

## Phenylephrine induced fixed drug eruption: a rare case of cross sensitivity

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### ABSTRACT

Fixed drug eruption (FDE) is a type of dermatosis characterized by recurrent lesions at exactly the same sites with each administration of the causative agents. FDEs are common types of drug eruptions amongst all cutaneous drug-induced side effects, mostly by intermittent exposure. Multiple drugs with common chemical structure can cause same type of lesions at same site called as cross sensitivity. There are many causative agents and the incidence of FDEs for a particular drug depends on the frequency of its use. Though usually not severe or fatal, cosmetic embarrassment is main problem, especially when they recur on the previously affected sites leaving behind residual hyperpigmentation. Phenylephrine is a sympathomimetic agent, given orally for the symptomatic relief of nasal congestion. It is also commonly combined with other ingredients in preparations intended for the relief of cough and cold symptoms. Considering the frequent use of Phenylephrine, associated drug eruptions generally appear to be rare, cross sensitivity with pseudoephedrine is even rarer. In our case phenylephrine was self-administered to control cold induced congestion and patient developed FDE on vermillion of upper lip, which healed after 2 weeks leaving hyperpigmentation and reappear on same site after re-challenge also. She has history of FDEs due to pseudoephedrine on same site on lips. This is a rare case of sympathomimetics induced FDE with cross sensitivity between phenylephrine and pseudoephedrine; hence we are reporting it here.

**Keywords:** FDE, Cross sensitivity, Phenylephrine, Pseudoephedrine sympathomimetics

### INTRODUCTION

Fixed drug eruption (FDE) is a type of dermatosis characterized by recurrent lesions at exactly the same sites with each administration of the causative agents. Brocq coined the term 'fixed eruption' in 1984 to describe a pattern of skin eruptions due to antipyrine. T-cell mediated FDE, is a localized variant of a delayed type hypersensitivity reaction in response to drugs and is characterized by sudden onset of single or multiple sharply demarcated, erythematous macules and plaques.<sup>1</sup> FDEs are common types of drug eruptions amongst all

cutaneous drug-induced side effects, mostly by intermittent exposure. Multiple drugs with common chemical structure can cause same type of lesions at same site. Itching or burning is usually associated with FDEs, well circumscribed, erythematous macules, patches, or plaques that leave hyperpigmentation after resolving. Occasionally vesicles or bullae may be seen. There are many causative agents and the incidence of FDE for a particular drug depends on the frequency of its use. Analgesics, antibiotics, muscle relaxants and anticonvulsants are common FDEs causing drugs. Besides drugs fruits, nuts, nutritional supplements,

artificial colouring agents are other uncommonly suspected culprits.

According to clinical features and type of lesions, different types of fixed drug eruption have been described.<sup>2,7</sup> These include pigmented fixed drug eruption, generalized or multiple, Linear, wandering, non-pigmented FDEs, bullous, eczematous, urticarial, erythema dyschromicum perstans like FDE, vulvitis, oral and psoriasiform. One more type recently observed is cellulitis like eruption.<sup>8</sup>

To identify the causative agent, re-challenge to the suspected offending drug is the only known test. Patch testing and oral provocation have been used to identify the suspected agent and check for cross-sensitivities to medications.<sup>9,10</sup> Skin biopsy is the procedure of choice for confirming diagnosis.

Only symptomatic treatment is there for fixed drug eruptions (FDEs), including systemic antihistamines and topical corticosteroids. If infection is there, antibiotics and proper wound care may be needed. Hyperpigmentation due to inflammation may take several months to resolve.

Phenylephrine is a sympathomimetic agent, given orally for the symptomatic relief of nasal congestion. They are also commonly combined with other ingredients in preparations intended for the relief of cough and cold symptoms. Considering the frequent use of phenylephrine, associated drug eruptions generally appear to be rare, cross sensitivity with pseudoephedrine is even rarer and any case report of this type is not documented in literature.

