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Levofloxacin-Induced Stevens-Johnson syndrome: A Case Report

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Abstract

Background: Adverse drug reactions (ADRs) are one of the leading causes of death and may vary from mild rashes to severe reactions such as Stevens-Johnson syndrome (SJS). Among various ADR, mainly Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare but potentially fatal reactions which endangers a patient's life. These reactions are characterized by mucocutaneous tenderness, typically haemorrhagic erosions, and erythema with more or less severe epidermal detachment, presenting as blisters and areas of denuded skin. Fluoroquinolones are widely used because of their broad spectrum activity. Their benefit-risk profile needs careful evaluation as they can induce T cell-dependent reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The majority of cases are drug-induced and; affect the oral and peri-oral region.

Case report: A 31 year old male presented with chief complaints of fever, generalized skin eruptions and mucosal erosions. On the day of admission his body surface was started to be covered by rash, blistering and epidermal peeling, extensive rashes on the skin of the face and neck. He complained ofburning and pricking sensation all over the body, headache, dark coloured urine, palpitations, joint pains and, muscle cramps. There was erythema of the conjunctiva, ulceration of eyelids and oral cavity along with difficulty in routine oral habits. The reaction was evoked 1 day after ingestion of a levofloxacin tablet 500mg and cyclopamtablet (Dicyclomine 20 mg+ Paracetamol 500 mg). The symptoms improved significantly after the offending drug was withdrawn. He was treated with intravenous and topical corticosteroids, anti-histamines, intravenous fluids, oral topical anaesthetics and other supportive therapies. After 5 days of therapy, symptomatic relief was observed and patient was discharged. Health care providers must be careful of the adverse effects of drugs, especially regarding Stevens- Johnson syndrome (SJS), which is a potentially fatal condition. The most common and widely prescribed drug regimens should also be used judiciously and continuously monitored to prevent a fatal adverse drug reactions.

Conclusion: This case report highlights the adverse drug reactions of levofloxacin and the need of regular monitoring in patients on long term therapy.

Keywords

adverse drug reaction; Stevens-Johnson syndrome; toxic epidermal necrolysis; fluoroquinolones

Introduction

Adverse reactions, although rare, still pose a major risk to the patient's welfare. Stevens-Johnson syndrome (SJS) is only one such fatal drug reactions. “A new eruptive fever with stomatitis and opthalmia” was described as a severe variant of erythema multiforme and was termed by Steven and Johnson in 1922. By the 1940's it was usually called as “Steven Johnson's syndrome (SJS)” [1]. Although SJS is rare with an incidence of 0.05 to 2 persons per 1 million per year; it has substantial influence on the community health due to its high morbidity and mortality [2].

Stevens Johnson syndrome (SJS) is a severe hypersensitivity reaction that can be triggered by infections such as herpes simplex virus or mycoplasma, vaccinations, systemic diseases, physical agents, foods and drugs [3,4]. The most common drugs that cause SJS are antibiotics (Sulphonamides), penicillins (amoxicillin, amoxicillin+clavulanic acid),fluoroquinolones (ciproflxacin, oflxacin, levoflxacin, ciproflxacin), anti-tubercular agents (isoniazid, rifampicin, pyrazinamide) antiepileptic's (phenytoin, phenobarbital, carbamazepine, lamotrigine), non-steroidal anti-inflammatory drugs (oxicam derivatives) and xanthine inhibitors (allopurinol), miscellaneous (metronidazole, tinidazole, quinine, furosemide, flconazole, chloroquinine) [5,6].

