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A STUDY OF FIXED DRUG ERUPTION: SINGLE CENTER ANALYSIS FROM CENTRAL INDIA

Dermatology

Chaitanya Namdeo* Department Of Dermatology, Venerology & Leprosy, Sri Aurobindo Medical College And PG Institute, Indore *Corresponding Author

Kailash Bhatia Department Of Dermatology, Venerology & Leprosy, Sri Aurobindo Medical College And PG Institute, Indore

Akshika Mukhija Department Of Dermatology, Venerology & Leprosy, Sri Aurobindo Medical College And PG Institute, Indore

Mohammad Rafi Pharmacovigilance Associate, PvPI, Department of Pharmacology, Sri Aurobindo Medical College and PG Institute, Indore

Susmit Kosta Central Research Lab, Sri Aurobindo Medical College and PG Institute, Indore

ABSTRACT

Background: Fixed drug eruption is a common cutaneous adverse drug reaction which is characterised by sharply demarcated skin lesions with recurrences at the same site with each subsequent exposure to the culprit drug. The causative drugs for fixed drug eruption (FDE) in any population changes depend on many factors. The knowledge of peculiar clinical features of FDE helps the treating physician to recognise at early stage and avoidance of mismanagement of such cases.

Material and method: In this context, we did a descriptive-analytical study of patients who were diagnosed with FDE in single center between Feb 2013 to Sep 2017 from central India.

Results: Ninety seven patients who developed FDE were studied in the study with 65% males and 35% females. Mean age at presentation in males and females were 34.95±16.90 and 37.12±12.98 years, respectively. Multiple lesions were present in 80.4% of patients. Seventy four percent of patients gave the history of prior episodes. In 68% patients, symptoms started and lesions developed within <24 hours of the drug exposure. Mucosal lesions were seen in 46.4% and skin lesions (non-mucosal) were seen in 36.1% and in rest 17.5% patients both mucosal and skin lesions were present. Antibiotics and NSAIDS were the most common group of medications to cause FDE. Thirty two percent of patients were caused by Fixed Dose Combinations of antibiotics and anti-protozoals.

Conclusion: In conclusion, FDE is a common acute cutaneous drug eruption that if not diagnosed timely leads not only to recurrences but also causes apprehension and morbidity.

KEYWORDS

Fixed drug eruption (FDE); Non-steroidal Anti-inflammatory drugs (NSAIDS), Fixed Dose Combination (FDC)

Introduction

Fixed drug eruption (FDE) is a common, benign form of drug reaction characterised by recurrences of skin and/or mucosal lesions at the same sites with each exposure to the medication[1]. FDE is a non-fatal condition and a lesion heals with drug-withdrawal. The only morbidity is the post-inflammatory hyper-pigmentation. Clinical presentation of FDE is highly characteristic yet equally enigmatic.

FDE was first described by Bourns in 1889 when he noticed recurrences of skin lesions over the same site after repeated exposure to antipyrine[2]. FDE develops from 30 minster 8-16 hours after the exposure to the drug[1,3]. However after the initial or first exposure to the culprit drug, lesions developed from few days to two weeks[4]. Mostly patients present with fewer lesions but multifocal presentation are also not uncommon. Oral and genital mucosal lesions are the commonly involved site with palms, soles trunk and proximal limbs are other involved sites. FDE has been reported in all age groups but adults are mostly involved. There is slight female preponderance[1]. The distribution of the lesions on the body and involvement of mucosa suggested affecting by the drug in question. FDE is considered to be a great immunological puzzle. Why some medications produce such a sharply defined lichenoid drug reaction in the same location each time exposure occurs is not completely understood. Expression of Intercellular adhesion molecule-1 (ICAM-1) and class II MHC antigen by keratinocytes and presence of antigen-specific T-cells are possible explanation of recurrences of lesions at the same site with each subsequent exposure to drug[5].