Certain assessment scales are helpful to establish the causality. The commonly used scales are Naranjo's assessment scale and WHO-UMC scale for standardized case causality assessment.

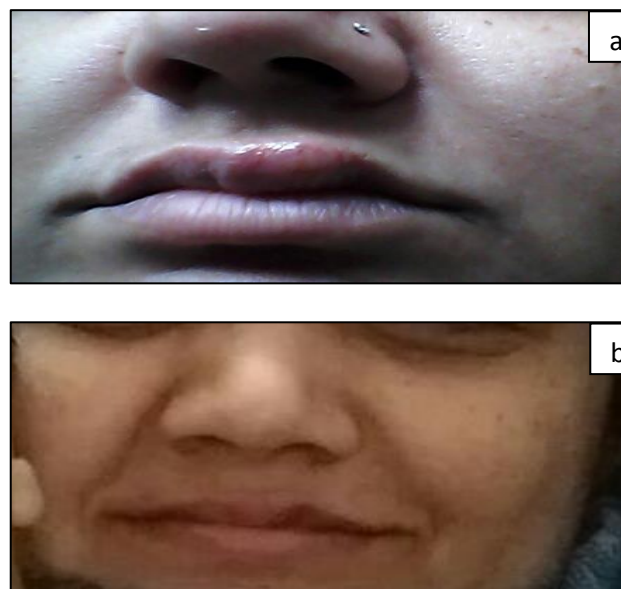
Re-challenge also called oral provocation test helps to establish the diagnosis as in our patient. Other methods include patch testing, prick test and intradermal skin test which have a positivity of 43%, 23% and 67% respectively.<sup>11</sup>

No case of this type has been reported previously. Here the first case report describes appearance of FDE over vermillion of lips in a 30 year old woman who had intermittent exposure to phenylephrine, also history of same FDE on lips with pseudoephedrine, a case of cross sensitivity. No specific treatment was instituted in this case and lesions healed over the time period of 2 weeks with encrustation.

## CASE REPORT

A 30 year old female patient presented with blisters measuring about 1 cm over vermillion of upper lip along

with burning and itching. History revealed that she has taken an OTC fixed dose combination drug MEDLER (paracetamol 325 mg, phenylephrine 10 mg, chlorpheniramine 2 mg and caffeine anhydrous 30 mg) 2 times a day. On 2<sup>nd</sup> day painful erythematous macule of 3-4 mm along with swelling of upper lip developed. On 3<sup>rd</sup> day blister of about 1cm filled with serous fluid developed on same site associated with burning and itching [Figure 1 (a)].



**Figure 1 (a and b): Initial presentation with bullous eruptions and healed lesion with hyperpigmentation on vermillion of upper lip.**

Patient was afebrile and there were no other associated systemic complaints. Her biochemical and haematological parameters were within normal limits. On examination she was alert, her pulse and B.P. were normal. She had no pallor, no icterus, no lymphadenopathy, no clubbing and no pedal oedema.

She had history of blistering type FDEs below the eyes, on cheeks, arms and abdomen from ibuprofen and mefenamic acid. History also revealed that she had FDEs on vermillion of lips several times after taking OTC SINAREST (paracetamol 500 mg, pseudoephedrine hydrochloride 10 mg, chlorpheniramine maleate 2 mg and caffeine anhydrous 30 mg). After consulting a doctor she stopped taking SINAREST and started self-medication with MEDLER whenever she had cold with same problem happening again 2 times. 3<sup>rd</sup> times she reported to the clinician with the same problem.

Based on patient history and clinical examination a provisional diagnosis of FDEs due to fixed drug combination was made. As patient had FDEs due to FDC containing pseudoephedrine 10 mg. Phenylephrine was considered as suspected culprit, as a case of cross sensitivity with pseudoephedrine. No skin biopsy was done. As patient had taken the FDC with antihistaminic

chlorpheniramine 2 mg, so patch test was not done, as test could give false results.

Drug was stopped and no specific treatment was given. She was asked to review in OPD after 2 weeks. The lesions healed with encrustation leaving hyperpigmented area of 3-4 mm on same site after removal of crust [Figure 1(b)].

