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Original Article

Current Causes and Clinical Pattern of Fixed Drug Eruption at a Tertiary Care Hospital

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ABSTRACT

Objective: To identify the current common causative drugs and the clinical pattern of FDE in Pakistani patients presenting to a Tertiary Care Hospital.

Study Design: Cross-sectional study.

Place and Duration of Study: Department of Dermatology Combined Military Hospital, Kharian Pakistan, from Nov 2018 to Oct 2021.

Methodology: Patients of all ages and sexes reporting in dermatology outpatient during the study period with Fixed drug eruption (FDE) were included in the study after taking informed consent. Diagnosis of FDE was based on the finding of well-demarcated erythematous patches or plaques and violaceous pigmentation. In cases where history was not suggestive, the drug was confirmed by an oral provocation test. In addition, the causative drug, site(s) affected, duration, number of skin lesions, history of FDE, and the purpose for using the drug were noted for each patient.

Results: Sixty-one patients were included in the study. Doxycycline (thirteen patients, 21.3%) was the commonest causative drug, followed by Quinolones and Paracetamol in ten (16.4%) patients each, Cotrimoxazole in eight (13.1%) patients and Nonsteroidal anti-inflammatory drugs (NSAIDs) in seven (11.5%) patients. Multiple lesions were common in patients with a history of FDE. The disease affected single-body sites in 16(26.23%) patients only. The most common site was the genital area in forty-two (71.19%) patients, followed by upper limbs in thirty-one (52.54%) patients and lips in twenty-eight (47.46%) patients. Only nineteen (31.1%) patients had developed the eruption for the first time.

Conclusions: Knowing the current causative drugs and carefully seeking a history of FDE may help prevent recurrent FDE.

Keywords: Causative drugs, Cutaneous adverse drug reactions, Fixed drug eruption.

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INTRODUCTION

Drug eruptions are common cutaneous disorders accounting for around 2 to 3% of dermatologic consultations.[1,2] Fixed drug eruption (FDE) is a specific type characterized by its recurrence at previously affected sites whenever the offending drug is readministered.[3,4]

The lesions may occur within half an hour to several hours after the intake of the offending drug.[5] It commonly involves mucocutaneous junctions, such as in areas around the mouth, lips, genitals, as well, as limbs and usually starts as itchy lesions with much irritation and burning sensation followed by eruption of well-demarcated erythematous to violaceous, round to oval plaques with a dusky center Blistering or erosions may occur in the lesion.[6,7] The lesions are sometimes multiple but commonly take the form of a few lesions. The severity varies from a small localized lesion to generalized involvement.[8,9] The lesions commonly heal with hyperpigmentation.

FDE is a common drug eruption representing approximately fourteen to twenty-two percent of all drug eruptions (0.28% to 0.66% of dermatologic consultations). 1-4 A large number of drugs are known to induce FDE.[2] Several studies from different parts of the world have described the causes and clinical patterns of FDE.[3,10] The frequency with which individual drugs cause FDE varies over time and in different countries. The causative drugs keep changing depending on clinicians' availability and prescription preferences. This study aimed to identify the current causative drugs and the clinical pattern of FDE in Pakistani patients presenting to the Hospital.

METHODOLOGY

The cross-sectional study was carried out at the Dermatology Outpatient of a Tertiary Care Hospital in central Punjab Pakistan, from November 2018 to October 2021. The Ethical Committee of the Hospital approved the study (Ref No 10 dated 30 Oct 2018).

Inclusion Criteria: Patients of all age groups and either gender reporting in Dermatology Outpatient during the study period with fixed drug eruption were included in the study.

Exclusion Criteria: All patients in whom the clinical diagnosis could not be established or cases in which at

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least 'probable' causality could not be established were excluded. Patients whose history did not reveal any compatible temporal relationship between drug exposure and rash were not included. Moreover, the cases where oral provocation tests could confirm no causative drug were also excluded from the study.

Informed consent was taken from all patients. Relevant history was taken from all patients included in the study, with special emphasis on the timings and dosages of all the drugs taken and the exact timings of the onset of drug eruption and its subsequent evolution. Patients were also inquired about the illness for which the offending drug was used. A detailed dermatological and systemic examination was performed on each patient. Diagnosis of Fixed drug eruption was clinical. It was based on the finding of clinically characteristic lesions attributable to a single identi-fiable drug with a history of compatible temporal relationship between drug exposure and rash. The disease was categorized as localized FDE or Genera-lized bullous fixed drug eruption (GBFDE) based on clinical findings and the course of the disease.[11] Diagnosis of FDE was made based on temporal correlation with the drug, eruption of well-demarcated erythematous macules with violaceous centre and surrounding erythematous concentric circles, in the absence of other systemic symptoms, and the rapid recovery that left residual hyperpigmentation after discontinuation of suspected drugs.

