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IP Indian Journal of Clinical and Experimental Dermatology

Journal homepage: www.innovativepublication.com

Original Research Article

A clinico-aetiological study of fixed drug eruption amongst the patient attending tertiary care centre

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ARTICLE INFO

Article history:
Received 15-11-2019
Accepted 25-11-2019
Available online 20-12-2019

Keywords:
Fixed drug eruption
Provocative tests.

ABSTRACT

Introduction: Fixed drug eruption (FDE) is a cutaneous adverse drug reaction characterized by recurrent well defined lesions occurring in the same sites each time the offending drug is taken. FDE typically presents 30 min to 8 h after drug exposure. An extensive list of medications are known to cause FDE and finding the underlying drug help in proper management of cases.
Aim: To study and analyse the causes and clinical pattern of FDE.
Materials and Methods: The study was performed in Silchar Medical College and Hospital, Silchar, Assam. A total of 50 cases of FDE were studied. Cases of FDEs encountered between July 2018 to June 2019 during routine pharmacovigilance activities were analyzed.
Result: Among 50 patients, 34 were male and 16 were female. Majority of patient were between the age of 18-40 years, mean age being 33.4 years. In 31 cases there was previous history of drug intake. Commonly affected sites include genitals and lips, palms and soles followed by extremities and other sites.
Most common causative drug was due to antimicrobial followed by NSAIDs.
Conclusion: Although clinical presentation of most of the patient was similar a detailed history, physical examination and drug provocation test helped us to reach most of the diagnosis.

1. Introduction

Fixed drug eruption (FDE) is a cutaneous adverse drug reaction characterized by recurrent well defined lesions occurring in the same sites each time the offending drug is taken. FDE is a drug eruption distinguished by its recurrence at the same sites on rechallenge, its short latency and benign nature. FDE typically presents 30 min to 8 h after drug exposure.[1] Fixed drug eruption though usually not fatal can cause enough cosmetic embarrassment if present on the exposed part.[2]

Although a large number of drugs have been incriminated to cause FDE, certain drugs are more often responsible for causing the same. Genitalia and lips were the are most commonly affected, but involvement of limbs and trunk is not uncommon.[3] Patients were further evaluated after taking proper consent. Complete physical examination including cutaneous examination was done.

2. Materials and Methods

This is a descriptive study which was conducted over a period of 12 months from July 2018 to June 2019 to find the etiology of FDE in patients attending Silchar Medical College and Hospital, Silchar, Assam. In the given period 50 cases of FDE were evaluated with relevent clinical history including history of drug intake. Patients with the FDE were interviewed for onset and duration of the disease with history of all drugs taken and a list of suspected drugs was made for each patient. When the patient was symptom free clinically, they were subjected to provocation test with all the suspected drugs taken by the patient with all necessary preventive measures. On the first day, the patient was given one-fourth of the therapeutic dosage. If there was no reaction during the next 24 hours, the patient was given half therapeutic dosage on the second day. If still there

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https://doi.org/10.18231/j.ijced.2019.069

was no reaction, on the third day the patient was given one day's full therapeutic dosage.[4] If still there was no reaction the drug was considered safe. In this manner each patient was tested with all the drugs thought to be responsible for the eruptions. A definite erythema at or around the existing lesion was considered as positive provocation test. Patient with known history of any other type of localized, generalized or systemic drug allergy were excluded from the study. The patients were explained about provocation test and written consent was taken for performing these tests. Emergency tray with injections of antihistamine, adrenaline and corticosteroids kept in hand to deal with any situation, if aroused.

3. Results

Out of 50 patients (34 were men and 16were women) with FDE, the mean age of the patients was 33.4 years, with a range from 12 to 66 years. Majority of the patients were adults between 18 and 40 years old. The lag period between intake of suspected drug and emergence of eruption ranged from 40 minutes to 5 days, with an average lag period of 1.02 days. Thirty one out of the 50 patients who developed lesions on the same day had previous history of FDE, while the 14 patient had a no previous history in the past. In 5 patients, the drug responsible for FDE in the past was not known. Commonly affected sites were genitalia (24), lips (16), head and neck excluding the lips (5) and extremities (5). Number of FDE lesions varied from 1 to numerous, with 20 patients presenting with a single lesion and another 26 presenting with 2–5 lesions. Four patients had 6 or m ore lesions, 2 of whom were classified as generalized bullous FDE which were due to fluconazole (Figures 2 and 1) and ciprofloxacin.

Fig. 1: Extensive FDE due to Fluconazole

Bullous FDE was seen in 2 cases of which one patient developed within 20-30 minutes of ornidazole [Figure 3], one after paracetamol (after 3 hours).

Fig. 2: FDE in same patient over arm

Fig. 3: Bullous FDE due to ornidzole

Antimicrobials (6 6%) and nonsteroidal anti-inflammatory drugs (22%) and others (12%) were the drugs implicated [Table 1].

