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A REPORT OF FIVE CASES OF FLUOROQUINOLONE-INDUCED EPIDERMAL NECROLYSIS AT A TERTIARY CARE TEACHING HOSPITAL IN NORTHERN KARNATAKA

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ABSTRACT

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are life-threatening, epidermal necrolytic adverse drug reactions (ADRs) considered to be within a spectrum of severe exanthematous vesico-bullous disorders, mostly attributable to drugs like anticonvulsants, NSAIDS and antimicrobials. Lately, the reports on Fluoroquinolone (FQ) induced SJS/TEN are rising. Our retrospective study conducted in this direction, brings in five such cases which manifested with severe epidermolyticmucocutaneous lesions after taking oral FQ therapy for gastrointestinal/ respiratory/genito-urinary indications. With the dechallenge of offending agents and adequate management of patients' clinical condition, four of them improved but the immunocompromised patient with TEN died despite intensive systemic corticosteroid and I.V-immunoglobulin therapy.

KEY WORDS: Stevens-Johnson syndrome, Toxic epidermal necrolysis, vesico-bullous disorders.

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, but potentially fatal adverse epidermolytic muco-cutaneous drug reactions, considered to be clinical entities within a spectrum differing only by their extent of body surface area

involvement which is less than 10% with SJS ,more than 30% with TEN and between 10% and 30% with "SJS-TEN overlap syndrome".[1] History of medication use exists in over 95% of patients with SJS and TEN [2],common ones being antimicrobials,anticonvulsants,NSAIDs, drugs for antiretroviral therapy (ART) and allopurinol.[3] Fluoroquinolones (FQs) represent approximately 11% of antibiotics prescribed worldwide to treat gastrointestinal, genitourinary and lower respiratory tract infections. Globally, the reported cases of FQ-induced SJS/TEN are in the rise since the last decade.[4,5,6,7] Hence we took up a retrospective study to determine the incidence of SJS/TEN due to FQs at our hospital.

Methodology

Ethical clearance for the study was obtained from the Institutional Ethics Committee. Spontaneously reported adverse drug reactions (ADRs) collected at the Hospital ADR monitoring cell between Oct,2011 and Jan,2013 were analysed. Central Drugs Standard Control Organisation (CDSCO-India) forms were used by the doctors for ADR reporting. ADRs were assessed for their causality using WHO-UMC scale, for their severity using the criterion developed by Hartwig *et al* and their prognostic assessment was done at admission time by "Severity of Illness Score for Toxic Epidermal Necrolysis" (SCORTEN) scale.[1,2]

Study results

A total of ten cases of SJS and four cases of TEN and two cases of SJS-TEN overlap were reported in our study duration accounting for a total of 16 cases in "SJS-TEN spectrum". Ten were females and six were males (female-to-male ratio 1.6:1). Eight of them were due to antimicrobials (50%), five due to anticonvulsants (31.2%) and three were due to NSAIDS (18.8%). FQs alone were responsible in five out of eight antimicrobial-induced SJS/TEN cases, of whom four were due to Ofloxacin and one due to Levofloxacin. Three of these five cases got admitted with SJS, and two with TEN of whom one patient was newly detected HIV-positive with disseminated tuberculosis during her recent hospital stay in Belgaum and was being prescribed Ofloxacin for diarrhea. She was not on either ART or ATT until her current admission into our hospital. The other case of FQ-induced TEN was a patient with type1-DM on regular insulin therapy. The three SJS cases had no h/o either comorbidities or concurrent medication(s). None of the cases had past history of drug hypersensitivity reaction(s). Taking all five cases together, the mean 'first dose-event interval' was 8 days. Mean duration of hospitalization was 14.8 days. The causal relationship with FQs showed to be"probable". The severity assessment showed that all of them were 'severe' ADRs. The

prognosis and the mortality risk assessment of individual cases is given in the table *(refer-Table).* The youngest patient was 19 year old and the eldest was of 55 years (mean age-35 years). In all 5 FQ-induced SJS/TEN patients, high grade fever and malaise preceded the appearance of rashes and desquamation by 4-7 days. Lesions involved the skin and two or more mucous membranes viz., conjunctival,oropharyngeal and anogenital(*see pic.1, 2, 3(a) and 3(b) which are of the patient with TEN, i.e case no.2 in the Table*).Three SJS cases and one TEN case developed systemic complications but gradually improved over a period of 2-3 weeks which could be attributed to early dechallenge of the offending agent followed by supportive,symptomatic and specific modes of treatment (*refer to the table*). At the end of 5 weeks, there was significant resolution of cutaneous and mucosal lesions in these four patients leaving behind mild post-inflammatory hyperpigmentation. The HIV positive patient with disseminated TB with TEN who showed a poor prognosis with a mortality rate of 35.3% based on SCORTEN rating, died of pneumonia, septicaemia and acute renal failure 10 days after onset of TEN, despite early intensive specific treatment with systemic corticosteroids, intravenous immunoglobulins and an initial empirical antimicrobial therapy with Inj.ceftriaxone 1g i.v. B.D. for 5 days followed by specific antibiotics (as per the antibiotic-sensitivity report of the organisms in the blood culture viz.,*Pseudomonas aeruginosa* and *Klebsiella pneumonia*) - Inj.cefotaxime 1gi.v. TDS and Inj.amikacin 15mg/kg/di.v. in 3 divided doses for the next 4 days. The average pharmacy cost incurred in the management of the 4 cases with improved outcome was Rs 8,020±210 and that of the TEN case which died was Rs 15,240±118.

