WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 4, 852-860. Case Report ISSN 2277– 7105

CEPHALOSPORIN INDUCED STEVEN-JOHNSON SYNDROME- AN ADVERSE DRUG REACTION

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Article Received on
23 Jan. 2019,

Revised on 13 Feb. 2019,
Accepted on 06 March 2019

DOI: 10.20959/wjpr20194-14208

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ABSTRACT

Introduction: In the management of patients with the modern day drug therapy, the indimidating remrak remains to be an adverse drug reaction. Drug hypersentivity is one such Adverse drug reaction which is a major clinical problem. Steven johnson syndrome(SJS) is a rare, severe life threatening immune complex- mediated hypersensitivity reaction involving skin and the mucous membrane which emerges in reponse to medication intake in more than 80 percent of cases. **Case Report:** We report a case of 20 year old female patient who presented to the medicine out patient Department with complaints of Swelling and painful ulceration in the oral cavity since 10 days together with fever, vomitings, throat pain and generalised body pains. Prior to its onset she had a history of twice daily intake of cefixime 200 mg, which was prescribed by a local emergency room physician for her lower respiratory tract infection. On the 7th day of antibiotic use the patient had complains of fever with chills, vomitings and throat pain which was followed by the gradual development of ulcers in the oral mucosa, extending over both upper and lower lip and around the angles of mouth. The lesions worsened progressively accompanied by rise in body temperature. Cefixime was immediately withdrawn and tablet cepodem was prescribed. On the next day the patient complained of worsening of oral ulcers with inability to eat and drink accompanied by severe headache and polyarthralgia. Tablet cepodem was immediately discontinued and the patient was declared as sensitive to cephalosporins. Causality assessment of the adverse drug reaction was done using the WHO UMC criteria and Naranjo's algorithm which revealed the adverse drug reaction as probable with a score of 6 and severity assessment was done using the Hartwigs severity assessment scale and the reaction was classified as severe. The patient was managed accordingly. Our case therefore

appears to be the first case in which SJS was triggered by cefixime and exacerbated by cefpodoxime, a hypothesis confirmed by the prompt clinical status resolution. **Conclusion:** Although SJS is a very rare complication of medication use, the occurrence of sjs associated with the use of cephalosporins is unclear. Early recognition of the Adverse drug reaction and immediate withdrawal of the offending agents are critical for minimizing secondary infections and subsequent complications of Stevens-Johnson syndrome(SJS). To date, no cases have been reported concerning the onset of SJS by cefixime and exacerbated by cepodem. It is important to be aware that SJS may be the cause of the affected mucosal tissues in childrens and young adults even in the absence of skin lesions.

INTRODUCTION

In the management of patients with the modern day drug therapy, the indimidating remrak remains to be adverse drug reaction. Drug hypersentivity is one such Adverse drug reaction which is a major clinical problem. Among the different types of adverse drug reactions (ADR) Steven johnson syndrome(SJS) is one of the rare, serious and life threatening drug hypersensivity reaction. Adverse drug reaction accounts for about 6% of the total hospital admissions with death as a major complication in 0.3-7% of the hospitalised patients, eventually resulting in increased economic burden on the health care system and drug removal from the market.[1,2,3]

The term steven jhonson syndrome(SJS) was coined by Albert mason stevens and Frank chambliss johnson in the year 1922.[4] Steven jhonson syndrome is expressed as a severe variant of erythema multiforme as “A new eruptive fever with stomatitis and opthalmia.” Steven johnson syndrome is acute, self limited and rare complication of medication use which mainly occurs with the drugs like Antibiotics, Anti epileptics and NSAIDS, among antibiotics which is responsible for 45% of cases antiretrovirals are the most common follwed by antitubercular, sulphonamides, fluroquinolones and penicillins.[4] The incidence of SJS is 1-7 cases per million persons per year.[17] It is most commonly seen in childrens but a higher mortality rate is observed among elderly.[5] Moreover patients suffering from certain conditions like systemic lupus erythmatosis, herpes simplex or HIV are at a higher risk of developing SJS.[6,7,8] Pathophysiologically is not well documented but genetic predisposition and disorders of immune system have been implicated in development of steven johnson syndrome in some cases.[2]

The beginning clinical features of SJS are prodromal symptoms like fever, malaise, cough, sore throat, vomiting and chest pain followed by rapid onset of mucocutaneous ulcers.[9,17] The main characteristic features of SJS mostly as an ADR to drug are[10]:

1. Erythematous cutaneous reaction associated with blister formation.
2. Haemorrhagic erosions of mucous membrane such as stomatitis, balanitis, colpitis, severe conjuctivitis and blepharitis.

