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An Observational Study of Fixed Drug Eruptions Among Patients Attending a Tertiary Care Hospital in Eastern India

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Abstract: ***Background:*** *Adverse reaction to drugs are common and often manifested as a cutaneous eruption. Fixed drug eruption (FDE) is unique type of adverse cutaneous drug reaction, the diagnostic hallmark is its recurrent eruption occurring on the same site after re-exposure to offending agent.*
Objective: *The aim and objective was to study the clinical features, demographic details, and to determine various offending drugs causing FDE.*
Materials and Methods:*The study was carried out from June 2017 to June2019 in the Department of Dermatology, Venereology and Leprosy at tertiary care hospital of Jharkhand, India. A detailed history taking and thorough clinical examination were done for all the patients having FDE and were recorded in predesigned proforma.*
Results:*A total of 67 patients were studied for FDE among which 42(62.6%) were males and 25(37.3%) were females. Majority of the patients were adults aged between 18 to 52 years (53.7%). Commonly affected sites were trunk, extremities, lips, palm & sole, genitals and mucosa. Antimicrobials (28.3%) were most common group of drugs causing FDE followed byNon steroidal anti-inflammatory drugs (22.3%). History of FDE was positive in 46.3% of the patients. The most common complaintsafter intake of offending drug was pain & burning sensation over the lesion.*
Conclusion:*FDEs are common adverse cutaneous drug reactions withAntimicrobials drugs being the most common group causing FDE, with increased possibilities of generalized and extensive lesions in patients with history of FDE.*
Keywords: *adverse cutaneous drug reaction, fixed drug eruption, antimicrobials, non steroidal anti-inflammatory drugs,*

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I. Introduction

Theterm 'fixed eruption' was coined by Brocq in 1984[1].It is one of the most common forms of drug induced exanthems. Fixed drug eruption (FDE) is a form of classical delayed-type hypersensitivity reaction characterized by development of one or more well definedannular or oval patches with erythema and edema, sometimes surmounted by blister, as a result of systemic exposure to a drug or agent, these reactions normally resolve with post inflammatory hyperpigmentation. Repeated exposure to the offending drug may cause new lesions to develop in addition to 'lighting up' the older hyperpigmented lesions.[2] It can be seen over any part of the body such as trunk, face, extremities, oral and genital mucosa.Its incidence varies from 2.5% to 22% of all drug eruptions[3] including data from the Indian population[4]. The number of FDE cases are increasing because of increased use of drugs these days.FDE has been reported in both sexes and all ages. However,it is more common in adults, particularly in the age range of 20-50 year olds. FDE typically present 30 min to 8 h after drug exposure. Almost any drug can induce skin reaction; however, the commonest culprit drugs are antimicrobials, non-steroidal anti-inflammatory drugs (NSAIDs), and anti-epileptics, have drug eruption rate approaching 1-5%.[5]. The need for this study is to identify the common drugs responsible for causing FDE.

II. Materials And Methods

An observational cross sectional study was carried out in Department of Dermatology, Venereology and Leprosy at a tertiary care hospital in Jharkhand, eastern India, over a period of 2 years from June 2017 to June 2019. All patients with history of drug intake followed by development of classical FDE lesions and those who had a definite or probable adverse reaction according to the Naranjo probability score[6] were included in this study, after taking written consent. In every case, a detailed history was taken with regards to drug intake, its temporal correlation with FDE, duration and morphology of the rash, associated mucosal or systemic involvement, previous history of similar rash and improvement of lesion on withdrawal of the drug. If multiple

drugs were taken, then the most likely drug causing such reaction was stopped and patient was observed for any improvement in skin lesions. Patch testing or oralprovocation were not performed.

III. Results

A total of 729 adverse cutaneous drug reaction were reported during the study period, from June 2017 to June 2019. Of which 67 patients (42 males and 25 females) with FDE were enrolled for study, making it 9.2% of total ACDRs. Past history of FDE was positive in 31 patients (46.3%). The mean age of the patients was 35.3 years, with age range from 7 to 63 years. Majority of the patients were adults between 18 to 52 years old.

