Journal of Pharmaceutical Care
jpc.tums.ac.ir

Stevens Johnson Syndrome Associated with Fluoroquinolones: A Case Series

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Received: 2022-09-13, Revised: 2022-10-02, Accepted: 2022-10-11, Published: 2022-12-31

ARTICLE INFO

Article type:
Case report

Keywords:
Steven Johnson Syndrome;
Norfloxacin;
Ciproflocaxin;
Fluroquinolones;
Adverse Drug Reaction

ABSTRACT

Stevens Johnson Syndrome is a rare autoimmune disorder which includes skin and mucous membrane. In India, the incidence of Stevens Johnson Syndrome (SJS) is 1.2 to 6 million patients per year. SJS is a very serious and life-threatening hypersensitivity reaction that can occurs due to infections (mycoplasma pneumonia) or as side effects of drugs (Sulfa Drugs, Phenytoin, Carbamazepine, Lamotrigine, Phenobarbital, Allopurinol, Piroxicam, Nevirapine and Diclofenac). Antibiotics can cause SJS and their contribution is around 40%. Fluoroquinolones are prescribed globally (11%) to treat lower respiratory tract infections, gastrointestinal and genitourinary infections. Norfloxacin and Ciprofloxacin are rarely associated with drug induced SJS. Most of the informative data, available on drugs induced SJS are based on case reports or case series. Here, we present three case reports of Fluoroquinolones induced SJS. In the following cases, patients had developed symptoms of SJS within two days. Whereas in Antibiotic induced SJS, it is reported that symptoms of SJS can appear within few days or even after a single dose of taking antibiotics. Therefore, we alleged that Fluoroquinolone could be the possible causative agent in our cases. The causality assessment had done based on the WHO-UMC causality scale and it was probable in all three cases of Fluoroquinolone induced SJS. This assessment generates a strong evidence that Fluoroquinolone induced SJS in all three cases. These patients were treated symptomatically with corticosteroids, parenteral solution and other non-pharmacologic agents and discharged after complete recovery.

J Pharm Care 2022; 10(4): 237-240

► **Please cite this paper as:**
Hotha PP, Naidu D, Zachariah NE. Stevens Johnson Syndrome Associated with Fluoroquinolones: A Case Series. J Pharm Care 2022; 10(4): 237-240.

Introduction

Stevens Johnson Syndrome (SJS) is a rare autoimmune disorder which includes skin and mucous membrane. In India, the incidence of SJS is 1.2 to 6 million patients per year (1). SJS is a very serious and life-threatening hypersensitivity reaction that can happen as a result of infections like mycoplasma pneumonia or as side effects of group of drugs like antibacterial drugs, anti-epileptic drugs and non-steroidal anti-inflammatory drugs etc. (2). Treatment of SJS mainly focuses on eliminating the suspicious cause which is responsible to cause SJS, caring for wounds, controlling pain and minimizing complications. Among antibiotics, sulphonamide group of drugs are most commonly associated with SJS (3). Fluoroquinolones (FQs) are recommended globally to treat lower respiratory tract infections, gastrointestinal and genitourinary infections (4). Norfloxacin and Ciprofloxacin are rarely associated with drug induced SJS (5,6). Here, we present three case reports of FQs induced SJS.

Case 1

A 69-year-old female patient came to OPD with complained of burning sensation when urinating and passing frequent small amounts of urine. She was diagnosed with urinary tract infection. She was prescribed Tablet Norfloxacin 400mg once a day. On second day at home, she had developed erosion in corner of lip, fever and fluid bullous in the left chest below breast and she was admitted in the hospital. At the time of admission, she was conscious, apprehensive,

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co-operative and well oriented to time, place and person at the time of hospital admission. Her temperature was 99 °F, pulse was 110/minute, respiratory rate was 22/ minute, blood pressure was 130/90 mmHg and her random blood sugar level was 215 mg/dl. Her medical history revealed that she had type 2 diabetes mellitus and hypertension since 5 years. Other systemic, cardiovascular, abdominal, respiratory and nervous system investigations were normal. After her clinical examination, clinicians were diagnosed it as a case of Norfloxacin induced Stevens Johnson syndrome and Tab Norfloxacin was immediately withdrawn. She was treated with intravenous fluids, Inj. Dexamethasone 8mg once daily IV for 7 days and for rest of the therapy, patient switched over to oral prednisolone 1 mg/day, Tab. Azithromycin 500mg once daily, Fusidic acid cream and Mupirocin ointment for local application. She completely recovered and was discharged after 25 days of treatment. This Case report of SJS associated with Norfloxacin was stated to PvPI with worldwide unique ID number IN IPC 300453314.

