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# RECURRENT FIXED DRUG ERUPTION INDUCED BY OFLOXACIN-ORNIDAZOLE COMBINATION: A CASE REPORT AND LITERATURE REVIEW

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## ABSTRACT

Fixed drug eruption (FDE) is a distinctive variant of cutaneous adverse drug reaction marked by the dramatic re-appearance of well-demarcated erythematous or violaceous plaques in precisely the same location whenever the patient is re-exposed to the culprit drug. Although classic triggers include sulfonamides, tetracyclines and non-steroidal anti-inflammatory drugs, recent pharmacovigilance data highlight an increasing contribution from broad-spectrum antimicrobial fixed-dose combinations (FDCs). Here we describe a 36-year-old man who, within 24 hours of ingesting this FDC, developed multiple sharply circumscribed hyper pigmented macules in his penile region, the identical sites affected during an episode one year earlier after taking the same tablet. No systemic involvement or mucosal lesions were noted. Withholding the drug led to gradual resolution, leaving residual slate-grey pigmentation characteristic of FDE. This case reinforces the importance of meticulous drug histories, rational prescribing and patient education. Recognizing FDE early not only prevents needless investigations but also averts potentially more extensive reactions on future exposure particularly relevant given the widespread, often unsupervised use of antimicrobial FDCs.

**KEYWORDS:**

## INTRODUCTION

Combination products, also known as fixed dose drug combinations (FDCs), are combinations of two or more-active drugs in a single dosage form. The Food and Drug Administration, USA defines a combination product as 'a product composed of any combination of a drug and a device or a biological product and a device or a drug and a biological product or a drug, device, and a biological product'. The recent 14th model list of essential drugs preparedby the WHO (March 2005) includes 312 formulation of which 18 are fixed dose drug combinations.[2] FDCs of quinolones and nitroimidazoles (e.g.norfloxacin + metronidazole, ciprofloxacin + tinidazole, ofloxacin + ornidazole) have not been recommended inany standard books but continue to be heavily pre-scribed drugs in GI infections, pelvic inflammatory disease, dental infection, etc., to cover up for diagnostic imprecisionand the lack of access to laboratory facilities.[1]

Ofloxacin is a synthetic fluoroquinolone antibiotic that acts by inhibiting bacterial DNA gyrase and topoisomerase IV enzymes, which are essential for bacterial DNA replication, transcription, repair, and recombination. This inhibition leads to DNA strand breaks and bacterial cell death, making ofloxacin bactericidal.[3,4] It is effective mainly against Gram-negative bacteria and some Gram-positive strains. Sensitivity patterns show good activity against pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*.[5,6] Resistance to ofloxacin often arises via mutations in gyrA and parC genes or increased efflux pump activity, posing clinical challenges.[9]

Ornidazole, a nitroimidazole derivative, exhibits its antimicrobial effect by causing DNA strand breakage and destabilization in anaerobic bacteria and protozoa, through the reduction of its nitro group to reactive intermediates inside anaerobic cells.[7] It is particularly efficacious against *Bacteroides fragilis*, *Clostridium* spp., *Entamoeba histolytica*, and *Giardia lamblia*. Ornidazole shares similar indications with metronidazole but with a longer half-life and better tolerability.[8]

Tinidazole and ornidazole are more efficacious than metronidazole because they have considerably longer serum half-lives than metronidazole.[10]

Therapeutically, ofloxacin is widely used for urinary tract infections, respiratory tract infections, skin infections, and certain gastrointestinal infections caused by susceptible bacteria.[5] Ornidazole is indicated in anaerobic infections, protozoal infections such as amoebiasis, trichomoniasis, and giardiasis, and as a combination therapy for mixed infections.[8] Overall, both drugs remain valuable agents in infectious disease management, though increasing resistance necessitates careful susceptibility testing and prudent use.

Fixed Drug Eruption (FDE) is a well-characterized cutaneous adverse drug reaction, marked by the recurrence of skin lesions at the same site each time the offending drug is administered. Clinically, it presents as sharply demarcated, round or oval erythematous macules or plaques, which may develop into bullae or erosions and resolve with post-inflammatory hyper pigmentation. Commonly involved areas include the lips, genitalia, face, and extremities.[11] The pathogenesis of FDE is primarily mediated through a type IV hypersensitivity reaction, involving CD8+ effector memory T-cells residing in the basal epidermis of the previously affected sites. Upon re-exposure to the causative agent, these cells release cytokines like interferon-gamma (IFN-γ), which initiate keratinocyte apoptosis, leading to inflammation and visible lesions.[12] This explains the recurrence of the lesion at the exact anatomical location on subsequent exposures.

