

FIXED DRUG ERUPTION DUE TO METRONIDAZOLE: REVIEW OF LITERATURE AND A CASE REPORT

Wahlang JB, Sangma KA, Marak MD, Brahma DK*, Lynrah KG, Ksih A

NORTH EASTERN INDIRA GANDHI REGIONAL INSTITUTE OF HEALTH AND MEDICAL SCIENCES (NEIGRIHMS), Mawdiangdiang, Shillong - 793018, India

ABSTRACT:

Fixed drug eruption (FDE) is common type of drug eruption seen in skin clinics. FDE usually occurs within hours of administration of the offending agent. Most commonly implicated are sulphonamides, salicylates, oxyphenbutazones, tetracycline, dapsone, chlordiazepoxide, barbiturates, phenolphthalein, morphine, codeine, quinine and derivatives, phenacetin, erythromycin, griseofulvin, mebendazole, meprobamate etc. We hereby report a case of fixed drug eruption on glans penis due to metronidazole, a nitroimidazole-derivative clinically indicated in trichomoniasis, amebiasis, giardiasis, anaerobic and mixed antibacterial infections. A patient administered metronidazole IV developed erythematous superficial non-tender ulceration over the glans penis on the second day of treatment with Inj. Metronidazole. A provisional diagnosis of metronidazole induced fixed drug eruption was made, metronidazole inj. was stopped and the patient was managed with Tab. Prednisolone 30mg/day tapered over 10 days and Fusidic acid+Betamethasone cream.

KEY WORDS: Fixed drug eruption, Glans penis, Metronidazole

INTRODUCTION:

A drug-induced reaction should be considered in any patient who is taking medications and who suddenly develops a symmetric cutaneous eruption. ^[1] Although the true incidence of adverse drug reactions (ADRs) is difficult to quantify, there is abundant evidence that cutaneous drug reactions (CDRs) are among the most frequent adverse events in patients receiving drug therapy. ^[2] Among all hospitalized patients, the incidence of CDRs has been found to range from 1 to 3%. ^[3,4]

Fixed drug eruption (FDE) is common type of drug eruption seen in skin clinics. FDE represents a unique CDR pattern characterized by skin lesion(s) that recur at the same anatomic site(s) upon repeated exposures to an offending agent. Most commonly, the skin lesion is a dusky erythematous macule and is usually found on the extremities, lips, genitalia and perianal areas, although any skin or mucosal surface may be involved. The skin lesions may be associated with a burning sensation and may be present in multiple numbers or progress to the development of central vesicles and bullae, particularly after the repeated use of an agent. ^[2] Persistent hyperpigmentation at the site of the lesion is normally seen after healing. Cross-sensitivity may occur with structurally similar drugs. The offending drug is thought to function as a hapten that preferentially binds to basal keratinocytes, thereby releasing lymphokines and antibodies thus damaging the basal cell layer. ^[5] The skin findings may be associated with nonspecific constitutional symptoms, including fever, malaise, nausea, and

* Corresponding Author:

Dr. Dhriti Kr. Brahma
Assistant Professor of Pharmacology
NORTH EASTERN INDIRA GANDHI REGIONAL INSTITUTE OF HEALTH AND MEDICAL SCIENCES
(NEIGRIHMS)
Mawdiangdiang, Shillong – 793018
Email: dbdhriti168@gmail.com

vomiting. FDE usually occurs within hours of administration of the offending agent. Most commonly implicated are sulphonamides, salicylates, oxyphenbutazones, tetracycline, dapsone, chlorthalidone, barbiturates, phenolphthalein, morphine, codeine, quinine and derivatives, phenacetin, erythromycin, griseofulvin, mebendazole, meprobamate etc.^[6,7,8] Certain medications also appear to have a tendency for certain anatomic locations (e.g., tetracyclines: genitalia). Many drugs such as dapsone, griseofulvin, erythromycin etc. are commonly used but FDE occurs rarely.^[9] Most commonly involved site of FDEs is glans penis.^[8]

We report a case of fixed drug eruption (FDE) due to metronidazole. We also carried out the causality and severity assessment associated adverse drug reactions (ADR) as per the Naranjo algorithm^[10], Hartwig scale^[11] and Modified Schumock and Thornton^[12] scales respectively.

METHOD:

The case was detected in the Dermatology department following referral from the inpatient department of Surgery and subsequently treated by dermatology department. The case was also informed to the Department of Pharmacology by a Senior Resident Doctor of Dermatology Department.

