

**Original Article**

A Study to Evaluate the Role of Patch Test in the Etiological Diagnosis of Fixed Drug Eruption

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Abstract

Background: *The fixed drug eruption is a common adverse drug reaction. Clear identification of the culprit drug is not always possible in the clinical setting, and oral rechallenge may induce new lesions or severe reactions.*

Objectives- *The main purpose of this study was to evaluate the role of patch testing in establishing an etiological diagnosis in fixed drug eruptions.*

Method: *85 patients with clinical diagnoses of fixed drug eruption were submitted to patch test in a period of one year July 2015 to June 2016 Dermatology Department IGMC Shimla.*

Results: *Patch test on lesional site were applied in 55 patients and positive results were seen in 20(36.4%). Non-lesional patch test were applied on upper back in 30 patients of mucosal FDE and all were negative. Most common drug implicated was tinidazole 6(30%), followed by ornidazole 4(20%), ciprofloxacin 3(15%), doxycycline 3(15%), paracetamol 2(10%), cotrimoxazole 1(5%), cetirizine 1(5%).*

Conclusion: *Patch test can be employed for the etiological diagnosis of fixed drug eruption, being safe, simple, inexpensive and reasonably sensitive. In fixed drug eruption patch test should be done only on the lesional site. Patch test applied on non-lesional sites give negative results.*

Keywords: *Fixed drug eruption, Drug Patch test, Cutaneous adverse drug reaction.*

Introduction

A fixed drug eruption (FDE) can be defined as a fixed exanthema (fixed eruption) which is induced

by drugs. It is an unusual type of cutaneous adverse drug reaction which is characterized by recurrent site-specific lesions each time when the

drug responsible is taken. Fixed eruptions can also be induced by ultraviolet (UV) light (UVA and/or UVB)² or foods³.

The credit for initial documentation of fixed drug eruption goes to “Bourns,⁴” who in (1889) described sharply demarcated hyperpigmentation of the lips and tongue after ingestion of antipyrine. Broq⁵ in 1984 coined the French term “eruption erythemato pigmentee fixe” from which the term fixed drug eruption is derived. Fixed drug eruption is known to arise from variety of medications like analgesics, anticonvulsants, antibiotics, antifungal agents and certain food particles.

Fixed drug eruption may account for as much as 16-21% of all cutaneous drug eruption⁷. The peak incidence of FDE is seen in 21-30 years, although any age may be affected and ratio of male : female is generally equal. Genetic susceptibility to develop FDE with an increased incidence of HLA-B22 has been reported⁹.

FDE usually appears as a solitary or a few number of well circumscribed, erythematous macules that evolve into edematous plaques. These lesions typically recur at exactly the same sites with each administration of the causative drug, but upon the discontinuation resolve spontaneously, leaving hyper pigmentation. After clinical resolution, the lesions remain quiescent and typically present as gray-brown macules or plaques on the skin, mucous membranes or on both for prolonged periods unless the causative drug is given.¹⁵

The lesions usually flare within 30 min to 8 hours¹⁵ after drug intake; mean length of time from drug intake to the onset of symptoms is approximately 2 hours.

The previously involved sites do not necessarily flare with each exposure, which is known as the refractory period¹⁶. The duration of this period is also variable, lasting from a few weeks to several months¹⁷. There are various clinical types of fixed drug eruption – most common is-pigmenting followed by generalized or multiple, erythema-multiforme-like¹⁹, toxic epidermal necrolysis-like²⁰, linear²¹, wandering,¹⁷ non pigmenting and

bullous fixed drug eruption. Drug patch tests (DPTs) represent a method of diagnostic testing which is low-risk, as they can reproduce delayed hypersensitivity to drugs and entail only a moderate exposure of the patients to the offending drugs. Pure drug form should be used for patch testing whenever possible in a concentrations of 1-10% in petrolatum, water or alcohol.^{22,23} Alternatively, liquid preparations or powder obtained from capsules or pulverized tablets or pills can be used at concentrations up to 30%²².