DISCUSSION

Worldover, the reported average incidence varies from 1.2-6 per million patient-years for SJS and from 0.4-1.2 per million patient-years for TEN. The incidence rises with increasing age and is 1000-fold higher in patients with HIV/AIDS.[1]A South Indian study reported a higher percentage of these cases with FQs.[8]The EuroSCAR study showed that FQs carry a potential risk for SJS with univariate relative risk of 10.7% (3.8-30, 95% CI) and multivariate relative risk of 6.9% (1.8-27, 95% CI).[3]In our study, FQs took the major share among antimicrobials (62.5%) as causative agents for SJS/TEN, probably due to their frequent inclusion in prescriptions. Immunological reactions, reactive drug metabolites or interactions between these two are proposed as possible underlying patho-mechanism. Extensive keratinocyte apoptosis induced by activated T-lymphocytes via Fas(CD95)-Fas ligand interaction is considered to be the hallmark of SJS/TEN.Granulysin is also a key mediator for disseminated

keratinocyte death in SJS and TEN.[9] Loss of the muco-cutaneous barrier leaves patients vulnerable to infections from fungi and bacteria resulting in sepsis. Mucous membrane involvement can result in gastrointestinal haemorrhage, respiratory failure, ocular abnormalities, and genitourinary complications. Death is caused either by sepsis or by respiratory failure. More than 50% of patients surviving TEN suffer from long-term sequelae of the disease.[10]

Legend Table

FQ-Fluoroquinolone

LRTI-Lower Respiratory Tract Infection

URTI- Upper Respiratory Tract Infection, UTI-Urinary Tract Infection

Dexamethasone – 8mg i.v. bid for 4 consecutive days in the early phase of SJS

IV-Ig – Intravenous immunoglobulins (at a total dose of 3g/kg over 3 consecutive days)

*****- Interval between the first dose of the drug and the onset of adverse drug reaction

† - supportive therapy with intravenous fluids & patient counseling

‡ - symptomatic therapy (including for complications)- topical antiseptics & skin sootheners; On suspicion of clinical infection, empirical antibiotic treatment- Inj.ceftriaxone 1g i.v. bid for 5 days followed by specific antibiotic course based on blood culture and antibiotic-sensitivity report ; Artificial tears & antibiotic eye drops administered both prophylactically and therapeutically; Prophylactically - Proton pump inhibitors (pantoprazole/esomeprazole) and antiseptic mouth gargles.

Table : Patient Characteristics

Case	ADR Diagnosed	Sex/age	Causative FQ	Indication	Co-morbidities	H/o pre-existing liver/ kidney disease	Onset* (in Days)	Treatment	Hospital Stay (in days)	Complications	SCORTEN score (max score-7)	Mortality rate (%) As per SCORTEN score [score of 0-1 = 3.2% 5 or more = > 90%]	Outcome
1	SJS	F/19 yrs	Ofloxacin	LRTI	None	No	9	Dexamethasone Supportive† Symptomatic‡	14	Mild bilateral conjunctivitis	0	3.2	Improved
2	TEN	F/29 yrs	Ofloxacin	Fever with URTI	None	No	8	Dexamethasone IV-Ig Supportive† Symptomatic‡	14	Neutrophilia, Mild bilateral conjunctivitis	2	12.1	Improved
3	SJS	M/55yrs	Ofloxacin	Fever with UTI	None	No	7	Dexamethasone Supportive† Symptomatic‡	16	Eosinophilia, severe bilateral conjunctivitis with purulent discharge	2	12.1	Improved
4	TEN	F/35 yrs	Ofloxacin	Abdominal pain with Diarrhea	HIV+ve with Disseminated tuberculosis	Mild hepatomegaly with mild elevation of liver enzymes but asymptomatic	7	Dexamethasone IV-Ig Supportive† Symptomatic‡	9	Highly elevated liver enzymes, pneumonia, septicaemia, acute renal failure	4	58.3	Died
5	SJS	M/36yrs	Levofloxacin	LRTI	Type1 DM	No	9	Dexamethasone Supportive† Symptomatic‡	21	Infective keratitis	1	3.2	Improved