CASE REPORT:

Metronidazole is a synthetic, nitroimidazole-derivative clinically indicated in trichomoniasis, amebiasis, giardiasis, anaerobic and mixed antibacterial infections.^[13, 14] It's a prodrug that is activated by reduction of the nitro group by susceptible organisms^[15] and acts by getting reduced to a product which interacts with DNA to cause a loss of helical DNA structure and strand breakage resulting in inhibition of protein synthesis and cell death in susceptible organism.^[16] Side effects rarely are severe enough to discontinue therapy. Common side effects are headache, nausea, dry mouth, and a metallic taste. Vomiting, diarrhoea, and abdominal distress are experienced occasionally. The most dangerous side effects are Neurotoxic side effects (e.g., dizziness, vertigo, and very rarely, encephalopathy, convulsions, incoordination, and ataxia) mandate metronidazole discontinuation. The drug also should be withdrawn if numbness or paresthesias occur. Urticaria, flushing, and pruritus are indications of drug sensitivity. It rarely causes toxic epidermal necrolysis.^[13] Metronidazole and other nitroimidazole-derivative, tinidazole, ornidazole, secnidazole and satranidazole have been used for a long time including self medication without any serious side effects. Increasing reports of FDEs caused by metronidazole and tinidazole are available now.^[17, 18] Reports of FDE caused by ornidazole are also available in recent time.^[19, 20] However, genital FDE on glans penis due to metronidazole occurs rarely so much so, in books it is not mentioned in the list of causative drugs.

This is the case of a 22 year old male patient. He was admitted in the General Surgery ward of North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong, Meghalaya for Appendicitis. He was administered Metronidazole infusion 500 mg IV 12 Hourly, Inj. Cefotaxime 1 gm IV/IM 12 Hourly, Inj. Ranitidine 50 mg IV/IM 8 Hourly, inj. Metoclopramide IM/IV stat & sos basis and IV fluids. He developed itching in some part of the body including glans penis on the very first day of above treatment and noticed erosion over the glans penis on 2nd day. The case was referred to Dermatology department next day. On examination, vitals were stable and there was no pus discharge. He was nondiabetic and he denied history of any sexual exposure. There was single superficial non-tender ulceration with erythematous halo over the glans without lymphadenopathy.



The case was provisionally diagnosed as FDE due to metronidazole considering the previous history of pruritus and FDE secondary to metronidazole and patient was advised to stop IV Metronidazole. Our provisional diagnosis was supported by literature review which revealed the presence of fixed drug eruption due to metronidazole.

Complete blood count, random blood sugar and serum electrolyte showed within normal limits. The patient was advised to continue with IV fluid, Inj. Cefotaxime, Tab Paracetamol sos and Tab Ranitidine 50 mg 12 hourly.

The FDE was managed with Tab. Prednisolone 30 mg/day tapered over 10 days, along with Tab. Ranitidine, Tab. Cetirizine 10 mg 1 tablet HS and Fusidic acid+Betamethasone cream.

Follow up on the 4th day of treatment, there was no pruritus, erythematous ulceration was subsiding. On the 11th day no lesion was seen except a hyperpigmented area. Patient and his attendants were counseled not to consume metronidazole in future. The assessment showed probable (Score - 5), moderate (level - 4) and preventable type of ADR as per Naranjo algorithm,^[10] Hartwig scale^[11] and modified Schumock and Thornton Scale^[12] respectively.

DISCUSSION:

The exact pathogenesis of FDE is unknown, although antibodies, antibody-dependent cell-mediated cytotoxicity, and serum factors have been implicated.^[21] According to one hypothesis FDE is classified as a type IVc immunologic reaction because of latent cytotoxic T cells in the lesions, which may become reactivated. There is also an association with HLA class I antigens, suggesting that there may be a genetic predisposition to these reactions.^[22] The peak incidence of FDE is 21-30 years and male:female incidence is generally equal, although any age/sex may be affected. Genetic predisposition to FDE appears to occur in individuals with a family history of diabetes mellitus, atopy, and drug allergies.^[23]

FDEs have a predilection for the glans Penis^[8] and erosions are usually well demarcated erythematous areas which may be bullous and subsequently ulcerated. In one of the reports oral Metronidazole caused fixed drug eruptions on Penis.^[9] In another report, FDE started on the 2nd day in a patient administered intravenous metronidazole.^[24] FDEs due to metronidazole usually occur within 30 min to 8 hours following administration of drug.^[19] In one of the study, ADR started after 8 hour of Metronidazole,^[25] and in another study reaction started only after 3rd day of Re-challenge.^[26] In our case also metronidazole was administered IV and the reaction started on the 1st day onwards on penis. This early onset may be due to the IV route of the drug. Our patient is a 22 years male which is within the common age group of FDEs (21 to 30 years).

Laboratory findings of a patient with FDE demonstrate interface dermatitis with basal vacuolization and necrosis of keratinocytes, which may lead to sub-epidermal blistering in florid lesions. Lymphocytes and incontinent melanocytes are often found in the epidermis.^[27] Biopsy may be one tool for the diagnosis of FDE, but systemic re-challenge is currently the standard method for diagnosis.

CONCLUSION:

We presented this case of FDE as it was detected in the initial days of starting the Dermatology OPD facilities at our Institute. Our Institute is the only teaching medical Institute in the state of Meghalaya, India having started its UG and PG medical teaching programmes in the year 2008 and 2009 respectively. This is the first ever ADR reporting literature from our Institute and also from the state of Meghalaya, India. We want to make a point here is that the state of Meghalaya in India is having an ethnic tribal population of 85.9% as per the Census of India 2001. Therefore, ADR and related data from the Hospitals of this region may be important from the point of view of identifying new information about hazards associated with medicines towards promoting safer use of medicines. A vibrant Pharmacovigilance activity is the need of the hour in this region.

COMPETING INTERESTS:

There are no competing interests to declare.

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