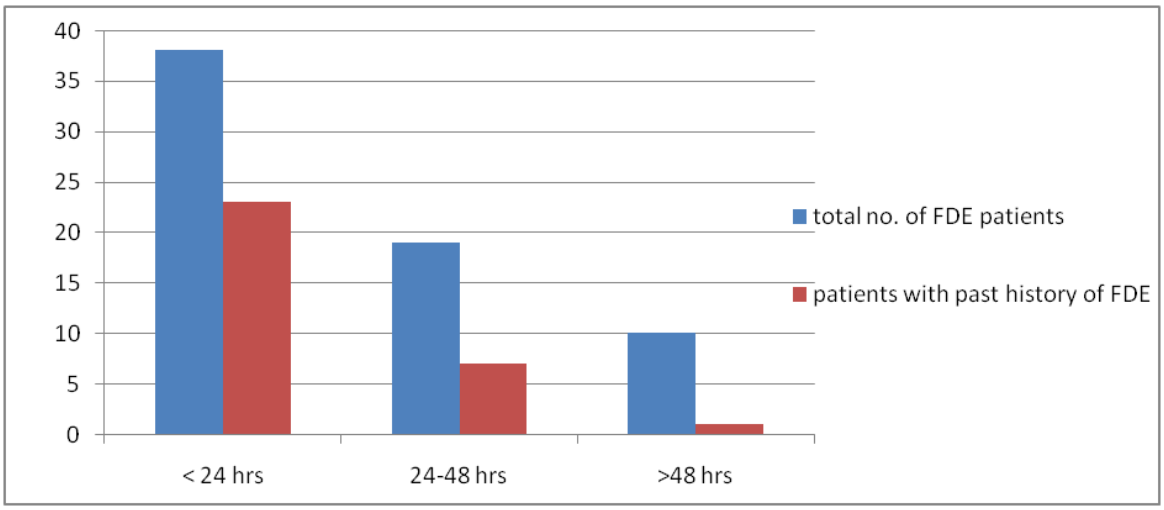


Fig 1. Onset of FDE in total number of the patients as compared with patients with recurrence

The lag period between intake of suspected drug and developement of lesion ranged from 0 (lesions appeared on the same day) to 1 month, with an average lag period of 1.3 days. 30 out of 57 patients who developed lesions within 48 hours had previous history of FDE,9 patients with a lag period of onset of FDE of a few hours gave no previous history of occurrence of similar lesion or any other drug reaction.Commonly affected sites were trunk (40.3%) extremities (37.3%) & lips. We had only 2 cases with involvement of genitalia.Number of FDE lesions varied from 1 to >5. Majority of the patients had well defined hyperpigmented patches, blisters were seen in 4 patients, and one patient had ulcerated lesion on buttock.The most common presenting complaint was burning sensation and pain at the hyperpigmented erythematous patch.

Antimicrobials and nonsteroidal anti-inflammatory drugs were the drugs implicated in a majority of patients. Fluoroquinalones were the most common antibiotic involved, accounting for 29 (43.2%) of the FDE cases, other drugs responsible for an FDE were ornidazole, amoxicillin, diclofenac, nimesulide, clonazepam, phenytoin. The drugs were prescribed in 43 patients and self medication in 24 patients. Fever was the most common illness for which patients had taken the culprit drug followed by gastroenteritis.

FDEs were treated by discontinuing the offending drug, topical corticosteroids and oral antihistamines. The lesion took 2-3 week to resolve but there was persistent post inflammatory hyperpigmentation till last follow-up.Diagnosis of FDE was clinical in all the patients.

According to Naranjo ADR probability scale showed probable in 43 (64.2%) cases, possible in 17 (25.4%) cases, and definite in 7 (10.4%) cases.

