

## FIXED DOSE COMBINATION OF OFLOXACIN AND ORNIDAZOLE WITH CROSS-SENSITIVITY TO METRONIDAZOLE INDUCED FIXED DRUG ERUPTION

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### ABSTRACT

Fixed drug eruption (FDE) is a recurrent, clearly defined lesion that consistently develops at the same location after taking the offending substance [1]. The lips, face, hands, feet, and genitalia are the typical sites for the lesions [2]. It can be identified by its benign character, short latency, and recurrence at the same places on re-challenge. Resting FDE lesions contain CD8+ T-cells with a memory characteristic that were situated at the dermal-epidermal junction and are silent until the drug is re-challenged after healing. Most FDE cases have excellent prognoses and are self-limiting. After the acute incident, post-inflammatory hyperpigmentation can be noticeable and last for several months. Ofloxacin is a fluoroquinolone of second-generation that prevents the synthesis of microbial DNA. Ornidazole is a 5-nitroimidazole with antibacterial and antiparasitic properties. Metronidazole has broad-spectrum cidal action against anaerobic protozoa. It is frequently given in combination with other antimicrobial agents to treat polymicrobial infections with aerobic and anaerobic bacteria. The most frequent combination causing fixed drug eruption among the anti-microbial FDC is fluoroquinolones + nitroimidazole. We report a case of ornidazole with cross-sensitivity to metronidazole-induced fixed drug eruption in an adult male of thirties treated for diarrhea.

**KEYWORDS :** Fixed drug eruption, Fixed dose combination, Cross sensitivity

### INTRODUCTION

Fixed drug eruption (FDE) is a recurrent well-defined lesion that occurs at the same site each time when the offending drug is taken [1]. Ofloxacin is a second-generation fluoroquinolone interfering with microbial DNA synthesis. Ornidazole is a 5-nitroimidazole having anti-bacterial and anti-parasitic activity. Metronidazole has broad spectrum cidal activity against anaerobic protozoa. Among the anti-microbial fixed-dose combination (FDC), fluoroquinolones + nitroimidazole combination is the most common combination causing FDE. Only a few cases of the FDC of ofloxacin and ornidazole with cross-sensitivity to metronidazole-induced FDE are reported. Among them, this is a classic case with bullae, vesicles, and mucosal erosion developed over both hands, legs, abdomen, and penis.

### Case Report:

An adult male in thirties came to the dermatology outpatient department (OPD) with complaints of itchy, multiple fluid-filled swelling over the hands, legs, abdomen, and penis. On examination, there were multiple bullae and vesicles over both hands (figure 1), single bulla over both medial sides of the right leg (figure 2) and left leg (figure 3), multiple vesicles clustered together over the abdomen (figure 4), and mucosal lesion over the glans penis (figure 5).

Three days ago, he went to a drug store with complaints of diarrhea (3 episodes in a day) and the pharmacist gave him a fixed-dose combination (FDC) of ofloxacin 200mg + ornidazole 500mg twice a day (BD) without doctor's prescription. On the second day of treatment, lesions developed and he went to the dermatology OPD.

He mentioned similar history was present in the past with the same clinical picture at the same location before 6 months due to tablet Metronidazole 400mg prescribed by a pharmacist without doctor's prescription for diarrhea (2 episodes in a day). During that time, he went to a medical practitioner where he was advised to discontinue tablet metronidazole and also not to take it in the future. Later the lesions healed after 7 days leaving residual hyperpigmentation.

Histopathology of the present lesion shows some necrotic keratinocytes, mild vacuolar changes at the dermal-epidermal junction, and papillary dermal edema. Oral rechallenge test was positive for FDC of ofloxacin and ornidazole; ornidazole; metronidazole but not for ofloxacin. Dechallenge test was positive which was done by discontinuing the drug causing adverse events. Based on the patient's past and present medical history; dechallenge and rechallenge test; histopathology, the diagnosis is concluded as

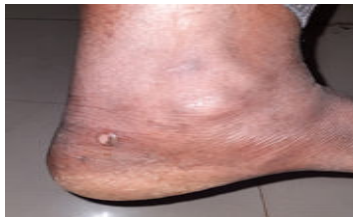
FDE caused by ornidazole with cross-sensitivity to metronidazole. The dermatologist advised him not to take the nitroimidazole group of drugs.



**Figure 1:** Multiple bullae and vesicles over both hands



**Figure 2:** Single bulla over the medial side of the right leg



**Figure 3:** Single bulla over the medial side of the left leg



**Figure 4:** Multiple vesicles clustered together over the abdomen



**Figure 5:** Mucosal lesion over the glans penis

### Who-umc Causality Categories<sup>[3]</sup>:

#### Certain:

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

#### Probable/Likely:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

#### Possible:

- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

#### Unlikely:

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)
- Disease or other drugs provide plausible explanations

#### Conditional/Unclassified:

- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination

#### Unassessable/Unclassifiable:

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

### RESULT:

According to WHO-UMC (World Health Organization – Uppsala Monitoring Center) causality assessment<sup>[3]</sup> and Naranjo Adverse Drug Reaction (ADR) probability scale<sup>[4]</sup>, it is a 'certain' reaction. The case was reported to the ADR monitoring center (AMC) and uploaded through Vigiflow. Previous literature suggests that an antigenic relationship between the drugs or their metabolites forms the basis of cross-sensitivity<sup>[5]</sup>.

### CONCLUSION:

A total of 311 cases of FDC containing ofloxacin and ornidazole-induced FDE were reported to WHO accessed through Vigiaccess. 377 cases of metronidazole-induced fixed drug eruption were reported to WHO. 109 cases of ornidazole-induced FDE were reported to WHO<sup>[6]</sup>. Cross-sensitivity was reported with nitroimidazole derivatives like metronidazole and tinidazole<sup>[7]</sup>; ornidazole and secnidazole<sup>[8]</sup>. Cross-sensitivity between metronidazole and FDC of ofloxacin and ornidazole is reported in this article. The objective of this manuscript is to create awareness among the doctors and public that not only the same drug causes a fixed drug eruption but also the cross-sensitivity among the same group of drugs also causes a fixed drug eruption

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