

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Overlay Associated with Self-Medication of Sulfadoxine-Pyrimethamine Overdose in a Patient with HIV/AIDS Infection: A Case Report

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Abstract: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) overlap is a severe delayed-type hypersensitivity reaction causing widespread blistering and necrosis of skin and mucosa. Sulfadoxine-pyrimethamine (SP) and HIV/AIDS infection are associated with hypersensitivity reactions, including SJS and TEN. A 20-year-old female with HIV/AIDS presented with fever, body pain, and skin blisters on her face, neck, trunk, and perineum. She was non-compliant with antiretroviral therapy. The lesions developed three days after self-administering SP for malaria, taken as two tablets every 12 hours for three days. The skin involvement was 23% of total body surface area (TBSA). The Naranjo Adverse Drug Reaction Scale Score of four suggested a possible association between SP and SJS/TEN overlap, considering HIV/AIDS can precipitate this reaction. The severity-of-illness score of toxic epidermal necrolysis (SCORTEN) score was one, with predicted mortality of 3.2%. The patient received conservative treatment including fluids, antimicrobials, nutrition, and wound care, leading to complete recovery. It is imperative that the medicine regulatory authority and healthcare professionals educate HIV patients to avoid self-medication with antibiotics such as SP due to the increased risk of serious adverse drug reactions, including SJS/TEN.

Keywords: Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity, Sulfadoxine-pyrimethamine, HIV/AIDS infection, case report

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare and potentially fatal medical conditions that are considered delayed-type hypersensitivity reactions to medicines and represent significant medical emergencies.^{1,2} They are variants of the same pathological process and are distinguished by the extent of total body surface area (TBSA) affected. The diagnosis of SJS is based on a TBSA affected of less than 10%, and that of TEN is based on a TBSA of > 30%. The TBSA involvement between 10 and 30% is designated as SJS/TEN overlap.³

SJS/TEN can be elicited by exposure to certain medications and less frequently to pathogens. A substantial number of medications including sulfonamides, beta-lactams, allopurinol, anticonvulsants, and certain nonsteroidal anti-inflammatory drugs have been associated with SJS/TEN.⁴ Moreover, risk factors for the development of SJS/TEN include certain human leukocyte antigen (HLA) haplotypes; variations in cytochrome p450 metabolism; pathogens such as *Mycoplasma pneumoniae* and Herpes simplex virus (HSV); human immunodeficiency virus (HIV) infection regardless

of treatment status, systemic lupus erythematosus (SLE), connective tissue disorders, psoriasis, epilepsy, malignancy, cerebrovascular accident, and diabetes mellitus.^{2,5}

Although the biological intricacies of the disease process are yet to be fully elucidated, it is hypothesized that cytotoxic CD8+ T lymphocytes and natural killer cells specific to the causative medication or infection release cytokines and chemokines which recruit other immune cells including neutrophils, monocytes, and eosinophils into the skin and mucosa. HIV specifically attacks and eliminates CD4+ T cells, which include regulatory T cells (Tregs) that help control immune activation. In the absence of Tregs, CD8+ T cells and pro-inflammatory cytokines become more prevalent, heightening the likelihood of immune reactions to SP.⁶⁻⁸ This can result in the development of an erythematous, then blistering, and ultimately desquamating rash and cellular necrosis which can involve the skin, eyes, and mucosa of the mouth, pharynx, gastrointestinal tract, respiratory tract, and genitals.^{1,9} The cessation of exposure to the inciting agent and supportive care will result in re-epithelialization of the affected areas. Treatment necessitates a multidisciplinary approach to managing the wounds and complications, utilizing systemic and topical therapies, often requiring hospitalization at the burn and reconstructive plastic surgery units.¹⁰

The use of sulfadoxine-pyrimethamine (SP) in People Living with HIV/AIDS (PLWHA) has been associated with hypersensitivity reactions and reported to cause a spectrum of SJS and TEN.¹¹ This warrants continuous documentation and reporting to competent authorities to augment pharmacovigilance and provide healthcare professionals with data for evidence-based decision-making. We present a case of SJS/TEN overlap associated with SP use in a patient with HIV/AIDS, highlighting the importance of understanding drug overdose and severe skin reactions to prevent life-threatening complications in vulnerable HIV/AIDS populations.

