

# Metronidazole Induced Bullous Fixed Drug Eruptions: A Case Report And A Review Of Literature

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## Citation

S Gupta, K Alam, S Palaian, M Singh, B Dwari, S Prabhu, M Prabhu, P Mishra. *Metronidazole Induced Bullous Fixed Drug Eruptions: A Case Report And A Review Of Literature*. The Internet Journal of Dermatology. 2006 Volume 5 Number 1.

## Abstract

Metronidazole is a synthetic nitroimidazole drug indicated in trichomoniasis, amebiasis, giardiasis and anaerobic and mixed bacterial infections. The common side effects due to this drug include GI disturbances, weakness, dizziness, ataxia, headache, drowsiness, insomnia, maculopapular skin eruptions, urticaria, pruritus, and occasionally erythema multiforme. We hereby report a case of bullous drug eruption due to metronidazole with an established causality, severity, preventability and predictability in a 99 year old male. Patient gave history of three days treatment with Inj. Metronidazole following which he developed severe generalized itching within one day of the above treatment and noticed the blisters on the second day. A diagnosis of metronidazole induced bullous eruption was made, and the patient was managed with Tab. Prednisolone 30mg/day tapered over 10 days, along with Tab Ranitidine, tab Fexofenadine, tab Cetirizine, Gentian violet paint and Fusidic acid+Betamethasone cream.

## INTRODUCTION

Metronidazole is a synthetic, nitroimidazole-derivative antibacterial and antiprotozoal agents.<sup>1</sup> It is indicated in trichomoniasis, amebiasis, giardiasis, anaerobic and mixed antibacterial infections.<sup>2</sup> It 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.<sup>3</sup> It produces dose related adverse effects, the commonest of which are gastro intestinal disturbances, especially nausea, vomiting and diarrhoea. Furred tongue, glossitis and stomatitis may be associated with over growth of candida, weakness, dizziness, ataxia, headache, drowsiness, insomnia, and change in mental state, maculopapular skin eruptions, urticaria, pruritus, and occasionally erythema multiforme.<sup>4</sup> However, bullous drug eruption due to metronidazole is rare. Hereby we report a case of bullous fixed drug eruption (FDE) due to metronidazole. We also carried out the causality, severity, preventability and predictability associated adverse drug reactions (ADR) as per the Naranjo algorithm,<sup>5</sup> Hartwig scale<sup>6</sup> and Modified Schumock and Thornton scales,<sup>7</sup> respectively.

## CASE REPORT

A 99 year old male presented to Dermatology Out Patients Department, Manipal Teaching Hospital, Pokhara, Nepal,

with complaints of itching and blisters over hands, legs and feet. Patient was a known case of hypertension, and was on antihypertensive medication. Patient gave past history of FDE secondary to Tab Metronidazole and diloxanide furoate. There was also past history of generalized pruritus after taking a single 400 mg tablet of metronidazole.

There was a three day history of treatment with Inj. Metronidazole 500mg iv Q8H, Inj. Cefotaxime 1gm IV 12<sup>th</sup> hourly, Tab Paracetamol 500mg 8<sup>th</sup> hourly, Tab. Enalapril 5 mg once daily in the night, Inj. Metoclopramide 1 ampoule IV stat and on SOS basis, and IV fluids. He developed severe generalized itching within one day of the above treatment and noticed the blisters on the second day.

On examination, vitals were stable. There was erythema over palms and mild edema over face, dorsae of hands and feet. Single erosion (measuring approximately 2.5x 3 cms) was present over right leg, with multiple intact bullae of sizes, ranging from 2x2 to 3x4 cms over right arm and forearm, dorsum of right hand, right knee and leg and few vesicles. (Figure 1-4) There was blanching macular erythema over the chest with patchy hyperpigmentation over dorsae of hands and over forearms. No target lesions were evident. There was no oro-genital mucosal involvement.

**Figure 1**

Figure 1-4: Multiple intact bullae of sizes ranging from 2x2 to 3x4 cms over dorsum of legs



**Figure 2**



**Figure 3**



**Figure 4**



Considering previous history of pruritus and FDE secondary to metronidazole, provisional diagnosis of Bullous fixed drug eruption was made and patient was advised to stop Inj Metronidazole / Inj Cefotaxime. Our provisional diagnosis was supported by the literature review which revealed the presence of reports of bullous eruptions due to Metronidazole.