Although oral drug re-challenge is gold standard but is rarely used because of the risk of generalised bullous FDE (GBFDE). Patch testing done specifically over the lesional site is positive only in 50 % patients, so diagnosis in most cases is based on clinical examination and specific drug history. More than 100 drugs have been implicated but the common drugs are tetracyclins, sulphonamides and non-steroidal anti-inflammatory drugs(NSAIDS)[3].In this study the causative drug, number of lesions, number of episodes, clinical patterns of various drug groups are identified.

Material and Methods

This cross-sectional study was done at Sri Aurobindo Medical College& PG Institute, Indore. The study period was 5 years from Feb 2013 to Sep 2017. The culprit drug was identified by meticulous history with taking into consideration the entire drugs taken by the patients in the past 30 days. Prior history of any such episodes and both the drugs and the conditions for he/she took medications were any into account.

Age, gender, number of episodes, site of involvement (face, upper limbs, lower limbs and trunk), mucosal involvement (oral and genitals), clinical features and other demographic data were recorded.

Statistical Analysis

All the informations were carefully recorded in a specially designed proforma. Disruptive analysis means with standard deviation and cross-sectional statistics was used to show feature and characteristic of data. Significance preferential site of involvement due to specific drugs was statistically evaluated by Fischer's exact test. P value of < 0.05 was considered to be statistically significant. The statistical analysis was carried out only for drugs that caused lesions in more than ten patients.

Results

Ninety seven patients were studied in the study with 63 (65%) males and 34 (35%) females. In both male and female patients maximum numbers of patients were in the age group of 20-40 years (Table 1). Mean age at presentation in males was 34.95±16.90 years and in females were 37.12±12.98 years. Multiple lesions were present in 78(80.4%) of patients. Seventy two (74.2%) patients gave the history of prior lesions over the same sites. In 66(68%) patients, symptoms and lesions started within <24 hours of the drug exposure. In most the cases patients used single drug 59(60.8%). Mucosal lesions were seen in 45(46.4%) and skin lesions (non-mucosal) were seen in 35(36.1%) and in rest 17(17.5%) patients both mucosal (oral and genital lesions) and skin lesions were present (Table 2). Maximum and minimum age at presentation was 99 years and 07 years both were males.

Multi-drug consumption was reported in 38(39.2%) while most of the patients when presented had history of single drug intake 58(60.8%) (Fig.1). The most common drug group to cause FDE when history of single drug consumed was Non-steroidal Anti-inflammatory drugs (NSAIDS) 31 (31.9%) followed by antibiotics 20 (20.6%), anti-protozoals 4 (4.1%), anti-fungals 3 (3%) and anti-depressants 1(1%). The most common drug combination to be implicated was ofloxacin and ornidazole combination in 18 (18.5%) patients followed by norfloxacin and tinidazole combination in 14 (14.4%) patients (Fig. 3 and Table 3). However when considering individual drug groups to be implicated to cause FDE in our study, antibiotics were the most common drug group to cause FDE in 56(57.7%) patients followed by NSAIDS in 37(38.1%) patients, anti-protozoal drugs 34(35.1%), anti-fungal drugs 6(6.2%) and antidepressant drugs 1(1%).

In the antibiotic group the most common site of involvement was the upper limbs 24 (26.63%) followed by lips 21(23%), lower limbs 18(19.7%), trunk 14(15.3%), genitals 12(13.1%) and face 2(2.1%). In the anti-protozoal drug group the most common site of involvement was the lips 17(32%), upper limbs 12(22.6%) and trunk 8(15%), genitals 8(15 %) and lower limbs 8(15 %). In the anti-fungal group, the most common site of involvement was the upper limbs 03(42.8%) followed by trunk 02(28.7%), lower limbs 01(14.2%) ,lips 01(14.2%) with none of the patients developed FDE over genitals an face.In the NSAIDS group the most common site of involvement was the upper limbs 19(28.7%) followed by lower limbs 15(22.7%), trunk 11(16.6%), lips 10(15.1%), genitals 10(15.1%) and face 1(1.5%). Anti-depressant was the culprit drug in only one patient who developed lesion of FDE on the trunk (Fig.2).

