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Case Report

# Ofloxacin/ornidazole induced fixed drug eruptions: a case report

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## ABSTRACT

The term fixed drug eruption describes the development of one or more annular or oval erythematous patches as a result of systemic exposure to a drug; these reactions normally resolve with hyperpigmentation and may recur at the same site with reexposure to the drug. Repeated exposure to the offending drug may cause new lesions to develop in addition to "lighting up" the older hyperpigmented lesions. A 53 year old male on taking Ofloxacin + Ornidazole complained of generalized itching followed by the appearance of rashes over the extremities and the trunk, and lesions over the buccal mucosa and urethral region. The subject had a history of allergic reaction to the same combination in the past. Since the eruptions occurred in the same site on reexposure to the same drugs, a diagnosis of fixed drug eruptions was made. According to the Naranjo Adverse Drug Reaction Probability Scale, the association between the drugs implicated and the adverse drug reaction was found to be probable (Score - 7).

**Keywords:** Fixed drug eruptions, Ofloxacin, Ornidazole, Cutaneous eruptions, Erythema multiforme, Bulls' eye target lesions

## INTRODUCTION

Adverse reactions to medications are common and often manifest as a cutaneous eruption. Drug-induced cutaneous disorders frequently display a characteristic clinical morphology such as morbilliform exanthem, urticaria, hypersensitivity syndrome, pseudolymphoma, photosensitivity, pigmentary changes, acute generalized exanthematous pustulosis, lichenoid dermatitis, vasculitis, Stevens-Johnson syndrome, or fixed drug eruption (FDE).[1]

The term fixed drug eruption describes the development of one or more annular or oval erythematous patches as a result of systemic exposure to a drug; these reactions normally resolve with hyperpigmentation and may recur at the same site with reexposure to the drug. Repeated exposure to the offending drug may cause new lesions to develop in addition to "lighting up" the older hyperpigmented lesions.[1]

Fixed drug eruptions may account for as much as 16-21% of all cutaneous drug eruptions. The actual frequency may be higher than current estimates, owing to the availability of a variety of over-the-counter medications and nutritional supplements that are known to elicit fixed drug eruptions.[1]

Ofloxacin belongs to a class of drugs called quinolone antimicrobials and is used to treat a variety of bacterial infections. Ornidazole is a nitroimidazole which is antibacterial and antiprotozoal drug used to treat anaerobic enteric protozoa. It is a drug that cures some protozoan infections.

According to Food and Drug Association (FDA), the combination of Ofloxacin and Ornidazole is irrational but is still prescribed and used extensively for treatment of acute gastrointestinal infections. Both Ornidazole and Ofloxacin are known to cause FDE individually as well as in combination. We report a case of FDE with fixed dose combination of Ofloxacin and Ornidazole.

## CASE REPORT

A 53 year old male on taking Ofloxacin + Ornidazole fixed dosed combination tablet complained of generalized itching followed by the appearance of rashes over the extremities and the trunk, and lesions over the buccal mucosa and urethral region (Figures 1, 2 & 3). The rashes were painful and associated with itching and burning sensation. The nature of the rashes was bulls' eye lesions (target lesions) resembling erythema multiforme. The rashes were noticed approximately 4 hours after medication. Fever and lymphadenopathy were not seen. Antihistaminics were administered. The rashes subsided within 2 days followed by hyperpigmentation. The drug prescription was for hemorrhoids.