An oral provocation test confirmed drugs suggested by history after the informed consent of the patients. Patients were subjected to provocation tests after recovering from the presenting episode and being off medications for at least 48 hours. An oral provocation test was carried out by administering half of the therapeutic dose of the suspected drug. The test was considered positive for a particular drug if there was a reactivation of the lesions in the form of itching and/or erythema during the next twenty-four hours after administration of the drug being tested. In cases there was no reaction, the next drug was tried after a gap of forty-eight hours. The data collected for each patient on a predesigned proforma included: age, gender, drug exposure, the period between drug exposure and the onset of lesions, duration, number and sites of lesions, and the number of previous episodes.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 21, and descriptive statistics (mean, percentages, and frequency distribution) were used to evaluate the results.

RESULTS

An oral provocation test was performed on 73 patients and was found to be positive in sixty-one patients. The 12 cases where oral provocation tests could confirm no causative drug were excluded from the study. Of the sixty-one patients included in the study, fifty-four (88.5%) were male, and seven (11.5%) were female. The male-to-female ratio was 7.7:1. Age at presentation ranged from eight years to eighty-seven years with a mean of 38.04±15.87 years and a median of thirty-three years. Forty (65.6%) patients were aged between twenty to forty years.

Duration of the disease at presentation ranged from one to fourteen days with an average of 4.57±3.21 days. The size of the lesions ranged from less than one centimetre in diameter to very large lesions with a diameter of more than fifteen centimetres (Figure-1 & 2).

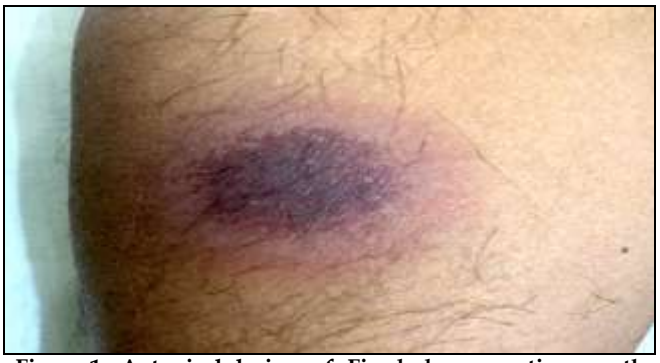

Figure-1: A typical lesion of Fixed drug eruption on the Forearm

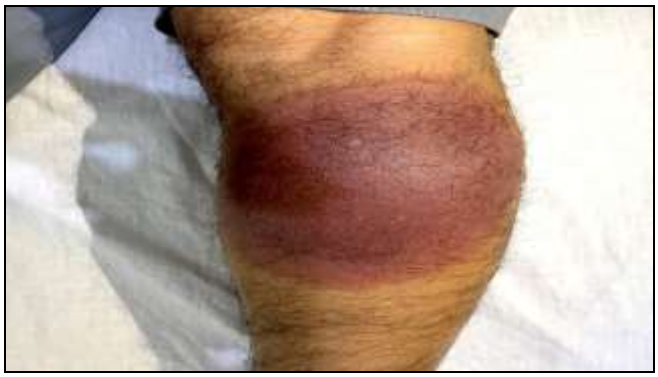

Figure-2: A Large Lesion of Fixed Drug Eruption on the back of the Leg

The number of skin lesions ranged from a single lesion to twenty lesions with a mean of 4.07±3.237 lesions. FDEs frequently develop as multiple lesions. A single solitary lesion was observed in ten (16.9 %) patients. FDE lesions were widespread in fourteen (23.73%) patients. Generalized bullous fixed drug

eruption was found in two patients. Thirty (50.8%) out of fifty-nine patients with a Localized type of disease had three or less than three lesions. Ten or more than ten lesions were found in only four patients. The frequency of drugs causing FDE is shown in Table-I.

Table-I: Frequency of Drugs causing Fixed Drug Eruption (n=61)

Drug category	Drug	Frequency
Antibiotics	Doxycycline	13(21.3%)
	Ciprofloxacin	9(14.8%)
	Levofloxacin	1(1.6%)
	Cotrimoxazole	8(13.1%)
	Metronidazole	2(3.3%)
	Lincomycin	1(1.6%)
	Total	34(55.7%)
Acetaminophen	Paracetamol	10(16.4%)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Diclofenac	4(6.6%)
	Mefenamic acid	2(3.3%)
	Flurbiprofen	1(1.6%)
	Total	7(11.5%)
Antifungals	Fluconazole	1(1.6%)
	Terbinafine	1(1.6%)
	Total	2(3.2%)
Antihistamines	Cetirizine	1(1.6%)
Proton Pump inhibitors	Omeprazole	1(1.6%)
Herbal	Toot Siah	1(1.6%)
Opioid analgesics	Tramadol	1(1.6%)
	None	1(1.6%)
	Total	61

In thirty-four (55.7%) patients, FDE was caused by antibiotics. Doxycycline (thirteen patients, 21.3%) was the commonest causative drug in our patients. In four (6.6%) patients, no drug history was found; out of these four patients, three had developed FDE for the third time, and one had developed FDE for the fourth time.