Several classes of drugs have been implicated in FDE. The most common offenders include antibiotics (e.g., sulfonamides, tetracyclines, fluoroquinolones), non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, and anticonvulsants.[11]

In a prospective study by Kumar and Reddy, out of 32 confirmed cases of Fixed Drug Eruption (FDE), 2 cases were linked to the fixed-dose combination of ofloxacin and ornidazole, highlighting their role as causative agents. Fluoroquinolones were the most commonly implicated antimicrobials overall. Lesions typically appeared within 48 hours of drug intake and presented as well-defined hyperpigmented patches. Management included discontinuation of the drug, antihistamines, and topical corticosteroids, though pigmentation often persisted. The study emphasizes the need for cautious use of ofloxacin–ornidazole FDCs to prevent recurrent FDEs.[13] Notably, ofloxacin, a fluoroquinolone, and ornidazole, a nitroimidazole, have been increasingly recognized as causative agents, especially when prescribed together in fixed-dose combinations (FDCs). These FDCs are frequently used in gastrointestinal infections in countries like India and are often available over-the-counter, contributing to misuse and underreported adverse effects. The irrational and unsupervised use of such combinations increases the risk of hypersensitivity reactions, including FDE. Clinicians should take detailed drug histories in patients presenting with pigmented or bullous lesions and avoid re-prescribing suspected medications. Rational use of antibiotics and discouragement of unnecessary FDCs are key to preventing such adverse reactions.

## CASE REPORT

A 36-year-old male with no significant medical co morbidities presented with complaints of acute onset watery diarrhea, 5–6 episodes per day for the past two days, associated with mild abdominal discomfort. He denied fever, vomiting, or blood in stool. Clinical examination was unremarkable with stable vital signs, no signs of dehydration, and a soft, non-tender abdomen. Based on the clinical presentation and regional prescribing patterns, he was empirically started on a fixed-dose combination (FDC) of ofloxacin 200 mg and ornidazole 500 mg (Tab OFLOX-OZ), twice daily for five days, along with supportive therapy. The diarrheal symptoms resolved within 48 hours of treatment initiation. However, on the third day of therapy, the patient developed a well-demarcated, round, erythematous patch approximately 3 cm in diameter on the penile region, associated with mild pruritus and burning. No systemic symptoms or mucosal involvement were noted. The lesion was managed conservatively with oral antihistamines (levocetirizine 5 mg daily) and a topical corticosteroid, resulting in resolution within a week, leaving post-inflammatory hyperpigmentation. At that time, the reaction was presumed to be a non-specific dermatosis.

Six months later the patient re-presented with similar diarrhoea and was again prescribed the same ofloxacin-ornidazole combination by another practitioner. Twenty-four hours after the second dose he developed an identical lesion at the exact previously affected site, progressing to the same size and intensity. No new lesions emerged. Laboratory parameters, including complete blood count and liver/renal profiles, were normal. The possibility of a fixed drug eruption (FDE) triggered by the ofloxacin-ornidazole FDC was strongly considered. The offending drug was discontinued; the cutaneous reaction was managed with cetirizine 10 mg nightly, mometasone furoate 0.1 % cream twice daily, and emollients. Complete resolution occurred within 10 days, again with residual hyperpigmentation.

## DISCUSSION

Ofloxacin–ornidazole FDCs are disproportionately represented among antibiotic-related FDEs in South-Asian pharmacovigilance data; irrational over-the-counter use compounds the problem. Cross-reactivity can occur both within fluoroquinolones (ciprofloxacin ↔ ofloxacin) and within nitro-imidazoles (ornidazole ↔ secnidazole), but is not universal, so structured provocation or patch testing aids safe substitution. FDE may involve unusual sites (sole, genitalia, oral mucosa)

or present with bullae; a high index of suspicion is required when lesions recur at stereotyped locations after re-exposure.

Sarkar MK et al, described a 25-year-old man who repeatedly self-medicated for gastro-enteritis with an ofloxacin 200 mg + ornidazole 500 mg FDC. After each course the patient developed sharply circumscribed, hyper-pigmented plaques on the trunk and thighs that re-flared at the identical sites upon re-exposure, fulfilling clinical criteria for a FDE. Causality was "probable" (Naranjo +7), and the patient was counselled to avoid the combination permanently.[14] Pal A et al[15], reported a young man who relied on multiple fluoroquinolone–nitro-imidazole FDCs (including ofloxacin–ornidazole) for recurrent diarrhoea. Each episode triggered more numerous and intense FDE plaques, illustrating the risk of sequential cross-sensitisation within the class. Definite causality (Naranjo +9) led the authors to emphasise strict antibiotic stewardship and patient education.

