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Title
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Journal
Dermatology Online Journal, 24(6)

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Publication Date
2018

DOI
10.5070/D3246040693

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Pheniramine maleate: an apparently safe drug causing bullous fixed drug eruption

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Abstract

Fixed drug eruption is a delayed type hypersensitivity reaction to a drug seen most frequently with antibiotics such as tetracyclines, sulfonamides, and NSAIDs such as naproxen and ibuprofen. Although H1-antihistamines rarely elicit cutaneous adverse effects, there have been a few reports in the literature implicating them in causing fixed drug eruption, particularly the piperazine derivatives (hydroxyzine, cetirizine, levocetirizine), and loratadine. However, cutaneous drug reactions with the alkylamine derivatives like pheniramine maleate are extremely uncommon and fixed drug eruptions have not been reported with any of the alkylamine antihistamines to date. We herein report a case of multifocal bullous fixed drug eruption following ingestion of pheniramine maleate.

Keywords: fixed drug eruption, pheniramine maleate

Introduction

Fixed drug eruption (FDE) is an uncommon cutaneous adverse drug reaction characterized clinically by the appearance of round to oval, well defined, dusky-red macules involving the skin and/or mucosae associated with itching and burning sensation. Sulfonamides, tetracyclines, NSAIDs such as naproxen, and ibuprofen are the most commonly implicated drugs [1]. H1-antihistamine are considered relatively safe drugs, with only a few isolated reports of FDE in the literature, mainly related to the piperazine derivatives and loratadine. However, cutaneous drug reactions with the alkylamine derivatives like chlorpheniramine and pheniramine maleate are extremely rare. We herein report a case of a 27-year-old woman with a multifocal bullous FDE following oral ingestion of 25mg of pheniramine maleate.

Case Synopsis

A 27-year-old woman presented to the dermatology outpatient department with multiple erythematous lesions over the trunk and extremities for the past

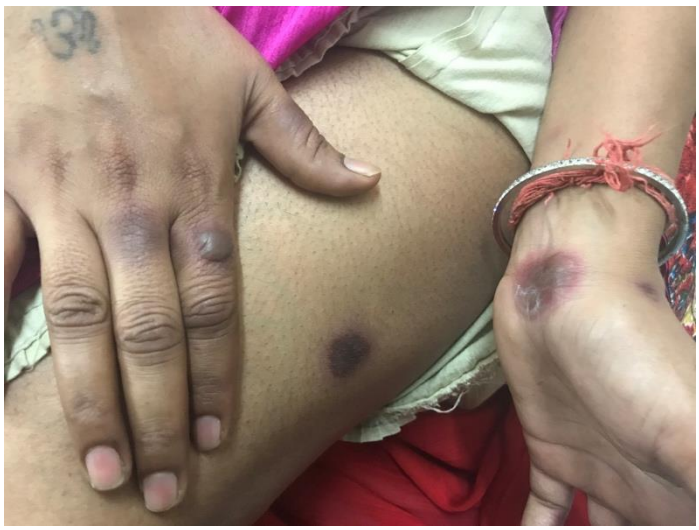

Figure 1. *Well defined, round, erythematous lesions with central duskiness and bullae present on the fingers and thighs developing 8 hours after intake of pheniramine maleate.*

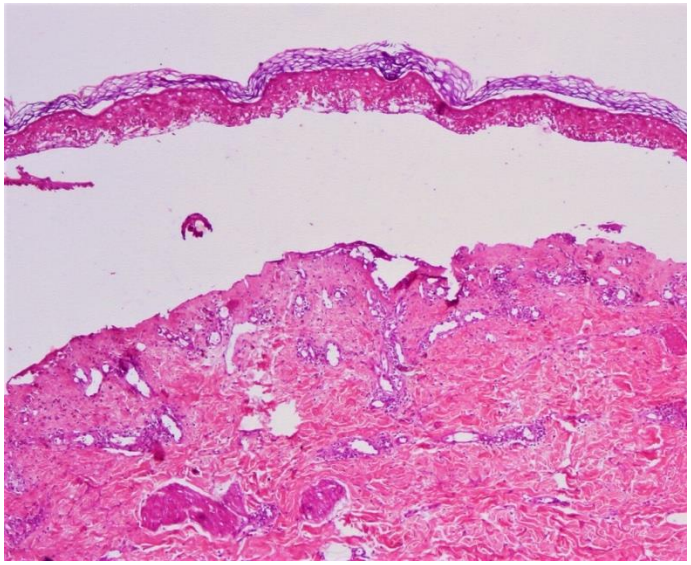

Figure 2. *Photomicrograph showing full thickness necrotic keratinocytes and separation of epidermis from the dermis. H&E, 40×.*