Mucosal ulceration is the main characteristic feature in approximately 90% of the cases and may exist in the absence of skin lesions, although the <10% of the body surface area that is involved in SJS. Apart from mucosal involvement the other organs most commonly affected is eye (i.e, corneal ulceration, conjuctivitis, uveitis, keratitis etc) followed by urethral and Gastrointestinal erosions and rarely respiratory tract involvement is observed.[17]

CASE REPORT

A 20 year old female patient presented to the medicine out patient Department with complaints of swelling and painful ulceration in the oral cavity since 10 days together with fever, vomitings, throat pain and generalised body pains. She was apparently alright, when she had a history of twice daily intake of cefixime 200 mg, which was prescribed by a local emergency room physician for her lower respiratory tract infection. On the 7th day of antibiotic use the patient had complains of fever with chills, vomitings and throat pain which was followed by the gradual development of ulcers in the oral mucosa, extending over both upper and lower lip and around the angles of mouth. On the 8th day the lesions worsened progressively with the development of swollen, painful fluid filled blisters on the lower lip. There was rise in body temperature associated with acute pharyngitis.

On admission to the hospital Cefixime was immediately withdrawn and tablet cepodem and mucopaine gel was prescribed for her respiratory tract infection and allergic reaction. On the next day the patient complained of worsening of oral ulcers with inability to eat and drink accompanied by severe headache and polyarthralgia. Tablet cepodem was immediately discontinued and the patient was declared as sensitive to cephalosporins.

Intra oral examination revealed yellowish brown crusting over the lower lip along with swollen multiple fluid filled, foul smelling mucocutaneous ulcers in the oral cavity extending to pharynx. No other lesions were found else where on the body or on the genital areas.

Ocular and fundoscopic examination was normal. Patient had no history of scarring of skin or GI bleeding, ocular complications or any other infections.

Physical examination of the patient revealed raised body temperature
Temperature :102° F
Pulse rate =86 b/min,
Blood pressure : 100/60mm Hg and
Respiratory rate =20b/min.

Cardiovascular, Respiratory, Gastrointestinal and joint examination was normal except for mild tenderness in the ankles and knees. Rest of the physical examination was normal. Upon further investigation, patient had nil comorbidities and no previous history of ulceration in the oral or genital areas, photosensitivity or allergic reactions to any drug. Further patient declined intake of any herbal, dietary or over the counter medication.

Laboratory findings such as Sr. Creatinine, liver function tests parameters and Hematology report was normal, except for leucocytosis on the 5th day. Electrolytes were within the normal limits. Total iron binding capacity (TIBC) and Iron levels were reduced.{Iron :28 microgram/dl, TIBC: 250.6 microgram/dl}. Other relevant test were performed to rule out any other causes that might have induced the reaction. Malarial parasite pathology report, Dengue ELISA Ig M and Ig G serology report, Salmonella Typhi Ig M ELISA report and Immunoserology report for Enteric fever were all negative. Skin biopsy was not performed as the patient had absence of skin lesions.

Considering the Clinical history of cefixime intake prior to the development of ulcers, worsening of symptoms upon tablet cepodem administration, clinical examination, laboratory findings as well as absence of any other underlying etiology, the patient was diagnosed as a case of cephalosporin induced steven johnson syndrome.

The patient was managed accordingly with analgesics, antipyretics, corticosteroids, antihistamines, anti-emetics, local treatment of lesions and nutritional supplements. Tablet Omnacortil 10mg twice daily (corticosteroid) was prescribed followed by mucopain gel(local anesthetic) and Lexanox(amlexanox) paste for local application to reduce inflammation and to heal the mucosal ulcers. Antihistamines and anti-emetics were prescribed as prophylactic as well as to prevent further damage to the underlying ulcers. Regular monitoring of the

patient for symptomatic improvement was observed. Upon discharge the patient was symptomatically better and was able to tolerate oral fluids well. The patient was adequately recommended to restrain further use of cephalosporins to prevent further damage and to avoid any other complications. At her follow up visit, she was doing well with significant improvement in the symptoms.

