



Full Length Case Report

FDE WITH FIXED DOSE COMBINATION OF OFLOXACIN AND ORNIDAZOLE WITH CROSS-SENSITIVITY TO METRONIDAZOLE: A NOVEL CASE

¹Dr. C. Dinesh M Naidu, ²Dr. Mabu Shareef, ^{3*}Dr. Nishat Ahmed Sheikh.

¹Professor of Pharmacology, Department of Pharmacology, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, Andhra Pradesh, 508254, India

²Asst. Professor of Pharmacology, Department of Pharmacology, Kamineni Institute of Medical Sciences, Narketpally, Nalgonda, Andhra Pradesh, 508254, India

³Associate Professor of Forensic Medicine and Toxicology, Department of Forensic Medicine and Toxicology, Kamineni Institute of Medical Sciences, Narketpally Nalgonda, Andhra Pradesh, 508254 India

ARTICLE INFO

Article History:

Received 05th July, 2014

Received in revised form

13th August, 2014

Accepted 24th November, 2014

Keywords:

Fixed Drug Eruption,
Ornidazole-Oloxacin combination,
Cross-sensitivity,
Unusual Site.

ABSTRACT

Ornidazole is a (synthetic) newer 5-nitroimidazole derivative and is commonly prescribed for amoebic dysentery in developing countries. Ornidazole has low incidence of side effects, but sometimes may cause significant allergic reactions such as fixed drug eruption (FDE). FDE is a rare adverse drug effect characterized by onset (appearance) of round or oval, erythematous macules on the skin or mucosa that can be associated with itching and burning sensation. It is a distinctive variant of drug-induced recurrent dermatosis occurring at the same site of the skin or mucous membrane. It is characterized by the appearance of a skin lesion in the instant of drug administration. The exact mechanism causing FDE is unknown. We report a case of Ornidazole induced FDE on the sole of right leg, an unusual site, in a 38 year old male patient treated for infective diarrhoea.

Copyright © 2014 Dr. Dinesh M Naidu et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

A fixed drug eruption (FDE) is an unusual and common adverse cutaneous reaction to an ingested drug. Lesions usually develop 1-2 weeks after the first exposure. But with subsequent exposures, they appear within 24 hours. FDE is characterised by the formation of one or a few, round, sharply demarcated erythematous and oedematous plaques, bulla, or erosions. The lesions usually occur on the lips, face, hands, feet and genitalia. If the patient is re-challenged with the offending drug, the FDE occurs repeatedly at the identical skin site (i.e. fixed). They fade over several days, leaving a residual post-inflammatory hyper-pigmentation. The most important characteristic feature of FDE is recurrence of skin lesions at the same site of a previous involvement whenever the offending drug is taken. Ornidazole is a synthetic newer 5-nitroimidazole derivative and is commonly prescribed for amoebic dysentery in developing countries as it has excellent activity against protozoa and anaerobic microorganisms.

Only Metronidazole and Tinidazole have been reported to cause FDEs with cross sensitivity to each other (Kanwar *et al.*, 1990 and Thami *et al.*, 1998). On the other hand, Ofloxacin is a synthetic antibiotic and belongs to the second-generation Fluoroquinolone and is used to treat various bacterial 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, with cross sensitivity to Metronidazole.

Case Report

This is a case of 38 year old male patient. He presented in the Dermatology OPD with an itchy, erythematous and painful patch (lesion) on the plantar aspect of right sole. On history, he revealed self-medication with tablet containing Ofloxacin 400 mg and Ornidazole 500 mg twice daily for infective diarrhoea since 2 days. He noticed that the lesion appeared after 6 hours

*Corresponding author: Dr.C. Nishat Ahmed Sheikh MBBS, MD, CTM, DFME.
Department of Forensic Medicine and Toxicology, Kamineni Institute of Medical Sciences, Narketpally Nalgonda, Andhra Pradesh, 508254 India

of third dose of the tablet (Ornof). There was no history of insect bite at that site. On detailed enquiry, the patient himself reported that he is a diagnosed case of recurrent skin lesion at similar site following ingesting of oral metronidazole tablets, but such lesions were not noted with Ofloxacin tablets. The previous lesion healed spontaneously without any treatment and after discontinuing the drug. On detailed dermatologic examination, a single, round, well defined purple coloured plaque of 1 x 1 cm in size was observed on the right sole (Fig). No such lesion was noted on the left sole. He was afebrile and there was no involvement of mucous membrane.