Stevens–Johnson syndrome, is a milder form of toxic epidermal necrolysis but nevertheless a life-threatening skin reaction, in which cell death causes the epidermis to separate from the dermis. The syndrome is assumed to be a hypersensitivity complex that affects the skin and the mucous membranes [7,8]. These conditions were first recognised in 1922 [9]. A classification first published in 1993, that has been adopted as a unanimity definition, recognizes Stevens–Johnson syndrome, toxic epidermal necrolysis; and SJS/TEN overlap. All three are part of a spectrum of severe cutaneous adverse reactions (SCAR) which affect skin and mucous membranes. The distinction between SJS, SJS/TEN overlap; and TEN is centered on the type of lesions and the percentage of body surface area with blisters and erosions. Blisters and erosions cover 3%-10% of the body in SJS, 11–30% in SJS/TEN overlap, and over 30% in TEN. The skin pattern most commonly associated with SJS is widespread, often joined or touching (confluent), red spots (macules) or even slight blisters or hefty blisters which may also link together [10].

SJS may present as a non-specific febrile illness (malaise, headache, cough, rhinorrhea) with polymorphic abrasions of skin and mucous membranes characterized by acute blisters and erosions [4]. Stevens-Johnson syndrome, otherwise known as erythema multiforme major, is thought to denote a continuum of disease, the most benevolent type of which is erythema multiforme, whereas toxic epidermal necrolysis is the most severe [11]. The importance of our case is that it is a case of SJS secondary to drug therapy instituted for a UTI which consisted of drugs that are very common and widely used. One must use caution and comprehensive history of past drug intakes or adverse drug reactions even when treating common cases with frequently prescribed drugs.

Fluoroquinolones are widely used because of their broad spectrum of activity. Their benefit-risk summary needs cautious evaluation as they can induce T cell-dependent reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [12]. Adverse drug reactions (ADR) account for 6% of the entire hospital admissions, rises economic burden on the healthcare system, and have serious consequences like withdrawal of drugs from the market and death [13,14]. Among several

(TEN) are rare but potentially fatal reactions which endanger patients' lives.

Aim: The main aim of this article is to present a case of Steven Johnson syndrome secondary to drug therapy consisting oral levofloxacin 500mg and cyclopam (dicyclomine 20 mg+ paracetamol 500 mg) prescribed for a minor urinary tract infection (UTI) in a primary health care centre by a general practitioner. It is important for clinicians to be aware of its presentation. It is critical to identify the causative agent as early as possible and its withdrawal is necessary for critical management.

We report a case of levofloxacin induced SJS in a 31 years old male patient who was prescribed levofloxacin and cyclopam for abdominal pain and UTI. The following case report demonstrates the necessity of prompt recognition and initiation of appropriate therapy to reduce the potential sequelae of Stevens–Johnson syndrome.

Case Presentation

A 31years old male visited the outpatient department of general medicine department of the Mandya Institute of Medical Sciences and Teaching Hospital, Mandya, Karnataka, India. He presented with chief complaints of fever and generalized skin eruptions and mucosal erosions. On the day of admission his body surface was started to be covered by rash, blistering and epidermal peeling, extensive rashes on face and neck, burning and pricking sensation all over the body, headache, dark coloured urine, palpitations, joint pains and; muscle cramps, erythema of conjunctiva, ulceration of eyelid and oral cavity along with difficulty in routine oral habits. The reaction was evoked after 1 day of ingestion of levofloxacin 500mg tablet and cyclopamtablet (dicyclomine 20 mg+paracetamol 500 mg) (Figure 1).

Prior day to presentation he noticed passage of dark coloured urine, pruritus and rash over his extremities, which over the next day progressed to his chest, trunk, back, legs and face associated with blistering and epidermal peeling. Past medical history of patient revealed that he had received treatment for UTI from the primary health care centre and the general physicion prescribed levofloxacin 500mgtablet, and cyclopam tablet for 5 days, in which he consumed for 2 days and he developed this sort of reaction. No history of diabetes mellitus, hypertension, tuberculosis, epilepsy, asthma and hypersensitivity reactions in the past.

Investigations: General Physical examination of the patient on day-1 examination-the patient was febrile and the body temperature was elevated to 39.8°C (103.6°F) with a heart rate of 82 beats/minute, respiratory rate of 17cpm and blood pressure of 102/74mmHg. The patient was well built and nourished, conscious, well oriented and appeared uncomfortable but not in distress. On examination, generalized maculopapular and bullous eruptions on the neck, face, external ear (Figures 1 and 2). The trunk and extremities were having well developed variable sizered coloured lesions. He also complained of burning micturition. The laboratory investigations are mentioned in Table 1.