Material and Methods

Study design: This study evaluated role of patch test in patients with clinical diagnosis of fixed drug eruption attending the Department of Dermatology Venereology & Leprosy, Indira Gandhi Medical College, Shimla over a period of one year w.e.f 1st August 2015 till 31 July 2016

Inclusion criteria -All clinically diagnosed patients of fixed drug eruption were patch tested after 6 weeks of resolution of the lesion

Exclusion criteria-Patient of <15 years of age, patients on oral steroids, Pregnant and lactating women.

Patch test procedure -Finn chambers of aluminium having 9mm internal diameter and 0.7mm depth and a volume of 43µl were used for patch test. Commercialised drug 30% in petrolatum base was applied using Finn chambers on scanpor tape on lesional site, except in the patients with the mucosal involvement, in those cases patch test were applied on upper back.

Results -Results were graded according to the International Contact Dermatitis Research Group criteria and were recorded on a pre-designed proforma

Results

Out of 85 patients, there were 54(64%) males and 31 (36%) females. The age ranged from 16 -76 years. Mean age was found to be 40.6± 15.3 years. Maximum patients were 25 (29.4%) seen in the age group of 26-35 years followed by 19 (22.3%)

patients in the age group of 36-45 years. In our study 20 (23.5%) patients lesions appeared within 2 hours of taking drug, in 55 (64.7%) patients lesions appeared 2-48 hours of taking drug and in 10 (11.8%) patients lesions appeared after 48 hours of taking drug. Most common type of FDE was pigmented type in 52(61.2%) patients, followed by bullous FDE in 24(28.2%) patients, non-pigmented type was seen in 5(5.8%) patients, and miscellaneous types: erythema multiforme like, SJS-TEN like, linear FDE was seen in 4(4.7%) patients. Cutaneous involvement was seen in 43(51%) , followed by mucosal involvement of 30 (35%) patients, and both cutaneous and mucosal involvement in 12 (14%) no. of patients. Extremities were involved in maximum number of patients 45 (52.9%), hands in 29(34.1%) patients, arms in 27 (31.8%), forearm in 26 (30.6%), feet in 14(16.5%), legs in 24(28.2%) and thigh in 11(12.9%) patients. Oral mucosal involvement was seen in 35 (41.1%) patients, Genital mucosa in 32(37.6%) patients, trunk involvement in 11 (12.9%) patients. Majority of patients 53(62.3%) revealed 2-5 lesions, while multiple lesions (>5)

were seen in 17(20%) patients, while 15 (17.6%) patients had only single lesion of FDE.

Patch test results-Patch test on lesional site were applied in 55 patients and positive results were seen in 20(36.4%). Non-lesional patch test were applied on upper back in 30 patients of mucosal FDE and all were negative .Patch test positivity is seen in 23.5% patients in our study. In 8 patients only mild itching at the site of patch test was reported. Most common drug implicated was tinidazole 6(30%), followed by ornidazole 4(20%), ciprofloxacin 3(15%), doxycycline 3(15%), paracetamol 2(10%), cotrimoxazole 1 (5%), cetirizine 1(5%). There were 2 patients of FDE to antihistamines (cetirizine) one of them had positive patch test.

Table 3: Clinical Type of fixed drug eruption

Type of FDE	No. of Patients	Percentage
PIGMENTED	52	(61.2%)
BULLOUS	24	(28.2%)
NON-PIGMENTED	5	(5.8%)
OTHERS(LINEAR,EM LIKE,SJS-TEN LIKE)	4	(4.7%)