Fig: Post-inflammatory reaction due to fixed dose combination.

There was also no involvement of face, trunk, back and upper extremities. Based on the patient's previous history and the clinical presentation, a provisional diagnosis of FDE due to fixed dose combination of Ofloxacin and Ornidazole was established. No investigations and skin biopsy was done. The patient was advised to discontinue the drug and not to take the drug in future. The patient was treated with Mesolastine 5 mg twice daily for 5 days (and local steroid ointment). The itching subsided after one day while erythema subsided after 2 days of taking Mesolastine. After 10 days, the bullous was formed and later it resolved completely. The causality assessment score carried out using the Naranjo's algorithm (Naranjo *et al.*, 1981) suggested a probable causality for Ornidazole total score was (Ozkaya, 2008).

DISCUSSION

Drugs most commonly implicated for causing FDE are (ME Docrat, 2005) Antimicrobial agents like Tetracyclines and Minocycline, Sulfonamide antibiotics; cross-reactions with anti-diabetic drugs (Sulphonyl urea) and diuretics or the thiazide group, Metronidazole (Flagyl), Non-steroidal anti-inflammatory drugs including Salicylates and Phenylbutazone and Oral contraceptive pill. Fixed drug reactions may occur when Ornidazole and Ofloxacin are used individually as well as when they are used as fixed dose combination. Cross-sensitivity is reported with chemically related Nitroimidazole derivatives like Metronidazole and Tinidazole (Kanwar *et al.*, 1990). Like Tinidazole, Ornidazole is also chemically related to metronidazole. Therefore in our patient the FDE resulted even though he is allergic to Metronidazole. Literature suggests that an antigenic relationship between the drugs or their metabolites forms the basis of cross sensitivity (Ozkaya, 2008). Weedon suggested that the causative drug acts as a hapten and preferentially binds to basal keratinocytes and causes release of lymphokines and antibodies thereby damaging the basal cell layer (Weedon, 2002). Sanmukhani *et al* reported a case of FDE

caused by Ornidazole which showed cross-sensitivity to secnidazole but not to Metronidazole, Tinidazole or Satranidazole (Jayesh Sanmukhani *et al.*, 2010). Marya *et al* reported a rare case of intra-oral Fixed Drug Eruption (FDE) induced by Ornidazole presenting on the hard palate, an extremely rare site for FDE, in a 40-year old male (Marya *et al.*, 2012). Gupta *et al.* reported a case of FDE induced by Ornidazole as a well-defined bullous erosion over the right side of the lower lip mucosa in a 26-year-old male (Gupta *et al.*, 2005). Similarly, Varma *et al* reported a case of FDE due to fixed dose combination of Ofloxacin and Ornidazole over the lip and perioral region in a 19 year old patient. Fixed drug eruption is a well-documented side effect of a drug and accounts for about 5-10% of cutaneous drug reactions (Varma *et al.*, 2013). It is almost impossible to predict which drug would produce FDE as its adverse effect. To add to this problem, fixed dose combinations also produces FDE. Most of fixed dose combinations in the market are not approved by FDA as they are usually irrational combination of two or more drugs. These FDC drugs are used in cases of inconclusive diagnosis, as a measure to get quick response from the therapy and over the counter for self-medication. Combination of Ornidazole and Ofloxacin is also an irrational fixed dose combination which is commonly used for acute gastroenteritis. In FDE, a topical or systemic provocation test is important to confirm the diagnosis. Topical provocation test is performed with the drug patch which is applied to a previously involved skin area. If the patch test is negative, then the oral provocation test with offending agents or drugs should be undertaken (Jafferany and Haroon, 1987). In our case, we did not perform any topical or systemic oral provocation test with Ornidazole, because our patient's previous and current medical history along with clinical signs was enough to diagnose FDE caused by Ornidazole. Moreover, lip and genital skin involvements were not observed in our case although these sites are the most common sites involved in FDE (Kanwar *et al.*, 1990).