Intra-oral examination revealed ulcerations of the vermilion surface of lips, labile mucosae, tongue and palate (Figure 2). The ulcers were haemorrhagic and tender on palpation. Haemorrhagic crusted erosions were also seen on both the upper and lower lips. The oral ulcerations were developed one day prior to development of the skin lesions. But he considered them as a routine. No other significant past medical history and drug allergies. No focal deficits were identified on neurological examination.

The patient was admitted to hospital with a presumptive diagnosis of drug-induced hypersensitivity reaction. At this point the differential diagnosis included drug induced hypersensitivity, erythema multiforme, toxic epidermal necrolysis, vasculitis, an exanthematous due to viral infection such as Epstein–Barr virus (EBV), cytomegalovirus (CMV) and auto-immune conditions such as systemic lupus erythematous.

Levofloxacin was withdrawn and the patient was monitored for signs of clinical recovery. On the day of admission patient condition worsened with increased facial skin peeling out and rash extending to his chest and abdomen.

Treatment: On day-1 the patient was treated with following medications- IV fluids, intravenous dexamethasone 8 mg TID, and intravenous chlorpheniramine 4 mg TID. Parenteral anti-biotic (ceftriaxone 1gm IV BD), parenteral proton-pump inhibitor (pantoprazole 40 mg IV OD), syrup rantac MPS 10 ml TID, topical corticosteroid-mometasone cream, oral steroids-Tess 0.1% ointment (triamcinolone acetonide), ANABEL oral gel: choline salicylate 8.7 % w/w, benzalkonium chloride 0.01 % w/w, lignocaine hydrochloride 2 % w/w, chlorhexidine mouth wash. The symptoms have not been reduced. So the patient has been referred for dermatologist opinion. The dermatologist evaluated the patient and confirmed the case as Stevens–Johnson syndrome and advised to withdraw levofloxacin and use alternative drugs for UTI. No fresh complaints on day-2 and patient were continued with the same medications. This Stevens–Johnson syndrome was mainly due to the levofloxacin.

Levofloxacin is a deoxyribonucleic acid (DNA) gyrase inhibitor that inhibits the relaxation of supercoiled DNA, thus promoting DNA strand breakage. Well-known adverse reactions of levofloxacin are gastrointestinal (nausea and vomiting approximately 5 %), anaphylaxis, photosensitivity, central nervous system (CNS; seizure <1 %, psychosis), cardiovascular (arrhythmia <1 %), and musculoskeletal (tendinitis <1 %, tendon rupture, tendon inflammation) [15].

On day-2, the physician dechallenged the drug after that patient was recovered from the presenting symptoms and an alternative urinary tract anti-infective agent was prescribed; Norfloxacin 400 mg twice daily was prescribed. The rashes and fever persisted for about 6 days. Liquid & soft diet was advised. It is important to caution patients to stop the drug once rashes develop. In this patient, medical attention was not sought immediately and the patient continued on levofloxacin till day 2 of the rash. The key prognostic marker in Stevens–Johnson syndrome is the prompt identification and withdrawal of the causative drug.

Outcome & Recovery: After 13 days of stay in hospital, he attained complete recovery. At the time of discharge, only mild rashes were present. During the discharge, the following medications such as wysolone 10mg tablet 2-1-0; pantoprazole 40mg tablet 1-0-1, avil tablet 25 mg 1-0-1, anabel Oral gel 1-0-1, chlorhexidine mouth wash, momate ointment 1-0-1 for one week was advised.

