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Original Research Article

A clinicoepidemiological study of fixed drug eruptions at a tertiary centre of North India

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ABSTRACT

Background: Various studies have found the overall incidence of cutaneous adverse drug reactions (CADR's) in developed countries as 1-3%, while the incidence in developing countries is thought to be higher between 2 and 5%. FDEs' share is seen to be about 15 -30% of all CADR's as reported in various studies. Aim of the research work was to study the clinical and epidemiological features of fixed drug eruptions and to identify probable culprit drug or drugs using Naranjo ADR probability scale and to provide information to the patient regarding the drug responsible for his/her drug rash.
Methods: A total of 180 patients of fixed drug eruptions were taken up for study who presented to skin OPD at a tertiary centre of North India. Diagnosis was made on the basis of history of drug intake prior to drug eruption, repetition of similar lesions on same as well as new sites on intake of same drug with improvement of skin lesions on discontinuation of the causative drug. Further on examination, skin lesions with typical morphology compatible with FDE were seen. Causality of the FDE was assessed according to the NARANJO ADR probability scale.
Results: A total of 180 patients of FDE were studied. Males outnumbered the females. The most common class of drug implicated was antimicrobials seen in 115 patients followed by NSAIDS 65 patients. Regarding the clinical presentation both skin and mucosal involvement was seen. The most common skin lesions were erythematous to hyperpigmented and violaceous macules followed by bullous FDE.
Conclusions: In summary, early recognition of FDE is important not only for the dermatologists but also for the clinicians of other specialties, so that the culprit drug is recognized and stopped immediately. Drug reactions are a common reason for litigation and has medicolegal pitfalls.

Keywords: CADR, Causality, Fixed drug eruptions

INTRODUCTION

WHO defines adverse drug reactions (ADR's) as any response to a drug which is noxious, unwanted or unintended. Cutaneous adverse drug reactions (CADR's) have been seen to be one of the most common ADR's in various studies. The incidence in developing countries is thought to be higher between 2 and 5%.[1] Although the true incidence is difficult to quantify but still the incidence of cutaneous adverse drug reactions is about 2.2% of all reported ADR's in India as reported in various studies.[2-4] FDE was first reported in 1889 by Bourns, when he described a lesion that repeatedly developed at the same limited sites after antipyrine was administered. In 1894 Brocq named this type of lesion an "eruptio-erythemato-pigmentee fixed Eruption erythémato-pigmentée fixé due à l'antipyrine. FDE's account for 15 -30% of all CADR's as reported in various

studies.[2] These are characterized by skin lesion (s) that recur at the same anatomic site (s) upon repeated exposures to an offending agent. Most commonly, the skin lesion is a dusky erythematous macule and is usually found on the lips and genitalia, although any skin or mucosal surface may be involved. The skin lesions may be associated with a burning and/or, itching. With repeated use of the drug the lesions increase in number and may even progress to the development of central vesicles and bullae.[3] The lesions usually heal leaving behind residual hyperpigmentation. Withdrawal of the causative drug usually improves the condition but symptomatic treatment in the form of antihistaminic and topical steroids are sometimes required.[5] Because of its characteristic features, FDE can be diagnosed with relative ease compared to other drug eruptions. This study was undertaken at a tertiary centre of north India with an aim to study the clinical and epidemiological features of fixed drug eruptions and to identify probable culprit drug or drugs using Naranjo ADR probability scale and to provide information to the patient regarding the drug responsible.[6]

METHODS

A total of 180 patients of fixed drug eruptions were taken up for study who presented to skin OPD at a tertiary centre of North India. Diagnosis was made on the basis of detailed history taking and examination of all patients. Regarding history taking, the following things were asked: history of drug intake prior to drug eruption indicating temporal association, repetition of similar lesions on same as well as new sites on intake of same drug with improvement of skin lesions on discontinuation of the causative drug. A further detailed history regarding drug intake, cutaneous eruptions and associated systemic symptoms, time gap between drug intake and skin eruption, dosage, duration, indication and class of drug taken and improvement in cutaneous eruption on stopping the drug was noted. History of cutaneous and systemic diseases, past history, family and any other relevant history was recorded.

The class of drug was noted down wherever the patient remembered. Further on examination, skin lesions with typical morphology compatible with FDE were seen. A complete detail general physical examination, cutaneous examination regarding morphology, pattern and distribution of eruption and mucosal examination was done. Mucosa of the mouth and genitalia was seen.

All routine investigations like haemogram, urine, liver function tests, renal function tests were done in all patients. Other special investigations like VDRL, HIV were done wherever necessary. Other dermatoses mimicking FDE were excluded and biopsies were taken wherever necessary. Causality of the FDE was assessed according to the NARANJO ADR probability scale (Annexure 1).

All the findings were recorded in the proforma. At the end of the study the data was analysed and inferences were drawn using various statistical methods.

