Therapeutic Causes of Stevens - Johnson Syndrome - A Mini Review

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Abstract
Stevens-Johnson syndrome, a form of life-threatening, toxic epidermal necrolysis in which epidermis is separated from the dermis. Aromatic drugs with heteroatoms such as sulphur, nitrogen and oxygen can cause Stevens-Johnson Syndrome. Examples of such drugs are barbiturates, oxicam derivatives, sulphonamides, etc. Mouth, eyes, skin and urogenital parts are affected. The SJS/TEN could be genetic via granulysin and via immunogenic activity involving white blood cells, cytokines or by formation of antigen antibody complex. Adults and young humans can be affected. Consumption of meats that contain traces of some drugs could also cause SJS/TEN. Also drugs or compounds that are tautomeric may cause Stevens Johnson Syndrome and Parkinsonism.

Keywords: Therapeutic drugs; Stevens johnson syndrome; Analgesic; Steroid; Genome

Abbreviations: SJS: Stevens- Johnson Syndrome; TEN: Toxic Epidermal Necrolysis; LEV: Leviracetam; CTL: Cytotoxic T Lymphocytes; PCA: Principal Component Analysis; CADRS: Cutaneous Adverse Drug Reactions; DRESS: Drug Reaction With Eosinophilia and Systemic Symptoms; NCS: Nanocrystalline Silver

Introduction
Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening complications of drug therapy. But the conditions are associated with serious sequelae and a high mortality rate in adults and lower mortality rate in children respectively. However, half of affected children suffered long-term complications. The recurrence rate of SJS was high (1 in 5), suggesting vulnerability and potential genetic predisposition. Treatment regimens differ significantly [1] SJS can occur with recurrent erythema multiform that can respond to mycophenolate mofetil (lg twice daily) and prednisone (40-60mg/day) suggesting that the two drugs can be used in the management of SJS [2]. Both SJS and TEN are rare affecting 1 or 2per/million annually and are considered medical emergencies as they are potentially fatal, characterized by mucocutaneous tenderness, haemorrhagic erosions, erythema, blisters and areas of denuded skin. TEN and SJS are two ends of severe epidermolytic cutaneous reactions caused in most cases by drugs. Mycoplasma pneumonia and Herpes simplex virus infections are also causative agents.

Therapeutic causes of Stevens Johnson syndrome
The incriminating drugs are allopurinol, trimethoprim-sulfamathoxazole, sulphonamides, aminopenicillins, cephalosporins, quinolones, carbamazepine, phenytoin, phenobarbital, oxicam-type analgesics. Genetic susceptibility is observed in Han Chinese as exemplified by the human leukocyte antigen HLA-B 1502, and SJS induced by carbamazepine [3]. Diagnosis is by clinical signs and histology. Mortality rate of SJS is 1-5% and of TEN 25-35%. More than 50% of patients surviving TEN suffer long-term sequelae of the disease [4] reported that piroxicam can increase the withdrawal period of West African dwarf goats administered sulphadimidine. Hence, the two drug may likely cause SJS in susceptible individuals. Other causes of SJS are aromatic antiepileptic drugs AEDs [5], such as phenytoin, carbamazepine, oxcarbazepine, phenobarbital, lamotrigen and other aromatics [6] and leviracetam (LEV), the S-enantiomer of α-ethyl-2-oxo-1-pyrroloidine acetamide, is an AED with a novel mechanism of action [7] and can cause SJS [8].

Structure–activity relationship of Stevens Johnson syndrome
Growing digitalization of health care data enables detection of adverse drug reactions ADR using electronic health records, biomedical literature, drug labels, bioassays and quantitative, structure-activity relationship (QSAR) models [9-13]. Therefore, QSAR models could identify SJS active and inactive drugs
Molecular pathogenesis of Stevens Johnson syndrome

