty persists regarding the well defined treatment modalities of SJS/TEN other treatment protocols besides system corticosteroids are high dose immunoglobulin's (IVIG) [29-31], thalidomide [32], cyclosporine [33,34], TNF-antagonists [35], plasmapheresis/plasma exchange [36] and cyclophosphamide [37].

In view of the pharmacogenetic influences underlying great number of drug reactions like HLA-B 1502 being associated with SJS/TEN induced by CBZ, PHT, and LTG [38]. HLA-B 5801 with allopurinol induced SCARs [39] and HLA-B 5701 with abacavir hypersensitivity [40]. It is also suggested that ethnicity has a role to play in difference of the individual genetic susceptibility [41]. A pharmacogenomic study done on CBZ has shown a strong association of HLA-A-3101 and CBZ- hypersensitivity in Caucasian patients [42]. This association encompasses all forms of cutaneous eruptions besides SJS/TEN. This is in contrary to association of HLA-B 1502 which is specific for SJS/TEN in Chinese patients. The association with HLA-A 3101 and CBZ hypersensitivity has been replicated in Japanase [43], South Korean [44] and Canadian populations [45].

More recently, drug labels of various drugs have been altered by the US Food and Drug Administration (FDA) and by the European

S.No	Age/Sex	Drug Therapy	Dose	Indications	Days to onset	Concomitant drugs	Cutaneous manifestation
1	35/F	Lamotrigine (LTG)	12.5mg/day Initially Followed by 25mg/day, Then 50mg/day	Seizures with BPAD	20	Quetiapine SR 200mg Sodium valproate (600mg/day) Etizolam (1mg/day) Propanolol (40mg/day)	SJS
2	58/F	LTG	25mg/day for week Then 50mg/day second week Increased to 100mg/day	BPAD	15	Metoprolol SR 100mg/day Clonidipine 10mg/day Olmesartan 20mg/day Rosuvastatin 5mg/day Quetiapine 25mg/day Clopidogril 75mg/day Aspirin 75mg/day	SJS
3	30/F	LTG	25mg/day,	BPAD with depression	15	Paroxetine Clonezepam 12.5mg/day	TEN
4	30/F	CBZ	200mg/day,	Trigeminal Neuralgia	10	Naproxen -500mg/day	TEN
5	60/M	PHT	300mg/day	OLE post traumatic epilepsy	10	Gabapentin 400mg/day Nortryptiline 10mg/day Citicoline 500mg/day Piracetam 400mg/day Vit B complex	SJS
6	26/M	NSAID	NA	Ankylosing spondylitis	15	Thiocholchicoside 8mg/day	SJS
7	50/F	Levofloxacin	750mg/day	UTI	10	None	TEN
8	60/F	Piroxicam	40mg, i/m stat	LBA	2	None	SJS
9	27/F	Ibuprofen	1200mg/day For 2-3days	Osteoarthritis	4	Paracetamol 1000mg/day	SJS
10	24/F	Levofloxacin	500mg/day i.v infusion Followed by Levofloxacin 500mg/day Cefpodoxime 400mg/dayfor 5days	RTI	7	None	TEN
11	50/F	Piroxicam	40mg, i/m stat	LBA	2	None	SJS
12	35/F	Sulfasalazine (delayed release form)	1000mg/day for month	Rheumatoid arthiritis	1 month	Aceclofenac 100mg/day Thiocholchicoside 4mg/day	SJS
13	54/F	LTG	Initially 50mg/day increased within week to 100mg/day	GTCS	28	Valproate 1200mg/day Levothroxine 50mcg/day	TEN
14	20/F	CBZ	Initially CBZ CR 400mg/day CBZ CR 600mg /day	GTCS	2 months	None	TEN
15	17/F	CBZ/PHT	Initially PHT 250mg/day for 1 month Then CBZ-SR 200mg/day for 3days followed by CBZ SR 600mg/day then PHT 200mg/day	GTCS	2 months	None	TEN
16	22/F	PHT	PHT 300mg/day	Focal epilepsy	1 month	AKT-4 R-450/mg /day Z-1500mg/day E 800mg/day H-300mg/day	SJS

[Table/Fig-2]: Characteristic of 16 cases of SJS/TEN with different drug therapies
LTG: Lamotrigine, BPAD: Bipolar affective disorder, CBZ: Carbamazepine, PHT: Phenytoin, OLE: Occipital lobe epilepsy NSAID: non steroidal anti-inflammatory drug, UTI: urinary tract infection. RTI: respiratory tract infection, LBA: low back ache, FDE:fixed dose eruption. R: rifampin, Z: pyrazinamide, E: Ethmabutol, H:Isoniazid, CR: continous release, NA: not available

Medicine agency (EMA), which requires testing for HLA prior to the prescription of drug concerned.

Realizing the importance of these genetic susceptibilities it is highly recommended that genotyping be undertaken as a screening measure for these HLA-B alleles in North Indian ethnic population prior to prescription of these respective drugs.

CONCLUSION

The present study illustrates that inspite of rare occurrence of SJS/TEN North Indian ethnic population has great predisposition of SCAR's due to aromatic AED's, LTG, oxicam NSAID's and quinolones. These reactions need to be reported at an earliest as it has an instrumental role and forms an important component of pharmacovigilance programmes. Patients should be educated to avoid re-exposure to suspect drug (s) to yield outcome based results.

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