one day. She was suffering from an upper respiratory tract infection for which she was prescribed pheniramine maleate 25mg tablets along with paracetamol 500mg by a local practitioner on the previous day. Eight hours after taking the drugs, she developed redness and itching on the involved sites followed by bulla formation. Cutaneous examination revealed multiple, well defined, round, erythematous plaques with central hyperpigmentation and bullae present on the fingers, wrist, abdomen, and thighs (**Figure 1**). Oral cavity and genital mucosa were not involved. Patient had received paracetamol previously on several occasions without development of similar complaints in the past. The patient had a history of development of itchy erythematous lesions previously over fingers and thighs, involving the same sites, two years back, after intake of pheniramine maleate. Her past medical history and family history were unremarkable. Histopathological examination from the skin lesion on the thigh revealed full thickness necrotic keratinocytes and separation of epidermis from the dermis. The dermis showed pigmentary incontinence, proliferating vascular channels, and moderate perivascular inflammatory infiltrate with few eosinophils. (**Figure 2**). The patient was advised to stop pheniramine maleate and was given topical steroids (0.05% clobetasol propionate cream) to use twice a day on the affected areas along with oral prednisolone 30mg OD for 10 days. The lesions resolved within two weeks after withdrawal of pheniramine, with post inflammatory hyper-pigmentation as a sequela (**Figure 3**). De-challenge was thus satisfactory. Use of the Naranjo Adverse Drug Reaction (ADR) Probability Scale indicated a probable relationship between this cutaneous adverse effect and pheniramine maleate therapy in this patient. Based on the above findings, a diagnosis of bullous fixed drug eruption to pheniramine maleate was made. After resolution of lesions, patient was counselled for both oral provocation test and patch testing to confirm the diagnosis, but she declined both these tests owing to the fear of having the lesions again. Patient was advised not to take pheniramine maleate and other related antihistamines in the future.

Case Discussion

The term fixed drug eruption was used for the first time by Brocq in 1894. It is an uncommon cutaneous adverse reaction, which is almost always secondary to drug intake. Fixed drug eruptions are characterized by sudden appearance of annular, erythematous, pruritic macules, occurring within 30 minutes-8 hours following exposure to the causative drug [2]. These lesions usually resolve spontaneously after withdrawal of the offending drug with a characteristic residual hyperpigmentation. Recurrence

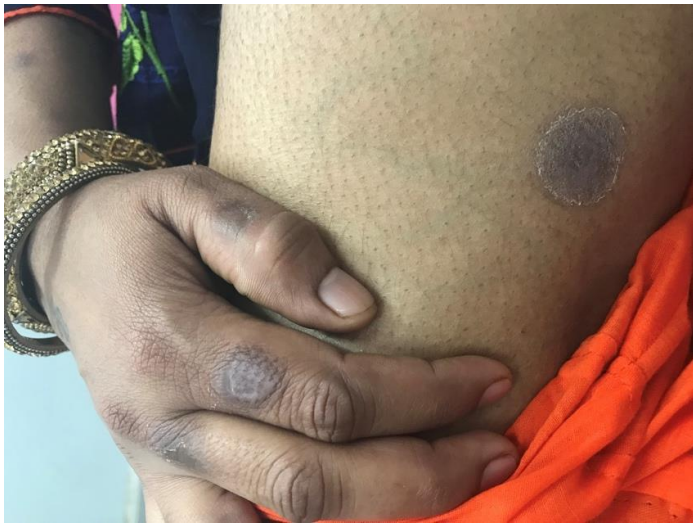

Figure 3. *Resolution of the lesions after withdrawal of pheniramines and with characteristic post inflammatory hyper-pigmentation as a sequela.*

of the reaction on same sites after re-administration of the drug is diagnostic.