Blister cells from skin lesions of SJS-TEN primarily consist of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, blister fluid and cells. Granulysin is responsible as qualified by polymerase chain reaction (PCR) and immunohistochemistry. Granulysin concentrations in the blister fluid were 2.4 orders of magnitude higher than perforin, granzyme B or soluble F as ligand concentrations, and depleting granulysin reduced the cytotoxicity. Granulysin (15-k Da) injected into mouse skin mimicked SJS-TEN, signifying that granulysin is a key molecule responsible for the disseminated keratinocyte death in SJS-TEN and highlight a mechanism for CTL-or Nkll mediated cytotoxicity that does not require cellular contact [18]. Principal component analysis (PCA) can be used to detect underlying differences in genetic ancestry [19]. T-cells activation and release of cytokines especially TNF-α and granzyme β causes immune-mediated activation of coagulation with increase in TAT, MCP-1, F1.2 and platelete microparticles and corresponding decrease in protein C1antithrombin, and PA1-1 which may progress to sepsis associated coagulopathy and overt disseminated intravascular coagulation [20]. Sulphonamide drugs are the most common cause of SJS with a combined prevalence of 0.8% HIV-1 infected patient treated with nevirapine developed SJS [21]. Penicillins are known to cause severe form of cutaneous adverse drug reactions (CADRS). Amoxicillin, dicloxacillin, and amoxicillin-dicloxacillin induced SJS have been reported [22] SJS causes bronchiolar submucosal fibrosis consistent with constructive bronchiolitis, eosinophilic micro-abscesses associated with permanent mucosal damage [23]. M. pneumonia-induced SJS manifests less severely than its drug-induced counterpart [24]. Didoenac, oximacs and propionic acid derivatives cause SJS characterized by mucosal erosions, propionic macules, and epithelial detachment involving less than 10% BSA in the trunk and face extremities. Sulphonamides and piroxicam can undergo photosensitization, especially the amide group [25] which may also be attributable to sulphur, nitrogen, oxygen (heteroatoms) leading to ulceration. Piroxicam metabolites may also act via melatonin [26]. However, S-O-O functional group present in sulphamethoxazole and piroxicam may be responsible for SJS. Piroxicam also has functional group similar to acetycholine, arecoline and nicotine signifying that cholinergic agents may also cause Stevens Johnson Syndrome. Since piroxicam can undergo keto-enol tautomerism every, tautomer may cause SJS and parkinsonism.

Therapeutic regimens of Stevens Johnson syndromes

Ciprofloxacin can cause photo-induced Stevens-Johnson Syndrome characterized by a red rash on the chest, difficult and painful swallowing, prednisone, famotidine and diphenhydramine were administered which further worsened the condition. But prednisone (60mg/day) for 7 days improved skin lesions and associated pain reducing skin sloughing to less than 5% of her body surface [27].

Although, drug reaction with eosinophilia and systemic symptoms (DRESS) known as hypersensitivity syndrome resembles SJS and caused 10% mortality prompt diagnosis and withdrawal of the fading are the most important preliminaries. After healing, follow-up is required for ophthalmic and mucous membrane sequelae. Sunblocks are recommended [28]. Despite its content of a long-acting sulfa, the manufacturers claim that the literature shows no case report of Stevens-Johnson Syndrome reaction to trimethoprim-sulphamethoxazole among Nigerians. However, a case report on an enlightened Nigeria who inadvertently took the drug a second time and had second and more reactions was reported [29] signifying that SJS may be related or connected with antigen-antibody reaction. But transplantation cryopreserved amniotic membrane in acute SJS/TEN can reduce inflammation and prevent scar formation in the conjunctival and corneal surfaces and in restoring corneal epithelial integrity [30].

Treatment of SJS/TEN involves the use of analgesic (including opiates) supportive therapy (immunotherapy) eye treatment (non-preserved hyaluronate, carmelleose-eye drops every 2hr, dexamethasone (0.1% twice daily), moxifloxacin (eye drop four times daily), silt paraffin ointment should be applied to the lips every 2hr, warm saline mouthwashes, benzylamine hydrochloride every 3hr before eating chlorhexidine (twice daily) and betamethasone sodium phosphate four times daily. But urogenital treatment includes white soft paraffin ointment to the urinary skin and mucosae every 4h, silicone dressing (e.g. mepitel) to erode areas. Psychological issues can follow treatment of SJS and there is no immune-modulating therapy at the moment [31] SJS triggered by sulfasalazine caused bilateral tarsal and forniceal conjunctiva and black pigmentation. There were stromal monocyte infiltration and conjunctival pigment of melanic origin which was not changed after treatment with topical steroid [32]. Sepsis in SJS/TEN is the main cause of mortality. Cytokines, metalloproteinasises, proteins cause intense destruction of extracellular matrix, major flood shifts, and systemic inflammatory response are life-threatening. Nanocrystalline silver (NCS) has antimicrobial activity and is effective in lower metalloproteinasises [33-36].

Conclusion

Stevens Johnson syndrome is an adverse drug reaction genetically related caused by drugs that contain heteroatoms. Such drugs can cause photosensitivity reactions. However, treatment of SJS is nonspecific and is associated with sequelae.
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