WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 6, 864-871 Case Report ISSN 2277– 7105

CO-TRIMOXAZOLE ASSOCIATED FIXED DRUG ERUPTIONS: A CASE SERIES

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Article Received on
24 Jan. 2018,
Revised on 14 Feb. 2018,
Accepted on 06 March 2018,
DOI: 10.20959/wjpr20186-11455

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ABSTRACT

Adverse drug reaction is defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, alteration of the dosage regimen, or withdrawal of the product. Trimethoprim-Sulfamethoxazole (Co-trimoxazole) is a commonly used antibiotic for treatment of a wide variety of bacterial infections. We report three cases of fixed drug eruptions due to sulfamethoxazole- trimethoprim in order to highlight the serious adverse reactions possible from this routinely prescribed, and easily available over-the-counter drug in India.

KEYWORDS: Adverse drug reaction, Trimethoprim- Sulfamethoxazole, Septran, Fixed Drug Eruptions.

INTRODUCTION

Introduced in the late 1960s, trimethoprim/ sulfamethoxazole (TMP/SMX) also known as co-trimoxazole, is an antibiotic used to treat a variety of bacterial infections. It consists of a fixed ratio of one part trimethoprim to five parts sulfamethoxazole.[1]

The concept of using this fixed dose of trimethoprim- sulfamethoxazole resulted from the recognition that bacteria are obligate folic acid synthesizers, while humans obtain folate through dietary sources.

TMP is a structural analogue of the pteridine portion of dihydrofolic acid that competitively inhibits dihydrofolate reductase, and consequently affects the production of tetrahydrofolic acid from dihydrofolic acid. This sequential blockade of two enzymes in one pathway results in an effective bactericidal action.[2]

SMX, a sulphonamide drug, is a structural analogue of para-aminobenzoic acid, and inhibits synthesis of intermediary dihydrofolic acid from its precursors.

During the past few decades, the fixed dose combinations of trimethoprim and sulfamethoxazole in the ratio 1:5 (80mg Trimethoprim and 400mg Sulfamethoxazole), has occupied a central role in the treatment of various commonly encountered infections, particularly urinary tract infections, MRSA (Methicillin- resistant Staphylococcus Aureus), skin infections, respiratory tract infections, traveller's diarrhoea and cholera, among others.[4]

Fixed drug Eruptions (FDE) are characterised by well circumscribed sharply demarcated erythematous patches or edematous plaques that appear after exposure to certain medications.[5] Lesions in FDE typically occur within a few hours, or days after exposure to the offending drug. These lesions may be localised in any part of the body, commonly seen in the sacral region and at the glans penis.

Drugs commonly associated with fixed drug eruptions include tetracyclines, acetaminophen, laxatives, sulphonamides and barbiturates. Few cases of cotrimoxazole have also been associated with Fixed Drug Eruptions.[6]

CASE REPORT

We present three cases of TMP-SMX induced FDE.

Case 1

A 14 year old male came to the dermatology OPD with chief complaints of generalised itching which was followed by high grade fever, and appearance of blisters over the genitalia that gradually progressed in size, extending to hips. On taking history, the patient revealed

that he had taken Tablet Septran (Cotrimoxazole) for a localised skin lesion two days back. The patient reported the appearance of similar lesions in the past with the same drug.

The patient was admitted and complete physical examination was done. The patient was of average built with normal nutritional status. His temperature was 98.4^0C, blood pressure 120/92 mm Hg and pulse rate 80/min. The skin lesions had become generalised with genital and oral mucosal involvement. The lesions were multiple, well defined, tender, brown to violaceous coloured plaques with rough surface and peri-lesional halo.

There was also presence of multiple flaccid bullae, which were well-defined with surrounding erosion and crusting present over hip and genitals (Fig 1). There was hyperpigmentation and swelling of lips, with inner lower lip having erosions. Less than 10% of the body surface was involved. A Tzank smear was performed, in which Tzank cells were seen along with Polymorphonuclear Neutrophils. Thus he was diagnosed as a case of Septran induced FDE.

Causality assessment was done and on Naranjo scale probability score was '9' which indicated a 'definite' relationship between TMP/SMX and occurrence of FDE in this patient. WHO Uppasala Monitoring Centre Causality Assessment Criteria also indicated a 'Certain' association with TMP/SMX as rechallenge was positive in this patient.

