

Phenytoin induced Stevens-Johnson syndrome exacerbated by cefepime

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ABSTRACT

Steven Johnson syndrome (SJS) is a rare drug induced mucocutaneous reaction. Here, we present an elaborate report of a 28-year-old female patient who developed Phenytoin induced SJS, which was exacerbated by cefepime.

Key words: Cefepime, phenytoin, Steven Johnson syndrome

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous cell-mediated hypersensitivity reactions that are generally rare, but potentially life-threatening and commonly drug induced.^[1,2] Both SJS and TEN are characterized by fever, malaise, facial puffiness, mucous membrane eruptions, skin lesions, vomiting, and skin eruptions.^[3,4] The incidence of SJS and TEN is 0.4-1.2/million and 1.2-6/million person-years respectively.^[4,5]

Phenytoin is the most commonly prescribed antiepileptic drug in adults. In a case-control study of 73 patients taking anti-epileptic drugs 14 patients were reported with the SJS associated with the phenytoin ingestion.^[1] In another retrospective study conducted for 10 years among 127 patients

in a hospital, 8 patients consumed anti-epileptic drugs and the incidence of phenytoin induced SJS was found to be 13.04% (six patients).^[6] Here, we report a case of a 28-year-old female patient who developed phenytoin induced SJS, which was exacerbated by the administration of cefepime.

CASE REPORT

A 28-year-old female patient with a medical history of left sided pleural effusion was started on anti-tubercular treatment (ATT) [Tablet (tab.) isoniazid, rifampicin, pyrazinamide and ethambutol] at a local hospital for 1 month. Although the patient was non-complaint to therapy, she developed ATT induced hepatitis with aspartate aminotransferase-136 IU/L, and alanine transaminase - 331 IU/L. Following this, ATT was promptly withdrawn. Patient had one episode of generalized tonic clonic seizures (GTCS) 1½ months after the stoppage of ATT medication. She was given a loading dose of phenytoin and was brought to a tertiary care hospital in southern India for further management.

On day 1, during the presentation in emergency room, patient developed an episode of seizures and was treated with Tab. phenytoin 300 mg at night. On day 2, patient developed

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one more episode of GTCS, Tab. Phenytoin 300 mg was continued and pleural effusion was managed with inj. amikacin 500 mg and ethambutol 800 mg. On day 3, patient had a mild fever (39.5°C), itching, and erythematous rash all over her body. Her fever was managed with tab. paracetamol 50 mg, in addition to tab. hydroxyzine 25 mg, calamine lotion and tab. embramine 25 mg for the management of erythematous rashes. Tab. phenytoin was stopped due to rash and tab. levetiracetam 500 mg bid was started.

On day 4, patient developed oral ulcers and generalized skin rash that was suspected to be SJS. Tab. paracetamol was stopped and inj. pheniramine maleate 25 mg, inj. hydrocortisone 100 mg were started and oral ulcer was managed with the candid mouth paint and choline salicylate. On day 6, patient's condition remained unchanged. Inj. hydrocortisone 100 mg was replaced with tab. methylprednisolone 6 mg and tab. levetiracetam and tab. embramine 5 mg were also discontinued.

From day 7 to day 19, there were no fresh complaints and rash was improving. Same medications were continued. On day 16 Inj. cefepime 1 g infusion was started for managing urinary tract infection (UTI) caused by multi drug resistance (MDR) *Klebsiella/Escherichia coli*. On day 20, patient presented with extensive skin peeling all over her body followed by pigmentation and scaling of skin managed with same medicines and was transferred to intensive care unit. Inj. tigecycline 50 mg bid was given for managing MDR *Acinetobacter* and tab. prednisolone was replaced with inj. methylprednisolone 40 mg.

On day 21, inj. cefepime 1 g infusion was stopped. Skin lesions worsened, considering her condition physician planned for tapering of steroids. Possibility of involvement of collagen vascular disease was high hence advised for skin biopsy and antinuclear antibody. On day 22, the patient's condition was unimproved and managed with saline compressor, silver sulphadiazine cream and paraffin gauze dressing. On days 23 and 24, skin lesions persisted and the patient complained of burning sensation over the lesions, chills and rigors, and redness of skin-reduced.

On day 25, inj. methylprednisolone 40 mg was changed to 40 mg tablet. Skin lesions and peeling along with desquamation of the skin was present, redness was decreased and lesions on the trunk were dried. On day 28, inj. tigecycline was stopped and inj. polymyxinE 1 million units was started for the treatment of MDR *Acinetobacter* and MDR *Klebsiella*. Patient had one episode of fever, skin lesions and peeling were present, redness and new skin eruptions were observed. On day 29, tab. methylprednisolone dose was decreased from 40 mg to 32 mg. Skin lesions showed signs of healing, and no new skin eruptions were observed.

