Case Report

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A Case Series Study of Oral – Paracetamol induced SJS/TEN in Hospitalized Patients in Dermatology

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Abstract

Aims: *Drugs' reaction is common, it occurs in almost 10-20% of hospitalized patients and 7% of general population. The severity varies from self- limiting to life threatening conditions. This study aims to evaluate the prognoses of SJS/TEN due to paracetamol intake during September -November of 2014 in dermatology department of Herat Regional Hospital- Afghanistan.*

Methods/Methodology: *A case series prospective cross sectional study was designed to evaluates the condition of 3 patients who were admitted to the hospital due to oral paracetamol intake.*

Results: *Out of 3 patients, 2 were male and 1 was female. Average age of the patients was 21.3±12.8 (M, SD), the average distance between clinical symptoms and hospital admission was 3±0.3 (M, SD). Involvement of at least 2 mucosal site (eyes, urogenital, and mouth) seen in all 3 cases. Hb was lower than normal range in 2 cases and in normal level in one. LFT was high in one patient and thrombocytosis also seen in the same patient, while both these parameters were in normal level in the other 2 patients. The causative medicine was confirmed to be paracetamol in 2 patients and suspected in 1. Average BSA involvement and epidermal detachment were 70% and 30%, respectively.*

Conclusion: *this study shows that even by taking a simple OTC medicine such as paracetamol, fatal conditions as SJS/TEN might occur.*

Keywords: Drug Reaction, SJS, Paracetamol, life threatening.

Introduction

Hypersensitivity reaction to drug varies from very mild to the fatal conditions requiring hospital admission and immediate advanced care. SJS/TEN are the least common but the most serious types of allergy to drug, the incidence is 6 cases and 1 cases per million persons year for SJS and TEN, respectively (BOLOGNIA et al., 2012).

Etiology: Although a clear etiology for SJS/TEN is not understood, several factors, such as; medicines, malignancies, viral infections, chemical substances has been reported in literatures, out of these, medicines come to top causative factor, and among the medicines, antibiotics and neuroleptic are in the top first causative medications, few studies have reported rule of paracetamol in SJS/TEN.

Age& Sex: SJS/TEN can affect human throughout lifetime, but the incidence peaks after 4 decades of life. Women are more affected than men are, as a ratio of 6: 1; the mortality rate varies from 10% to 30% in SJS/TEN, respectively.

Prognostic Factors: Some factors as; age, other medical conditions, % of BSA involvement, etc. are to be the contributing factor for mortality but not the dose of the drug used (Wolff et al., 2008) mucosal involvement seen in both SJS/TEN (oral, eyes, urogenital) and is one of the diagnostic marker.

Classification: several classifications on SJS/TEN has been suggested, the easiest way is the BSA epidermal detachment, up to 10% of BSA detachment is pure SJS, 10%-30% is overlapped, and more than 30% is pure TEN (BOLOGNIA et al., 2012).

Pathophysiology: Even if the precise sequence of molecular and cellular events is incompletely understood, several studies provide important clues to the pathogenesis of EN. The immunologic pattern of early lesions suggests a cell-mediated cytotoxic reaction against Keratinocytes leading to massive apoptosis. Immunopathologic studies have demonstrated the presence of CD8+ T killer lymphocytes in the epidermis and dermis in bullous adverse reactions, with some natural killer cell-like features, during the initial phase of EN, whereas monocytes are present more during the late phase.