She was again reviewed in OPD after 10 days and oral provocation test was applied with same FDC (Medler) after taking patient's consent, as previous reaction was local and without any systemic finding. This was a re-challenge which turned out to be positive (Figure 2). Then causality assessment was done using WHO-UMC scale as certain and case was reported to regional pharmacovigilance centre.<sup>12</sup>



**Figure 2: Recurrent lesion over vermilion of upper lip after 2 weeks on application of oral provocation test with same FDC.**

She has history of taking paracetamol 500 mg alone several times in past as analgesic and antipyretic without any eruption or reaction. So, paracetamol was excluded as culprit drug. Chlorpheniramine is antihistaminic, phenylephrine was considered as suspected drug.

She was advised against self-medication and not to take phenylephrine or pseudoephedrine either alone or as FDCs. After 9 weeks she had fever and rhinitis again. Subsequently she took paracetamol 500 mg and chlorpheniramine 4 mg as separate drugs. No hypersensitivity reaction occurred, excluding paracetamol and chlorpheniramine as suspected drug, confirming the diagnosis.

Thus patient was diagnosed as case of phenylephrine induced fixed drug eruption having cross sensitivity with pseudoephedrine on the basis of oral provocation tests and history.

## DISCUSSION

FDE is a cutaneous ADR which is characterized by recurrent eruptions when the offending drug is re-administered. The hallmark of FDEs is the recurrence in the same site on repeated administration of the offending drug.<sup>13</sup> Though usually not severe or fatal, cosmetic

embarrassment is main problem, especially when they recur on the previously affected sites leaving behind residual hyperpigmentation. In our case repeated lesion occur on same site after re-challenge with the offending FDC and individual offending drug was diagnosed after exclusion on the basis of history and oral challenge test.

This might be case of cross sensitivity between phenylephrine and other sympathomimetic drugs like pseudoephedrine. Both are included in the phenylamine family, having 2 main groups of drugs: phenylpropanolamine-derived (ephedrine, pseudoephedrine, and norephedrine) and phenylethanolamine-derived (phenylephrine and epinephrine). Potential cross reaction among them could be explained by very close chemical structures of these drugs. But the results reported in the literature are controversial, as no case report of cross sensitivity between phenylephrine and pseudoephedrine is mentioned. Although sympathomimetic drugs are used often, allergic reactions are rare, especially when the drugs are administered systemically. Cross-sensitivity may exist among catecholamine derivatives, although reported data on this are contradictory.<sup>14</sup>

The literature contains many reports of contact dermatitis to phenylephrine and FDEs due to pseudoephedrine.<sup>15,16</sup> One report of fixed drug eruption due to phenylephrine is also documented.<sup>17</sup> One report of cross sensitivity between phenylephrine and ethylephrine is also reported.<sup>18</sup> To best of our knowledge no such case of this type is reported in literature.

On WHO-UMC scale ADR is casually assessed as certain. A patch test might have been useful in this case, but it must be done on cases that are not on any immunosuppressants or anti-allergic agents in the past 48 hours. In our case, patient was on tablet Medler (FDC containing antihistaminic chlorpheniramine 2 mg) from past 72 hours. Hence, a patch test would have yielded false results.

## CONCLUSION

Phenylephrine and other sympathomimetics are commonly used as nasal decongestants as single agent or in FDCs available as OTC products. In our case fixed drug eruption will be related to phenylephrine due to suggestive relationship between drug intake and reaction onset, the relapse of eruption after withdrawal and reoccurrence on same site after re-challenge. Also history revealed cross sensitivity with pseudoephedrine. Thus, this report emphasizes a rare case of uncommon localization of FDE due to phenylephrine as well as cross sensitivity with pseudoephedrine. Clinicians should keep in mind and should be aware of the possibility of reactions to these drugs also, which are very frequently prescribed and available also as OTC drug products to manage symptoms of rhinitis.

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