Adverse Drug Reaction Analysis: After collecting the past and current medication history from the patient it was suspected that the patient had developed drug induced Stevens–Johnson syndrome. After analysing the ADR profiles of all the drugs that has administered to the patient, it was found that the most suspected drug for producing Stevens–Johnson syndrome was Levofloxacin. We have further analysed to establish the relationship between the drug and the observed ADRs, through causality assessment by

using Naranjo's scale, WHO-UMC ADR assessing scale as well as Karch and Lasagne scale, results were shown in Table 2. The Naranjo's criteria and WHO probability scale were applied to determine the causality for suspected ADRs. The causality assessment with both scales revealed that adverse reaction due to levofloxacin in this case was probable (Naranjo overall score: 7). The severity of ADRs were evaluated using Modifid Hartwig and Siegel, based on which it was categorized as severe level 5 reaction.

Severity: Severe level 5

Predictability: Unpredictable

Preventability: Probably preventable

Management of Adverse Drug Reaction: Generally, management of ADR includes withdrawal/suspension, dose reduction of suspected drug and administration of supportive therapy. Here in this case report the suspected drug levofloxacin was discontinued.

Fate of suspected drug: Drug withdrawn

Treatment Given: Specific

Outcome: Recovered

Discussion

Patients with epidermal detachment involving <10% of their body surface area are classified as having SJS, whereas patients with >30% of body surface area affected are classified as having Toxic Epidermal Necrolysis [16,17]. Treatment includes according to the symptoms, usage of corticosteroids along with alteration or deletion of the causative drug. In the present case patient showed complete improvement once the drug was stopped and with the help of certain other supportive measures. Early diagnosis with the prompt recognition and withdrawal of all potential causative drugs is essential for a favourable outcome. Corticosteroids have for years been the mainstay therapy for SJS in most cases, as like in our case. Fluid balance and aseptic care of wounds is also important.

Conclusion

This case report of levofloxacin induced Stevens–Johnson syndrome helps to alert physicians about the toxic manifestations of levofloxacin in patients on long term therapy. Extensive period therapy with levofloxacin should be individualised based on the patient's clinical response and signs of toxicity. There is also need for regular follow up to assess compliance and response to therapy. Monitoring of ADRs should be done even when there are doubts of early toxic effects. It is important to obtain a history of allergy also as it was missed in one patient before prescribing the causal drug.

This report also highlights the importance of educating patients and their caregivers about the clinical manifestations of levofloxacin toxicity, so that it can be recognized early and treated appropriately. Hence, this case report serves to alert clinicians to remain clinically vigilant for such manifestation in patients with active cognitive lifestyles who are on long term levofloxacin therapy. Immediate withdrawal of the causative drug is mandatory to avoid a possible fatal outcome in Stevens–Johnson syndrome. Thus it is important to be aware and suspect this infrequent but fatal side effect of this commonly prescribed antibiotic. Even if there are little published data on levofloxacin

TEN/SJS, this fluoroquinolone can be concerned in these delayed ADR requiring early diagnosis and careful monitoring.

A robust ADR monitoring system with a feedback to and the education of the prescribers can help prevent, identify and manage this life threatening condition much more effectively. In conclusion, we would like to state that patients started with any common drug regimen may a potential risk of developing SJS. The oral erythema and ulcerations are usually the initial presenting complaint which the patient may ignore. There are documented reports in the literature where an early diagnosis of SJS could be made due to the presence of oral lesions. Symptomatic management of the oral lesions is necessary in order to enable the patient to have oral feeds to maintain nutritional balance. Increased clinical vigilance is required to identify hypersensitivity reactions like rash, vesiculo bullous lesions, and/or other clinical symptoms such as fever, nausea, and abdominal pain. Early diagnosis helps the clinician to elude secondary infection and subsequent complications. The offending drug should be discontinued and never be rechallenged.

