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Case Report

A Rare Case of Fixed Drug Eruption due to Ondansetron

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Abstract

Fixed drug eruption (FDE) is a unique type of cutaneous drug reaction that typically recurs in the identical locations on re-exposure to the attributed drug. FDE is characterized by the appearance of a single or multiple sharply demarcated violaceous erythematous plaques which heal with residual hyperpigmentation. A 27-year-old woman presented with multiple dark patches over her eyelids, mouth, lips, and shoulders of 1 week's duration. These lesions followed multiple erythematous plaques over the same areas which appeared within 4 hours of the intake of an ondansetron tablet, 12 days previously. The case was diagnosed as post-inflammatory hyperpigmentation following ondansetron-induced FDE. There was an identical episode 1 year earlier due to the intake of the same drug. The causality assessment pointed toward a probable/likely association as per the Naranjo algorithm and the WHO–UMC scale. There have been only a few cases of FDE due to ondansetron in the reported literature.

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What's Known

- Fixed drug eruption is very rare with ondansetron usage.
- A few cases on record are due to the parenteral usage of ondansetron.

What's New

- We describe a 27-year-old woman, who reported post-inflammatory hyperpigmentation following ondansetron-induced fixed drug eruption.
- This is the first recorded instance of oral ondansetron-induced fixed drug eruption.

Introduction

Fixed drug eruption (FDE), a unique type of cutaneous adverse drug reaction (ADR), was first described by Bourns in 1889 and later by Brocq as "eruption erythemato-pigmentee fixe". It is characterized by the appearance of a single or multiple sharply demarcated violaceous erythematous plaques that may blister and is often associated with pruritus.[1] The lesions generally leave behind some residual hyperpigmentation. These lesions typically appear within 30 minutes to 8 hours of the administration of the incriminated drug.[2] The usual sites of involvement are hands, feet, genitalia, and perianal region. However, these lesions are seen less commonly around the mouth and trunk.[2] There is a characteristic recurrence at the same sites on the repeat administration of the offending drug.[2] Here we present a rare case of FDE following the intake of ondansetron hydrochloride.

Case Presentation

A 27-year-old woman presented to the dermatology outpatient department of a tertiary care hospital with multiple sharply demarcated dark patches over her upper eyelids, over and around her lips, and on the upper part of her back (figure 1). There was slight itching associated with the currently presented lesions.

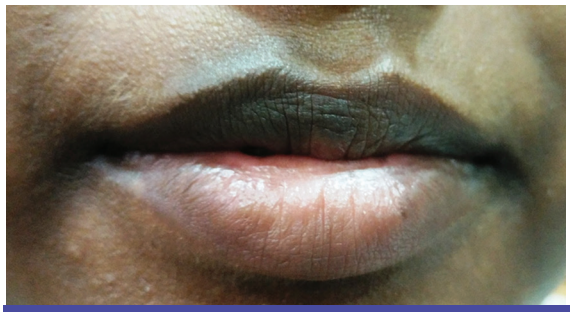

Figure 1: Photograph demonstrates post-inflammatory hyperpigmentation patches around the mouth and over the lips.

On enquiry, she narrated that 12 days earlier she had experienced nausea and a few bouts of vomiting, for which she was dispensed over the counter at a local medicine shop with oral ondansetron hydrochloride (4 mg). Within 4 hours of the intake of 1 tablet, multiple erythematous macular patches appeared in the same locations. She refrained from taking a 2nd dose of ondansetron as she remembered that she had had a similar episode of skin reactions appearing at the same sites, perhaps with the same or similar antiemetic medicine, 1 year before. She received no other treatment for these patches, which gradually resolved over 5 to 6 days leaving behind the dark patches with which she presented.

A complete blood count was done and it was found to be within normal limits. Clinically, the Nikolsky sign was negative. There were no significant past incidences of any other ADRs apart from this. The patient categorically denied taking any homeopathic or herbal remedies as well. She gave no history of allergies or any notable medical conditions which could have contributed to this. The personal and family history of the patient was unremarkable as well. A diagnosis of post-inflammatory hyperpigmentation following FDE was made based on this evidence. She was also given a steroid (mometasone 0.1%) cream and 5-mg levocetirizine tablets for 1 week. The hyperpigmented patches gradually reduced in size over a fortnight. The patient was advised to avoid taking ondansetron or its analogues like granisetron, palonosetron, tropisetron, or dolasetron in the future.

Written consent was obtained from the patient to report the case and relevant photographs.