NARANJO ADR probability scale

According to this scale, a series of questions were asked to the patients regarding the adverse event, and then a final score was calculated.

RESULTS

A total of 180 patients of FDE were studied. Males outnumbered the females. There were 114(63.3%) males and 66(36.6%) females. The youngest pt was of 14 yrs while the oldest was of 75yrs old. The mean age was 39.42 years. Maximum no. of patients were in the age group of 31-40 years. Age and gender distribution was shown in Table 1.

Table 1: Age and gender distribution of patients.

Age group	Males	Females	Both
11-20	5	3	8
21-30	35	13	48
31-40	42	35	77
41-50	18	9	27
51-60	8	4	12
>60	6	2	8
Total	114	66	180

Drug class distribution

The most common class of drug implicated was antimicrobials seen in 115 patients followed by NSAIDS 65 patients as shown in Figure 1.

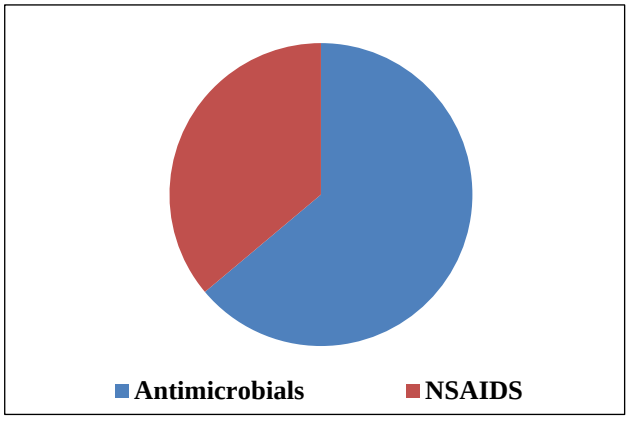

Figure 1: Class of drug implicated in fixed drug eruption.

Among antimicrobials-tinidazole and ornidazole were the most commonly implicated drugs seen in 81 patients whereas among NSAIDS-paracetamol was implicated in

42 patients. Multiple drug etiology was seen in 10 patients in which the patients had taken more than 1 drug.

The distribution of various individual drugs in the causation of FDE has been shown in Table 2. The time between the intake of drug and onset of signs and symptoms varied from 5minutes to 10 days amongst all patients with FDE.

Table 2: Distribution of individual drugs causing FDE.

Drug Implicated	No. of patients
Tinidazole	45
ornidazole	36
Ciprofloxacin	16
Amoxycillin	11
Cefuroxime axetil	10
Fluconazole	7
Paracetamol	42
Diclofenac, piroxicam, ibrufen, etoricoxib	19
Levocetirizine	5

Clinical presentation of FDE

Regarding the clinical presentation both skin and mucosal involvement was seen. A total of 95 (53%) patients presented with only skin lesions with 51 males and 44 females. 58 (32%) patients presented with both skin and mucosal lesions out of which 41 were males and 22 were females. 27 (15%) presented with only mucosal lesions. Out of skin lesions, the most common site of involvement was upper limb. The most common skin lesions were erythematous to hyperpigmented and violaceous macules followed by bullous FDE. Some lesions presented with erosions as well (Figure 2).

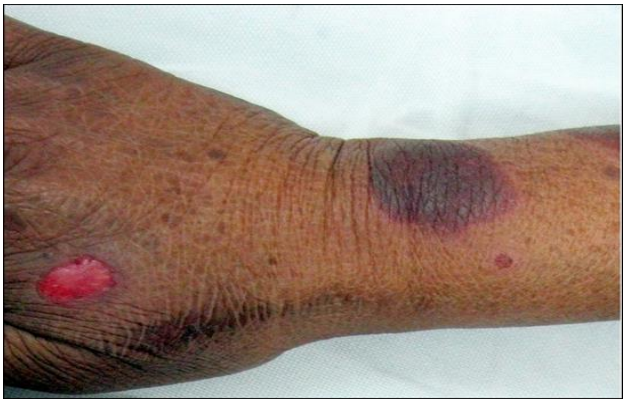

Figure 2: Fixed drug eruption with erosion.

Around 123 patients presented as solitary lesions (18%), whereas 57 presented with multiple lesions (82%). Most common site was upper limbs followed by lower limbs and abdomen. Oral and genital mucosa was also seen among patients.

Improvement after stopping drug was observed in 55 patients and in rest 125 patients this could not be studied as patients didn't return for follow up. Applying the NARANJO ADR probability scale- 96 patients had a probable association, 61 highly probable and 23 a possible association (Figure 3).

