Original Research Article

Analysis of causation of Stevens Johnson Syndrome in a patient of rheumatoid arthritis with increased dose of methotrexate

Manab Nandy[1], Sangeeta De[2*], Mustafa Asad[2], Nirmal Polle[3]

[1]Associate Professor, Department of Pharmacology, Medical College, Kolkata, West Bengal, India
[2]Post Graduate Trainee, Department of Pharmacology, Medical College Kolkata, West Bengal, India
[3]Consultant AMRI Hospital, Kolkata, West Bengal, India
[*]Corresponding author email: **drsangieta2013@gmail.com**

International Archives of Integrated Medicine, Vol. 4, Issue 12, December, 2017.

Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P)ISSN: 2394-0034 (O)

Received on: 22-10-2017 **Accepted on:**03-12-2017
Source of support: Nil **Conflict of interest:** None declared.

How to cite this article: Manab Nandy, Sangeeta De, Mustafa Asad, Nirmal Polle. Analysis of causation of Stevens Johnson Syndrome in a patient of rheumatoid arthritis with increased dose of methotrexate. IAIM, 2017; 4(12): 132-136.

Abstract

Rheumatoid arthritis (RA) is an autoimmune disease affecting about 1% of people, with the highest incidence between 40 and 70 years. Methotrexate is a folic acid antagonist that has good efficacy and safety in the treatment of RA. Methotrexate (MTX) and non-steroidal anti-inflammatory drugs are often concomitantly administered in clinical practice for the treatment of RA. In this case report 46 year old male patient, a known case of rheumatoid arthritis was admitted with history of knee joint pain and swelling. Methotrexate was initially started in a dose of 7.5 mg per week, dose was then increased to 15 mg per week. Six weeks later, the patient complained of oral ulcerations, erythematous, itchy and edematous rash on all four limbs and trunk. The patient was re-evaluated and was diagnosed with Stevens-Johnson syndrome. All the previous medications were stopped. The patient was treated with steroids, prophylactic antibiotics and antifungal drugs. The lesions started to heal after 5 days of hospitalization. Thus the treatment of Rheumatoid arthritis with methotrexate should be carefully considered due to its increased toxicity and risk of severe skin reactions.

Key words

Methotrexate, Stevens-Johnson syndrome, Increased dose.

Introduction

Methotrexate (MTX) is a potent competitive inhibitor of dihydrofolatereductase (DHFR), a key enzyme in the generation of reduced folates crucial for the biosynthesis of purines and thymidylic acid. Methotrexate has good efficacy and safety in the treatment of Rheumatoid arthritis (RA).

Stevens-Johnson syndrome (SJS) is a minor form of toxic epidermal necrolysis, with less than 10% body surface area (BSA) detachment. Stevens-Johnson syndrome is idiopathic in 25-50% of cases. Drugs and malignancies are most often implicated as the etiology in adults and elderly persons. Pediatric cases are related more often to infections [1].

SJS usually begins with fever, sore throat, and fatigue. Ulcers and other lesions begin to appear in the mucous membranes, almost always in the mouth and lips, but also in the genital and anal regions. Those in the mouth are usually extremely painful and reduce the patient's ability to eat or drink. Conjunctivitis of the eyes occurs in about 30% of children who develop SJS.A rash of round lesions about an inch across arises on the face, trunk, arms and legs, and soles of the feet, but usually not the scalp [2].

Materials and methods

46 year old male patient, a known case of rheumatoid arthritis was admitted with history of knee joint pain and swelling. Methotrexate was initially started in a dose of 7.5 mg per week, dose was then increased to 15 mg per week. The patient was also getting naproxen (500mg) concomitantly. Six weeks later, the patient complained of oral ulcerations, erythematous, itchy and edematous rash on all four limbs and trunk. The patient was re-evaluated and was diagnosed with Stevens-Johnson syndrome.

The physical examination was remarkable for cutaneous involvement of all the four limbs and trunk (**Figure - 1, 2**). Erythematous and itchy rash were seen (**Figure - 3, 4**). Oral lesions were also seen. The vital signs recorded were as follows: temperature (axillary) - 38.5ºC; pulse rate- 88/min; respiration rate - 18/min; blood pressure - 150/80 mmHg. Laboratory investigations revealed hemoglobin 8.9 g/dl, white blood cell count 8500 mm^3, platelet count 4,20,000 mm^3, serum creatinine 1.1 mg/dl, blood urea nitrogen 18 mg/dl, liver function test was normal. Blood and urine cultures were sterile. Chest X- ray and ultrasound abdomen was normal.

Figure – 1: The skin lesions in SJS.