Treatment was started in the form of H_1 blockers (Tab. Fexofenadine 180mg), Oral steroids (Tab Omnacortil 20mg, gradually tapered to 10mg, and later withdrawn) and a topical steroid (Keracort orabase gel). His lesion gradually improved with a few sequelae on the skin. He was advised to apply Elovera Imf Cream (Aloe Extract with Vitamin E acetate and Allantoin Hyaluronic Acid) on his residual lesions after discharge from the hospital.

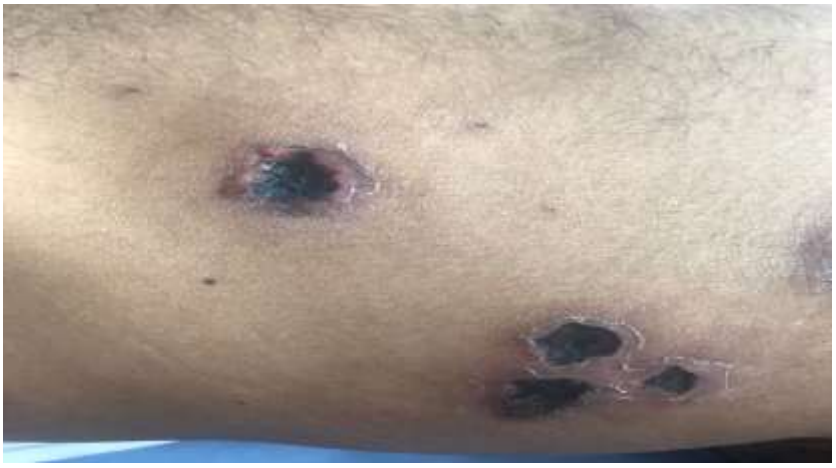

Fig 1: Cotrimoxazole induced lesions localized to upper leg, hip and genitalia.

Case 2

A 20 years old female patient came to the OPD with complaints of acute onset of lesions all over the abdomen and flexural fold of left shoulder joint which gradually increased in size from last 8 days. On taking history, the patient's attendant revealed that she had taken Tab. Septran (80mg Trimethoprim and 400mg Sulfamethoxazole) twice for sore throat 9 days back. Her vitals and general condition was stable.

On examination, she showed well-defined, resolving erythematous patches over the right supraclavicular fossa, over the abdomen, and also over the right calf and above the right lateral malleolus (fig 2). She was diagnosed as a case of Septran induced FDE.

Naranjo adverse drug reaction probability score was '5' which indicated a 'probable' relationship between TMP/SMX and occurrence of FDE in this patient. WHO Uppasala Monitoring Centre Causality Assessment Criteria also indicated a 'Probable' association with the drug.

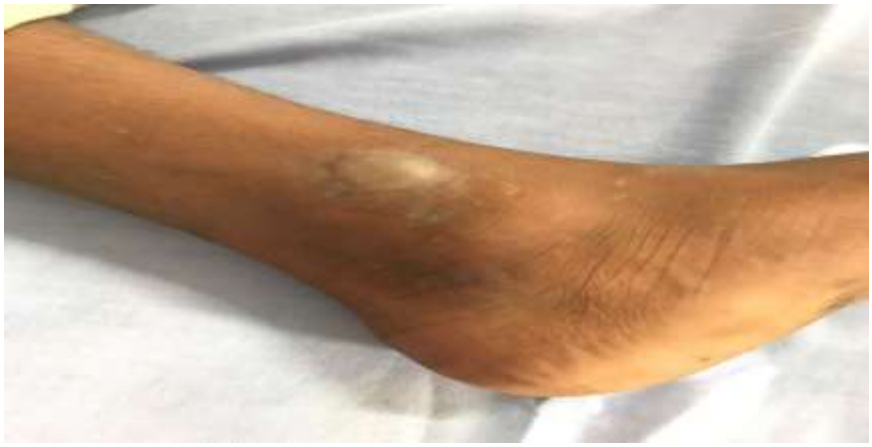

Fig 2: Well defined erythematous blisters over the patient's right lateral malleolus.

The drug was withdrawn, and she was administered topical corticosteroid (Mometasone furoate; 0.1% in 15g) twice daily along with antihistaminic (Tab Levocetrizine 5mg) twice daily.

One week later, her lesions completely subsided.