Out of the 50 cases, as in 5 cases the drug was not known, so rechallange was done in 45 cases and the rechallenge test was positive in 34 patients with various dos es of drugs, as shown in Table 2. In rest 11 cases it was negative. The onset of the lesion was noticed as early as 30 minutes t o a maximum of 23 hours (mean=5.3 hours) after the administration of the drug. Ornidazole was the most common offending agent, affecting 7 patients, followed by Metronidazole, ofloxacin, co-trimoxazole and paracetamol (4 each) and by other drugs. The test was positive for half the drug dose in 14 cases, followed by 1/4th dose of the drug in 12 cases and full dose in 8 cases. Result of provocation test is given in Table 3.

Route of administration was oral for all causative drugs.

The FDEs were treated by discontinuing the offending drug, topical and systemic corticosteroids, oral antihistamines and with other supportive measures. Majority of the patients recovered within a week, while in rest of patients, the lesions took up to 3 weeks to resolve. In all these patients, there was persistent hyperpigmentation of the affected site till last follow -up. Diagnosis of FDE was clinical and on the basis of drug provocation in all the patients.

4. Discussion

Although our cases are less to give definitive trends, there was a predominance of male (34 male and 16 female). A slight male trend has been reported in some studies[5,6] while some analyzes report a female dominance.[7] The most frequently affected sites in our series were the genitalia (48%)[Figure 4], followed by the lips (32%)[Figure 5]. Both these sites have been recognized as common sites of involvement in several studies.[7–9] We had only five cases with involvement of the extremities. Antimicrobials and NSAIDs are well- known triggers for an FDE[10–12] and were the common culprits in our series too [Table 1]. This is in keeping with several other reports of FDE with these drugs as these drugs are increasing used in our country.[13]

In 62% of patient, there was history of an FDE. Many authors have reported a high proportion of recurrent FDEs[14] [Table 2]

Fig. 4: FDE over lip

Majority of the patients (25 out of 31 or 80.64%) whose lesions appeared within minutes to hours of suspected drug intake had previous history of FDE. Furthermore patients with multiple lesions also had previous history of FDE. Although the number of cases was too small for statistical significance, it might be possible to expect that patients with a history of FDE were more likely to have a faster onset (lesions appeared within minutes to hours) as well as more number of lesions. Furthermore, two out of four patients with extensive FDE had previous history of FDE. The increase in number and severity of lesions on re exposure is related to the pathophysiology of FDE, which is still incompletely understood. FDE is a form of classical delayed- type hypersensitivity reaction and skin resident T cells are believed to be the key mediators in eliciting FDE. Long after clinical resolution, 'resting' FDE lesions

Fig. 5: FDE over Genitalia

contain CD8+ T cells with an effector /memory phenotype. These cells are located at the dermal–epidermal junction and remain quiescent until drug re-challenge. On re - exposure to the drug, there is activation and expansion of these CD8+ lymphocytes with the release of interferon (IFN)- γ and cytotoxic granules resulting in keratinocyte apoptosis. At the end of the immune response, regulatory T cells are recruited into the lesions and limit further damage by inhibiting the cytotoxic T cells. Expanded and activated cytotoxic T cells are removed by apoptosis but a small population is prevented from apoptosis by keratinocyte derived interleukin(IL)-15 and remain as skin-resident memory T cells until the next activation cycle.[1]

Provocation tests were done in 45cases with the suspected drugs. It was observed that 75 % of cases showed positive results. The likely cause of negative results in the remaining cases may be due to wrong drug history, smaller provocation test dosage, patient in refractory period with temporary lack of response to the test dosage. Our observations were more or less similar to the observation of Kauppinnea et al.[15]

5. Conclusion

From the above study we can conclude that the pigmentation persist for long time and prevention is the key. This can be done by knowing about the common causative drugs, the likelihood of recurrence with same or similar drugs, and use of alternative drug where possible.

Table 1: Drugs implicated in fixed-drug eruptions

Drug	Number of patients* (%)
Antimicrobials	**33(66)**
Ornidazole	10(20)
Co-trimoxazole	6(12)
Metronidazole	6(12)
Ciprofloxacin	5(10)
Erythromycin	2(4)
Rifampicin	1(2)
Sulfasalazine	1(2)
Omeprazole	1(2)
Amoxicillin	1(2)
NSAIDs	11(22)
Paracetamol	7(14)
Aceclofenac	3(6)
Nimesulide	1(2)
Others	1(2)
Fluconazole	1(2)
Unknown	5(10)
Total	**50**

Table 2: Number of patient showing positive drug provocation test.

Suspected Drugs	With 1/4 th Dose	With $\frac{1}{2}$ Dose	With full Dose	Total
Ornidazole	2	3	2	7
Co-trimoxazole	1	2	1	4
Ciprofloxacin	2	1	1	4
Omeprazole	-	1	-	1
Metronidazole	1	2	1	4
Sulfasalazine	1	-	-	1
Erythromycin	1	-	1	2
Rifampicin	1	-	-	1
Amoxicillin	-	1	-	1
Paracetamol	1	2	1	4
Nimesulide	1	-	-	1
Aceclofenac	1	2	-	3
Fluconazole	-	-	1	1
Total	12	14	8	**34**

Table 3: Result of provocation test

Total Number of cases	Positive(%)	Negative(%)
45	34(75.5)	11(24.5)

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Sahu VK, Gupta B. A clinico-aetiological study of fixed drug eruption amongst the patient attending tertiary care centre. *Indian J Clin Exp Dermatol* 2019;5(4):332-335.