Drugs implicated in causing Fixed Drug Eruptions	
DRUG	Number of cases
• **Antimicrobials**	**33**
Ofloxacin + ornidazole	10
Ciprofloxacin + tinidazole	7
Norfloxacin	6
Metronidazole	3
Amoxicillin + clavulanic acid	3
Doxycycline	2
Cefixime	1
Ceftriaxone	1
• **NSAIDs**	**18**
Diclofenac	5
Nimesulide	4
Paracetamol	4
	2

Mefenamic acid	2
Aceclofenac	1
Ibuprofen	**4**
• **Antiepileptics**	3
Phenytoin	1
clonazepam	**4**
• **Antitubercular**	2
Isoniazide	2
Rifampicin	**3**
• **Ayurvedic & herbal medicines**	**5**
• **Others**	
TOTAL	**67**

IV. Discussion

The prevalence of adverse cutaneous drug reaction has been reported to be 1-5%. FDEs range from 15-20% of all ACDRs. Although our cases numbered too few to give definitive trends, there was a predominance of men (42 male 25 female). A slight male trend has been reported in some studies[7,8]. FDE can occur in any age,according to some authors, FDEs account for 14-22% of cutaneous drug reactions in children[9,10] but in our study there were only 2 children, 7 and 10 year old.

The most frequently affected sites in our study was trunk (40.3%) followed by extremities.Antimicrobials and NSAIDs are well known triggers for FDE[2,3] and were common culprits in our study too. Among the antimicrobials, fluoroquinolones were most commonly involved. Among NSAIDs diclofenac was found to be most commonly associated with FDE.

Genetically, FDE has been linked with HLA-B2[11,12]. Although the exact mechanism is not known, a cell mediated process is involved in initiating both the active and quiescent lesions. The offending drug acts as hapten that preferentially binds to basal keratinocytes, leading to an inflammatory response, via liberation of cytokines such as TNF-alpha, keratinocytes upregulate expression of the intercellular adhesion molecule-1 (ICAM-1). ICAM-1 acts as stimulus for activating CD8+ effector /memory T-cells play an important role in the reactivation of lesion with re-exposure to the offending drug or structurally related one[13,14] they produce a large amount of interferon-gamma, cytotoxic granules such as granzyme B & perforins, tumor necrosis factor alpha and cause tissue damage.

Re-challenge/provocation tests, intradermal tests, or skin prick tests are of significant value in identifying the culprit drug, but they need expertise, or may even re-precipitate life threatening ADRs that may raise ethical issues.

The high percentage of patients with recurrent FDEs underlines the importance of recognizing an FDE as well as avoiding administration of same or structurally related drug to the patient who once developed an FDE. Both patient as well as prescriber awareness is required to avoid inadvertent and unnecessary rechallenge with a causative drug.

The limitation of the study was no objective test was conducted to confirm the offending drug. Also, only that drug which was most likely to cause drug reaction was recorded instead of mentioning all the drugs in given patient.

V. Conclusion

Due to a wide variety of drugs available over the counters, FDE is an important type of ACDR frequently seen nowadays. Since FDE cannot be reversed and the pigmentation often persist indefinitely, prevention is the key. This can be done by better awareness about the causative drugs, the likelihood of recurrence with same or similar drugs and use of alternatives where possible.