Case 2

A 54-year-old male patient was presented to hospital with redness and fluid filled blisters over both palms and feet after taking Tab. Norflox-TZ 1 g twice a day (Norfloxacin 400mg and Tinidazole 600 mg) as self-medication for groin infection. The time between drug administration and onset of reaction was 12 hours. The patient continued to take the drug even after he noticed fluid filled erythematous lesions. Within two days, he gradually developed oral and genital lesion. He took 3 doses of Tab. Norflox-TZ before being brought to the hospital. On admission, his physical examination revealed crusting over lips, multiple erosions over genitals, bullae and vesicles with clear fluid in the palms and soles. The final diagnosis concluded by clinician was Stevens Johnson Syndrome associated with Norflox-TZ. After diagnosis of SJS, Tab. Norflox-TZ was stopped. The patient had no significant past medical history of such episode. He was an occasional alcoholic. On admission his blood pressure was 130/65 mmHg, pulse rate was 86 beats/ min. and blood sugar was 112 mg/dL. Lab investigations showed serum creatinine-

1.3 mg/dL, sodium- 131 meq/L, and SGOT- 60 U/L. Other systemic examinations were normal. During his hospitalization, the patient responded well with the treatment and recovered after being treated with Tab Azithromycin 500mg once daily for groin infection, Inj. Dexamethasone 8mg once daily IV for 7 days, Tab. Pantoprazole 40mg once daily, Inj Pheniramine 2 ml 4 hourly, Saline compresses followed by the topical application of Fusidic acid cream for the multiple erosions over genitals and lip, aspirate fluid from bullae and given saline sitz bath. The patient recovered was discharged after 1 week. This Norfloxacin induced SJS case report was informed to PvPI with worldwide unique ID number IN IPC 300484047.

Case 3

A 29-year-old male patient was referred to the Hospital with complaints of generalized itching and blister formation all over the body since past 2 days following intravenous administration of Inj. Cifran-TZ (Ciprofloxacin 500mg and Tinidazole 600mg) and Inj. Flagyl (Metronidazole 500mg in 100 ml). He received these two injections for loose stools and fever in the nearby Primary Health Centre. Within an onset time of 1 hour, the patient complained of itching over hands, feet and lips followed by multiple blister formation. He observed hypopigmentation and peeling over hand and legs in the following days. On admission, the local examination of trunk and inner aspects of the thighs showed confluent erythematous macules. Oral and genital mucosal eruptions were also present. The patient was diagnosed as Cifran-TZ induced Stevens Johnson Syndrome and Inj. Cifran-TZ was stopped. The patient had no significant past medical history. During admission, his blood pressure was 136/110 mmHg, pulse rate was 118 beats/min. and his oxygen saturation was 98%. His lab investigations were as follows International Normalised Ratio (INR)- 1.6 INR, Random Blood Sugar (RBS)- 55 mg/dL, urea- 104 mg/dL, creatinine- 1.9 mg/dL, sodium- 128 meq/L, potassium- 3.6 meq/L, bilirubin total- 1.0 mg/dL, SGOT- 84 U/L, SGPT- 38 U/L and alkaline phosphatase- 118 U/L. Other systemic examinations were within normal limits. During his hospital stay, no new lesions were developed and the patient responded to the treatment with Inj. Hydrocortisone 100mg IV for 7 days and then switched to oral prednisolone 1 mg/ day, Inj. Cefotaxime 1g IV twice daily, Inj Pheniramine 2 ml 4 hourly, Saline compresses over lip, topical application of Fusidic acid cream for mucosal eruptions, saline mouth gargle with candid mouth paint thrice daily for oral eruption and saline sitz bath. The patient recovered satisfactorily and was discharged after 2 weeks. This case report was reported to PvPI with world unique ID number IN IPC 300451716.

