Fixed Drug Eruptions Due To/Caused by Levocetirizine and Cetirizine: An Uncommon Adverse Cutaneous Drug Reaction to Commonly Used Piperazine Derivatives

Dear Editor,

Piperazine derivative antihistamines like cetirizine and levocetirizine are commonly used anti-pruritic agents. Fixed drug eruption (FDE) is a rarely reported side effect of these drugs. Identification of causative agent becomes challenging since patients and doctors often do not suspect easily available and safe antihistamines. Here, we report three cases of FDE due to the piperazine class of antihistamines.

Case 1

A 38 year old man presented with pigmented FDE on the trunk, upper arms, thighs [Figure 1] and lower lip. There had been five such episodes, the last being a year and a half back with medications for fever, cough, and sneezing. Suspected drugs included amoxicillin, paracetamol, etoricoxib, dextromethorphan and cetirizine.

Case 2

A 28 year old man developed bullous FDE over the palm [Figure 2], penile shaft and glans, after taking a drug for urticaria. There had been seven such episodes in the last 15 years associated with medications consumed for rhinitis and fever. Suspected drugs included cetirizine, levocetirizine, fexofenadine, hydroxyzine and loratadine.

Case 3

A 17 year old female presented with pigmented FDE on multiple sites [Figure 3] including the lips after taking medicines for recurrent sinusitis and generalized weakness. This was her fourth episode and the suspected drugs included paracetamol, multivitamins, ferrous sulfate, levocetirizine and cetirizine.

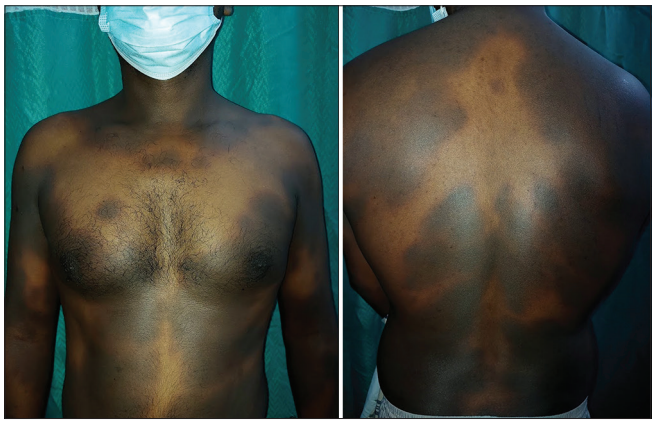

Figure 1: Case 1: Multiple large well-defined hyperpigmented patches on the trunk and arms

Recurrent episodes had led to drug phobia and patients took only alternative medicine or no treatment at all for their ailments. Oral drug provocation was done as per the institute protocol to alleviate her fear.[1] Supervised drug administration was done after taking an informed consent in a blinded manner, by starting from the least suspected drug. Drug provocation was initiated at 1/4th the routinely prescribed dose and then escalated to a full dose, if no reaction was noted. Drugs were administered every 12 hours to shorten the hospital stay. Oral challenge with cetirizine in case (1) and levocetirizine in cases (2) and (3) was positive.

Patients responded favorably to topical corticosteroids and alternative class antihistamines. Oral challenge with levocetirizine after 8 weeks was negative for case (1) but cases (2) and (3) denied further provocation. Usage of the Naranjo adverse drug reaction (ADR) probability scale suggested a probable relationship for all cases.[2]

Twenty one cases of FDE to piperazines have been reported till date [Table 1].[3-19] Mean age of presentation was 37.5 years (4–73 years) with male preponderance (Male:Female - 2.4:1). Clinical presentation was macular or bullous, as in our cases. Cetirizine and levocetirizine

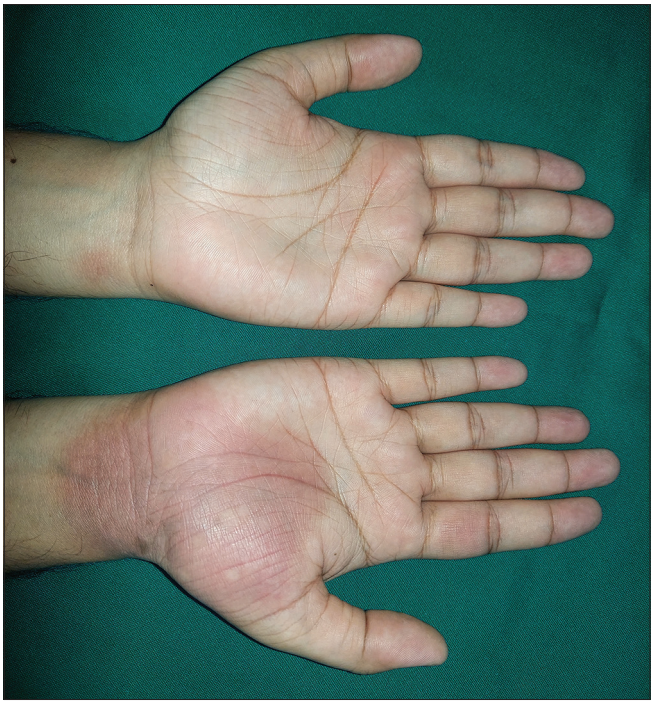

Figure 2: Case 2: Erythematous macule over right hand compared to the normal left palm