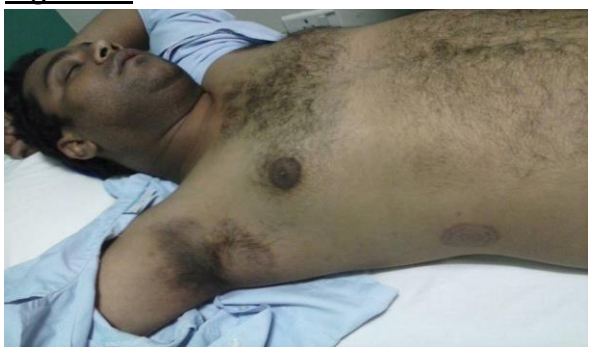


Figure – 2: The skin lesions in SJS.

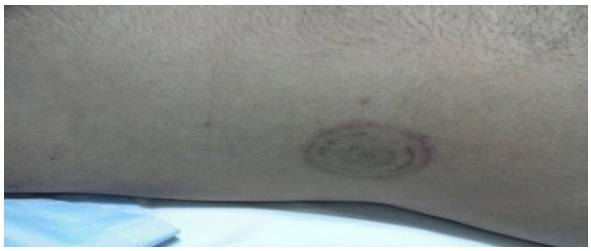
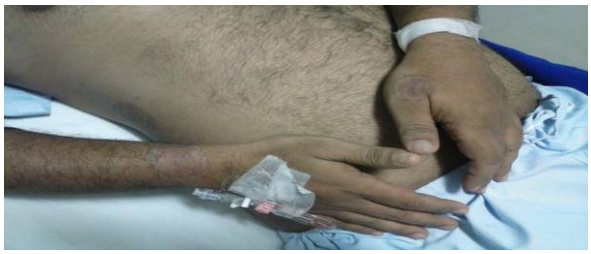
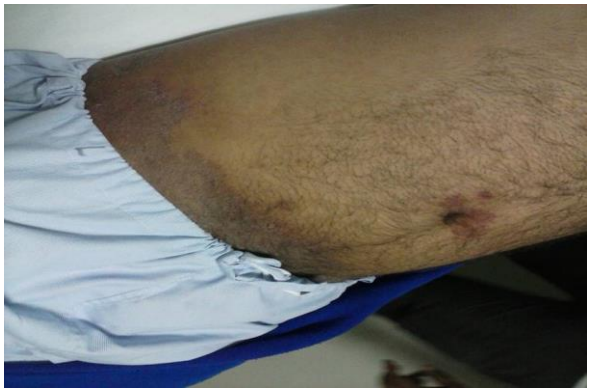


Figure – 3: The skin lesions in SJS.



After the patient's assessment, consultations by a dermatologist were availed. The diagnosis of SJS was concurred. All the previous medications taken by the patient were discontinued. Apart from methotrexate, the previous medications included hydroxychloroquine 200 mg, folic acid 1 mg, pantoprazole 40 mg, naproxen 500 mg, leflunomide 20 mg.

Figure – 4: The skin lesions in SJS.



The patient was treated with steroids, prophylactic antibiotics and antifungal drugs. Anaemia was corrected. The lesions started to heal after 5 days of hospitalization.

Results

The diagnosis and management of severe cutaneous adverse drug reactions like SJS require meticulous recording of the case history of the patient. The etiology of SJS is not clear and could be due to drug induced immunological mechanism [3]. The most frequently involved groups of therapeutic agents cited in the literature are sulphonamides, anticonvulsants, non-steroidal anti-inflammatory drugs and beta lactam antibiotics [4]. Although SJS is an immune mediated hypersensitivity reaction, it is debatable whether they are dose related or caused by drug-drug interaction, but in our case it is quite clear that it is the increased dose of methotrexate that caused the skin reaction.