Figures With Legends

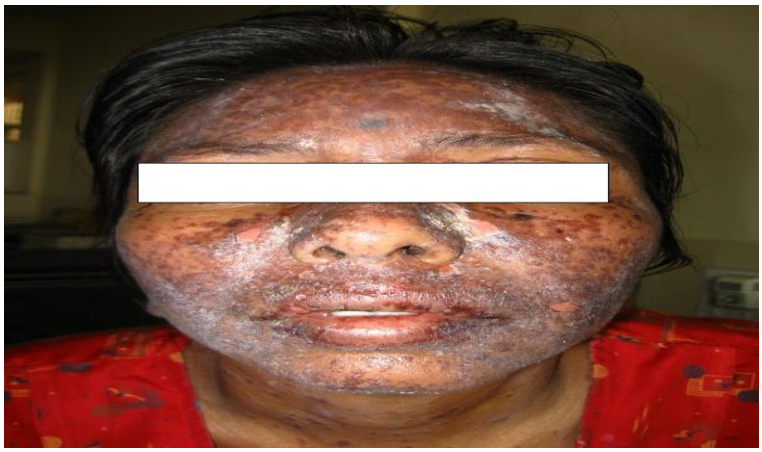

Fig.1 : Patient with TEN showing characteristic epidermal erosions coated with greyish-white pseudo-membrane over the face and vermilion margins of lips. (Conjunctival erosions were present but not shown in the picture to maintain confidentiality of patient'sidentity)

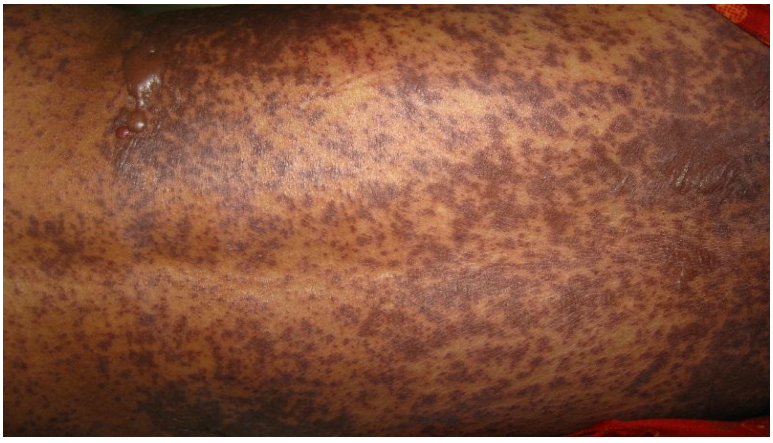

Fig.2 shows extensive epidermal erosions and bullae on the back of the same patient as in Fig.1

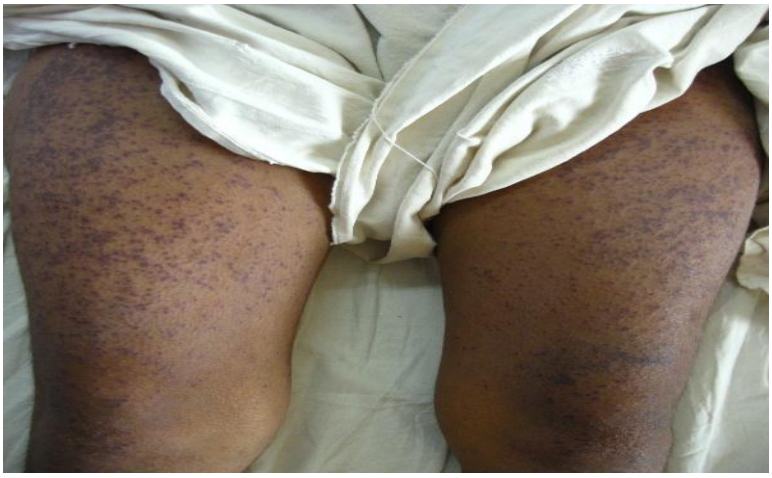

Figure-3 : shows hemorrhagic erosions on the proximal limbs

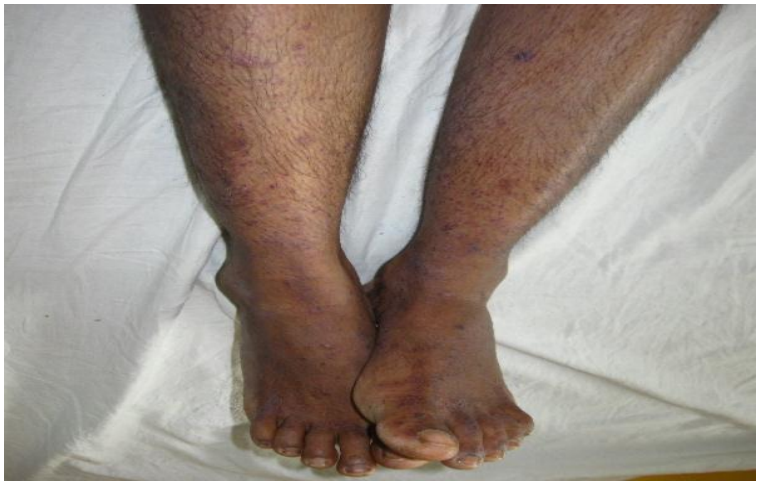

Figure-4 : shows relative sparing of the distal region of lower limbs.

CONCLUSION

Drug induced SJS and TEN is of great concern in the field of therapeutics as the reported global mortality rate for SJS is approximately 5% and for TEN is up to 30%[1].The use of FQs which possesses a potential risk for these life-threatening ADRs, demandsa vigilant monitoring which could possibly aid early recognition and aggressive management of these conditions, thereby reducing the morbidity and mortality in the affected cases.

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