



## Case Report on Fixed Drug Eruption

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### Abstract

Fixed drug eruption is a well-documented drug side effect and accounts for about 5–10% of cutaneous drug reactions. A fixed-dose combination of Ofloxacin and Ornidazole is one of the most commonly used medications for acute gastroenteritis and causes a red, raised macule, which turns into a blister and is later followed by post-inflammatory hyperpigmentation. The history, clinical examination, and normal laboratory parameters led to the diagnosis of ofloxacin and ornidazole-induced hypersensitivity reactions, and the patient was successfully treated with corticosteroids and antihistamines. Hypersensitivity reactions to fluoroquinolones are rare, with an incidence of 0.4% to 2%. The pharmacovigilance programme and self-reporting of all ADRs by healthcare workers can aid in ensuring judicious drug use and drug safety and thus lower associated morbidity and mortality. The fixed drug reaction caused in this case was a black, raised macule, which turned into a blister and was later followed by post-inflammatory hyperpigmentation. The delayed type IV hypersensitivity reaction is most probably the reason for the mechanism of fixed drug reaction.

**Key words:** Fixed drug eruption, hyperpigmentation, ofloxacin, ornidazole, de-challenge

### Introduction

Fixed drug eruption (FDE) is an unusual and rare adverse drug reaction. The term "FDE" was first introduced by Brocq in 1894. This type of reaction is actually a delayed type of hypersensitivity reaction that occurs as lesions recurring at the same skin site due to repeated intake of an offending drug. Ornidazole is a relatively new 5-nitroimidazole having a low molecular weight with excellent activity against anaerobic microorganisms and protozoa. They are the first-line drugs for hepatic and intestinal amoebiasis in developing countries. <sup>(1)</sup> Hyperpigmentation is a common dermatologic problem that may have a substantial impact on the patient since it affects the appearance and quality of life. It is defined as the darkening of the skin's natural color, usually due to an increase in melanin deposition (hyper melanosis) in the epidermis or dermis, an increase in chromophores of nonmelanic origin (hyperchromia), or to dermal deposition of endogenous or exogenous pigments such as hemosiderin, iron, or heavy metals. <sup>(2)</sup> Ofloxacin

is a synthetic chemotherapeutic antibiotic belonging to the second-generation fluoroquinolone and used to treat various bacterial infections. This combination is irrational according to Food and Drug Association (FDA) but still used extensively for treatment of acute gastroenteritis. We would like to present a case of FDE following treatment with fixed dose combination of Ofloxacin and Ornidazole as both the drugs are causative in fixed drug eruption. <sup>(1)</sup> Drug-induced hyperpigmentation is estimated to account for 10% to 20% of cases of acquired hyperpigmentation, although these figures are probably highly speculative, as most cases are idiopathic, especially in elderly patients. The incidence of drug-induced hyperpigmentation varies according to the drug involved, ranging from isolated cases to 25% of patients receiving treatment. Some drugs are associated with the development of hyperpigmentation of the skin or mucous membranes. <sup>(2)</sup> 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. According to the Food and Drug Association (FDA), the combination of Ofloxacin and Ornidazole is irrational but is still prescribed and used extensively for the treatment of acute gastrointestinal infections. Both ornidazole and ofloxacin are known to cause Food Drug Eruption individually as well as in combination and case of FDE with a fixed dose combination of Ofloxacin and Ornidazole. <sup>(3)</sup> 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 an antibacterial and antiprotozoal drug used to treat anaerobic enteric protozoa. It is a drug that cures some protozoan infections. <sup>(4)</sup> 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. <sup>(5)</sup>

## CASE REPORT:

A male Patient with the age of 24years bearing Ip number A03624 in department of general medicine was admitted on 15/06/22 and discharged on 18/06/22 with chief complaints of abdominal pain, vomitings, loose stools (Diarrhea) and generalized weakness (fatigue) since yesterday night.

