WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 2, 888-895. Case Study ISSN 2277– 7105

DRUG-INDUCED STEVENS-JOHNSON SYNDROME: A CASE SERIES.

Jatin Arora*[1], Usha D. S.[2], M. R. Manisha[3], Tuhin Das[4], Subhranil Deb Roy[5]

[1,2,3,4,5]Department of Pharmacy Practice, KLE College of Pharmacy, KAHER, Bengaluru, Karnataka, India.

Article Received on
25 November 2022,
Revised on 15 Dec. 2022,
Accepted on 05 Jan. 2023
DOI: 10.20959/wjpr20232-26676

***Corresponding Author**
Jatin Arora
Department of Pharmacy Practice, KLE College of Pharmacy, KAHER, Bengaluru, Karnataka, India.

ABSTRACT

Stevens-Johnson Syndrome (SJS) is one of the rare but life-threatning cutaneous reaction which can lead to symptoms like skin lesions, rash, hyperpigmentation of lips, blisters and various other painful symptoms. We represented five cases of SJS caused due to Nimesulide, Cefixime, Paracetamol, Ibuprofen and Allupurinol. In all the cases onset of symptoms took place after five-six days of medication administration. All the patients were treated using steriods, anti-histamines along with supportive care which included mouth wash and cream for topical application, and before initiation of therapy, the causitive medication was discontinued immediately after diagnosis. Disease prognosis was terminated in all the cases and patients wounds started healing as well. As advice patients were adviced not to consume the causitive medication prior consulting the physician to prevent the disease recurrence.

KEYWORDS: Stevens-Johnson Syndrome, Hyperpigmentation, Steroids, Anti-histamines.

INTRODUCTION

Stevens-Johnson Syndrome (SJS) is a mucocutaneous disorder which exhibits epidermal detachment because of keratinocyte death.[1] It is a life-threatening, rare, and serious reaction.[2,3] SJS ranges from 7 to 49 cases per million person per year and it is more incident in males as compared to females with a mortality rate of 10-75%.[4,5] A severe variant of erythema multiforme (EM) that is "A new eruptive fever with ophthalmia and stomatitis" was termed as Steven Johnson in year 1922.[6] It is less severe than Toxic Epidermal Necrolysis (TEN) but it can lead to mucosal and skin eruptions due to hypersensitivity to certain drugs which can be potentially fatal.[7] The most common classes of drugs that can led

to SJS are antiepileptic drugs, sulfa drugs, antirheumatic drugs, Nonsteroidal Antiinflammatory Drugs (NSAIDs) and antimicrobial drugs.[8] Clinical manifestations of Stevens-Johnson Syndrome include headache, cough, malaise, and rhinorrhea along with mucous membrane and skin lesions usually characterized by acute blisters and erosions.[9] The mechanism behind the onset of symptoms is delayed-type four hypersensitivity response to certain drugs which is usually mediated by CD8, CD4, and T lymphocytes which releases cytotoxic mediators that result in the apoptosis of keratinocytes.[10,11] There is no specific criteria for diagnosis of SJS but the history of drug exposure and skin biopsy can confirm the diagnosis.[12,13] Discontinuation of suspected or causative agents along with proper intake of balanced diet, and electrolytes is a supportive treatment and in order to prevent the prognosis of symptoms patient should be treated in isolated conditions.[14,15] Surgical approach can be adopted to remove the infected skin layer and protect the affected wound through proper dressing. Different type of pharmacological therapies like immunomodulatory agents, glucocorticosteroids, and cyclosporines have been proven effective in SJS.[16]

This article mainly contains six case reports which shed light on different drugs that can lead to Steven Johnson Syndrome in the general population.

Case Report 1

Salwa Mehrin *et al*., studied a case in which a 27 years old female patient came with complaints of vesicular rupture which was first seen in the eye and then proceeded to the oral cavity, throat along with an external genital area for a period of four days. In addition, the patient was febrile with past history of burning micturition. On examination, her vitals were stable but she was dull and further examination indicated lesions on her lips which were itchy and painful along with erosions, erythema with crusting, hyperpigmentation on lips with oral mucosa congestion and diffuse fissures. Other examinations showed both eyes bilaterals were watering with collection of whitish material in medial canthus. Dorsum of foot, palms, and hands had erythematous papules.

