

A study of fixed-drug reactions at a rural-based tertiary care center, Gujarat

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Abstract

Introduction: Nowadays, due to the widespread availability of various drugs, adverse cutaneous drug reactions (ACDRs) have become very common. One type of ACDR that dermatologists encounter frequently these days is Fixed-drug reaction (FDR). FDR is a characteristic type of adverse cutaneous reaction, which occurs at the same site whenever a particular drug is taken. That is why there is a need to identify the drugs causing FDR and to counsel the patients properly to avoid recurrence.

Aim and Objective: The aim and objective was to study the demographic details, clinical patterns, and the culprit drugs causing FDR.

Setting and Design: We have conducted a cross-sectional, observational study.

Materials and Methods: We have conducted an observational cross-sectional study from April 2010 to March 2018 at the Department of Dermatology, Venereology and Leprology at Shree Krishna Hospital, Pramukhswami Medical College, Karamsad, Gujarat, after taking approval from the research ethical committee of our hospital. All patients coming to the skin out patient department who were diagnosed clinically as FDRs were included in the study, irrespective of age and sex. In every case, a detailed history was elicited and proper clinical examination was carried out and it was recorded in a proforma. The data collected was analyzed using proportions, frequencies and chi-square test. All the patients were counseled and given a list of drugs causing FDR to avoid recurrence.

Results: In our study, we enrolled 78 patients of FDR in which there were 43 (55.12%) males and 35 (44.88%) females. In these patients, the most frequent condition for which the offending drug was taken was fever (in 18 [23.08%] patients), while the most common complaint after intake of offending drug was pigmented patch (in 32 [41.03%] patients) followed by mucosal lesions (in 20 [25.64%] patients). Overall, antimicrobials (31 [39.74%]) were the most common group of drugs which caused FDR followed by nonsteroidal anti-inflammatory drugs (28 [35.90%]). Considering a single molecule, diclofenac (16 [20.51%]) was the most common drug causing FDR followed by metronidazole (6 [7.69%]) and then cotrimoxazole, fluconazole and ciprofloxacin (5 [6.41%]) each.

Conclusion: Among ACDRs encountered in dermatology patients, FDRs form an important part. Antimicrobials are the most common group while diclofenac is the most common drug causing FDR.

Keywords: Fixed-drug reaction, Adverse cutaneous drug reactions, Antimicrobials, NSAIDS

Introduction

Out of all reported adverse drug reactions (ADRs), adverse cutaneous drug reactions (ACDRs) comprise of 10%–30%.^{1,2} It occurs in 2%–3% of hospitalized patients.³ Most of the ACDRs are usually mild and self-limiting, but severe ACDRs such as Stevens–Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms cause significant morbidity and mortality.⁴ FDR is defined as a cutaneous drug eruption that recurs at the same site when the same drug is administered and heals with residual hyperpigmentation, which is an indicator of site recognition.⁵ If the diagnosis of FDR is missed, it can cause recurrent eruptions whenever the culprit drug is administered again.⁶ It can be caused by any medicine but certain drugs like nonsteroidal anti-inflammatory drugs (NSAIDs); antibiotics and anti-epileptics induce reaction in 1%–5% of patients.⁷ The lesions of FDR are well defined, round or oval patches with erythema and edema, sometimes accompanied by a blister. With time, it becomes purplish or brownish. Any part of the body can be involved such as face, trunk, upper limbs, lower limbs, genitals and oral mucosa. It is important that skin reactions should be identified at the earliest and documented in the patient records so that their recurrence can be avoided. This study was done to identify the drugs that are responsible for FDR.

Materials and Methods

We have conducted an observational cross sectional study from April 2010 to March 2018 at the Department of Dermatology, Venereology and Leprology of Shree Krishna Hospital, Pramukhswami Medical College, Karamsad, Gujarat, after taking approval from the research ethical committee of our hospital. All patients coming to the skin out patient department who were diagnosed clinically as FDRs were included in the study, irrespective of age and sex. Written consent of each was taken. In every case, a detailed history was elicited and a thorough clinical examination was carried out. In order to find the causative agent, we enquired in detail about history of drug intake, duration of the lesion, morphology of the eruption, associated mucosal or systemic involvement, temporal correlation of lesions with the drug and improvement of lesions on withdrawal of drug. All other possible etiologies were ruled out and then the diagnosis of ACDR was reached. When two or more drugs were thought to be responsible, the most likely drug was noted and the impression was confirmed when the symptoms reduced on withdrawing the drug.