A patient was apparently normal till today's evening (15/06/22). Patient presented with abdominal pain, vomitings, loose stools (Diarrhea) and generalized weakness (fatigue) because of food poisoning. No past illness and family history, social History was Nonsmoker & nonalcoholic. By above complaints patient was diagnosed as **Food Borne Illness**. Later the patient was prescribed with immediate advice of medications like Infusions (IV) i.e., Ciprofloxacin 200mg, Metronidazole 500mg and Intramuscular (IM) Inj. Dicyclomine 10mg followed by fluids (2 units RL with Methyl cobalamin 1000mcg injection). on discharge, The Patient was prescribed the following treatment with discharge summary were T. Pantoprazole 40mg, T. Cyclopam-MF, T. Ondansetron 4mg, Sporolac sachets, T. Loperamide 2mg, T. Ofloxacin 200mg + T. Ornidazole 500mg (Ocebran-Oz) and the treatment follow up by 3 days of therapy.



**Figure. 1**

A patient developed a hypersensitivity reaction to T. Ofloxacin 200mg + T. Ornidazole 500mg (Ocebran-Oz) "**Black Pigmentation Patches**" on various regions of the body.

## Discussion

In the overall study, it was observed that fluoroquinolones (33.3%) were the major etiological agent in causing FDE, followed by nitroimidazole antibiotics (26.6%), NSAID's (24.4%), penicillin and antifungals (6.7%), and antitubercular drugs (2.2%). In a survey of recent studies performed before 2000, the most common causative agent of FDE was trimethoprim-sulfamethoxazole. <sup>(6)</sup> Fixed drug reactions have been reported by Ornidazole and Ofloxacin individually, but this was the first time it is being reported by their fixed dose combination. The exact mechanism for this fixed drug eruption is still unclear, but it has been postulated that FDE is due to a delayed classical Type IVc hypersensitivity reaction mediated by CD8+ T cells. The drug binds with basal keratinocytes and stimulates the inflammatory process by causing the release of lymphokines, mast cells, and antibodies, which in turn causes damage to basal cells. CD8+ on activation causes the release of interferon (IFN) and cytotoxic granules into the local microenvironment, which may contribute to further damage to basal cells. <sup>(1)</sup> According to the Naranjo, adverse drug reaction probability scale, the fixed dose combination of Ofloxacin and Ornidazole is the probable cause of fixed drug eruptions in this case (Overall Score = 8). In our case, the fixed drug eruption and hyperpigmentation is probably associated with the fixed dose combination of Ofloxacin and Ornidazole. An Adverse Drug Reaction (ADR) due to hypersensitivity to any drug has a genetic predisposition and have higher incidence in individuals with a history of atopy, family history of drug allergy and the presence of Human Leukocyte Antigen-B22 (HLA-B22). <sup>(4)</sup> Ofloxacin is a 2<sup>nd</sup> generation fluoroquinolone and is a racemic mixture of 50% Levofloxacin and 50% dextrofloxacin. Fluoroquinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA Gyrase) and Topoisomerase IV. It has a half-life (t<sub>1/2</sub>) of 5-7 hours with an oral bioavailability up to 95%. Ofloxacin is administered for both gram negative and gram-positive bacteria and is administered in a dose of 400 mg once a day. <sup>(5)</sup> According to Ravi Shankar Manchukonda et.al., 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. 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. A genetic susceptibility to developing a fixed drug eruption with an increased incidence of HLA-B22 is possible. 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).

In the clinical situation, there was a temporal association between the administration of Ofloxacin and Ornidazole and the onset of eruptions. The manifestations were reduced on discontinuing the offending agents.<sup>(3)</sup> Although it is irrational to use, a combination of Ofloxacin and Ornidazole was commonly used for acute gastroenteritis in developing countries. Those individuals who are known to be allergic to the constituents of the combination or have had skin eruptions following consumption of the drug should be warned against its future use. In this case, the patient was advised not to take self-medication, use moisturisers for soothing effects on the skin due to the associated black pigmentation pruritis. In this case, the fixed drug eruption and hyperpigmentation are probably associated with the fixed dose combination of Ofloxacin and Ornidazole.<sup>(4)</sup> Because of the widespread use of fluoroquinolones, it is important to consider these as possible etiologic agents of FDE. The great majority of reports of FDE due to fluoroquinolones have been recent, possibly indicating environmental or evolutionary components.<sup>(5)</sup> The diagnosis of hyperpigmentation is complicated due to the lack of providing direct evidence or inadequate information to the physician.<sup>(2)</sup> So, to conclude, we have reported the fixed drug eruptions due to certain drugs. No doubt, these drugs are only like a few drops in a large sea, but the continuous addition of a few drops would result in the formation of a large sea.<sup>(6)</sup>

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