Methotrexate has 100,000 times greater affinity than folic acid for the dihydrofolatereductase enzyme [5]. This mechanism of methotrexate to reduce the tetrahydrofolate and attentuate the DNA synthesis in proliferating cells, makes it an ideal disease modifying agent for rheumatoid arthritis. Methotrexate is metabolized into a series of polyglutamate derivatives that increase linearly with the concentration and duration of exposure. Therefore, higher doses of methotrexate administered for prolonged duration can result in greater toxicity [6]. MTX is reversibly bound to albumin in plasma and can be displaced by other drugs that are administered simultaneously [7]. A recent Cochrane systematic review documented 17 publications on concurrent use of MTX and NSAIDs; however, none reported systemic adverse drug reactions or other major toxicity [8]. Previously in few patients skin ulcerations, necrosis, erosions of the psoriatic plaques and bullous acral erythema, have been reported as adverse effects of methotrexate [9, 10]. In a study, by Lawrence and Dahl, seven patients were treated with low dose of methotrexate and NSAIDs for psoriatic plaque and pre-existing dermatitis. Ulcerations occurred in four patients, who received long term MTX therapy, either after increasing the MTX dosage or taking NSAIDs; the skin ulcerations healed after reducing MTX dose in these patients [10]. In our patient, MTX was initially started in a dose of 7.5 mg per week, dose was then increased to 15 mg per week. The patient was also getting naproxen (500mg) concomitantly. Six weeks later, the patient complained of oral ulcerations, erythematous, itchy and edematous rash on all four limbs and trunk. This could be possibly due to the reason that naproxen oral increases levels of methotrexate sodium by decreasing renal clearance. Concomitant administration of NSAIDs with high dose methotrexate has been reported to elevate and prolong serum methotrexate levels, resulting in deaths from severe hematologic and GI toxicity. NSAIDs may reduce tubular secretion of methotrexate and enhance MTX toxicity [11]. Methotrexate being an anti-folate molecule may arrest normal epidermal cell proliferation at high doses. Thus, SJS may be a dose dependent adverse drug reaction in susceptible individuals.

We used Naranjo Adverse Drug Reaction Probability Scale to calculate the probability of methotrexate in the causation of SJS [12]. In our case, we got a score of 5 (**Table - 1**) which clearly tells the probable causal relation between the occurrence of SJS after the higher dose of MTX administered.

Table – 1: Scoring of probability of methotrexate in causation of SJS by Naranjo Adverse Drug Reaction Probability Scale.

Questions	Yes	No	Do not 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 event reappear when the drug was re-administered?	+2	-1	0	0
5.Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	-1
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in 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	+1
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	+1
Total score				5

Discussion and Conclusion

The treatment of RA with methotrexate should be carefully considered due to its increased toxicity and risk of severe skin reactions. Higher doses of methotrexate administered for prolonged duration can result in SJS. The SJS caused by medication with MTX was clinically diagnosed, and the methotrexate was discontinued in our patient due to adverse reaction. Our case demonstrates that the SJS can occur following 15mg weekly dose of methotrexate in RA. The syndrome was not present until before increasing the dose of MTX. These arguments provide a strong support for a causal relationship between the SJS and higher dose methotrexate administration in our case. Thus the treatment of RA with methotrexate should be carefully considered due to its increased toxicity and risk of severe skin reactions.

References

1. http://emedicine.medscape.com/article/1197450-overview. (Last seen on 20/10/2017).
2. https://en.wikipedia.org/wiki/Stevens%E2%80%93Johnson_syndrome#Signs_and_symptoms.(Last seen on 20/10/2017)
3. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnsons syndrome. Orphanet J Rare Dis., 2010; 5(39): 1-11.
4. Jezierska-Krupa B, Hyla-Klekot L. Toksycznanekrolizanaskórka a zespótStevensa-Johnsona (Polish). Ped Pol., 1996; 60: 615–19.
5. Weinstein GD, Goldfaden G, Frost P. Methotrexate mechanism of action on DNA synthesis in psoriasis. Arch Dermatol., 1971; 123: 1303-07.
6. Madani TA, Zafad S, Harif M, Quessar A, et al. Methotrexate-induced toxic epidermal necrolysis: a case report.

International Journal of Medicine and Medical Science, 2009; 1(4): 99-101.

7. Maeda A, Tsuruoka S, Ushijima K, Kanai Y, Endou H, Saito K, et al. Drug interaction between celecoxib and methotrexate in organic anion transporter 3–transfected renal cells and in rats in vivo. Eur J Pharmacol., 2010; 640(1-3): 168-71.
8. Colebatch AN, Marks JL, van der Heijde DM, Edwards CJ. Safety of non-steroidal anti-inflammatory drug and/or paracetamol in people receiving methotrexate for inflammatory arthritis: A Cochrane Systematic Review. J Rheumatol Suppl., 2012; 90: 62-73.
9. Roenigk HH Jr, Auerbach R, Maibach HI, Weinstein GD. Methotrexate in psoriasis: revised guidelines. J Am AcadDermatol., 1988; 19: 145-56.
10. Lawrence CM, Dahl MG. Two patterns of skin ulceration induced by methotrexate in patients with psoriasis. J Am AcadDermatol., 1984; 11(6): 1059-65.
11. http://www.rxlist.com/drug-interactions/methotrexate-sodium-oral-and-naproxen-oral-interaction.htm.(Last seen on 20/10/2017)
12. Naranjo CA. A method for estimating the probability of adverse drug reactions. ClinPharmacolTher., 1981; 30: 239-245.