Another case by Manchukonda RS et al[16], discussed 38-year-old male developed hyperpigmented, erythematous lesions with burning and itching after taking a fixed-dose combination of ofloxacin and ornidazole. The patient had a similar reaction a year prior with the same FDC, though affecting fewer sites. Other medications taken (omeprazole, paracetamol) had been previously tolerated without issue. The recurrence at identical and new sites supported a diagnosis of FDE. A Naranjo score of 9 confirmed a definite causal relationship with the FDC. This case underscores the need to avoid re-exposure to ofloxacin–ornidazole in sensitized individuals.

Kameswari PD et al[17], presented a bullous FDE caused by ciprofloxacin that recurred one year later with ofloxacin despite prior counselling, again demonstrating quinolone class cross-reactivity. Withdrawal and topical therapy cleared lesions within a week; the authors stressed the importance of a drug-alert card to prevent inadvertent rechallenge. Slim R et al[18] documented a 40-year-old male who developed genital bullous FDE 24 h after a single ofloxacin tablet. Interestingly, patch testing revealed cross-reactivity with ciprofloxacin and levofloxacin, underscoring the piperazinyl ring as a shared allergenic determinant among fluoroquinolones.

Here we discussed the literature articles of FDE caused solely by ornidazole. Emre S et al[19] described an unusual localisation: a 48-year-old woman developed a solitary violaceous plaque confined to the plantar sole after each course of ornidazole for genitourinary infection. Three recurrences over six months confirmed site-specific FDE; avoidance of ornidazole prevented further episodes. Sanmukhani J et al[20], discussed a detailed case of an adult with ornidazole-induced FDE who also reacted to secnidazole but tolerated metronidazole and tinidazole. Oral provocation confirmed cross-sensitivity limited to certain side-chain structures, highlighting the need for careful alternative selection within the nitro-imidazole family.

Marya CM et al[21], reported a 40-year-old man who developed a 3 × 3 cm erythematous macule on the hard palate—an exceptionally rare mucosal site—within hours of taking ornidazole. Lesions resolved completely after drug withdrawal, leaving no scarring; this case broadened the spectrum of intra-oral FDE presentations.

Ramesh et al[22], emphasized that clinician awareness is crucial, as FDE is often misdiagnosed as infectious or autoimmune dermatoses. They highlighted that recurrence at the same site is a key diagnostic clue and that a detailed drug history, including over-the-counter medications, is essential for detection. In their study, nearly 16% of reported cutaneous adverse drug reactions were FDEs, suggesting the need for dermatologists and general practitioners to maintain high vigilance for this presentation. Effective management of fixed drug eruptions (FDEs) requires prompt recognition and immediate withdrawal of the causative agent. Clinicians should suspect FDE in any patient presenting with sharply demarcated, erythematous or violaceous patches that recur at the same anatomical site after drug re-exposure.

Early identification can prevent progression to more severe reactions, including bullous or mucosal involvement. Symptomatic treatment includes topical corticosteroids for local inflammation and oral antihistamines for pruritus. Severe or generalized lesions may warrant short-term systemic corticosteroids for rapid resolution. Drug avoidance is the mainstay of treatment, and antihistamines can reduce associated pruritus. Raising awareness of this condition will increase the likelihood of prompt diagnosis leading to resolution within days to weeks after the offending drug is discontinued.[23]

In our case, the patient developed a recurrent, well-demarcated hyperpigmented lesion following re-exposure to a fixed-dose combination of ofloxacin and ornidazole, consistent with fixed drug eruption (FDE). The Naranjo causality assessment score was +8, indicating a probable adverse drug reaction. Clinically, the presentation aligned with classical FDE features: rapid onset after re-exposure, recurrence at the same anatomical site, and residual pigmentation post-resolution. There were no systemic symptoms or mucosal involvement, supporting a localized cutaneous reaction. The diagnosis was made based on temporal association, morphology, and clinical history. The patient was counselled extensively about the nature of FDEs and the risk of recurrence with re-exposure. The patient was strongly advised to permanently avoid all ofloxacin- and ornidazole-containing medications. A written drug-alert card was provided to the patient for use in future clinical encounters. The patient was instructed to inform all

healthcare providers of his hypersensitivity history to prevent accidental re-prescription.

In conclusion, successful FDE management is multidimensional rooted in rapid diagnosis, targeted symptomatic therapy, increased clinician awareness, and structured patient counseling. These steps not only resolve acute lesions but also significantly reduce morbidity from future episodes. This case highlights the importance of clinician vigilance and patient education in the prevention of recurrent drug-induced reactions.

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