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Case Report

Cefixime and ornidazole combination induced fixed drug eruption: a case report

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ABSTRACT

Cefixime, a third generation cephalosporin and ornidazole, a nitroimidazole is used for a wide variety of conditions like urinary tract infections, otitis media, pharyngitis, uncomplicated gonorrhea and anaerobic infections. Fixed drug eruption (FDE) is commonly associated with anticonvulsants, antimicrobials and NSAIDs. Here we report a case of a rare cefixime and ornidazole combination induced fixed drug eruption. A 39 year old male developed hyper-pigmented patches over both forearms and left thigh after consuming fixed dose combination of cefixime and ornidazole tablet for the treatment of urinary tract infection.

Keywords: Cefixime, Ornidazole, fixed dose combination, Fixed drug eruption, Hyper-pigmented patches

INTRODUCTION

Fixed drug eruption (FDE) is a specific cutaneous drug reaction which characteristically recurs in the same location after re-exposure to the same or related medications. The skin lesions manifest as either generalized non-bullous FDE with well-defined erythematous to violaceous round plaques or as generalized bullous FDE with vesicular or bullous lesions.[1] The common sites of FDE are on the lips, trunk, hands and genitals and it usually resolves with a residual hyperpigmentation. They are responsible for about 10% of all adverse drug reactions. The common agents causing FDE are antibiotics (trimethoprim sulfamethoxazole, tetracycline, penicillin, and erythromycin) followed by nonsteroidal anti-inflammatory drugs (diclofenac sodium, aspirin, naproxen, and ibuprofen).[2] Cephalosporins and nitroimidazoles are commonly used medication for a wide variety of disease states like urinary tract infections, otitis media, pharyngitis, uncomplicated gonorrhea anaerobic protozoal infections. Cefixime, a semi synthetic broad spectrum third generation cephalosporinis active against both Gram-positive and Gram-negative aerobic bacteria. It is orally effective against urinary tract infection caused by *Escherichia coli* and *Proteus mirabilis*.[3] Ornidazole, a nitroimidazole, is active against a wide variety of anaerobic protozoal parasites and anaerobic bacteria. Hypersensitivity to third generation cephalosporins and nitroimidazoles has been previously reported individually.

CASE REPORT

A 39 year old male presented to the Dermatology Department of our hospital with complaints of multiple hyper-pigmented patches over both forearms and left thigh with no itching/burning sensation for the past 2 months. He did not have any systemic complaints. History revealed that symptoms developed following consuming the fixed dose combination (FDC) of cefixime and ornidazole tablet for urinary tract infection prescribed by the Surgery Department of our hospital. Past history revealed a similar kind of allergic reaction 1 year back to an antibiotic (not recalled) at the same site.

On examination, the patient was conscious, afebrile and vitals were stable. There were no signs of anaemia, cyanosis and clubbing and the lymph nodes were normal. Local examination showed multiple, well defined, violaceous patches on both forearms and left thigh (Figure 1A and B). The genital examination was insignificant. Blood investigations were normal. Based on the clinical examination and history, the patient was diagnosed as cefixime/ornidazole combination-induced FDE. Patch test was not done as the patient did not give consent. The offending drug was stopped immediately. Patient was conservatively managed with topical corticosteroids and oral cetirizine. The lesion improved gradually in the next 15 days leaving residual hyperpigmentation. He was advised to avoid cefixime and ornidazole in future. This case was reported to the nearby adverse drug reaction monitoring centre.

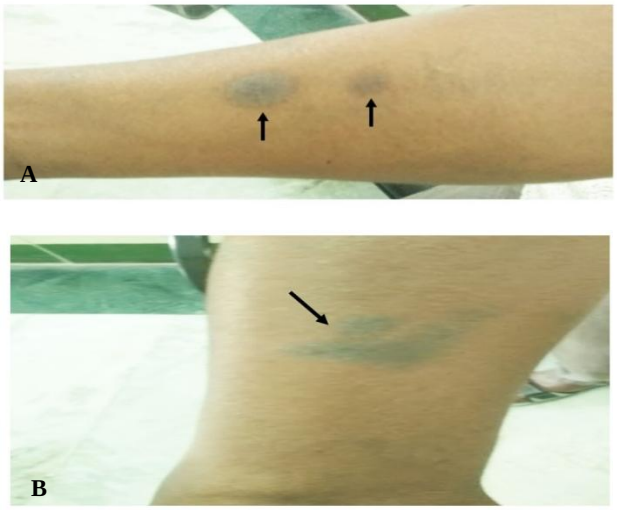

Figure 1 (A and B): The arrow indicates well defined, violaceous patches.