These cytotoxic CD8+ T cells express α-β T-cell receptors and are able to kill through perforin and granzyme B but not through Fas or Trail. It is now well established that this oligoclonal CD8+ expansion corresponds to a drug-specific, major histocompatibility complex-restricted cytotoxicity against keratinocytes. Furthermore, regulatory CD4+CD25+ T cells have been demonstrated to be potentially important in the prevention of severe epidermal damage induced by reactive cytotoxic T lymphocytes. Important cytokines such as interleukin 6, tumor necrosis factor-α (TNF-α), and Fas ligand (Fas-L) are also present in the lesional skin of EN patients. Viard et al. suggested that keratinocyte apoptosis in lesional skin was associated with increased expression of Fas on their membranes and was blocked by high concentrations of human immunoglobulins that interfere with the interaction of Fas and Fas-L. TNF is probably also important. This molecule is present in lesional epidermis, in blister fluid, and in peripheral mononuclear cells and macrophages (Wolff et al., 2008; BOLOGNIA et al., 2012).

Slow acetylation was found in patients with sulfonamide-induced TEN, which suggests an increased production of reactive metabolites. However, the immunologic response is directed against the parent drug rather than reactive metabolites

Finally, genetic susceptibility could play an important role. A strong association was observed in Han Chinese between the human leukocyte antigen HLA-B1502 and SJS induced by carbamazepine and between HLA-B5801 and SJS induced by allopurinol. However, the association between carbamazepine-induced EN and HLA-B1502 is not present in European patients who do not have Asian ancestry (BOLOGNIA et al., 2012).

Increased amount of reactive (oxidative) metabolites of drugs, decreased products of normal soluble atoxic metabolite, and or decreased ability to detoxyfi reactive metabolite. Release of granulysin by CD8 Cytotoxic T cells and natural killer cells within the epidermis resulting apoptosis of keratinocyte. Apoptosis may also results from the degranulation of perforin and granzymes by CD8 Cytotoxi T Cell and the ligation of Fas on keratinocytes by Fas-Ligand (FasL). The source of FasL still unclear with CD8 and keratinocyes proposed as a candidate. Cytotoxic immune reaction at keratinocyte by antigen complex formed through interaction between reactive metabolite and host tissue, leading to apoptosis or planed cell's death. In early stage, cytotoxic t cell (CTC) express coetaneous leukocyte antigen (CLA). Other cytokines: IL6, TNF ά, and FasL, TNF ά may induce directly apoptosis or attracting CD8+ CTC or both. Fas (CD95) and FasL (CD95L) is a receptor -ligand pair that triggers apoptosis, in normal skin low level of FasL are expressed by keratinocytes intracellularly, in TEN high level of FasL are expressed in cells surface, FasL rapidly signals the keratinocytes by apoptosis, this extensive keratinocyte apoptosis leads to cell necrosis which clinically observed. Wide spread apoptosis leads to necrosis and dermo – epidermal separation at stratum spinosum level.

Method and Materials

This was prospective case series cross-sectional study with a universal sampling method. Inclusion criteria were the patients admitted during the reporting period having either pure SJS/TEN or a combination regardless the age, ethnicity, and causative agents, all other patients admitted during the study time excluded. Data were analyzed using EPI info 7 software. The patients photographed by using personal mobile after getting consent approval of the caretakers or parents (BOLOGNIA et al., 2012; Nassif et al., 2002).

Results/Findings

3 patients were admitted in provisional diagnosis of SJS/TEN. Mean age was 21.3±12.8 (M,SD), pure paracetamol thought to be the causative factor in the male patients aged over 18, while paracetamol plus pheneramine was taken by one of the under 18 female patient, rule of paracetamol was in doubt in the last under 18 male patient.

Mean BSA involvement was 70%± 10% (M, SD) and average epidermal detachment was 33% ±7% (M, SD), oral mucosa was involved in all 3 patients. Eye complications (xerophtalmia) seen in one patient. Average length of stay was 9 ± 4.3 days (M, SD). Allergy to the same or any other medicine was positive in one patient, two patients had Hb lower than the normal range, glycemia was normal in all three patients, serum electrolyte was not checked because of unavailability of this service in the public hospital. Prednisolone, fluid therapy, antibiotics, and primary nursing care were the management interventions.