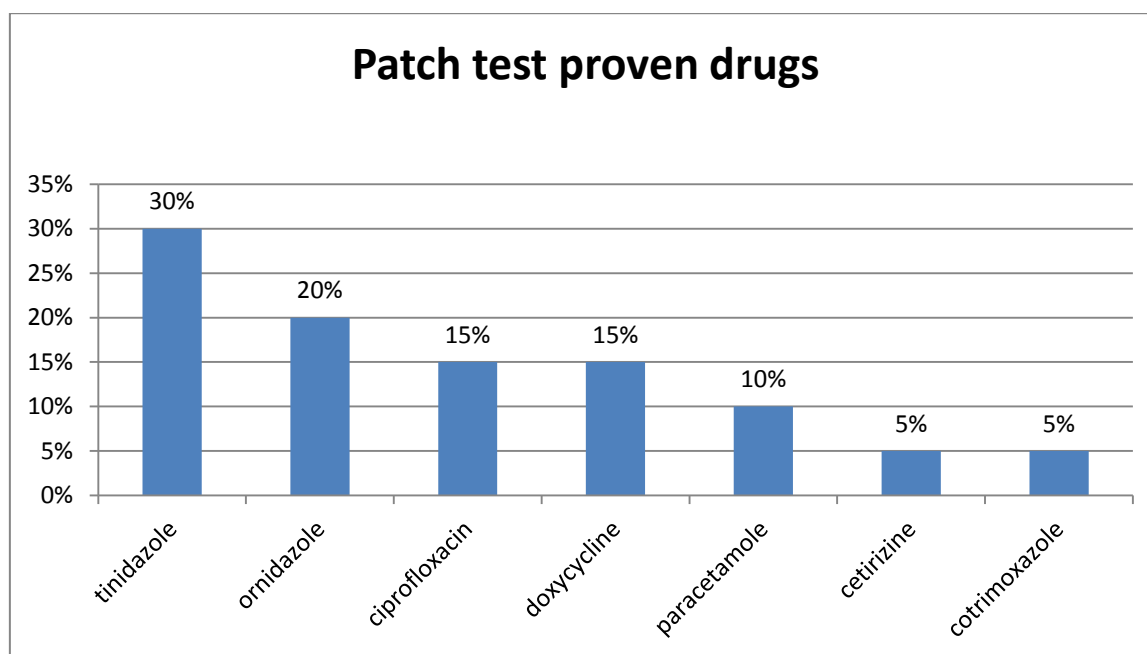


Figure 9: Patch test proven drugs

Table 11: Patch test results

Type Of Patch Test	Lesional	Non –Lesional
Total no of patients	55	30
Positive	20	0
Negative	35	30



Discussion

In situ drug patch tests have been recommended for a long time in investigating the responsible drug for FDE in order to avoid a provocation test, which remains the gold standard for the etiological diagnosis of FDE. Indeed, patch testing has proved a simple and safe method to confirm drug accountability, mainly when multiple drugs are suspected.

A total of 85 patients of FDE were included in the study .Out of 85 patients, 54(64%) were males and 31(36%) were females. In the present study the age ranged from 16 -76 years with mean age of 40.6±15.3 years. Maximum patients were 25 (29.4%) in the age group of 26-35 years followed by 19 (22.3%) patients in the age group of 36-45 years. This finding is consistent with the previous studies by Pai VV et al⁴⁴ and Andrade et al³¹ in which age groups involved were 18-78 years and 20 to 78 years respectively.

Regarding the clinical presentation majority of patients 53(62.3%) revealed 2-5 lesions, while more than 5 lesions were seen in 17(20%) patients and 15(17.6%) patients had only single lesion. In a study by Pai VV et al⁴⁴, the number of FDE lesions were 5 or less in 37(65%) patients and 20 (35%) patients with more than 5 lesions consistent with our study. In our study single episode was reported in 36 (42.3%) patients and multiple episodes in 49(57.6%) patients which is similar to the study by Pai VV et al, where history of recurrence was seen in 33 (57.8%) patients.

Majority of patients 55(64.7%) developed drug eruptions in 2-48 hours while in 20 (23.5%) patients lesions appeared rapidly within 2 hours and in rest 10 (11.8%) patients lesions appeared after 48 hours of drug intake. Pai VV et al and Aoum et al³³ reported the onset of lesion in majority of the patients within the first 48 hours of drug intake their findings are comparable to our study.

In our study lesions were most commonly located over oral mucosa in 35(41.2%) patients, followed by genital mucosa in 32(37.6%) patients, hands in 29(34.1%), arms in 27 (31.8%), forearm in 26 (30.6%), feet in 14(16.5%), legs in 24 (28.2%) and thigh in 11(12.9%) of patients.