On day 30, skin biopsy revealed interface dermatitis with pityriasis versicolor. On day 31, tab. methylprednisolone dose was decreased to 24 mg and to 20 mg on day 34. Patient complained of itching over the face. Facial edema, generalized hyperpigmentation and desquamation were observed. On day 35, Inj. amikacin and tab. ethambutol were stopped, as there was no conclusive evidence of tuberculosis. On day 40, skin peeling was reduced and methylprednisolone dose was decreased to 12 mg. On day 43, polymyxinE was stopped and all other medications were continued. On days 44 and 45, lesions were healed and the dose of methylprednisolone was decreased to 8 mg and to 4 mg on 46th day.

On day 48, patient had recurrent UTI and urine culture showed *Pseudomonas* which was sensitive to cefepime. On day 49, patient was given a test dose of cefepime and was observed for any signs of SJS. When no adverse reactions were observed, a full dose of cefepime 1 g was administered. 2 h later, she developed burning sensation on both upper limb and epigastrium. Patient complained of fever, vomiting (5-6 episodes), generalized weakness, chills and rigors. She was therefore administered inj. pheniramine 1 amp i.v. On day 50, inj. cefepime was stopped. Patient had burning sensation and fever. On day 51, no fresh complaints were observed and patient was better. Hence, she was planned for discharge.

DISCUSSION

Patient was admitted to emergency ward for the management of GTCS and developed itchy erythematous rashes 2 days after consumption of phenytoin 300 mg. It is a delayed type of hypersensitivity reaction. Patient had an initial exposure to i.v phenytoin at a local hospital 1 week prior to admission to our hospital. A case-control study reported that the short term use of phenytoin increases the risk of SJS and TEN for a period of less than 8 weeks. In such case, the offending drug should be withdrawn.^[1] The time between the 1st administration and development of SJS/TEN is 1-4 weeks in majority of the cases.^[6] In a clinical report, it was shown that onset of exposure to occurrence of SJS was after 10 days of Phenytoin consumption in a patient.^[6] In our patient, it was developed on the 3rd [7] day of administration of Phenytoin and it was present for 1 week and was withdrawn on the same day of development of rash. Until day 19, there were no fresh complaints, but skin rash was present. On day 20, patient presented with extensive skin peeling all over the body followed by pigmentation and scaling of skin following the 5th day of administration of cefepime. Hence, the progression of SJS may be due to cefepime as β lactam carbonyl group of cephalosporins readily undergo nucleophilic attack by water to form inactive cephalosporic acid. It has been speculated that one of the causes of cephalosporin allergy may be due to formation of antigenic cephalosporyl proteins *in vivo* by the reaction of

nucleophilic groups with the lysine ϵ amino groups of proteins to form cephalosporyl proteins, which are major antigenic determinants.^[8] Rechallenge of cefepime was carried out on day 49, following which she developed burning sensation on both upper limb and epigastrium, fever, vomiting 5-6 episodes, generalized weakness, chills, and rigors. According to World Health Organization-Uppasala Monitoring Centre causality assessment scale phenytoin induced SJS is probable and progression of SJS due to the cefepime is certain.

The study by Sanmarkan *et al.* showed that SJS is more common in males.^[6] Whereas, our patient is female. Other studies reported patients are in mean age group of 10-40 years.^[6,9,10] In our case, she is a 28-year-old patient. Patient also developed UTI-MDR *Klebsiella/E. coli* and was on Inj. cefepime for 6 days since microorganism was resistant to the drug it was discontinued. Inj. tigecycline was changed to inj. polymixinE as it had a better spectrum of action for MDR *Acinetobacter*.

Patient was administered methylprednisolone for the treatment of SJS. Gradually, rashes started decreasing and she was shifted to female general ward. On day 20, she developed skin peeling and recurrence of lesions in the evening followed by pigmentation and scaling of skin and was shifted to intensive care unit. All medications were discontinued, but lesions worsened hence tapering of steroids was planned, which was found to be beneficial in this patient. Our experience was similar to that reported by Michaels b and Cheriyan *et al.*^[11,12] The skin biopsy showed interface dermatitis and pityriasis versicolor. A study conducted by Whitney and Milton. Stated that glucocorticoids are more effective in cases in which the biopsy shows inflammatory changes (more lymphocytes), compared to those cases in which the biopsy is paucicellular.^[13] She was given i.v methylprednisolone 40 mg q 8 h for 5 days. The next 2 days, she was administered tab. methylprednisolone 40 mg and tapered to 32 mg over the next 5 days, 24 mg for 3 days, 20 mg for 4 days, 16 mg for 2 days, 12 mg for 4 days, 8 mg for 2 days and 4 mg for 6 days. Patient's condition was normalized, no lesions were observed. Hence, the patient was planned for discharge.

CONCLUSION

Here, we report a rare case of phenytoin induced SJS that was exacerbated by the cefepime administration. We could not find any cases in the literature review of such unique reactions. The possible cause of aggravation of SJS may be due to the reaction of nucleophilic groups with lysine ϵ amino groups of proteins to

form cephalosporyl proteins. However, the mechanism of this drug reaction is currently unknown. It is therefore advised that cefepime should be administered with the caution in patients with history of drug induced SJS.

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