Tables

Table 1: Patient laboratory investigations

	LABORATORY INVESTIGATIONS									
	DAY-1					**DAY-5**				
Haemoglobin	10.9 gm %					12.6 gm %				
White Blood Cells	15,900 cells/cmm					18,600 cells/cmm				
Differential Count	N	L	M	E	B	N	L	M	E	B
	78%	14%	4%	3%	01%	73%	22%	2%	2%	01%
Platelet Count	2.69 lakh cells/cmm					3.3 lakh cells/cmm				
ESR	30 mm/hr					39 mm/hr				
RBS	159 mg/dl					167 mg/dl				
Blood Urea	24 mg/dl					31 mg/dl				
Serum Sodium	135.3 mmol/l					136.6 mmol/l				
Serum Potassium	4.03 mmol/l					4.25 mmol/l				
Serum Chloride	100.5 mmol/l					102.39 mmol/l				
Serum Creatinine	1.5 mg/dl					1.6 mg/dl				
Total Bilirubin	1.3 mg/dl					1.5 mg/dl				
Direct Bilirubin	0.5 mg/dl					0.6 mg/dl				
Total Protein	6.2 g/dl					6.6 g/dl				
Serum Albumin	4.5 g/dl					5.01 g/dl				
Serum Globulins	3.9 g/dl					4.2 g/dl				
SGOT	47 U/L					49 U/L				
SGPT	45 U/L					51 U/L				
ALP	49 U/L					50 U/L				

Table 2: causality assessment of suspected ADRs

Suspected drug	Consequence of suspected drug (ADR)	Naranjo's scale	WHO-probability scale	Karch and Lasagnas scale
Levofloxacin	Stevens–Johnson syndrome	Possible	Probable	Probable

Figures

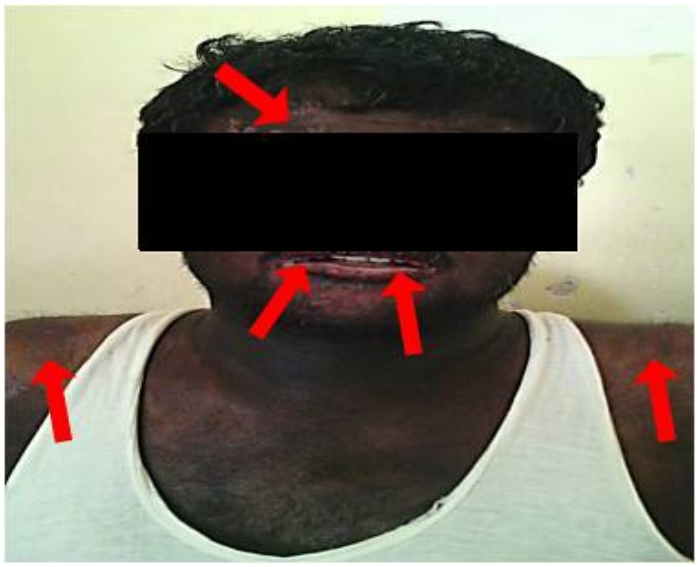

Figure 1: Maculopapular rash over the face, forehead and neck.

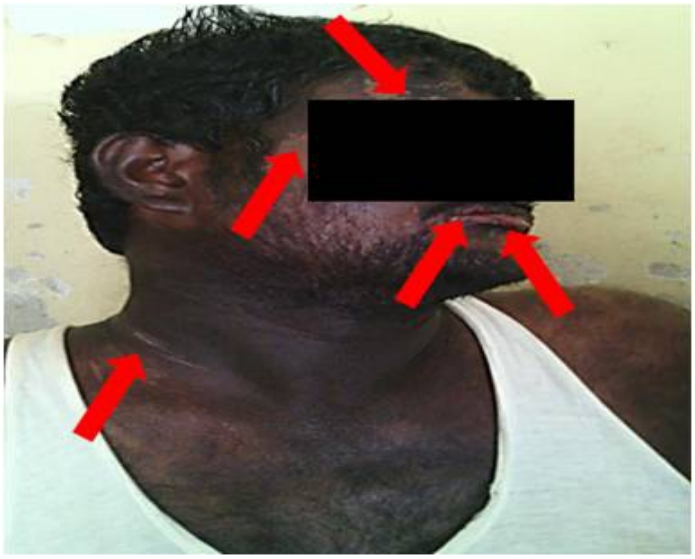

Figure 2: Ulcerations and bloody crusting lesions of vermilion surfaces of lips.

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