Case Report

This report details the case of a 20-year-old non-pregnant woman with Retroviral Disease (RVD) who did not adhere to her Tenofovir/Lamivudine/Dolutegravir antiretroviral treatment regimen. She sought medical attention at the Connaught Hospital, part of the University of Sierra Leone Teaching Hospitals Complex. She presented with a four-day history of fever and generalized body pain, accompanied by a three-day occurrence of skin blisters on her face, neck, upper torso, and genital area (Figures 1 and 2). The skin lesions appeared three days after she consumed an excessive dose of SP, taking two tablets every 12 hours for three days, which was not the recommended amount. The recommended dose of SP is three tablets taken together as a single dose, in which each tablet contains 500mg Sulfadoxine plus 25mg Pyrimethamine. The patient had obtained the SP over the counter from a local pharmacy to treat malarial symptoms



Figure 1 Picture showing the skin detachment of the patient while on admission at Connaught Hospital.



Figure 2 Picture showing the facial skin blisters of the patient while on admission at Connaught Hospital.

she experienced while preparing for her high school diploma West African Senior School Examinations (WASSCE). Initially seen at the antiretroviral clinic, she was subsequently transferred to the Intensive Care Unit because of the extensive nature of her condition. Drug history revealed previous exposure to SP for treatment of malaria two months ago.

On examination at the intensive care unit (ICU), she had signs of acute illness, dehydration, and conjunctivitis. Skin blisters were observed on her face (including eyelids), neck, upper trunk (front and back), and labia, affecting 23% of her TBSA. Her body temperature was 38.6°C, with 98% oxygen saturation in room air. The cardiovascular and respiratory examinations yielded unremarkable results.

Blood tests revealed mild anemia (Hb:10.9 g/dl), neutropenia (41.4%), and monocytosis (18.5%), while liver function (serum glutamic oxaloacetic transaminase, serum glutamate pyruvate transaminase, total protein, albumin, bilirubin, alkaline phosphatase), kidney function, and electrolyte levels were within normal ranges.

Treatment included rehydration, pain relief, multivitamin supplementation, antibiotic therapy (metronidazole and ceftriaxone), omeprazole, prednisolone, and tetracycline eye drops. The blisters were ruptured and the wounds were thoroughly debrided and cleaned with lukewarm saline before being dressed with paraffin oil. The patient was able to consume food orally on admission with minimal discomfort and adhered well to a high-protein diet recommended by the nutritionist. Wound dressings were changed on alternate days initially and then once every three days as the wound improved. Her clinical recovery progressed satisfactorily, leading to her discharge two weeks after admission, with complete wound healing and no scarring.

The Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN) score was 2, indicating a possible link between SP ingestion and the observed adverse reaction, considering the presence of an alternative cause.¹² Also, the Naranjo Adverse Drug Reaction Probability Scale score of 4 further suggested a possible relationship between SP and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), as the reaction followed a temporal sequence post-medication administration, potentially aligned with a recognized pattern for the suspected drug, but could be explained by the HIV/AIDS.¹³ The patient had not been taking any other medications alongside the sulfadoxine-pyrimethamine before symptom onset. The severity-of-illness score of toxic epidermal necrolysis (SCORTEN) was determined based on one out of seven parameters: TBSA detached $\geq 10\%$ on day one.¹⁴ According to the p-method, the preventability score classified this as a preventable Adverse Drug Reaction (ADR) due to four critical factors: (1) Incorrect dosage (2) Necessary medication not provided (3) Self-medication with prescription medicine (4) Inappropriate indication.¹⁵

Discussion

The combination of SP and HIV/AIDS appears to increase the risk and intensity of SJS/TEN, considering pre-exposure, and its occurrence can increase by a factor of one thousand.^{11,16} The exact mechanism underlying this effect remains unclear, but it is likely related to immune system disruption caused by HIV infection. A compromised immune system in patients with HIV/AIDS may result in altered drug metabolism and increased vulnerability to hypersensitivity reactions.