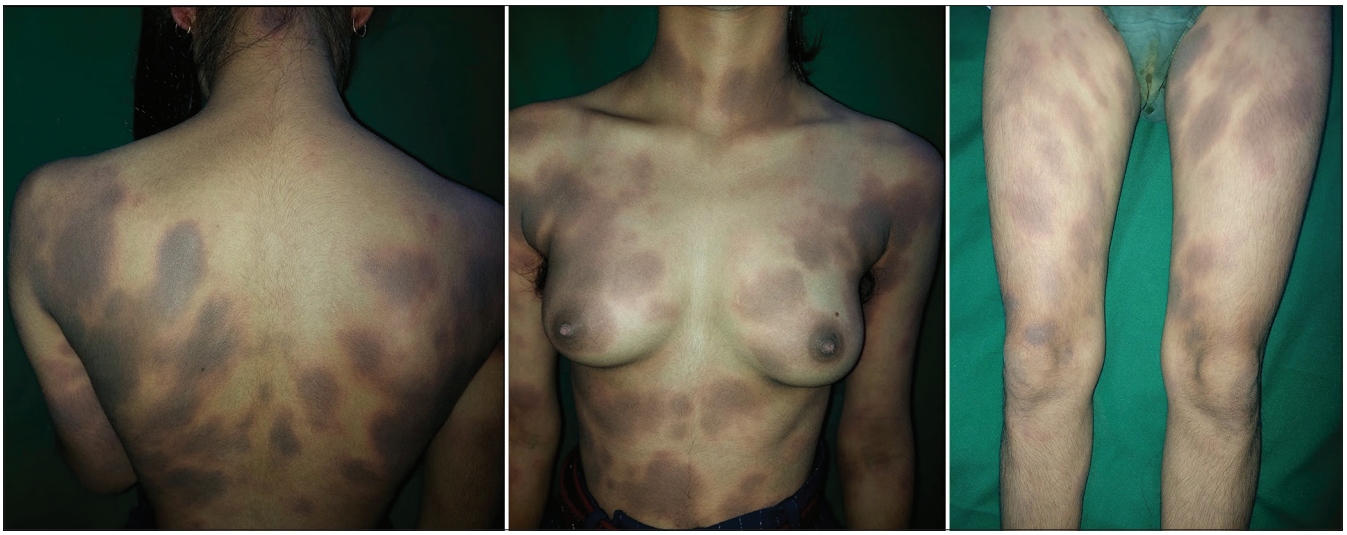

Figure 3: Case 3: Dusky erythematous macules over chest, abdomen, back and thighs

Table 1: Reported cases of fixed drug eruption to piperazine class of antihistamines

Study	Age/Sex	Presentation	Drugs implicated	Tests
Pereira *et al*.[3]	18/M	Pigmented FDE	Levocetirizine	Patch test positive for levocetirizine, hydroxyzine, and cetirizine
Bhari *et al*.[4]	21/M	Pigmented FDE	Levocetirizine	Patch test with hydroxyzine was positive at 48 h; oral re-challenge positive for levocetirizine
Mahajan *et al*.[5] (First report of FDE to levocetirizine)	34/M	Pigmented FDE	Levocetirizine (as well as cetirizine)	Oral re-challenge positive
Cravo *et al*.[6]	45/F	Multifocal bullous FDE	Cetirizine	Patch testing with hydroxyzine, cetirizine, and levocetirizine was positive
Ramos *et al*.[7]	21/M	Pigmented FDE	Hydroxyzine, cetirizine and aripiprazole	Patch test positive for hydroxyzine
Lee *et al*.[8]	4/M	Pigmented FDE	Levocetirizine and ketotifen	Skin-prick positive for levocetirizine; oral re-challenge positive for both
An *et al*.[9]	45/M	Pigmented FDE	Levocetirizine	No tests performed
Kim *et al*.[10]	73/F	Multifocal bullous FDE	Levocetirizine	Patch test was positive with levocetirizine
Jhaj *et al*.[11]	49/F	Multifocal bullous FDE	Levocetirizine	No re-challenge as lesions recurred on the same sites as previous episodes
Guptha *et al*.[12]	52/M	Pigmented FDE	Levocetirizine	Oral re-challenge positive
Ardeshna *et al*.[13]	21/M	Pigmented FDE	Cetirizine	No tests done
Gopal *et al*.[14]	34/F	Pigmented FDE	Cetirizine	No extra tests as no consent
Inamdar *et al*.[15]	45/M	Pigmented FDE	Cetirizine	Oral challenge positive
Assouère *et al*.[16]	73/M	Non-pigmented FDE	Cetirizine and hydroxyzine	Patch tests with cetirizine and hydroxyzine were negative
Gharami[17]	24/M	Solitary pigmented FDE	Cetirizine	Oral challenge positive
Kränke *et al*.[18]	27/M	Multifocal bullous FDE	Cetirizine	Patch test positive with cetirizine
Cohen *et al*.[19]	Four children-other details NA	Pigmented FDE	Hydroxyzine	Macrophage migration inhibiting factor (MIF) assay with hydroxyzine was positive
Gupta *et al*.[20]	52/F	Pigmented FDE	Levocetirizine and cetirizine	Oral re-challenge positive

were more commonly implicated than hydroxyzine. However, cross-reactivity between antihistamines of the same class has been reported.[3-6] Cetirizine has two enantiomers, levocetirizine and dextrocetirizine, which may differ significantly in their pharmacological properties like bioavailability, metabolism, excretion, potency and selectivity for receptors and toxicity.[20] This may explain a positive challenge to cetirizine but not levocetirizine in our case. A combination of *in vivo* tests such as prick and intradermal skin testing, patch testing and oral challenge is

generally considered the gold standard for diagnostic testing of any drug allergy. Patch testing shows positive results in up to 43% of cases. The prick test and intradermal skin test have a positivity of 23% and 67%, respectively.[21] We couldn't perform patch tests in our cases as an interval of at least 3 weeks is recommended after an episode before performing a patch test.[5]

In conclusion, we aim to highlight the importance of taking a detailed history of all medications taken by the patient and preparing a drug chart before undertaking diagnostic tests in case of an Adverse Cutaneous Drug Reaction (ADR).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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