Case 3

A 58 year old male presented with sudden onset of painless, blistering lesions over the forehead and right upper eyelid with swelling over the eyelid. In the centre of one of the lesions, there was an erosion where a flaccid blister had broken.

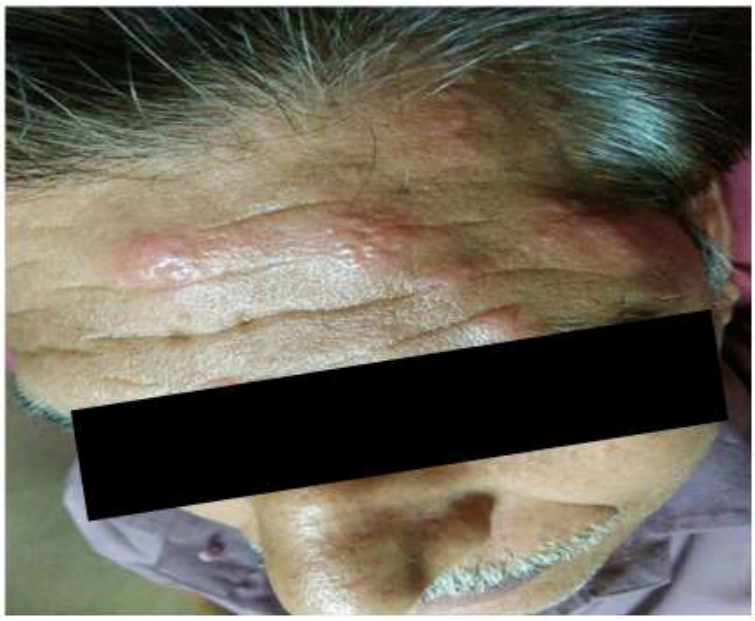

Fig 3: Blistering lesions over the forehead and right upper eyelid.

He had experienced two episodes in the past in which identical lesions had appeared in the same site. These lesions appeared after taking Tablet Septran (80mg Trimethoprim and 400mg Sulfamethoxazole) for urinary tract infection.

Histological examination of a biopsy specimen revealed a deep and superficial perivascular infiltrate of lymphocytes and eosinophils.

Patient was diagnosed as bullous FDE and was treated with intravenous corticosteroid (methylprednisolone 125mg), antihistaminics (Chlorpheniramine maleate 4mg) and a topical steroid (Clobetasol Topical 0.05%) His lesions completely resolved within a week.

On the Naranjo adverse drug reaction scale, the probability score was '7' which indicated a 'probable' relationship between TMP/SMX and occurrence of FDE in this patient. WHO Uppasala Monitoring Centre Causality Assessment Criteria also indicated a 'Probable' association with the drug.

DISCUSSION

According to the World Health Organization, an adverse drug reaction (ADR) may be defined as "A response to a drug which is noxious and unintended, and which occurs at doses normally used or tested in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[7] Reactions resulting from drug hypersensitivity account for about one-sixth of all ADRs.

Drug allergy is one type of unpredictable adverse drug reaction that encompasses a wide spectrum of immunologically mediated hypersensitivity reactions with varying mechanisms and clinical presentations. It accounts for approximately 5–10% of all the ADRs.[8]

Fixed drug eruption (FDE) is a rare adverse drug effect. Brocq in 1894 first introduced the term FDE.[9] FDE is characterized by onset of oval or round, well-defined erythematous macules located on the skin and/or mucosa associated with intense itching and burning sensation.

The exact pathogenesis of FDE is unknown, although it has been seen that antibodies, antibody-dependent cell-mediated cytotoxicity and serum factors have a role to play. Interleukin (IL)-mediated survival of memory T cells is considered the most probable mechanism for development of FDE. CD8+ cells, liberating interferon-gamma, are found in large numbers in FDE lesions and seem to play a major role in the initiation of epidermal injury.