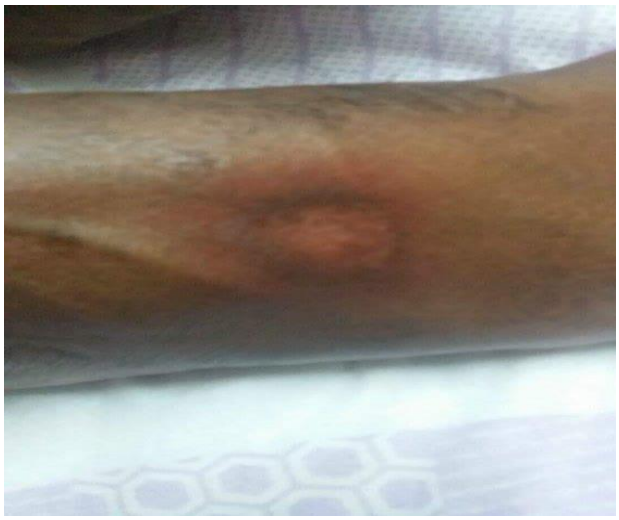

**Figure 1: Ofloxacin/Ornidazole induced fixed drug eruptions.**

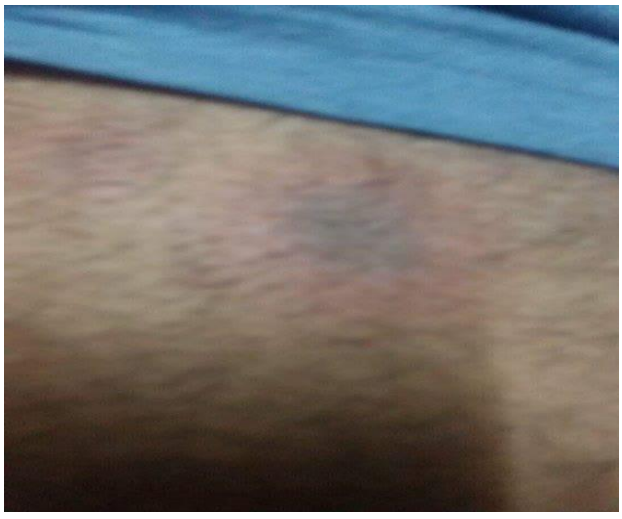

**Figure 2: Ofloxacin/Ornidazole induced fixed drug eruptions.**

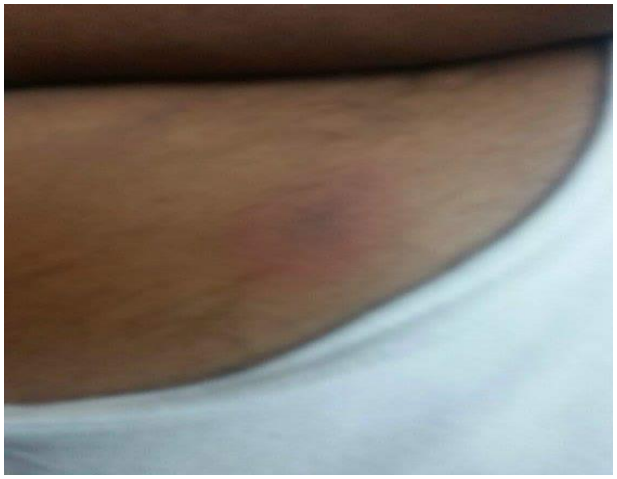

**Figure 3: Ofloxacin/Ornidazole induced fixed drug eruptions.**

The subject had a history of allergic reaction to the same combination in the past. The previous episode was associated with the vesicular eruptions in the same areas and oral lesions followed by hyperpigmentation. Itching and burning were reported. The patient had been admitted in a hospital for dehydration due to gastrointestinal infection. Since the eruptions occurred in the same site on reexposure to the same drugs, a diagnosis of Ofloxacin/Ornidazole induced fixed drug eruptions was made.

## DISCUSSION

Several variants of fixed drug eruption have been described, based on their clinical features and the distribution of the lesions.[2-8] These include the following:

- Pigmenting fixed drug eruption
- Generalized or multiple fixed drug eruption
- Linear fixed drug eruption
- Wandering fixed drug eruption
- Non pigmenting fixed drug eruption
- Bullous fixed drug eruption
- Eczematous fixed drug eruption
- Urticarial fixed drug eruption
- Erythema dyschromicum perstans–like fixed drug eruption
- Vulvitis
- Oral
- Psoriasiform
- Cellulitis like eruption[9]

Although the exact mechanism is unknown, recent research suggests a cell-mediated process that initiates both the active and quiescent lesions. The process may involve an antibody-dependent, cell-mediated cytotoxic response.[10] $CD8^+$effector/memory T cells play an important role in reactivation of lesions with re-exposure to the offending drug.[11,12]

The offending drug is thought to function as a hapten that preferentially binds to basal keratinocytes, leading to an inflammatory response.[13] Through liberation of cytokines such as tumor necrosis factor-alpha, keratinocytes may locally up-regulate expression of the intercellular adhesion molecule-1 (ICAM1).[14] The up-regulated ICAM1 has been shown to help T cells (CD4 and CD8) migrate to the site of an insult.[15,16]

The newly arriving and residential CD8 cells likely perpetuate tissue damage by their production of the inflammatory cytokines interferon-gamma and tumor necrosis factor-alpha. CD8 cells isolated from active lesions have also been shown to express alpha E beta 7, a ligand for E-cadherin, which may further contribute to the lymphocyte's ability to localize to the epidermis. Other cell surface molecules, such as CLA/alpha4beta1/CD4a, that bind E-selectin/vascular cellular adhesion molecule-2/ICAM1 help to further attract CD8 cells to the area.[10]

Changes in cell surface markers allow vascular endothelium to select CD4 cells for migration into active lesions. These regulatory CD4 cells likely produce interleukin 10, which has been shown to help suppress immune function, resulting in a resting lesion.[10] As the inflammatory response dissipates, interleukin 15 expression from keratinocytes is thought to help ensure the survival of CD8 cells, helping them fulfill their effector memory phenotypes. Thus, when reexposure to the drug occurs, a more rapid response develops in the exact location of any prior lesions.[10]

In the United States, the prevalence of drug eruptions has been reported to range from 2-5% for inpatients and greater than 1% for outpatients.[17]

The international prevalence is variable but is likely similar to that in the United States. Most studies report fixed drug eruptions to be the second or third most common skin manifestation of adverse drug events.[18]

