Fixed drug eruption to cetirizine – role of patch testing

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Abstract

Antihistamines are prescribed for a wide variety of disorders like urticaria, eczema, allergies and infestations. Adverse reactions due to them is unusual and the incidence of fixed drug eruption is scarce. They are characterized by a sudden onset of edematous, erythematous plaques appearing at the same sites following an oral provocation with the drug and is proposed to be due to the epidermal $CD8^+$ T cells resident at the sites of these residual post inflammatory hyper pigmented macules. Antihistamines sharing a similar chemical structure have an increased likelihood of showing cross reactions and a patch test based evaluation can be carried out to deduce the offending drugs, cross reactions and alternative medications

Keywords: Antihistamines, Fixed drug eruptions, Patch testing.

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Introduction

Allergy to an antiallergen, although rare, is a remote possibility. Antihistamines serve as one of the commonest medications prescribed by a dermatologist for a wide variety of disorders. Fixed drug eruption (FDE) following the intake of cetirizine is a rare entity[1,2,3] and we report this case to emphasize upon this uncommon reaction to a commonly used drug and more importantly to highlight the significance of patch testing in such cases.

Case Report

A 15 year old girl presented with numerous, well circumscribed, pruritic, erythemato- violaceous plaques over the trunk and extremities (Fig. 1). History revealed consumption of tablet cetirizine 10mg the previous night which was prescribed by a dermatologist for hypertrophic lichen planus. Mucous membrane involvement was absent. There was no history of application of herbal medications or consumption of any other over the counter preparations. She claimed the current episode was preceded by several similar instances of identical lesions upon consumption of the aforementioned drug which appeared not only at the same sites, but with additional new sites each time. They tended to linger for about two weeks leaving behind brownish macules which were quiescent, except for an occasional impulse to itch. Previous medical history included congenital choledochal cyst excision with Roux-en-Y hepaticojejunostomy with re-exploration of the anastomosis for hepatic stones at 10 years of age. A battery of tests proved to be unremarkable.

Based on the typical history, a diagnosis of FDE to cetirizine was made and a patch test was carried out six weeks later (to overcome the refractory period)[4] upon the back and over the residual hyperpigmented macules (non-lesional and lesional skin). Commercially available antihistamines such as cetirizine, levocetirizine, hydroxyzine, chlorpheniramine, cyproheptadine, ebastine, loratidine and fexofenadine were used and their tablet formulations were powdered and petroleum jelly was used to make appropriate 10% concentrations of the drug which were employed in the patch testing.

The lesions were reviewed 20 minutes after the removal of the patches on day 2 and day 4.[4] Reactivation of the lesional skin in the form of erythema, infiltration, papules and itching (score ++)[5] was perceived for cetirizine, levocetirizine, hydroxyzine (Fig. 2). No reaction was observed to any of the drugs over the normal skin (Fig. 3). Oral administration of ebsatine, cyproheptadine, loratidine and fexofenadine yielded no reactions and were thus prescribed as suitable alternatives**.**

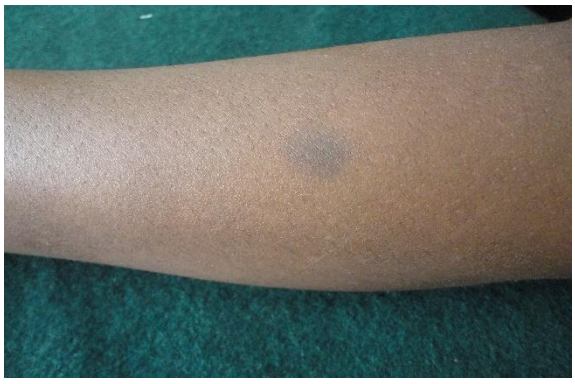

Fig. 1: Fixed drug eruption to cetirizine

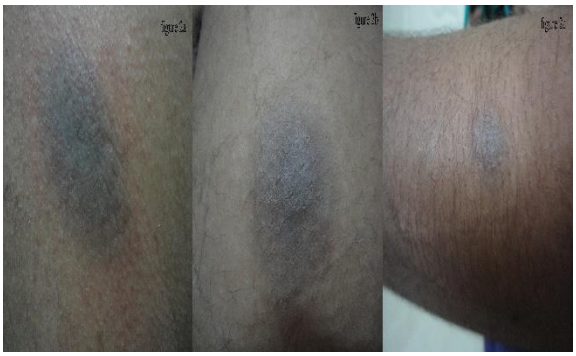

Fig. 2: Positive patch test over the lesional skin
2a: Cetirizine
2b: Levocetirizine
2c: Hydroxyzine