The reason for recurrence of lesions at the same site may be explained by the persistence *in situ* of CD8+ memory T cells. The involvement of CD8+ T cells may implicate a role for cell-mediated hypersensitivity in the pathogenesis of FDE.[10,11]

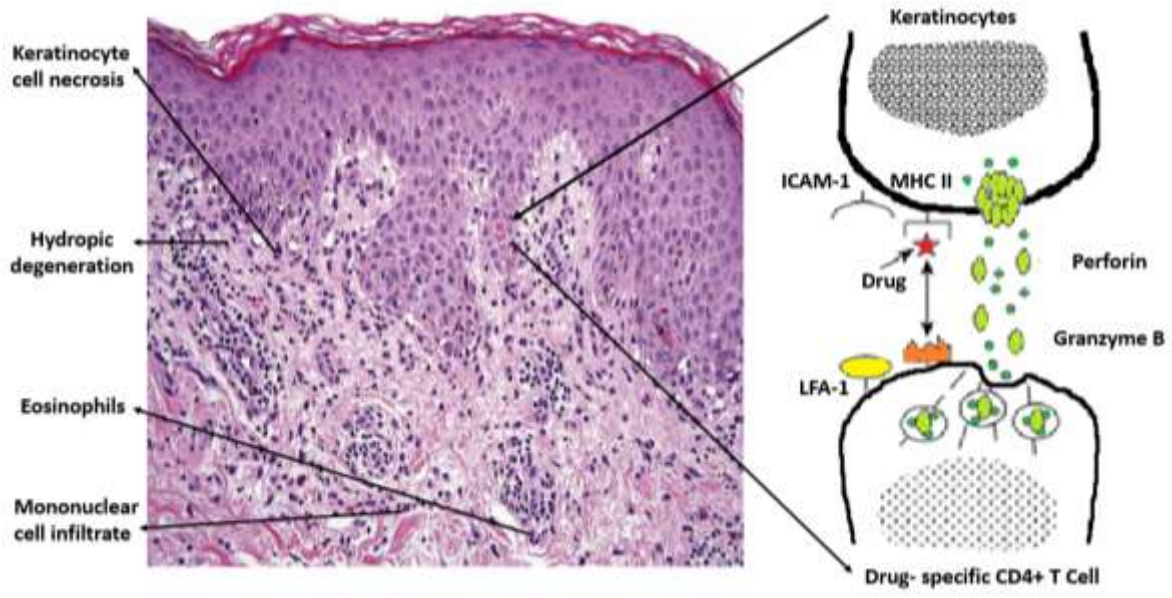

Fig 4: Mechanisms Underlying Fixed Drug Eruptions.

Left: Histologically, there is presence of hydropic degeneration of keratinocytes, necrosis of keratinocytes, and lymphocyte and eosinophil infiltrations into dermis and epidermis.

(Hematoxylin–eosin; original magnification, x 250.) **Right**: Keratinocytes are stimulated to express MHC class II and intercellular adhesion molecule-1 (ICAM-1), a ligand for leukocyte function-related antigen-1 (LFA-1). Infiltrating T cells interact with the drug through their T-cell receptor (TCR) for antigen, together with the MHC class II molecules on keratinocytes, and kill them by a mechanism dependent on perforin and granzyme B, which are B are important mediators of cell-mediated cytotoxic reactions.

Drug literature suggests the use of oral provocation tests (rechallenge) and patch tests to confirm the diagnosis of FDE.[12] However, evidence regarding the efficacy of these tests is still lacking. Tests were not performed in the present cases due to severity of the episodes.
Since its introduction more than 3 decades ago, trimethoprim-sulfamethoxazole has played a key role in the treatment of a wide variety of clinical infections. It certainly retains a special role in the prophylaxis and treatment of certain HIV-associated infections, and as first-line therapy for various infections (organisms affected include Streptococcus, Staphylococcus, Salmonalla, Vibrio, *P carinii*, *S maltophilia* and other nonfermentative gram-negative bacilli, *Isospora*, *Cyclospora*, *Nocardia*, and *T whippelii*).[3]

Co-trimoxazole was claimed to be more effective than either of its components individually in treating bacterial infections, although this was later disputed.[13] Since it has a higher incidence of adverse effects, including mental confusion, thrombocytopenia, bone marrow depression and anorexia, its use has been restricted in many countries to very specific circumstances where its improved efficacy has been demonstrated.[14] Therefore, the judicious use of trimethoprim-sulfamethoxazole may ultimately serve as a model for the future appropriate use of broad-spectrum antibiotics.

CONCLUSION

This was a case series of Co-trimoxazole induced Fixed Drug Eruptions. Inducing awareness among physicians about this side effect of co-trimoxazole is important since more such cases may be reported with extensive usage of the drug in future.

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