Table 4 shows the correlation of lips involvement with involvement of genitals, upper limb, lower limb, trunk and face in different drug groups. Lips and genitals are involved in 11/97 patients (11.3%) with antibiotics and anti-protozoal were the cause each in 4 patients and NSAIDS in 03 patients. Lips and upper limb were involved in 11/97 patients (11.3%) with antibiotics were the cause in 05, anti-protozoal in 03 patients, NSAIDS in 03 patients. Lips and lower limbs were involved in 08/97 patients (8.2%), with antibiotics were the cause in 04 patients, anti-protozoal in 02 patients, NSIADS in 02 patients. Lips and trunk were involved in 05/97 patients (5.1%), with antibiotics were the cause in 01 patients, NSIADS in 03patients and antidepressant in 01 patient. None of the patients in the study have concomitant involvement of face and lips.

Table shows the correlation of genitals involvement with involvement of upper limb, lower limb, trunk and face in different drug groups. Genitals and upper limbs are involved in 12/97 patients (12.3%) with NSAIDS were the cause in 05 patients, antibiotics and anti-fungals each in 03 patients and anti-protozoals in 01 patient. Genital and lower limb were involved in 08/97 patients (8.2%) with NSAIDS were the cause in 04 patients, antibiotics in 02 patients, anti-protozoal and anti-fungals each in 01 patient. Genitals and trunk were involved in 09/97 patients (9.2%), with NSAIDS were the cause in 03 patients, antibiotics and anti-fungals each in 02 patients and anti-protozoal and antidepressants each in 01 patients. NSAIDS was the cause of FDE concomitantly over face and genitals in only 1 patient. The correlation of upper limbs involvement with involvement of lower limb, trunk and face in different drug groups. Upper limbs and lower limbs are involved in 21/97 patients (21.6%) with NSAIDS were the cause in 10 patients, antibiotics in 09 patients and anti-protozoals in 03 patients. Upper limb and trunk were involved in 18/97 patients (18.5%) with antibiotics were the cause in 08 patients, NSAIDS in 06 patients and anti-protozoal and anti-fungals in 04 patients.Upper limb and face were involved in 02/97 patients (2%), with NSAIDS and antibiotics were the cause each in one patient.

Table shows the correlation of lower limbs involvement with involvement of trunk and face in different drug groups. Lower limb and trunk were involved in 19/97 patients(19.5%) with NSAIDS and antibiotics were the cause each in 7 patients, anti-protozoals in four patients and anti-fungals in one patient.Antibiotics was the cause of FDE concomitantly over lower limb and face in only one patient. In the present study none of the 97 patients developed FDE concomitantly only over trunk and face.

Discussion

Fixed drug eruption (FDE) is a specific adverse cutaneous reaction which is characterised by development of skin and /or mucosal lesions with each exposure to the culprit medication. Lesions of FDE develop as sharply demarcated round to oval erythematous and edematous plaques with a dusky hue and becomes erosive at times. Over a period of several days, lesions tend to fade and mostly heal with postinflammatory hyperpigmentation. If remain undiagnosed, on subsequent exposure to same drug, apart from the involvement of previous lesions, additional sites may involve[4]. Patients usually complaints of burning and stinging sensation over the lesions and some may have malaise, fever and abdominal discomfort[3].Onset of skin lesions of FDE usually occurs few days to two weeks after the first exposure of the culprit medication, while on subsequent exposure the onset is within 24 hours[4]. In the present study, two-third (66%) of the cases developed FDE lesions within 24 hours of drug intake.

Our study showed males (65%) were more affected than females (35%) with maximum cases of FDE in their third and fourth decades. Jung et al. in their study of 184 patients with FDE reported males (51%) are more affected and that too in their fourth decade[6]. In contrast to our study, Mahboob et al. in their study of 450 patients with FDE reported male to female ratio of 1:1.1[7].