Later, the patient informed us that she had consumed a nimesulide tablet because of headache six days back from her admission. The hematology reports suggested low hemoglobin levels, other values were normal and the major diagnosis was concluded as Nimesulide induced Stevens-Johnson Syndrome. Patient was administered with two daily dose of intravenous dexamethasone for a period of three days, which reduced to once daily with addition of cephalosporin as a prophylaxis. Mouthwash and cream were advised for oral lesions along

with other supportive medications. Patient was prescribed with ten miligram omnacortil to be consumed thrice daily for three days, then twice daily for three days and at the end once daily for three days along with supportive care upon discharge. During follow up treatment the patient was symptomatically stable and was recovering fast.[17]

Case Report 2

Abhigan Babu Shrestha *et al.,* described a case of 40 years old man who was presented with complaints of fever, painful swallowing (odynophagia), itchy cutaneous lesion with burning. The same patient had history of previous admission sever days back because of road accident for which he was given the required therapy. Upon discharge patient was prescribed with cefixime (200 mg) twice daily along with paracetamol and tramadol (325 mg + 37.5 mg) once daily only if required for a period of ten days. Upon examination, patient informed that he was consuming only antibiotic from past six days and he started developing cutaneous lesio after that.

Patient history revelaed that there was no such case before along with no autoimmune disease, no known hypersensitivity. Further examination showed multiple hyperpigmented lesions all over the face along with reddish-purple target macules. Erythematous rash and blisters were also present with ulcerative lesion in oral cavity with hemorrhagic eorsion of lips and nose. At the time of admission the prognosis assessing SCORTEN score was two and vitals were in normal range, hematological investigation reported low hemoglobin levels. The diagnosis was made as Cefixime induced Stevens-Johnson Syndrome. Patient was treated with prednisolone (20mg) for period of 12 days in tapering doses along with fexofenadine (120 mg) once daily and chlorpheniramine (4 mg) for period of ten days. In addition, omeprazole (20 mg) twice daily for twelve days with paracetamol (500 mg) thrice daily along with supportive therapy of nasal drops and gargles was also advised. Patient was discharged after twelve days of hospital course in stable condition and was advised to take proper precaution before taking antibiotics in future.[18]

Case Report 3

Manasa Bollampally *et al.,* analyzed a case of two years old male who came to the hospital with complaints of lips discoloration with swelling, and lesions of skin over the past four days. There was sudden black discoloration of the face that spread over whole body. There was previous history of fever from past two weeks for which required therapy was given at the local hospital, which included syrup paracetamol that was substituted by suspension

flexon (Ibuprofen 100mg + paracetamol 125 mg) since patient was not responding and fever was not subsiding. Systemin examination were normal and hematological findings indicated low levels of hemoglobin and there was evidence of maculopapular rash along with crusting over lips. All the features indicated towards Stevens-Johnson Syndrome secondary to Ibuprofen therapy. The patient was given fluid therapy along with listerine mouth wash for gargling and oral corticosteroid Prednisolone on day one. Fusidic cream and lotion along with liquid paraffin were given for local application on second day and it continued for a period of six days. Patient was discharged with the advice of continuous application of fusidic cream and liquid paraffin along with gargling.[19]

Case Report 4

Rajan Rajput *et al.*, represented a case of 14 years old male who was admitted with complaints of mouth ulceration which lead to difficulty in opening of mouth and eating from past five days. The history revealed that prior to ulcers there was burning sensation in oral cavity along with chest, arms and other body parts as well. There was evidence of watery discharge and eye redness. Patient past medical history revealed fever and pain from past two weeks for which he was prescribed with tablet crocin for seven days. Upn therapy patient started feeling burning sensation and onset of ulcer formation in mouth. The examination revealed mixed white and red lesions on buccal mucosa. There was swelling in both upper and lower lips along with bleeding, laboratory examination showed elvated number of leukocytes along with very high values of C-reactive proteins. Based on all the examinations, the patient was diagnosed with Paracetamol induced Stevens-Johnsons Syndrome. Therapy was initiated with Tablet Prednisolone (30mg) twice daily for period of seven days which was reduced to (20mg) twice daily for more seven days and similarly reduced to (10mg and 5mg) for two consecutive weeks. Along with oral medication, topical application was also given which included Gentian violet thrice daily along with Kenacort. Upon review, patient was seen healing significantly and was stable.[20]

Case Report 5

Manik Chhabra *et al.*, showed a case of 50 years old female patient who came with the complaints of lesions were spread to whole body including chest, back, abdomen and limbs which were red in colour from last six days which was progressing at slow ratealong with development of mouth ulcers from last five days. History revealed that patient took self medication of allopurinol for joint pain and after two days of administration she started

developing lesions and rashes. She also had red eyes with photophobia and discharge from both eyes. There was history of burning micturation and epistaxis as well and patient was on irregular medication for hypothyroidism from past three months. Upon examination, the patient was semiconscious with the normal systemic examination. Hematological examination revealed low levels of hemoglobin. The patient developed high-grade fever and was managed with paracetamol.