Serum electrolytes / random blood sugar and complete blood count estimation were done. They were all within normal limits. The patient was advised to continue IV Fluids, Tab Paracetamol 500mg SOS, and Inj metoclopramide 1amp SOS.

The bullous eruptions were managed with Tab. Prednisolone 30mg/day tapered over 10 days, along with Tab Ranitidine 150mg 1tab B.D. (a.c.) for 10 days, Tab Fexofenadine 180mg 1tab OD for 6days, Tab Cetirizine 10mg 1 tab HS, Gentian violet paint over intact bulla and Fusidic acid+Betamethasone cream topical application twice daily

over eroded lesions.

On follow up, after 3 days, fever and loose stools subsided, pruritus had decreased, erythematous macular rash was subsiding and bullae were healing. On follow up after 10 days, no lesions were evident except patchy hyperpigmentation over hands. Patient and his attendants was counseled and advised not to consume Metronidazole in future. The causality assessment as per the Naranjo algorithm<sup>5</sup> revealed the ADR to be Probable (Naranjo score 8). The severity of the ADR was found to be [Moderate (Level 3)] as per the Modified Hartwig scale.<sup>6</sup> It was found that the ADR could have been definitely preventable as per the Modified Schumock and Thornton Scale.<sup>7</sup>

### DISCUSSION

Fluid filled blisters of diameter more than 0.5 cm are termed as bulla.<sup>8</sup> Bullous eruptions are commonly caused by primary irritants, allergic contact dermatitis, physical trauma, sunburn, insect bites or visceral infection with herpes; other cause includes pemphigus, dermatitis herpetiformis, erythema multiforme, epidermolysis, pemphigoid and drugs eruptions.<sup>9</sup> Common drugs causing bullous eruptions are Barbiturates, Captopril, Furosemide, Iodides, Nalidixic acid, Penicillamine, Phenylbutazone, Rifampicin, Salicylates and Sulphonamides. There are isolated reports of bullus eruption due to Metronidazole.<sup>10</sup>

The mechanism of most drug induced eruptions is unknown. However, most bullous drug reactions are the result of an immunologically mediated inflammatory response, although pseudo-porphyrria cutanea tarda (pseudo-PCT) is not associated with significant inflammation. Recent studies have reported the preferential activation of drug-specific CD8<sup>+</sup> T cells in the pathophysiology of some bullous drug eruptions.<sup>11</sup>

There are reports of bullous eruption due to oral Metronidazole. In one of the study the ADR started after 8 hr of oral Metronidazole,<sup>12</sup> where in another study the reaction started only after 3 days of rechallenge.<sup>13</sup> In our patient ADR developed on the second day. Moreover, the previous reports suggest that the patient developed bullous eruption due to oral Metronidazole earlier as well. In our case, the patient was on intravenous Metronidazole, which may account for the comparatively early onset of the lesion. This is also the first case report of bullus fixed drug eruption due to Metronidazole from Nepal.

Laboratory studies in a patient with FDE may show

leukocytosis, hypereosinophilia, and hypergammaglobulinemia. However, clinical and histologic features are the mainstay of diagnosis which reveal an interface or spongiotic dermatitis pattern. In the acute phase, the epidermis is characterized by dyskeratotic cells, exocytosis, edema, nuclear pyknosis, and hydropic degeneration of basal cells. An acute infiltrate consisting of lymphocytes, histiocytes, neutrophils, and eosinophils may be found around superficial and deep blood vessels. The quiescent lesion contains macrophages replete with melanin in the upper dermis. Papillary dermal fibrosis may develop consequent to prior episodes of FDE at the same site. Corticosteroids are the mainstay in the management of bullous drug eruptions. Our patient responded to steroid therapy and improved significantly after the treatment.

### CONCLUSION

Metronidazole is a commonly used drug in the management of conditions like amoebiasis, giardiasis and anaerobic infections. Although dermatological reactions such as bullous eruptions are not common with Metronidazole, one should be cautious while using Metronidazole. If an ADR is suspected, the drug should be stopped immediately and the patient should be managed carefully.

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