In our study we found that 25.8 % of cases had history of similar episodes. However Jung et al.in their study of 184 patients of FDE reported 83% of cases had recurrences and Kavoussi H et al. reported 39 % of patients had more than 3 episodes[6, 8]. Increased awareness and early recognition of FDE both in general physician and general population are the most probable explanation.

FDE can occur any part of skin and/or mucosa. However the lesions of FDE presenting on lip mucosa, genital mucosa and sometimes perineal area are dramatic in presentations due to their associated symptoms. In our study, mucosal involvement (lips and genitals) alone was present in 46.4 % of patients while only skin involvement was present in 36.1 % of patients. A solitary lesion present on a limb or trunk can be often missed for an arthropod bite. In our study 19 % patients presented with single FDE lesion. Jung et al. reported single lesion FDE in 30.6% of patients with upper limb as the most common site[6], however in our study lips are the most commonly involved (7%) when single lesion FDE was present.

Generalised FDE is a distinct subgroup of FDE that presents with multi-focal lesion defined as at least 3 anatomical site involvement and minimum of 10 lesions.(8) In our study 13% of patients presented with GFDE. Although not qualify to be GFDE, but 78 % of patients in our study presented with multiple skin lesions, which is similar to the finding in the study by Jung et al. upper limb is the most common site of involvement when patient present with multiple lesions[6].

The causative drug pattern and the incidence of FDE in any population varies with relative use of the implicated drugs, geographical location, climatic factors and even the follows the trend of the disease for which these medications are prescribed. In our study the most common drug group when patient took the drug as mono-therapy was NSAIDS 31 (31.9%)followed by antibiotics 20 (20.6%). Finding of our study are similar to the study by Jung et al. who reported NSAIDS to be the most common drugs in 71.1% patients followed by antibiotics in 15.8% patients[6]. However, Kavoussi H et al in their study of generalised FDE reported antibiotics to be the most common drug group in 60% patients followed by NSAIDS in 7 % patients[8].

In our study of 97 patients of FDE, we reported three cases of FDE caused by fluconazole. Fluconazole as a cause of FDE has rarely been reported[9]. Single case of Fluoxetine, an anti-depressant drug, induced FDE also reported in our study. We reported 18 patients developing FDE after the intake of drug combination of ofloxacin and ornidazole. We also reported 14 patients developing FDE after the intake of drug combination of norfloxacin and tinidazole. These fixed dose combinations of quinolones and nitroimidazoles are commonly used for gastro-intestinal infections, pelvic inflammatory diseases and dental infections. Not recommended in any standard textbooks, these FDCs are used mostly used to cover diagnostic imprecision and lack of laboratory facilities[10].Not only these FDCs are irrational to use due to difference in anti-microbial spectrum, pharmacodynamics and pharmacokinetics, but also may cause increased incidence of adverse cutaneous reactions[11].

Conclusion

In conclusion, FDE is a common acute cutaneous drug eruption, the

diagnosis of which if missed leads to recurrences and increased morbidity in form of generalised FDE. The most commonly offending drugs belong to antibiotics and NSAIDS. The causative drugs for FDE in various areas may depend on frequency of use that particular medication in any community[12], and genetic susceptibility[13]. Early diagnosis of FDE, identification and prompt withdrawal of the culprit drug based on the meticulous and detailed history is very important. We recommend increase awareness among not only among treating physiciansand paramedics but also among general public and obtaining detailed history to identify the culprit drug.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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Table 1: Descriptive analysis according to age and gender

	Male	Female	Total
<20	6 (6%)	2(2%)	8 (8%)
21-40	43(43%)	21(21%)	64(64%)
41-60	7(7%)	8(8%)	15(15%)
>60	7(7%)	3(3%)	10(10%)
Total	63(63%)	34(34%)	97(97%)

Table 2: Clinical finding in FDE

Lesion	
Lesion	
Mucous	45(46.4%)
Non-Mucous	35(36.1%)
Both	17(17.5%)
No. of Lesion	
Single	19(19.6%)
Multi	78(80.4%)
Episodes	
Single	72(74.2%)
Multi	25(25.8%)
Onset of Lesion	
<24 HR	66(68%)
>24 HR	31(32%)