Nineteen (31.1%) patients had developed the eruption for the first time, and forty-five (73.8%) had had at least two episodes. Out of nineteen (31.1%) patients in whom the eruption had developed for the first time, four developed single lesions, and ten developed three or less than three lesions. On average, patients visited the Hospital after experiencing FDE 3.5 times. Most of our patients with FDE induced by antibiotics tended to visit the Hospital when they experienced FDE for the first time (n=11, 32.35%) or the second time (n=9, 26.47%). The third episode reported twenty-seven (79.41%) patients with FDE induced by antibiotics. Most of our patients with NSAID-induced FDE (57.14%) visited our outpatients when they had experienced repeated FDE, i.e. after more than three episodes (Table-II).

Generalized bullous fixed drug eruption (GBFDE) was seen in two patients. The disease affected single-

Table-II: Drug Episodes (n=61)

Drugs	Number of patients with Episode Numbers									Total
	1	2	3	4	5	6	7	8	11	
Paracetamol	3(4.9%)	3(4.9%)	1(1.6%)	0%	1(1.6%)	0%	0%	0%	2(3.2%)	10(16.4%)
Fluconazole	0%	0%	0%	1(1.6%)	0%	0%	0%	0%	0%	1(1.6%)
Terbinafine	1(1.6%)	0%	0%	0%	0%	0%	0%	0%	0%	1(1.6%)
Total Antifungals	1(1.6%)	0%	0%	1(1.6%)	0%	0%	0%	0%	0%	2(3.3%)
Ciprofloxacin	4(6.6%)	2(3.2%)	2(3.2%)	0%	1(1.6%)	0%	0%	0%	0%	9(14.8%)
Cotrimoxazole	1(1.6%)	2(3.3%)	2(3.3%)	1(1.6%)	0%	1(1.6%)	0%	1(1.6%)	0%	8(13.1%)
Doxycycline	5(8.2%)	5(8.2%)	3(4.9%)	0%	0%	0%	0%	0%	0%	13(21.3%)
Levofloxacin	0%	0%	0%	1(1.6%)	0%	0%	0%	0%	0%	1(1.6%)
Lincomycin	0%	0%	0%	0%	0%	0%	1(1.6%)	0%	0%	1(1.6%)
Metronidazole	1(1.6%)	0%	0%	0%	1(1.6%)	0%	0%	0%	0%	2(3.3%)
Total Antibiotics	11(18%)	9(14.8%)	7(11.5%)	2(3.3%)	2(3.3%)	1(1.6%)	1(1.6%)	1(1.6%)	0%	34(55.7%)
Cetirizine	1(1.6%)	0%	0%	0%	0%	0%	0%	0%	0%	1(1.6%)
Toot Siah	1(1.6%)	0%	0%	0%	0%	0%	0%	0%	0%	1(1.6%)
Diclofenac	0%	0%	2(3.3%)	1(1.6%)	0%	0%	0%	0%	1(1.6%)	4(6.6%)
Flurbiprofen	0%	0%	0%	0%	0%	0%	1(1.6%)	0%	0%	1(1.6%)
Mefenamic acid	0%	0%	1(1.6%)	0%	0%	0%	0%	0%	1(1.6%)	2(3.3%)
Total NSAIDs	0%	0%	3(4.9%)	1(1.6%)	0%	0%	1(1.6%)	0%	2(3.3%)	7(11.5%)
Tramadol	1(1.6%)	0%	0%	0%	0%	0%	0%	0%	0%	1(1.6%)
Omeprazole	1(1.6%)	0%	0%	0%	0%	0%	0%	0%	0%	1(1.6%)
None	0%	0%	3(4.9%)	1(1.6%)	0%	0%	0%	0%	0%	4(6.6%)

body sites in 16(26.23%) patients only. On the other hand, the most common site of FDE in fifty-nine subjects with Localized forms of FDE was the genital area in forty-two (71.19%) patients. The frequency of various body sites affected by FDE lesions was shown in Table-III.