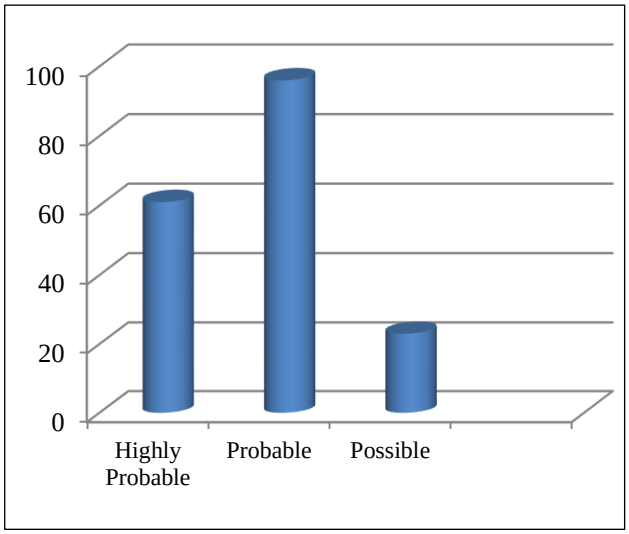

Figure 3: NARANJO ADR probability scoring.

DISCUSSION

Cutaneous adverse drug reactions are one of the most common ADR's.[7] The diagnosis of cutaneous ADR is one of the most challenging clinical problems in patients. The challenge is two-fold: firstly, to accurately diagnose cutaneous ADR and secondly, to attribute causality to a particular drug, if possible. Detailed history and clinical examination form the cornerstone of the diagnoses.

FDE's account for 15 -30% of all CADR's as reported in various studies.[2] These are characterized by skin lesion (s) that recur at the same anatomic site (s) upon repeated exposures to an offending agent. Most commonly, the skin lesion is a dusky erythematous macule and is usually found on the lips and genitalia, although any skin or mucosal surface may be involved. With repeated use of the drug the lesions increase in number and may even progress to the development of central vesicles and bullae.[3] It has been found that intraepidermal CD8+T cells with an effector-memory phenotype resident in fixed drug eruption lesions have a major contributing role in the development of localized tissue damage. Activation of these CD8+T cells is sufficient for triggering the lesion, however, this is not sufficient to cause extensive tissue damage observed in the fully evolved lesions. There was a male preponderance found in our study similar to that seen in another study where 450 cases of FDE were studied.[8,9] In our study the time between the intake of drug and onset of signs and symptoms varied from 5minutes to 10 days amongst all patients with FDE which was similar to other studies.[10] The most common site involved was upper limb followed by lower limbs

and abdomen ion our study. Another study reported variation in site according to causative drugs like tetracycline causing FDE at mucocutaneous sites.[11] The most common presentation was in the form of erythematous, hyperpigmented or violaceous macules seen in 38 patients (76%). A higher proportion of bullous FDE (24%) was seen in our study. 123 patients presented as solitary lesions (18%), whereas 57 presented with multiple lesions (82%). These findings were similar to that seen in another study. In their study they found single site involvement in 20.4% and multiple in 79.6% with a time lag of 10minutes to 10 days.[9]

Among drugs causing FDE, antimicrobials were the most common offending agent followed by NSAIDS in our study among FDE patients similar to that seen by two other studies.[4,11] Among antimicrobials we found antiamoebic tinidazole as the most common drug. Two other studies reported clotrimoxazole as the most common offending agent in contrast to our study.[4,11] This could be attributed to the regional and ethnic variations and variable patterns of drug usage. Various studies concluded that FDE causing drug class before 2000 was clotrimoxazole and NSAIDS were rare.[8,11,12] Few studies found NSAIDS to form a major share after year 2000 after antimicrobials, acetaminophin was the main NSAID implicated.[4,13,14]

In summary, early recognition of FDE is important not only for the dermatologists but also for the clinicians of other specialities so that the culprit drug is recognized and stopped immediately. Drug reactions are a common reason for litigation. Not warning a patient about potential adverse effects, prescribing a medicine to a previously sensitized patient or prescribing a related medication with cross-reactivity are the most common medicolegal pitfalls.

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ANNEXURE

S. No.	Questionnaire	Yes	No	Don't know	Score
1	Are there previous conclusive reports on this reaction?	+1	0	0	+1
2	Did the adverse event appear after the suspected drug was administered?	+2	--1	0	+1
3	Did the adverse reaction improve on discontinuation of the suspected drug?	+1	0	0	+1
4	Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	+1
5	Are there alternative causes other than drug that could on their own have caused the reaction?	-1	+2	0	+1
6	Did the adverse reaction reappear when a placebo was readministered?	-1	-1	0	-2
7	Was the drug detected in blood in concentrations known to be toxic?	+1	0	0	+1
8	Did the patient have similar reaction to the same or similar drug in any previous exposures?	+1	0	0	+1
9	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total score	**ADR Probability classification**				
9	Highly Probable				
5-8	Probable				
1-4	Possible				
0	Doubtful				