In our study patch test at the lesional site were applied in 55 patients and positive results were seen in 20(36.4%) patients. Non-lesional patch test which were done in 30 patients of mucosal FDE were all negative. Lesional patch test positivity is 36.4% whereas total patch test positivity is 23.5% in our study. In 8 patients only mild itching at the site of patch test was observed. Most common drugs proven on patch test were tinidazole 6(30%), followed by ornidazole 4(20%), ciprofloxacin 3(15%), doxycycline 3(15%), paracetamol 2(10%), cotrimoxazole 1(5%), cetirizine 1(5%). In a study by Andrade et al³⁵ patch tests on lesional skin were positive in 21 patients (40.4%), most common implicated group of drug was NSAIDs in 95% patients. 9 (42.8%) patients were patch test positive for nimesulide, 9(42.8%) for piroxicam, 3(14.3%) for etoricoxib and 1(4%) to antihistamine (cetirizine). Cheng-Han Lee et al⁴¹ did patch testing in 12 of the 39 patients of FDE with the suspected causative agents over the previous lesion sites, four (33.3%) of whom had a positive reaction to the suspected drugs. In a study of 30 patients by Alanko et al⁵² 26 (87%) patients had positive patch test.

Earlier, tetracyclines were the most frequent cause of FDE, followed by sulphonamides and NSAIDs.⁴⁹ With the increasing use of, Nitroimidazoles, fluoroquinolones, and their fixed

combination frequently available over the counter and widely prescribed by physicians is now a major cause of FDE as is seen in our study also. Nitroimidazoles are the first line drugs for hepatic and intestinal amoebiasis. All the nitroimidazoles: metronidazole, tinidazole, ornidazole, secnidazole have a similar nitroimidazole ring but different side chains.

In our study, tinidazole, ornidazole, ciprofloxacin/norfloxacin-tinidazole -fixed dose combination was responsible for the greatest number of cases of FDE. This reflects the widespread use of these drugs for gastrointestinal infections in our part of the country. Our case series also provided some interesting findings such as two cases of recurrent FDE to cetirizine patch test confirmed in one of the patient, while the other showed negative patch test which is a less common cause of FDE.

Topical provocation testing is a safe diagnostic step. 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)⁵⁰. Drug metabolites may be responsible for the FDE which cannot be recruited for the applying patch test. 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. Patch testing with the presumed culprit drug is performed in an old FDE lesion. False-negative reactions are frequently reported, but the reactions from patch tests have been simply recorded as positive or negative,⁵⁸ probably according to the International Contact Dermatitis Research Group (ICDRG) criteria for interpretation of allergic contact dermatitis. The interpretation criteria, which have been recommended by the ICDRG, require infiltration as well as erythema to be positive. However, these criteria were not always applicable for the interpretation of patch test results in fixed drug eruption. An erythematous

macular reaction or darkening from the patch test was proved to be positive by systemic provocation.

A certain degree of erythema and infiltration could be missed under the hyper pigmentation in the lesion of FDE. The results of skin tests provide a reference to decide the order of drugs for systemic provocation, the final step for diagnosis. Drugs showing no reaction in skin tests can be tried initially. It is necessary to be careful not to ignore minor reactions in the interpretation of skin test results. Mere pruritus or burning may sometimes be meaningful, and an erythematous reaction may be missed because of residual hyperpigmentation. If the skin test results are still inconclusive, rechallenge can be tried, using non reactant drugs first. Cross-sensitivity needs to be excluded after identification through skin tests and/or rechallenge. Patch test in FDE is a useful and safe diagnostic step to identify the culprit and the cross reacting drug.

Conclusion

It can be concluded that diagnosis of the etiology of fixed drug eruption can be difficult specially in patients on multiple drugs. Patch test can be employed for the etiological diagnosis of fixed drug eruption, being safe, simple, inexpensive and reasonably sensitive. In fixed drug eruption patch test should be done only on the lesional site. Patch test applied on non-lesional sites give negative results. Antihistamines can also be a rare cause of fixed drug eruption.

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