Fig 1. Naranjo's Algorithm.[11]

Questions	Yes	No	Don't know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	**1**
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	**2**
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	**1**
4. Did the adverse reaction reappear when the drug was re administered?	+2	-1	0	**2**
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	**0**
6. Did the reaction reappear when a placebo was given?	-1	+1	0	**0**
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	**0**
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	**0**
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	**0**
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	**0**
				Total score=6

*Score ≥ 9 = definite,5-8 = probable,1-4 = possible,0 = doubtful.

Fig 2: WHO-UMC causality categories.[12]

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to

	drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably compiled with

Fig 3: Hartwigs severity assessment scale.[11]

Level 1	An ADR occurred but required no change in treatment with the suspected drug.
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in length of stay (LOS)
Level 4	Any level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission.
Level 5	Any level 4 ADR which requires intensive medical care.
Level 6	The adverse reaction caused permanent harm to the patient.
Level 7	The adverse reaction either directly or indirectly led to the death of the patient.

DISCUSSION

SJS is a rare, severe life threatening immune complex- mediated hypersensitivity reaction involving skin and the mucous membrane which emerges in reponse to medication intake in more than 80 percent of cases.[13] To date, no cases have been reported concerning the onset of SJS by cefixime, cephalosporin of the third generation with a highly stability in the presence of beta-lactamase enzyme as well as broad spectrum antibacterial activity.

It is generally a well-tolerated drug for the treatment of respiratory tract infection, infections of genitor-urinary and pelvic tracts, skin and soft tissue infections, intra-abdominal infections, sepsis, pre and post-surgical surgical prophylaxis. The most commonly reported adverse events to cephalosporins include gastrointestinal (nausea, colitis, vomiting, diarrhea), neurological (cephalea) and cutaneous, or hypersensitivity reactions such as rashes, itchiness and urticaria. Apart from urticaria, the acute generalized exanthematous pustolosis and SJS/TEN caused by phenytoin and exacerbated by cefipime can be found among the skin conditions caused by cephalosporins described in scientific literature.[14,15,16]

The patient's presentation was most consistent with Stevens-Johnson syndrome. Cefixime was the only medication the patient was receiving at the time of her initial mucosal ulcers. Mucosal involvement with stomatitis presenting with painful and dry crusted lips, a common feature of SJS were present along with multiple mucocutaneous ulcers in her mouth. The development of her ulcers after 7 to 8 days of the antibiotic therapy, better correlates with the timing of the usual onset (seven to ten days) noted in drug-induced SJS. No skin lesions were found on her body, while her eyes were dry without signs of conjunctivitis. This patient was relatively free of any complications, except for her presenting complains and diagnosis of pharyngitis. Further, she denied intake of any over-the-counter medications or illicit drugs. Considering the timing of development of the ulcers upon the intake of cephalexin, worsening of the symptoms upon Rechallenge and lack of any other underlying cause preceding the onset of SJS, a differential diagnosis of cephalosporin -induced SJS was made.

Causality assessment of the adverse drug reaction was carried using WHO-UMC criteria(Fig 1) and Naranjo’s algorithm(Fig 2), according to which the adverse drug reaction was classified as probable. The severity assessment for the reaction was done using Hartwigs severity assessment scale(fig 3) and the reaction was classified as severe. Our case therefore appears to be the first case in which SJS was triggered by cefixime and exacerbated by cefpodoxime, a hypothesis confirmed by the prompt clinical status resolution.

CONCLUSION

Although SJS is a very rare complication of medication use, the occurrence of sjs associated with the use of cephalosporins is unclear. Early recognition of the Adverse drug reaction and immediate withdrawal of the offending agents are critical for minimizing secondary infections and subsequent complications of Stevens-Johnson syndrome(SJS). It is important to be aware that SJS may be the cause of the affected mucosal tissues in childrens and young

adults even in the absence of skin lesions. Furthermore, physicians and health care workers are encouraged to improve the documentation on SJS/TEN to strength the database to design effective treatment modalities.

Abbreviations: SJS: steven johnson syndrome, TEN: Toxic epidermal necrolysis, ADR: Adverse Drug Reaction, NSAIDs: Non steroidal anti inflammatory drugs, LOS:length of stay.

COMPLIANCE WITH ETHICAL GUIDELINES

CONFLICT OF INTERESTS: The authors declare that they have no conflict of interests.

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