The Naranjo's algorithm was used to assess the causal probability of the reaction occurring due to cefixime and ornidazole.[4] The following criteria were considered: There were previous conclusive reports on this reaction (+1); the adverse event appeared after cefixime and ornidazole was administered (+2); adverse event improved when cefixime and ornidazole was discontinued (+1); adverse event reappeared when cefixime and ornidazole was re-administered (0); alternate causes that could solely have caused the reaction (+2); the reaction reappeared when a placebo was given (0); drug detected in the blood (or other fluids) in a concentration known to be toxic (0); the reaction was more severe when the dose was increased or less severe when the dose was decreased (0); the patient had a similar reaction to cefixime and ornidazole in the previous exposure (0); the adverse event confirmed by objective evidence (0). A cumulative score of 6 was obtained suggesting a 'probable' association of reaction with cefixime and ornidazole. WHO-Uppsala Monitoring Centre causality assessment system showed that the adverse reaction was "probable/likely" with cefixime and ornidazole.[5] Severity assessed by using modified Hartwig and Siegel scale and found the severity level at 3.[6]

DISCUSSION

FDE is associated with sudden onset of well demarcated erythematous macules, evolving rapidly to violaceous edematous plaques; it recurs on the same site within 30 minutes to 1 day of drug administration and heals with residual pigmentation. This accounts for 16 to21% of all cutaneous reaction.[7] Morphologically, FDE initially manifests as single erythematous macule, which gradually transforms into an edematous plaque or sometimes to bullous form. The lesions are normally asymptomatic but they may be associated with pruritus and burning sensation and the lesions may be single or multiple and mostly affect the genitalia, lips, and hands with inflammatory changes and hyperpigmentation. The reactions are known as "fixed" as recurrent lesions occur at the original region following exposure to the same suspected drugs (re-challenge) and the lesion occur more rapidly than the previous exposure as it occurred in our case. The healing happens spontaneously after few days to weeks after the offending drug is discontinued leaving a hyperpigmented patch.[8]

FDE is proposed to be a delayed-type hypersensitivity reaction but still the exact mechanism is uncertain. The major causal factor in the development of localized tissue damage could be due to the activation of $CD8^+$ T cells which retain the immunologic memory in the lesions. The immunologic memory retained can trigger the lesion but it is not sufficient enough to cause extensive tissue damage. Moreover, the $CD4^+$ T cells are involved in the latter phase of lesion progress and get activated on re-challenge.[7,8]

FDE has four stages which include resting phase, drug intake phase, acute evolving phase and resolution phase. Histopathologically, FDE is characterised by marked, basal cell, hydropic degeneration with pigmentary incontinence. Epidermis and dermis shows scattered keratinocyte necrosis with eosinophilic cytoplasm and pyknotic nucleus, lymphocytes, histiocytes and neutrophils.[9] The peak incidence is between 21 to 40 years of age with high predilection for males compared to females.[10]

FDC of antibiotics have also shown to cause FDE.[11] Most of FDCs available in the market is usually irrational combination of drugs which are prescribed to get faster response with incomplete and improper diagnosis. These FDCs are consumed as over-the-counter medications.[12] Assessment of safety and rationale of antibacterial fixed-dose combinations in the private sector in Latin American countries reported that the majority of antibacterial FDCs lacked therapeutic benefit.[13] The FDC of cefixime and ornidazole is also an irrational combination used for many infectious conditions. Consumption of unsafe antibacterial

and those antibiotics lacking sufficient therapeutic benefit is likely to contribute antibacterial resistance and ADRs.

Among the irrational FDCs banned in India recently, the antibiotic combinations accounted for 19%.[14] Antibiotic resistance is of increasing concern worldwide, but initiatives to curtail inappropriate use should be improved. Despite repeated investigations into the shortcomings of some FDCs, such drugs are still being manufactured and promoted in the Indian drug market. Among the 118 antibiotic FDCs that are available in the Indian market, 80 (68%) of them are not registered with the Central Drugs Standard Control Organisation. Studies have shown that rising sales of antibiotic combinations in India could be undermining the global efforts to limit antimicrobial resistance, due to dozens of unapproved and some risky formulations available in the market.[15,16]

FDE have been reported by cefixime and ornidazole individually, but to best of our knowledge this is the first case to be reported following their use as a FDC.[17-19] FDE due to other antibiotic FDCs like fluoroquinolone with nitroimidazole combinations have been reported.[20,21] The present case was presented to document an uncommon side effect of a commonly prescribed FDC, particularly in India. Cross reactions can also occur with structurally similar compound like tinidazole and cephalosporin combination. Thus, our case elucidates the clinically significant but rare cutaneous reaction of cefixime and ornidazole FDC. Hence, clinicians should have a high index of suspicion and be aware of the possibility of this kind of reactions (FDE) in case of irrational prescriptions of cefixime and ornidazole combination.

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