The confirmatory diagnosis of Stevens-Johnson Syndrome was made after carrying out the causality of adverse drug reaction and allopurinol which came probable. Therapy adviced for management included Injection of Pheniramine (22.75mg) given twice a day, Injection of Hydrocortisone (100mg) given thrice daily, and Injection of Ranitidine (25mg) given once daily. Other supportive medication included mouthwash and cream. Patient was discharged in improved condition after 25 days of hospital course, with advice to not consume allopurinol.[21]

DISCUSSION

SJS is an immune-mediated hypersensitivity reaction that can be life-threatening which is caused due to medications as well as infections. Associated risk factors include malignancy, Collagen disease, viruses and bacteria as well.[22] In the case reports analyzed, we had observed drugs which were responsible for inducing Stevens-Johnson Syndrome. Nimesulide induced SJS is usually caused due to unusual use of nimesulide which can lead to adverse cutaneous reactions.[23]In one of the case the patient was administered with cefixime for six days which has led to cutaneous changes. In other cases also close association between cefixime and SJS has been observed and cephalosporins is considered to be one of the common antibiotic which can lead to SJS.[18] Although, non steroidal anti-inflammatory agents are most commonly known to cause cutaneous reactions[24], but Ibuprofen induced SJS was the first ever case to be reported, but still no proper mechanism is known by which NSAIDs are related to onset of SJS.[25] Apart from this, In the case of Ibuprofen Induced SJS, the levels of lymphocytes, Tumor Necrolysis Factor and cytokines secretion were found elevated.[26] Another rare case of SJS reported was due to ingestion of paracetamol, Being one of the common medication given for pain, fever and because of its easy availability adverse reaction associated with SJS has been reported.[27] Among various etiologies, one of the evidence of SJS is associated with allopurinol.[28] In order to prevent the prognosis of disease the causitive drug was immediately terminated if it was being administered while in

other cases, though exact pharmacological therapy is not clear yet, the symptomatic therapy was initiated along with supportive care and patients were reviewed.

CONCLUSION

Out of all the assessed case, SJS was caused majorly due to administration of NSAIDs, which should be controlled by consulting physician before consuming the medication and should be taken in appropriate dose. Apart from this, it is very essential to immediately discontinue the suspected drug to prevent the prognosis of disease into severe complications. Patient awareness is also important to prevent the reccurence of disease.

ACKNOWLEDGEMENT

The authors are thankful to the staff and patients of the hospitals for being supportive and we extend our thanks to the families of patients for giving their consent to perform the study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

SJS: Stevens-Johnsons Syndrome; **EM:** Erythema Multiforme; **TEN:** Toxic Epidermal Necrolysis; **NSAIDs:** Nonsteroidal Antiinflammatory Drugs.

SUMMARY

The studied cases indicated that there is close association between SJS and drugs belonging to class NSAIDs along with some antibiotics as well. For which pharmacological therapy includes Steroids along with anti-histamines.

REFERENCES

1. E.N. Ergen, L.C. Hughey, Stevens-johnson syndrome and toxic epidermal necrolysis, JAMA Dermatol, 2017; 153: 1344, https://doi.org/10.1001/jamadermatol.2017.3957.
2. Fitzpatrick‟s dermatology in general medicine, Editors: Irwin m. Freeberg, Arthur Z. Eisen, Klans Wolff, K. Frank Austin, Lowell A. Goldsmith, Stephen I. Katz, 6th edition, Mc Graw Hill, 2003; 543-57.
3. Ghislain PD, Roujeau JC. Treatment of severe drug reactions: Stevens Johnson Syndrome, toxic epidermal necrolysis and hypersensitivity syndrome. Dermatol Online J., 2002; 8: 5.

