



Original Article

A STUDY OF DRUGS CAUSING FIXED DRUG ERUPTIONS

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Abstract

Fixed drug eruption (FDE) is a distinctive type of cutaneous drug reaction that characteristically recurs in the same site or sites each time a particular drug is taken. FDEs are among the most frequent problems encountered by the dermatologists. The present study was carried out to recognize offending drugs, to educate the patients and to avoid self-administration of drugs and re-administration of the offending drugs. The study was conducted in Skin & VD outpatient department of Rajshahi Medical College Hospital, Rajshahi over a period of one year. One hundred ten cases with established FDE were evaluated clinically. The causative drugs were identified and confirmed by provocation tests. Cotrimoxazole (25%) was the most common cause of FDE. Other drugs incriminated were NSAID (21.8%), Tetracycline (15.4%), Ciprofloxacin (10%), Amoxicillin (7.2%), Metronidazole (5.4%), Griseofulvin (2.7%) and Fluconazole (1.8%). The lesions were found to be distributed on the oro-genital mucosa, trunk and the acral regions. The main presentation of FDE was circular hyperpigmented lesion.

Key words: Fixed drug eruption, Cotrimoxazole.

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Introduction

Fixed drug eruption is characterized by recurrence of lesions at the same site on

re-administration of the drug.¹ With each exposure the number of involved sites may increase.² The term FDEs describe the development of one or more annular or oval erythematous patches as a result of systemic exposure to a drug which usually resolves with a residual hyperpigmentation.³ Repeated exposure to the offending drug may cause new lesions to develop in addition to “lighting up” the older hyperpigmented lesions.⁴ Medications inducing FDEs are usually those taken intermittently.⁵ It is

responsible for about 10% of all adverse drug reaction.⁶

The initial eruption is often solitary and frequently located on the lip or genitalia. With the initial FDE attack, a delay of up to 2 weeks may occur from the initial exposure to the drug to

the development of the skin lesion. Subsequent re-exposure to the medication results in a reactivation of the site with inflammation occurring within 30 minutes to 16 hours.⁷

The lesions usually develop within 30 minutes to 8 hours of taking the drug.² The re-activation of old lesions may be associated with the development of

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new lesions at other sites.⁷ FDE may present with itching or burning. Vesicles or bullae may occasionally be seen.⁸ Sites of predilection include lips, genitalia, trunk, legs and arms.⁹ Fifty percent of cases of FDE occur on the oral or genital mucosa. FDE represent 2% of all genital ulcers. Lesions of the genital and oral mucosa usually present as erosions. Most lesions are 1 to several centimeters in diameter but larger plaques may occur.⁵

The skin lesions disappear when medication is discontinued but it can sometimes result in permanent pigmentation.¹⁰

Both the immunological and toxic mechanisms have been implicated but conclusive evidence is lacking.¹¹

FDEs are common. There are many causative agents and the incidence of FDE for a particular drug depends on the frequency of its use. Therefore, the list of etiologic drugs varies from country to country and from time to time.⁸

The aim of the present study was to recognize the offending drugs responsible for FDE in our country, to educate the patients and to avoid self-administration of drugs and re-administration of the offending drugs.

Material and Methods

It was a clinical observational study conducted in Skin & VD outpatient department of Rajshahi Medical College Hospital, Rajshahi over a period of one year (June 2015-May 2016).

Patients with drug induced fixed eruptions, of both sexes, under all age group were included. Fixed eruptions due to other causes (Cashew, liquorice) and other cutaneous eruptions caused by drugs (Stevens Johnson syndrome, Toxic epidermal necrolysis) were excluded.

A detailed history regarding the drug intake, mode of drug administration, nature of illness for which the drug was taken, total number of doses taken, whether had been prescribed by a Registered Medical Practitioner or taken over the counter was evaluated. A thorough clinical examination was carried out to establish the etiologic drug; attention was paid to the history of drug intake, approximate

incubation period, improvement of lesions on withdrawal of the drug and recurrence of lesions on re-challenge. All the informations were carefully recorded in a specially designed proforma.

Oral provocation tests were carried out after informed consent of the patients once they had recovered from the presenting episode and were not taking any medication. One-tenth of the daily therapeutic dose of the drug was given on the first day and the patient was observed for any reaction. The test was repeated with one-fourth, one-half and full dose at 24 hours interval. If no reaction was observed with that drug, the next suspected drug was tested in the same manner.

One hundred thirty clinically diagnosed cases of FDE were selected for this study. Only 110 cases (Male 60, Female 50) confirmed by provocation tests were analyzed.

Results

Of 110 patients studied, there were 60 males (54.5%) and 50 females (45.5%). The youngest patient was one year old and the oldest was 80 years (mean=30.5).

The distribution of cases in relation to age and sex are shown in Table-1.