Discussion

Adverse Drug Reactions (ADRs) are one of the leading causes of morbidity and mortality. In India, around 2.9 - 5.6% hospital admissions occur due to ADRs (7). SJS is a rare and severe cutaneous ADR which requires hospitalization. According to the involvement of body surface area (BSA), the disease can be classified into SJS (<10% BSA), Toxic Epidermal Necrolysis (TEN) (>30% BSA) and SJS–TEN overlap (10%–30% BSA) (8). Previously, FQs induced TEN were reported (4). Most common drugs at high risk of triggering SJS are Sulfa Drugs, Phenytoin, Carbamazepine, Lamotrigine, Phenobarbital, Allopurinol, Piroxicam, Nevirapine and Diclofenac (9). Antibiotics contribute around 40% of drug induced SJS (10). Among Antibiotics, Sulphonamides and Penicillins are the commonest antibiotics causing drug induced SJS (11, 12). Among FQs,

Norfloxacin (0.01% to 0.1%) (5) and Ciprofloxacin (less than 0.01%) (6), very rarely cause drug induced SJS.

HLA-B gene variations cause the immune system to react abnormally to the suspected drugs known to cause SJS. Due to the failure to clear reactive metabolites, the drug causes cytotoxic T cells and natural killer cells to release granulysin that abolishes cells in the skin and mucous membranes. The death of these cells causes the blistering and peeling of skin, which is a characteristic feature of SJS. CD8+ T cells have been identified as important mediators of blister formation, and granulysin concentration in blister fluid correlates with the severity of SJS (13).

Early symptoms of SJS include fever and flu-like symptoms (14). Within 1 to 3 weeks after starting the suspected drug, the patient develops malaise, headache, cough, and kerato-conjunctivitis. Macules usually found on the face, neck, and upper trunk, are associated with large flaccid bullae and slough over a period of 1 to 3 days (15). In drug induced SJS cases, early skin symptoms appear 2–3 weeks after taking the suspicious drug, but antibiotics can act more rapidly i.e. within few days or even after a single dose (16, 17). In our case series, first, and third patients had developed symptoms of SJS on second day whereas the second patient developed symptoms within 12 hrs. Therefore, we suggest FQs was the causative agent for SJS in our cases. Along with FQs, Tinidazole was a concomitant drug in second and third cases. Tinidazole belongs to nitroimidazole group of drugs. Till now, a well-established case of SJS to Tinidazole have not been reported. In second and third cases, it may be possible that Tinidazole may aggravate SJS when given with FQs (4). Similar reports on Norfloxacin (18,19) and Ciprofloxacin (22) induced SJS were published by other authors.

Indian guideline for the management of SJS recommended immediate withdrawal of all suspected drug. If patients of SJS has been identified at a primary or secondary health-care, the treatment should be initialized then referred the patient to a tertiary care center and treatment should be carried out in an intensive care setting or in an isolated room with maintenance of sterile field. There should be consult dermatologist, physician, pediatrician, ophthalmologist, respiratory physician, intensivist, dietician and any other specialist if required. IV or IM corticosteroids therapy such as Prednisolone 1–2 mg/kg/day, dexamethasone 8–16 mg/day and pulse form employing slow intravenous infusion of methylprednisolone 500–1000 mg/day or dexamethasone 100 mg for 3 days should be given within 72 hrs. with total duration of 7–10 days. Assessment of appearing of new lesions, peri-lesional erythema and skin tenderness should be done daily. If steroid are contraindicated in patient i.e. in tuberculosis and severe hyperglycemia, Cyclosporine 3–5 mg/kg/day for 10–14 days should be used. Intravenous immunoglobulin 0.2–0.5 mg/kg in the first 24–48 hrs. may be given in the HIV patients, children and in the first trimester pregnant women. Strict avoidance of suspected drug is absolutely necessary. A drug card should be issued to patient of SJS (20,21). In our cases, the suspected drugs were immediately withdrawn after the diagnosis of FQs induced SJS and the patients were treated as per guideline with non-pharmacological care. As a result of adequate treatment, mortality risk was reduced. It is noted that mortality risk may be reduce by 30% for each day before development of blisters or erosion (1). In SJS, skin regrows over two to three weeks and complete recovery can take months (22). In our cases, all the three patients completely recovered within 3 weeks. The causality assessment done based on the WHO-UMC causality scale determined the causality to be probable/likely for all three cases of FQs induced SJS.

Conclusion

The incidence of SJS associated with Norfloxacin and Ciprofloxacin is very rare. The use of these drugs, which have the potential to cause SJS, needs vigilant monitoring. Health care professionals should prescribe Norfloxacin and Ciprofloxacin with caution and be alert for such rare ADRs.

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