Additionally, SP might cause an imbalance in inherent activation and detoxification processes and modify the innate immune response. HIV specifically targets and destroys CD4⁺ T cells, including regulatory T cells (Tregs), which are integral in suppressing immune activation. In the absence of Tregs, CD8⁺ T cells and pro-inflammatory cytokines become predominant, increasing the risk of immune responses to antibiotics such as SP.^{6,7} In individuals with HIV/AIDS, the chronic activation of CD8⁺ T cells may lead to the misidentification of drug metabolites as antigens, potentially triggering SJS/TEN through the induction of keratinocyte apoptosis, resulting in severe dermatological reactions. Furthermore, HIV depletes glutathione, an antioxidant essential for the detoxification of sulfonamide metabolites, which can subsequently activate cytotoxic T cells and provoke immune responses.^{6,7,17,18} Individual genetic predisposition also contributes to the development of SJS/TEN, indicating a complex interaction between drug exposure, HIV infection, and host factors.^{2,19}

These incidents can result in significant health complications, fatalities, and financial strain on the healthcare system. Consequently, healthcare professionals must promptly and proactively report these occurrences.

The patient in question engaged in self-medication, defined as the use or purchase of medicines without professional medical advice to treat self-diagnosed conditions, which carries risks such as the overdose that led to this serious adverse reaction.²⁰ Moreover, the dispensing of SP by an unqualified individual at the drug outlet was both unlawful and inappropriate, as the national malaria treatment guidelines do not recommend SP as the primary treatment for uncomplicated malaria in adults. In Sierra Leone, the first-line treatment for uncomplicated malaria is Artemether-Lumefantrine, with Artesunate-Amodiaquine as the second-line option.²¹

The non-prescription acquisition and consumption of SP has several important implications. SP is primarily recommended for the intermittent preventive treatment of malaria in children and pregnancy (IPTi and IPTp) in Sierra Leone. This highlights the complex nature of the antimalarial drug resistance dynamics. Unregulated use of SP could potentially accelerate the development and spread of drug-resistant parasites, compromising its effectiveness for IPT. In our setting, where drugs are poorly regulated and easily accessible from most pharmaceutical outlets, individuals can obtain them readily and may only seek proper medical attention when complications arise.²² Therefore, stricter regulation of SP availability and usage is crucial to maintain its efficacy for expectant mothers and children and reduce the development and transmission of resistant parasites. Treatment included fluid repletion, analgesics, multivitamins, antibiotics (metronidazole and ceftriaxone), omeprazole, prednisolone, and tetracycline ophthalmic solution. Vesicles were ruptured, lesions were debrided, and the wound was thoroughly cleaned with saline and dressed with paraffin oil. Despite mild discomfort, oral nutrition was possible, and a high-protein diet was prescribed. The patient showed progressive improvement and was discharged after two weeks when re-epithelialization of the wounds was complete and there was no residual scarring. Unfortunately, rechallenge was not done using a patch test.

Conclusion

It is crucial for the medicine regulatory authority and healthcare providers to inform HIV patients about the dangers of self-medicating with antibiotics like SP, as this can lead to severe adverse drug reactions, including SJS/TEN. Additionally, pharmacies should display warnings and precautions for individuals with HIV, advising them against purchasing antimicrobials without a prescription. Enforcing stricter regulations on the availability of antibiotics such as SP is necessary as a preventive strategy.

Consent for Publication

Permission was granted by Connaught Hospital to use patient case details. The patient granted permission for the publication of case details and accompanying images. Authorization was obtained through an informed consent process, ensuring the patient's agreement to share their medical information.

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Disclosure

The authors declare no conflicts of interest in this work.

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