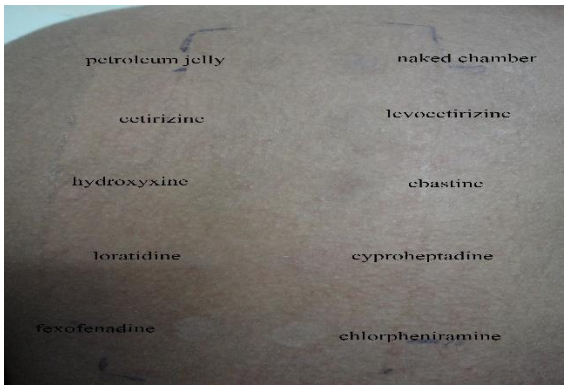

Fig. 3: Negative patch test over the non lesional normal skin

Discussion

H_1 Antihistamines are categorized on the basis of their chemical structure as ethanolamines, ethylenediamines, alkylamines, piperazines, piperidines and phenothiazines.[5] Catergorized under piperazine antihistamines are cylizine, chlorcyclizine, hydroxyxine, meclizine, buclizine, cetirizine and levocetrizine.[5]

Hydroxyxine is a first generation H_1 Antihistamine with two active metabolites i.e.; cetrizine and levocetirizine. 45% of hydroxyzine is transformed into cetirizine in the body.[1] Cetirizine is a second-generation antihistamine having a rapid onset of action and long half- life.[6] Levocetirizine, another second generation antihistamine is the active (R)-enantiomer of cetirizine and has twice of the affinity to H_{1-} receptor compared to cetirizine.

The positive lesional reactions to cetirizine, levocetirizine and hydroxyzine is explained by the cross reactivity to the common piperzine group and hence must be avoided.[1,2]

Systemically administered antihistamines rarely induce allergic hypersensitivity and is most often in the form of urticaria, morbilliform and scarlatiniform eruptions, erythema multiforme, photosensitivity and anaphylactic shock.[7]

FDE lesions are uncommon and appear when susceptible individuals are sensitized to a particular drug.[8] They occur as single or multiple, sharply demarcated, pruritic, erythematous macules which evolve into edematous plaques and recur when the implicated drug is taken, at precisely same sites.[9] They however disappear upon discontinuation of the drug and resolve spontaneously leaving behind hyperpigmentation.[8] These persist as gray-brown macules for prolonged periods unless the causative drug is given. Reactivation of the lesions typically occur within 24 hours following the drug intake.[9]

FDEs are a form of delayed-type hypersensitivity reaction showing the following stages:[8]

Stage 1: Resting phase - Intraepidermal $CD8^+$ T cells with an effector – memory phenotype reside in the areas of residual hyperpigmentation.

Stage 2: Drug intake - Intraepidermal $CD8^+$ T cells are activated to release IFNY and cytotoxic granules into the local microenvironment. The mast cells localized in the vicinity of epidermis also contribute to the activation of the intraepidermal $CD8^+$ T Cells via induction of intracellular cell adhesion molecules on the surrounding keratinocytes through the action of TNFα.

Stage 3: Acute evolving phase - Keratinocytes are killed by the direct action of the intraepidermal $CD8^+$ T cells and also $CD4^+$ T cells recruited later on from the the circulation.

Stage 4: Resolution phase - a proportion of intraepidermal $CD8^+T$ cells are prevented from undergoing apoptosis by IL-15 secreted by the keratinocytes which leads to the persistence of memory T cell population

A Patch test based assessment is an insightful option for the evaluation of FDE. The reactivity is observed only in the lesional skin (correlating with the localized collection of $CD8^+T$ cells)[8] and the rate of positivity may range from 20% to 43%[9,10]

Patch tests must be performed with the drug mixed in petroleum to 10-20% or diluted in water at the same concentration. Although positive tests maybe elicited using 50% of the drug it should not utilized as stronger delayed reactions may occur on day 3- 7, indicating patch test sensitization.[9] The merits of patch testing are- Firstly, it has a high safety profile contrary to the risky oral provocation tests.[9,10] Secondly, testing for multiple medications maybe carried out when a history of polypharmacy is present serving as a screening test and is therefore recommended as the initial diagnostic tool in FDE.[9] Thirdly, cross reactivity testing between related drugs can be carried out which is explained by the existence of similar immunogenic chemical structures which are recognized by the immune system as one. This is imperative as it serves to impose additional drug restrictions. Fourthly, evidence-based safe tolerable drugs can be determined.

However, the downfalls include a generous number of false negative results which may be attributed to the

timing of patch testing (should be performed 6 weeks after the resolution of lesions in order to avoid the refractory period).[4] Drug metabolites may be the inciting factor for the FDE which cannot be recruited for the study. There is a limited availability of pure substances and the commercially available preparations need to be employed for testing, thus making it difficult to rule out the possibility of additives and coloring agents as the offending agents. Another important drawback is that drugs with limited penetration or lipophilic properties cannot be tested.[1,9]

In conclusion, FDE to antihistamines is a very rare phenomenon with the propensity to show cross reactions. In the event of an encounter with such adverse reactions, an attempt must be made to carry out a patch test based evaluation which, unlike the risky oral provocation has the additional benefits of ascertaining the cause, cross-reactions and suitable alternatives.

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