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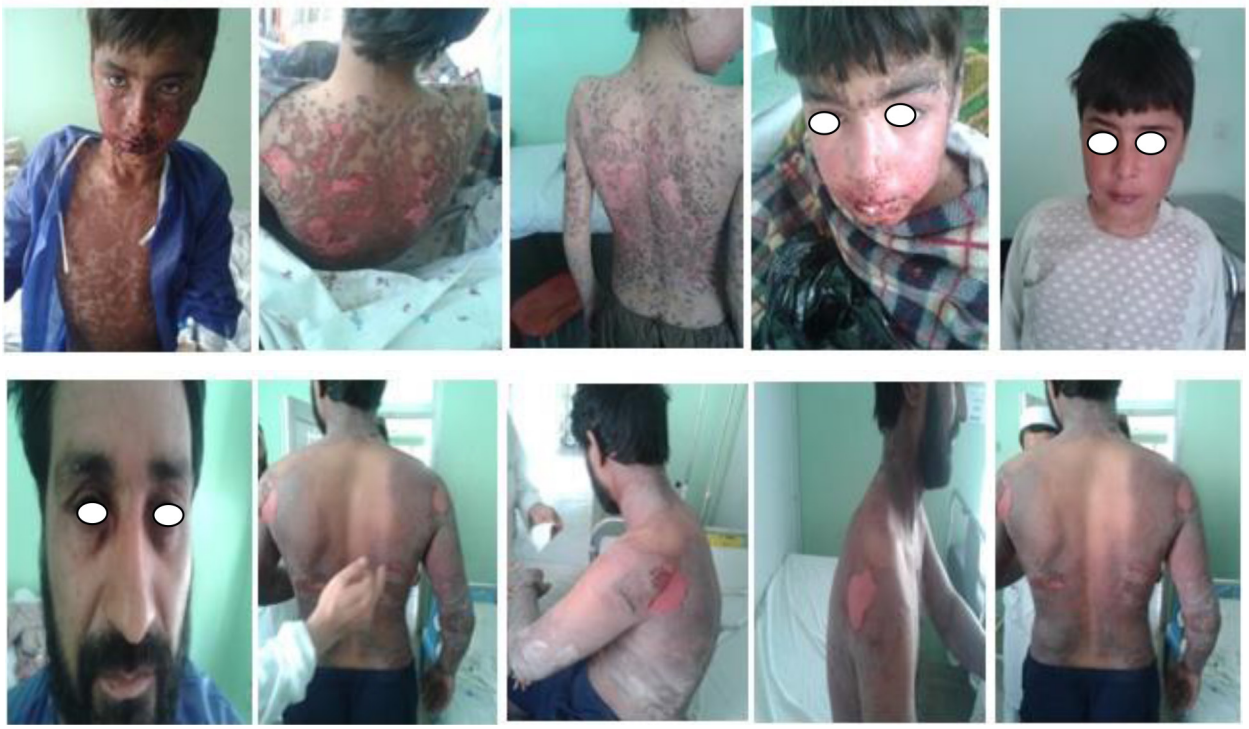

Discussion/Conclusions

3 cases of SJS/TEN within 3 months in a province with less than 3 million indicating a high incidence rate of SJS/TEN in our population particularly related to an OTC medicine (Paracetamol), having no access to very basic specialty care and good outcome of patients who need well advanced ICU care, needs further investigation. The causative agents in our study (paracetamol) brings to mind that drug safety is still a big challenge in our setting since the ministry of public health has no strong control on the imported medicines.

Challenges and Limitations

Delay in bringing patients to the hospital, incorrect and or incomplete information, no specialized laboratory services (RAST test, electrolyte level, etc), weak control on drug supply system by the government, short duration of the study and few samples all are the limitation of this study minimizing the chance of generalization of the findings of this study.

Suggestions/Recommendations

Raising the community awareness through mass media, strengthening of control system on imported medicines, training of medical staff on drug's reaction and its prognosis, improvement the lab services and initiation of specialized laboratory services, etc need further planning and budget allocation.

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