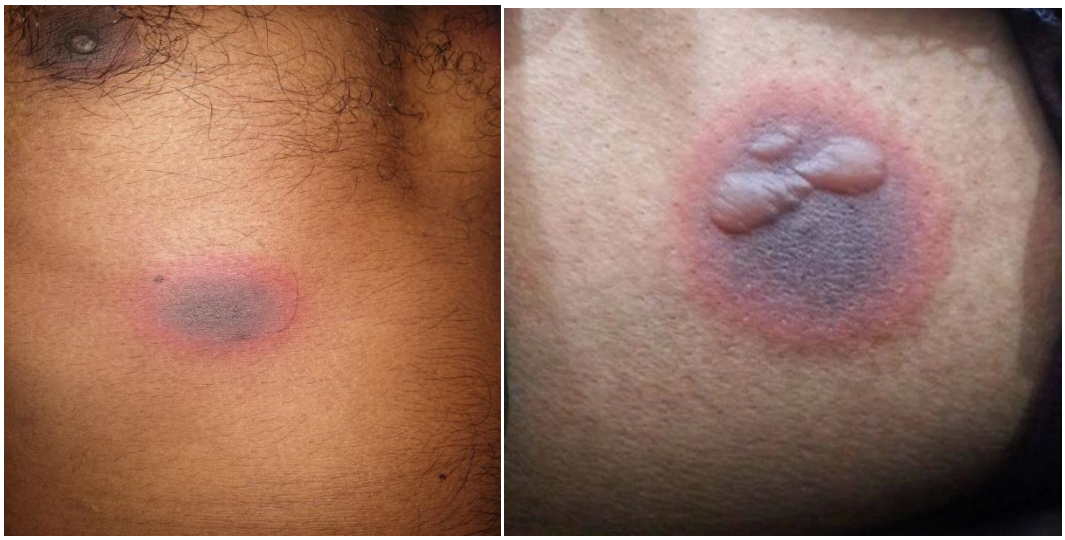


Fig 2, 3 showing a well defined patch of fixed drug eruption on the trunk, in fig 2 there is bullae formation in lesion of FDE

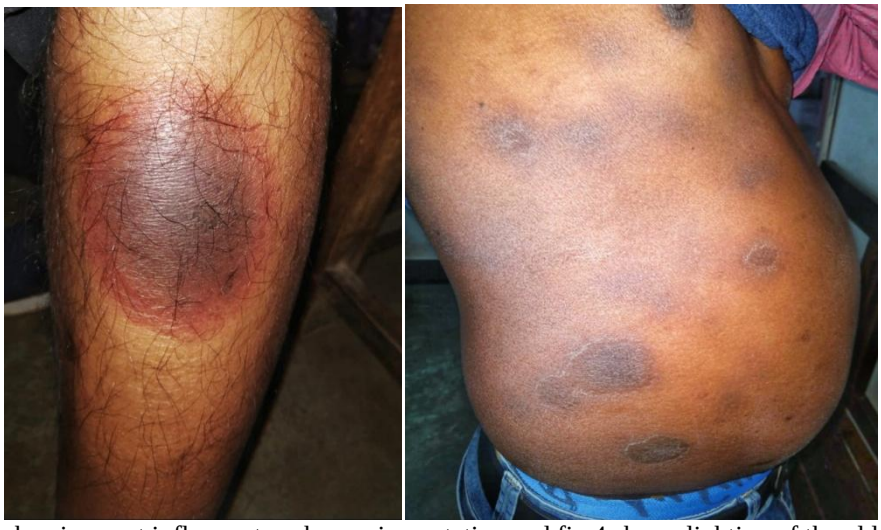
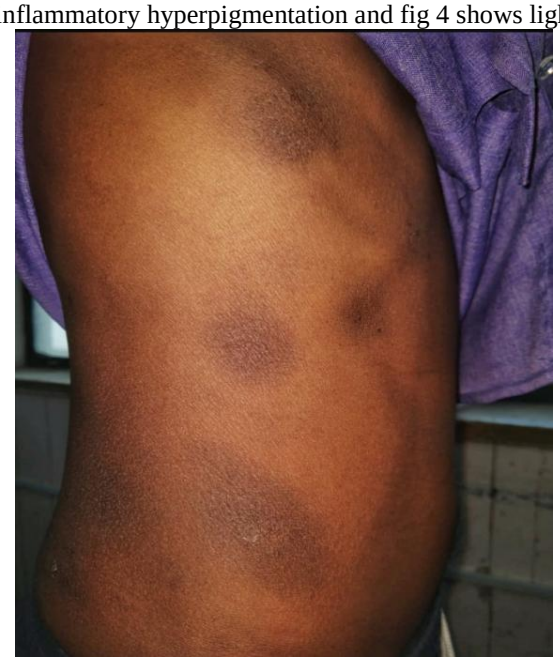


fig 4,5,6 showing post inflammatory hyperpigmentation and fig 4 shows lighting of the older lesion



VI. Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for 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.

VII.Financial support and sponsorship

Nil.

VIII.Conflicts of interest

There are no conflicts of interest.

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