Table-III: Sites affected by Fixed Drug Eruption (n=61)

Site of FDE lesions	Frequency (%)
Face (without lips)	3(5.08%)
Feet including soles	10(16.95%)
Genital area	42(71.19%)
Genitalia only	8(13.56%)
Genitalia and lips	23(38.98%)
Genitalia and lips (without other body parts)	5(8.47%)
Hands including palms	18(30.51%)
Lips	28(47.46%)
Lower limbs	22(37.29%)
Palms	8(30.51%)
Soles	3(5.08%)
Upper limbs	21(52.54%)

Multiple sites were affected in the majority of patients. For example, the drugs were taken for Upper respiratory tract infection in seventeen (27.9%) patients, diarrhoea in ten (16.4%) patients, boils in five (8.2%) patients, fever, toothache, and backache in four (6.6%) patients each, and headache in 2 (3.3%) patients.

DISCUSSION

Fixed drug eruptions (FDEs) is a distinctive drug eruption that tends to recur at the same site whenever the causative drug is administered again. The lesions may occur within half an hour to several hours after the intake of the offending drug. It commonly involves mucocutaneous junctions in areas around the mouth, lips, genitals, and limbs. Usually, it starts as itchy lesions with much irritation and burning sensation followed by eruption of a well-defined typical round to oval erythematous patch or plaque with a dusky red centre and a diameter ranging from 1-10centimeter.[12,13] Blistering or erosions may occur in the lesion. The lesions are sometimes multiple but commonly take the form of a few lesions. The lesions commonly heal with hyperpigmentation. The frequency with which individual drugs cause FDE is different in different countries and keeps changing over time depending upon the prevalence of various diseases in the population for which different drugs are prescribed, the availability of various drugs, and changing prescribing practices amongst General Practitioners and Consultants.[14,15]

In the studies published before 2000, drugs causing FDE commonly were not the same as those reported by the above-quoted studies published after 2000.[16] The common drugs reported by another sudy in 1970 included barbiturates, phenolphthalein, and oxyphenbutazone. Interestingly the three drugs that topped the list in 1970 were missing amongst the drugs causing FDE listed in 2001 after 31 years. This was because oxyphenbutazone was withdrawn from markets worldwide in the mid-1980s.[17] Barbiturates and phenolphthalein have been replaced by other better drugs and are infrequently prescribed. The common causative drugs revealed by another study were Tetracyclines, Metamizole, Oxyphenbutazone, Phenobarbitone, and sulfonamides.[18] The drugs most frequently associated with FDE, as were barbiturates, phenazone derivatives, and less frequently tetracyclines, sulphonamides, and acetylsalicylic acid. In the past, FDEs caused by NSAIDs and acetaminophen were rare, but in our study and most reports after 200010,[12-15] NSAIDs were the second most common drugs after antibiotics.

Similarly, in the past, tetracyclines were considered among the rarer causes of fixed eruptions, while in our patients, Doxycycline was the most common causative drug. Doxycycline is currently a popular antibiotic among General practitioners and quacks, which is why Doxycycline topped the list (21.3% of total cases). These findings indicate that the relative frequencies with which various drugs cause fixed drug eruptions keep changing occasionally. The number of cases of FDE caused by any drug is influenced by two main factors, which include the ability of the drug to cause an FDE, and how frequently the drug is being used. This in turn depends on the availability of a particular drug and the liking of General practitioners and Consultants for a particular drug in a country. In our country, Cotrimoxazole was the most common cause of FDE at 73% previously, but it was responsible for FDE in 13.1% of our patients. This is because of a decline in its use, likely due to its side effects and the tendency to prescribe newer and broad-spectrum antibiotics amongst General Practitioners. Due to the same reason, the frequency of FDE cases due to Paracetamol and NSAIDs has substantially increased.[16]

The average number of skin lesions was 4.07±3.237 lesions in our patients. FDEs frequently developed as multiple lesions, but a single solitary lesion was observed in 16.9% of patients. 31.1% of our patients had developed the eruption for the first time, and 73.8% had had two previous episodes. The most

common site of FDE was the genital area in (71.19%), followed by upper limbs (52.54%), lips (47.46%), and lower limbs (37.29%). These findings were in agreement with the previous studies.[15,17,18]

The present study has pointed clearly to the fact that the current causative drugs of FDE have changed in our population. The current causative drugs include Doxycycline, Quinolones, Cotrimoxazole, Paracetamol, and Nonsteroidal anti-inflammatory drugs (NSAIDs) in descending order of frequency. Paracetamol is a common cause of Fixed Drug Eruption and should always be suspected in all patients with FDE. An oral provocation test may help in identifying the causative drug.

CONCLUSION

Common drugs causing FDE were Doxycycline, Paracetamol, and Nonsteroidal anti-inflammatory drugs. Prevention is the key, as FDE cannot be reversed, and the number of lesions may increase with each episode causing considerable morbidity. This can be done by tracing the causative drug and using alternatives wherever available.

Conflict of Interest: None.

Author's Contribution

Following author has made substantial contributions to the manuscript as under:

AH: Conception, study design, data acquisition, data analysis, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

Author agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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