Table 1: Distribution of cases in relation to age and sex

Age in years	Males	Females	Total
<9	11	4	15
10-19	13	7	20
20-29	9	5	14
30-39	8	16	24
40-49	11	11	22
50 & above	8	7	15
Total	60	50	110

Females were predominating among the age group between 30 and 39 years (mean=34.1). The drugs were taken commonly for fever, upper respiratory tract infection, urinary tract infection, dental pain or fungal infection.

The incubation period varied between 1 hour to 15 days. Twenty eight patients (25%) had taken the drug over the counter, without a proper

prescription from a Registered Medical Practitioner.

The causative drugs for FDE are shown in Table-2

Table 2: Drugs causing fixed drug eruptions

Drugs	No of patients	Percentage
Cotrimoxazole	28	25%
* NSAID	24	21.8%
Tetracycline	17	15.4%
Ciprofloxacin	11	10%
Amoxycillin	8	7.2%
Metronidazole	6	5.4%
Griseofulvin	3	2.7%
Fluconazole	2	1.8%
Unknown (OTC)	11	10%

Table 3: Localisation of lesion

Drug	Mucosa	Face	Trunk & extremities	Acral lesions	Total no of cases
Cotrimoxazole	22	2	4	-	28
NSAID	7	-	17	-	24
Tetracycline	7	-	10	-	17
Ciprofloxacin	2	2	7	-	11
Amoxycillin	-	-	-	8	8
Metronidazole	3	-	3	-	6
Griseofulvin	-	-	1	2	3
Fluconazole	-	-	1	1	2
Unknown	3	1	5	2	11
Total	44	5	48	13	110

Multiple lesions were present in 60% and solitary lesion in 40% of cases. Size of the lesions ranged between 1-10 cm. The mean presentation of the FDE was circular, hyperpigmented lesion. Less commonly FDE presented as :nonpigmenting erythema, urticaria, dermatitis, periorbital or generalized hypermelanosis. Most of the solitary lesions on the glans penis were exclusively bullous.

STEP-V:Data compilation and analysis with SPSS 12.0 program.

Discussion

In the present study male to female ratio was 1.2 : 1. One large study of 450 patients revealed a male to female ratio of 1 : 1.1. A slight male preponderance was observed in the previous studies.^{3,12}

In our study the youngest patient was 1 year old and the oldest was 80 years. FDEs have been reported in patients as young as 1.5 years and as old as 87 years.¹ In one study, the age of patients

OTC- Drugs taken over the counter, *NSAID- Diclofenac sodium, Indomethacin,

Ibuprofen, Mefenamic acid, Acetylsalicylic acid, Paracetamol.

Cotrimoxazole was the frequently offending drug. Regarding the pattern of distribution of the lesion, oro-genital mucosa was the most frequently involved sites among males; trunk and extremities among females. Cotrimoxazole preferentially caused FDE in the mucosa and NSAID in the skin. The localisation of lesions in relation to drugs is shown in Table-3.

ranged between 10 months to 70 years.³ In concordance with the findings³, females were predominating among the age group between 30 and 39 years in our study.

In the present study, most of the drugs were taken for fever, upper respiratory tract infections, urinary tract infections, dental pain or fungal infection. Majority of patients had eruptions following a single dose and few patients after three doses. Some patients had taken more than one drug over

the counter without proper prescription by a Registered Medical Practitioner. Similar findings were seen in a study conducted by Gowriet al.³

In concordance with the findings of others^{1, 3, 9, 11, 13} Cotrimoxazole was the most common drug causing FDE in our study. The prevalence varies with different studies.^{9, 13, 14} This is in contrast to a study from India where Metamizole and Tetracycline were incriminated in maximum number of cases. In one study, NSAID was the most common drug causing FDE.⁸ Savin¹⁵ in his study reported Barbiturates and Phenolphthalein as being the most common drugs causing fixed eruption. In one study, Ciprofloxacin was the most common drug causing FDE.¹⁶ Thus the relative frequency of drugs causing FDE varies from country to country and even from time to time in the same location depending upon the frequency of prescription.

In a study, Kanwar et al.¹⁷ showed that Cotrimoxazole induced FDE were mainly located on the oro-genital mucosa, followed by trunk and extremities.⁹ In two studies, Tetracycline was the only significant cause of FDE on male genitals, although Cotrimoxazole was the most common offender for FDE.^{9, 12} Similarly in the present study, Tetracycline had induced FDE on male genitalia. In concordance with the previous studies,¹⁸ NSAID induced FDE were located on the trunk and extremities. Amoxicillin induced FDE were confined to the palms and soles. Ciprofloxacin and Metronidazole had induced FDE on the extremities. In males oro-genital mucosa was commonly affected; whereas in females the lesions were distributed among the trunk and extremities.

Conclusion

Cotrimoxazole was the most common culprit drug in FDE. It is therefore, important to recognize the offending drug in each case of FDE, so that the drug may be avoided in future. Provocation test is the only reliable means of finding the causative agents of FDE.

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