Fixed drug eruptions have no known racial predilection. A genetic susceptibility to developing a fixed drug eruption with an increased incidence of HLA-B22 is possible.[19,20]

One large study of 450 patients revealed a male-to-female ratio of 1:1.1 for fixed drug eruptions.[2]

Fixed drug eruptions have been reported in patients as young as 1.5 years and as old as 87 years. The mean age at presentation is 30.4 years in males and 31.3 years in females.[2]

The initial eruption is often solitary and frequently located on the lip or genitalia. Rarely, the eruption may be intraoral. Other common locations of the initial lesion are the hip, lower back/sacrum, or proximal extremity. With the initial fixed drug eruption attack, a delay of up to 2 weeks may occur from the initial exposure to the drug to the development of the skin lesion.[21] Skin lesions develop over a period of hours but require days to become necrotic. Lesions may persist from days to weeks and then fade slowly to residual oval hyperpigmented patches.

Subsequent re-exposure to the medication results in a reactivation of the site, with inflammation occurring within 30 minutes to 16 hours.[22] The reactivation of old lesions also may be associated with the development of new lesions at other sites.

Patients may not be cognizant that a drug, nutritional supplement, over-the-counter medication, or, rarely, food (egg, fruits, nuts) triggered the skin problem. They may be convinced that an insect, particularly a spider, may be the culprit. A careful history is required to elicit the fact that a drug has been taken and is temporally related to the onset of the eruption. Medications taken episodically, such as pain relievers, antibiotics, or laxatives, are often to blame. When able to be identified, patients often report ingestion of one the following types of medications:[23]

- Analgesics
- Muscle relaxants
- Sedatives
- Anticonvulsants
- Antibiotics

Local symptoms may include pruritus, burning, and pain.[2] Systemic symptoms are uncommon, but fever, malaise, nausea, diarrhea, abdominal cramps, anorexia, and dysuria have been reported.[22,23]

Further questioning may reveal prior episodes of fixed drug eruption, atopic disease, or other past drug reactions. Family history may render a history of atopy, drug reactions, or diabetes mellitus.[2]

Several cases of fixed drug eruption on the genitalia have been reported in patients who were not ingesting the drug but whose sexual partner was taking the offending drug and the patient was exposed to the drug through sexual contact.[24-26]

The most common clinical manifestation is the pigmenting fixed drug eruption, which usually manifests as round or oval, sharply demarcated erythematous/edematous plaques located on the lip, hip, sacrum, or genitalia.[3] These erythematous patches or plaques gradually fade with residual hyperpigmentation. The center of the patch may blister or become necrotic. Other less common variants may manifest as lesions resembling erythema multiforme, toxic epidermal necrolysis, eczema, urticaria, a linear pattern following Blaschko lines, bullous lesions, a migrating eruption, or a nonpigmenting form with no postinflammatory hyperpigmentation.[4]

Initially, a single lesion or a few lesions develop, but, with reexposure, additional lesions occur. The vast majority of patients present with 1-30 lesions, ranging in size of 0.5-5 cm, but reports of lesions greater than 10 cm have been published. Lesions may be generalized. The most common reported site is the lips, and these may be seen in up to half of all cases.[2]

Medications may also follow a site-specific eruption pattern. For example, trimethoprim-sulfamethoxazole (Bactrim) has been shown to favor the genital region (especially in males) and naproxen and the oxicams involve the lips.[3]

Resting/inactive lesions tend to appear as round or oval, gray, hyperpigmented macules.

Upon reexposure, the resting hyperpigmented macules activate, developing a violaceous center encircled by concentric rings of erythema. Re-administration of the medication poses the risk of increased pigmentation, size, and number of lesions.

Individuals with darker pigmentation may develop postinflammatory hypopigmented macules once the lesions have resolved.[13]

The major categories of causative agents of fixed drug eruption include antibiotics, antiepileptics, nonsteroidal anti-inflammatory agents, and phenothiazines, although numerous other agents and certain foods such as cashews and licorice have also been reported as causative agents. Ingestion of the causative agent may occur via any route, including oral, rectal, or intravenous.[23]

In this clinical situation, there was a temporal association between the administration of Ofloxacin and Ornidazole and the onset of eruptions. The manifestations reduced on discontinuing the offending agents. Since the patient had a history of the same combination inducing rashes in the same sites previously, a diagnosis of "Ofloxacin/Ornidazole induced Fixed Drug Eruptions" was made.

According to the Naranjo Adverse Drug Reaction Probability Scale, the association between the drugs implicated and the adverse drug reaction was found to be probable (Score - 7).

## CONCLUSION

Since the patient had cutaneous eruptions in the same sites on repeated exposure to the same drug combination, a diagnosis of "Ofloxacin/Ornidazole induced Fixed Drug Eruptions" was made. The importance of eliciting drug allergy through a case history is highlighted here. The offending drugs should not be prescribed again.

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