4. Tapan Shah, Yogesh BS, Amit Raval. Ibuprofen Induced Stevens Johnson Syndrome -A Case Report. Indian J. Pharm. Pract, Apr-Jun, 2010; 3(2).
5. Rannakoe Lehloenya. Management of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Current Allergy & Clinical Immunology, August 2007; 20(3).
6. Ramineni HB, Eluri P, Vipparla K, Suryadevara V. Phenobarbital induced Stevens Johnson syndrome: A case report. Int J Res Med Sci, 2015; 3: 492-3.
7. Khawaja A, Shahab A, Hussain SA. Acetaminophen induced Steven Johnson syndrome‐toxic epidermal necrolysis overlap. J Pak Med Assoc, 2012; 62: 524-7.
8. Gomes ER, Kuyucu S. Epidemiology and risk factors in drug hypersensitivity reactions. Curr Treat Options Allergy, 2017; 4: 239-57.
9. French LE. Toxic epidermal necrolysis and Stevens Johnson syndrome: Our current understanding. Allergol Int, 2006; 55: 9-16.
10. Ardern-Jones MR, Friedmann PS (2011) Skin manifestations of drug allergy. Br J Clin Pharmacol, 71(5): 672-683.
11. Lerch M, Mainetti C, Terziroli Beretta-Piccoli B, Harr T (2018) Current Perspectives on Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Clin Rev Allergy Immunol, 54(1): 147-176.
12. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, et al. (2010) alden, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther, 88(1): 60-68.
13. Rzany B, Hering O, Mockenhaupt M, Goerttler E, Ring J, et al. (1996) Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol, 135(1): 6-11.
14. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC, et al. (2000) Toxic epidermal necrolysis and Stevens- Johnson syndrome: does early with-drawal of causative drugs decrease the risk of death? Arch Dermatol, 136(3): 323-327.
15. Stern RS, Divito SJ (2017) Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Associations, Outcomes, and Pathobiology-Thirty Years of Progress but Still Much to Be Done. Journal of Investigative Dermatology, 137(5): 1004-1008.
16. Zimmermann S, Sekula P, Venhoff M, Motschall E, Knaus J, et al. (2017) Systemic Immunomodulating Therapies for Stevens-Johnson Syndrome and Toxic Epidermal

Necrolysis: A Systematic Review and Meta-analysis. Jama Dermatology, 153(6): 514-522.

17. Mehrin S, Parveen U, Sultana S, Rafi R. nimesulide induced stevens-johnson syndrome-an adverse drug reaction.
18. Shrestha AB, Shrestha S, Yadav PK, Adhikari L, Yadav A. Cefixime induced Steven Johnson syndrome: A case report from Bangladesh. Annals of Medicine and Surgery, 2022 Jul 1; 79: 104089.
19. Bollampally M, Praneeth G, Prithi A. Ibuprofen induced stevens-johnson syndrome.
20. Rajput R, Sagari S, Durgavanshi A, Kanwar A. Paracetamol induced Steven-Johnson syndrome: A rare case report. Contemporary clinical dentistry, 2015 Sep; 6(Suppl 1): S278.
21. Chhabra M, Gaur A. Allopurinol-induced Stevens–Johnson Syndrome and toxic epidermal necrolysis: A case report. Asian Journal of Pharmaceutical and Clinical Research, 2019 Feb 7; 5-7.
22. S.-C. Yang, S. Hu, S.-Z. Zhang, J.-W. Huang, J. Zhang, C. Ji, B. Cheng, The epidemiology of Stevens-Johnson syndrome and toxic epidermal necrolysis in China, J. Immunol. Res, 2018; 4320195, https://doi.org/10.1155/2018/4320195.
23. Rainsford, K. D. Relationship of Nimesulide safety to its pharmacokinetics: Assessment of adverse reactions. Rheumatology, 1999; 38(1): 4-10.
24. Patel TK, Barvaliya MJ, Sharma D, Tripathi C. A systematic review of the drug‐induced Stevens‐Johnson syndrome and toxic epidermal necrolysis in Indian population. Indian J Dermatol Venereol Leprol, 2013; 79: 389‐98.
25. Stevens Johnson Syndrome & Toxic Epidermal Necrolysis [http://dermnetnz.org/ reactions/sjs- ten.html.]
26. Neuman M, Nicar M. Apoptosis in ibuprofen induced Stevens-Johnson syndrome. Transl Res, 2007 May; 149(5): 254-9.
27. Kvedariene V, Bencherioua AM, Messaad D, Godard P, Bousquet J, Demoly P. The accuracy of the diagnosis of suspected paracetamol (acetaminophen) hypersensitivity: Results of a single‐blinded trial. Clin Exp Allergy, 2002; 32: 1366‐9.
28. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A, 2005; 102: 4134-9.