Discussion

Ondansetron is a prototypical antiemetic drug belonging to the serotonin 5-HT_3A receptor antagonist family, the other members being granisetron, palonosetron, dolasetron, and tropisetron. The 1st generation 5-HT_3 receptor antagonists have been the mainstay in the management of acute chemotherapy-induced nausea and vomiting and in preventing postoperative nausea and vomiting as demonstrated in clinical trials.[3,4] It is not helpful in motion sickness. The most frequently observed adverse effects are constipation or diarrhea, headache, and light-headedness. These agents have been shown experimentally to induce small but statistically significant QT-interval prolongation.[5] Ondansetron has been reported to cause extrapyramidal side effects in a considerable number of cases.[6] There have been only 2 reported cases of FDE due to ondansetron in the reported literature, which makes this case extremely rare.[7,8]

A study by Zhang et al.[9] indicated that ondansetron might have some role in the treatment of schizophrenia, as an adjunct to haloperidol. The authors reported the combination to significantly improve negative schizophrenia symptoms, with patients taking both drugs experiencing fewer of the adverse effects commonly associated with haloperidol. A previous trial by Zullino et al.[10] had found ondansetron to be of value in the treatment of antipsychotic-induced tardive dyskinesia in schizophrenic patients and the study patients also showed notable regression of the disease's symptoms.

The number of drugs capable of producing FDE is significantly high. The commonly incriminated drugs causing FDE are allopurinol, barbiturates, benzodiazepines, captopril, clindamycin, carbamazepine, cephalosporins, dapsone, gentamycin, gold, lithium, NSAIDs, penicillins, phenolphthalein, phenytoin, sulphonamides, tetracyclines, and thiazides. A large series from India reported by Sharma et al.[11] found that the most reported drugs causing FDE were sulphonamides and NSAIDs. Co-trimoxazole has been also implicated as the major drug causing FDE in another major study by Thankappann et al.[12] A 9-year-long Iranian study by Kavousii et al.[13] also reported that co-trimoxazole caused the most cases of FDE. A recent French study by Brahimi et al.[14] pointed to paracetamol as the most commonly incriminated agent.

It has been demonstrated that intraepidermal CD8+T cells with an effector-memory phenotype residing in FDE lesions have a major contributing role in the genesis of localized tissue damage.[15] Intraepidermal CD8+ T cells, when activated, destroy the adjacent keratinocytes and this leads to the proliferation of cytokines such as interferon-gamma and cytotoxic granules

into the milieu, thus causing tissue injury.[15] The lesional epidermis proliferates interleukin 15 (IL-15), which maintains the endurance of CD8+T cells, even without any antigenic stimuli. The intraepidermal ingress of IL-10-producing CD4+T cells and CD8+T cells, including Foxp3+ regulatory T cells, during the progression of a severe episode of FDE serves to reduce the epidermal damage.[16] The early release of histamine from mast cells or basophils has been demonstrated in FDE, based on suction blister fluid levels. Notably higher frequencies of HLAB22 and HLA-Cw1 antigens were found in 36 patients (in a study by Pellicano et al.[17]) with FDE and familial cases do occur, suggesting a genetic predisposition in the causative spectrum.

The ethical problem of ascertaining the causality of the offending drug by repeat administration has led to the use of assessment scales such as the Naranjo probability scale and the WHO–UMC scale. A detailed Naranjo assessment was carried out and it revealed a score of +7 (i.e. probable ADR).[18] There were previous conclusive reports (+1); the adverse event appeared after the use of the drug (+2); the adverse event improved when the drug was discontinued (+1); there were no alternative drugs which could have caused this reaction (+2); and the patient had a history of a similar reaction 1 year previously (+1). As regards the WHO–UMC criteria, the causality of the FDE due to ondansetron was probable/likely.[19] The preventability criteria via the Schumock and Thornton scale were definitely preventable (as the patient had a definite history of ADR with the same drug).Assessment of the Hartwig severity revealed a level 3 score (as the ADR required that treatment with the suspected drug be stopped and an antidote be given to counter the ADR).

Conclusion

Patients should be educated on the potential symptoms and signs and the chance of the recurrence of FDE after the intake of culprit medications. Our patient was counseled regarding medication in general and advised, in particular, to avoid the tendency to self-treat any future episode of nausea and vomiting. Through this rare case report we convey a message to prescribers about the possibility of encountering such an adverse reaction. It is the responsibility of consumers, caregivers, and prescribers to report any suspected ADR to the nearest pharmacovigilance center. This case should be taken as a primary signal for pharmacovigilance. Usually more than 1 report is required to generate a pharmacovigilance signal depending on the quality and seriousness of the report.

Conflict of Interest: None declared.

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