Table 3: Incidence of FDE in different drug groups

Mono-therapy (59)	
ANTIBIOTIC (20)	
Levofloxacin	5
Ciprofloxacin	3
Ofloxacin	3
Norfloxacin	1
Cloxacillin	2
Cotrimoxazole	2
Doxycycline	1
Amoxyclave	1
Cefuroxime	1
Cefotaxime	1
NSAIDS (31)	
Diclofenac	17
Nimesulide	6
Ibuprofen	3
Paracetomol	2
Asprin	2
Acelofenac	1
ANTIPROTOZOAL (4)	
Ornidazole	2
Tinidazole	1
Secnidazole	1
ANTIFUNGAL (3)	
Fluconazole	3
ANTIDEPRESSANT (1)	
Fluoxetine	1

Table 4: Correlation of FDE lesions with individual Drug Groups

	Antibiotic	Antiprotozoal	Antifungal	NSAIDS	Antidepressant	Total
Lips						
Genital	4	4	0	3	0	11
Upper Lip	5	3	0	3	0	11
Lower Lip	4	2	0	2	0	8
Trunk	1	0	0	3	1	5
Face	0	0	0	0	0	0
Genital						
Upper Lip	3	1	3	5	0	12
Lower Lip	2	1	1	4	0	8
Trunk	2	1	2	3	1	9
Face	0	0	0	1	0	1
Upper Lip						
Lower Lip	9	3	0	10	0	21
Trunk	8	4	0	6	0	18
Face	1	0	0	1	0	2
Lower Lip						
Trunk	7	4	1	7	0	19
Face	1	0	0	0	0	1

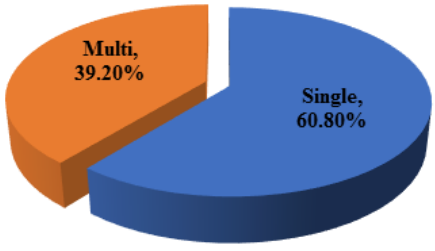

Figure 1: Drug consumptions

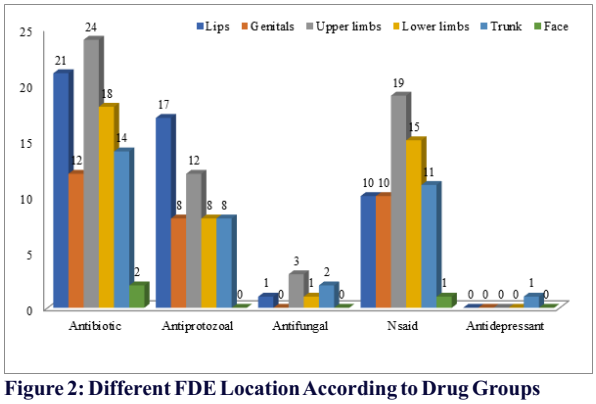

Figure 2: Different FDE Location According to Drug Groups

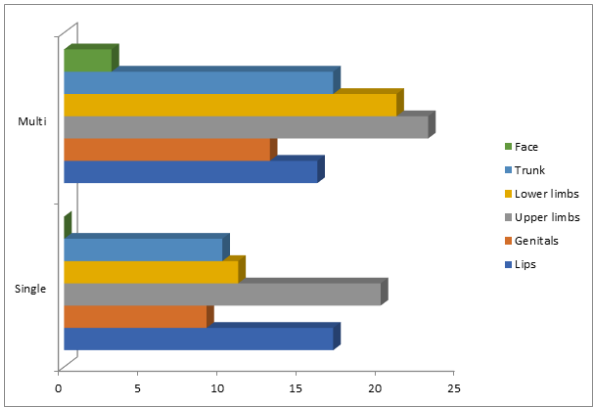

Figure 3: FDE Sites Involvement According to Single and Multiple Drug Intakes

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