Fixed drug eruption is a delayed type hypersensitivity reaction to a drug in a susceptible individual, mediated by intraepidermal effector-memory CD8+ T cells resident in the lesions. Reactivation of these CD8+ T cells on re-administration of the drug results in release of IFN-gamma and cytotoxic granules into the local microenvironment causing epidermal injury, thereby, triggering the lesions. Interleukin-20 has also been found to be responsible for the site-specificity of the lesions. [3].

The drugs most commonly implicated for causing FDEs include sulfonamides, tetracyclines, and NSAIDs such as naproxen and ibuprofen. H1-antihistaminics, used widely in clinical practice for the treatment of allergic disorders such as allergic rhinitis, urticaria, eczema, and other pruritic disorders, have an excellent safety profile and are uncommonly associated with adverse drug reactions (ADR). However, very rarely have they been implicated in causing cutaneous ADRs, including FDEs. The H1 antihistaminics that have been reported to elicit FDEs include mainly piperazine derivatives such as hydroxyzine, cetirizine, and levocetirizine; loratadine and diphenhydramine have been reported in a few cases [4-7].

Our patient presented with skin lesions suggestive of FDE after intake of a single dose of pheniramine maleate. Pheniramine maleate is a first-generation alkylamine H1-antihistamine. Alkylamines are characterized structurally by a carbon atom linking the diaryl moieties with the ethyl carbon chain and tertiary amino group (general structure: Ar (Ar1)-CH-CH_2CH_2-N-$(CH_3)^2$) [8]. Pheniramines are alkylamines containing a saturated carbon linking the phenyl and 2-pyridyl aryl groups. They consist of several congeners differing in the phenyl substituent at the para-position; H (pheniramine), the parent compound, and Cl (chlorpheniramine), Br (brompheniramine), (F) fluorpheniramine and (I) iodopheniramine, the halogenated pheniramines and their active dextro-enantiomers, dexchlorpheniramine or polaramine, and dexbrompheniramine, which are more potent and have a longer duration of action. Other alkylamines include the unsaturated analogues, pyrrobutamine, triprolidine, dimethindene, and phenindamine. Although there are isolated reports of cutaneous ADRs such as hypersensitivity reactions with chlorpheniramine and dexchlorpheniramine, FDEs have not been reported with any of the alkylamine antihistamines to date [9, 10].

In the present case, the patient presented with lesions with clinical and histological findings suggestive of FDE after intake of a single dose of pheniramine maleate. The presence of a temporal association between pheniramine intake with the development of the classical cutaneous lesions, the resolution of the lesions on withdrawal of the drug, and the history of similar lesions at the same sites in the past related to intake of pheniramine maleate, suggest that pheniramine was the culprit in our case. Although the patient had taken both acetaminophen and pheniramines simultaneously and there are a few reports of this drug causing FDE, the patient had received acetaminophen previously on several occasions without development of similar complaints suggesting that it was not the offender in our case. Also, Naranjo Adverse Drug Reaction (ADR) Probability Scale indicated a probable relationship between this cutaneous adverse effect and pheniramine maleate therapy in our patient. Although some authors consider oral re-challenge test and topical provocation test to be helpful in confirming the diagnosis of FDE, our patient refused these tests owing to fear of recurrence of the lesions. Moreover, the efficacy and safety of these tests remains doubtful.

Although the diagnosis of FDE is generally considered to be straightforward, it should be differentiated from other cutaneous drug reactions such as erythema multiforme (EM), Stevens-Johnson syndrome, nummular eczema, lichen planus, and discoid lupus erythematosus. There is considerable clinical and histopathological overlap between FDE and EM, but the presence of pigmentary incontinence in the dermis and eosinophils in the inflammatory infiltrate was more suggestive of FDE than EM in our case. Moreover, rapid onset of skin

lesions after drug intake, recurrence of the reaction on the same sites after re-administration of the drug, the presence of post inflammatory hyper-pigmentation as a sequela, the presence of only a few lesions without any acral predilection, and the absence of typical target lesions, mucosal involvement, and systemic symptoms pointed towards a diagnosis of FDE in our case.

Conclusion

Our patient presented with FDE related to a commonly used H1- antihistamine, pheniramine maleate. Since FDEs have a tendency of cross-sensitivity with other drugs, other alkylamine antihistamines and antihistamines belonging to other classes, such as diphenhydramine and doxylamine (ethanolamines) and tripelennamine (ethylenediamine), which have a structure similar to pheniramine, should be avoided by the patient in future.

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