Conclusion

Cutaneous eruptions are the most commonly manifested adverse drug reactions and are observed in about 1% of patients taking any particular medicine. It is almost impossible to predict which drug would induce FDE and what would be its course. A detailed present and previous medical history along with a careful physical examination is sufficient for diagnosing FDE. Therefore, it is mandatory that the physician should perform detailed enquiry into the patient's history. This is a rational approach to patients' treatment and further increase the quality of their life. The main goal of treatment is to identify the drugs that are causing these reactions to the patients and to avoid them in the future. The offending drug must be discontinued. To conclude, perform a detailed enquiry into patient's current and previous medical history, consider cross-sensitivity with other drugs of the same class, Ornidazole should be taken into consideration and added to the list of drugs causing FDE. Fixed Drug Eruption (FDE) is an adverse cutaneous drug reaction, which usually goes unreported due to the ignorance and negligence of patients as well as physicians. If the patient gives history of any reactions or allergy to a particular drug, then the same drug should not be used in future and he/she should consult medical practitioners in future. Moreover, the fixed dose combinations of such drugs should not be prescribed or used. On the other hand, a detailed history including the drug history

and meticulous physical examination are necessary for the diagnosis of FDE. A high degree of suspicion regarding the cross-sensitivity among the drugs is also helpful in diagnosing FDE. The main goal of management is to define the causative drugs responsible for such reactions and to avoid them in future.

Acknowledgement

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors/ editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

Ethical Approval: Ethical approval taken from the Institutional ethics committee.

Source of funding: Nil

Conflicts of Interest: Nil.

Author Disclosures

Authors have no conflict of interest. This study was a part of departmental research activities in Pharmacology and Forensic Medicine and Toxicology at Kamineni Institute of Medical Sciences, Narketpally.

REFERENCES

- Gupta, S., Jain, V.K., Aggarwal, K., Gupta, S. and Mahendra, A. Fixed drug eruption caused by ornidazole. *Contact Dermatitis*. 2005. 53: 300–301.
- Jafferany, M. and Haroon, T.S. Tinidazole-induced fixed drug eruption. *J Pak Med Assoc* 1987; 37: 136–7.
- Jayesh Sanmukhani, Viral Shah, Seema Baxi, Chandrabhanu Tripathi. Fixed drug eruption with ornidazole having cross-sensitivity to secnidazole but not to other nitro-imidazole compounds: a case report. *Br. J. Clin. Pharmacol.*, Jun 2010. 69(6): 703–704.
- Kanwar, A.J., Sharma, R., Rajgopalan, M. and Kaur, S. Fixed drug eruption due to tinidazole with cross sensitivity to metronidazole. *Dermatologica*, 1990. 180: 277.
- Korkij, W., Soltani, K. Fixed drug eruptions – a brief review. *Arch Dermatol*. 1984.120: 520-4.
- Marya, C.M., Sharma, G., Parashar, V.P., Dahiya, V. Mucosal fixed drug eruption in a patient treated with ornidazole. *J. Dermatol Case Rep.*, 2012. 6(1): 21-24.
- ME Docrat. Fixed Drug Eruption. *Current Allergy & Clinical Immunology*. March 2005. 18(1): 24.
- Naranjo, C.A., Busto, U., Sellers, E.M., Sandor, P., Ruis, I., Roberts. E.A., Janeczek, E., Domecq, C. and Greenblatt, D.J. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981; 30: 239–45.
- Ozkaya, E. Fixed drug eruption: State of the art. Review. *J. Dtsch Dermotol Ges.*, 2008. 6: 181–188.
- Thami, G.P., Kanwar, A.J. Fixed drug eruption due to metronidazole and tinidazole without cross-sensitivity to secnidazole. *Dermatology*, 1998. 196: 368.
- Varma, S.K., Nagpure, S., Misra, A.K., Dhanvijay, P. Fixed drug eruption due to fixed dose combination: A novel case. *Int J Health Allied Sci.*, 2013. 2:130-2.
- Weedon, D. *Skin Pathology*. 2nd. London: Churchill Livingstone; 2002. The lichenoid reaction pattern ('interface dermatitis') pp. 42–3.
