IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 1 Ser.18 (January. 2021), PP 45-47
www.iosrjournals.org

A Prospective Study of Pattern of Fixed Drug Eruptions in A Tertiary Care Hospital

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Abstract
Introduction: *A fixed-drug eruption (FDE) is an immunological cutaneous adverse reaction characterized by sharply defined lichenoid lesion/s which occur/s at the same location every time there is exposure to the causative substance. Exogenous agents are the only known cause of FDE. It does not occur spontaneously or following an infection. The skin lesion sometimes resolves when medication is discontinued, but it usually results in long-lasting or even permanent pigmentation. Because of its characteristic features, FDE can be diagnosed with relative ease compared to other drug eruptions.*
Materials and Methods: *An observational cross sectional study was carried out in Department of Pharmacology, Kurnool Medical College and Govt General Hospital in Kurnool, south India, over a period of 1 year from October 2019 to October 2020. 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 WHO probability score were included in this study, after taking written consent.*
Results: *A total of 120 adverse cutaneous drug reactions were reported during the study period, from October 2019 to October 2020. Of which 32 patients (22 males and 10 females) with FDE were enrolled for study, making it 26.6% of total ACDRs. Past history of FDE was positive in 11 patients (34.3%). 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.*
Conclusion: *FDE is an important type of ACDR frequently seen nowadays. Since FDE cannot be reversed and the pigmentation often persists 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.*
Key Words: *Fixed drug eruption, WHO, ACDR.*

I. Introduction

A fixed-drug eruption (FDE) is an immunological cutaneous adverse reaction characterized by sharply defined lichenoid lesion/s which occur/s at the same location every time there is exposure to the causative substance. Exogenous agents are the only known cause of FDE. It does not occur spontaneously or following an infection. The skin lesion sometimes resolves when medication is discontinued, but it usually results in long-lasting or even permanent pigmentation. Because of its characteristic features, FDE can be diagnosed with relative ease compared to other drug eruptions.

The number of diagnosed FDE cases is increasing steadily, due in part to increased awareness by physicians, but also because of increased use of drugs. Its incidence, from different reports, varies from 2.5% to a high of 22% of all patients with cutaneous adverse drug reactions (CADRs), including data from the Indian population. Fixed-drug eruptions occur in both sexes and in all age groups, including infants and the elderly, although a majority of cases are seen in the age range 20-40 years.

Techniques to identify the causative drug are intradermal testing, patch tests and invitro tests like flow cytometry and cytokine assays. But there are problems with the availability, applicability and reliability of these tests. It is now generally agreed that the only reliable method for finding the causative drugs is the provocation method. The present study is an attempt to find out the drugs commonly causing fixed drug eruption in and around Kurnool by provocation tests.

II. Materials And Methods

An observational cross sectional study was carried out in Department of Pharmacology, Kurnool Medical College and Govt General Hospital in Kurnool, south India, over a period of 1 year from October 2019 to October 2020. 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 WHO probability score 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 oral provocation were not performed.

III. Results

A total of 120 adverse cutaneous drug reactions were reported during the study period, from October 2019 to October 2020. Of which 32 patients (22 males and 10 females) with FDE were enrolled for study, making it 26.6% of total ACDRs. Past history of FDE was positive in 11 patients (34.3%). 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.

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. 20 out of 32 patients who developed lesions within 48 hours had previous history of FDE, 10 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 23 patients and self medication in 9 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 WHO probability scale showed probable in 17 (53.12%) cases, possible in 15 (46.8%) cases.

Drug	Number of cases
Antimicrobials	**12**
Ofloxacin + Ornidazole	2
Norfloxacin	1
Metronidazole	1
Amoxicillin + Clavulanic acid	2
Doxycycline	1
Cefixime	2
Ceftriaxone	3
NSAIDs	**9**
Diclofenac	3
Nimesulide	1
Aceclofenac	3
Ibuprofen	2
Antiepileptics	**6**
Phenytoin	3
Clonazepam	3
Antitubercular	**5**
Isoniazide	3
Rifampicin	2

Table 1: Drugs Causing Fixed drug eruptions

S.No	WHO Probability Scale	N (%)
1	**Probable**	17 (53.12%)
2	**Possible**	15 (46.8%)

Table 2: WHO Probability Scale

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.

FDE can occur in any age, according to some authors, FDEs account for 14-22% of cutaneous drug reactions in children 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 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. 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 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.

V. Conclusion

FDE is an important type of ACDR frequently seen nowadays. Since FDE cannot be reversed and the pigmentation often persists 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.

Acknowledgement

Authors acknowledge the support of NCC-PvPI, Indian Pharmacopoeia commission, Ghaziabad, UP, India.

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