Results

We had enrolled 78 patients in our study, which included 43 (55.12%) males and 35 (44.88%) females. 21–

30 years was the most common age group affected (20 [25.64%]) [Table 1]. 36 (46.15%) patients had past history of FDR, of which 8 (10.26%) had FDR due to the same drug. Those culprit drugs were paracetamol for 2 cases and 1 case for fluconazole, ciprofloxacin, chloroquine, isoniazid, cotrimoxazole and phenytoin. In all patients who had FDR from the same drug, the reaction was more severe than the previous reaction. The drugs were prescribed in 61 (78.21%) cases and self-administered in 17 (21.79%) cases. The most frequent complaint for which the offending drug was taken was fever (in 18 [23.08%] patients) followed by respiratory illness (in 16 [20.51%] patients), while the most common complaint after intake of offending drug were pigmented patch (in 32 [41.03%] patients) followed by mucosal lesions (in 20 [25.64%] patients) [Table 2]. In 58 (74.36%) cases, only skin was involved while in the rest 20 (25.64%) cases, there was mucosal involvement in which 12 (15.38%) cases had genital lesions, 5 (6.42%) cases had oral

lesions, 2 (2.56%) cases had conjunctival involvement and 1 (1.28%) case had anal involvement. Overall, antimicrobials (31 [39.74%]) were the most common group of drugs which caused FDR followed by nonsteroidal anti-inflammatory drugs (28 [35.90%]) [Table 3]. As a single molecule, diclofenac (16 [20.51%]) was the most common drug causing FDR followed by metronidazole (6 [7.69%]) and then cotrimoxazole, fluconazole, and ciprofloxacin (5 [6.41%]) each [Table 4]. According to the WHO causality categories 33(42.30%) cases were falling into possible categories, 38 (48.79%) into probable and 7 (8.97%) cases into certain. According to Naranjo ADR probability scale, 51 (65.38%) cases fell in probable category, 22 (28.20%) cases in possible and 5 (6.41%) cases in definite. Hartwig severity assessment showed level 2 in 36 (46.15%) cases, level 3 in 25 (32.06%), and level 4 in 17 (21.79) patients.

Table 1: Number of patients in different age groups.

AGE(years)	Male	Female	Total(%)
0-10	1	0	1(1.28%)
11-20	3	3	6(7.69%)
21-30	13	7	20(25.64%)
31-40	9	7	16(20.51%)
41-50	7	6	13(16.66%)
51-60	7	7	14(17.95%)
61-70	2	4	6(7.69%)
71-80	1	1	2(2.56%)
>80	0	0	0(0%)
Total	43(55.12%)	35(44.88%)	78

Table 2: Presenting complaints of patients.

Chief complaints	No of Cases
Pigmented patch	32(41.03%)
Mucosal lesions	20(25.64%)
Blisters	12(15.38%)
Redness of lesion	7(8.98%)
Burning sensation	2(2.56%)
Ulceration	3(3.85%)
Peeling of skin from lesional area	2(2.56%)
Total	78

Table 3: Drug groups causing fixed-drug reaction.

Causative drug groups	Number of cases (%)
Antimicrobials	31(39.74%)
NSAIDs	28(35.90%)
Antifungals	12(15.38%)
Antitubercular drugs	3(3.85%)
Antiepileptics	2(2.56%)
Antiretroviral drugs	1(1.28%)
Antispasmodics	1(1.28%)
Total	78

NSAIDs: Nonsteroidal anti-inflammatory drugs

Table 4: Drug molecule causing fixed-drug reaction.

Drugs	Number of cases (%)
Metronidazole	6(7.69%)
Ciprofloxacin	5(6.41%)
Levofloxacin	3(3.85%)
Ornidazole	2(2.56%)
Ceftriaxone	2(2.56%)
Cefuroxime	2(2.56%)
Cefadroxil	2(2.56%)
Cefixime	4(5.12%)
Chloroquine	2(2.56%)
Tinidazole	1(1.28%)
Doxycycline	1(1.28%)
Norfloxacin	1(1.28%)
Diclofenac	16(20.51%)
Ibuprofen	4(5.12%)
Nimesulide	6(7.69%)
Paracetamol	2(2.56%)
Griseofulvin	2(2.56%)
Fluconazole	5(6.41%)
Cotrimoxazole	5(6.41%)
Isoniazid	3(3.85%)
Clonazepam	1(1.28%)
Phenytoin	1(1.28%)
Buscopan	1(1.28%)
Nevirapine	1(1.28%)
Total	78

NSAIDs: Nonsteroidal anti-inflammatory drugs

Discussion

In outpatients and inpatients, the prevalence of ACDR has been reported to be 1% and 2%–5%, respectively.⁸ There are two types of ADRs: The majority (nearly 95%) are those which are dose dependent and predictable from the primary and secondary drug pharmacology known as Type A (augmented) reactions; while others are idiosyncratic, unpredictable from drug pharmacology and determined by patient-specific susceptibility factors, known as Type B (bizarre) reactions.⁹ According to most of the studies, FDR is the second or third common ACDR.¹⁰ and among all ACDRs, FDRs range from 16% to 21%. The real percentage may be more than these values because ACDRs are under reported due to increased selling of over-the-counter drugs. FDR has is associated with HLA-B22.^{11,12} The exact mechanism of FDR occurrence is not yet understood, but it is hypothesized that the active and quiescent lesions are caused due to a cell-mediated process. The culprit drug acts as a hapten, which creates an inflammatory response by binding preferentially to the basal keratinocytes. This causes the keratinocytes to release cytokines such as TNF-alpha, which upregulate the expression of intercellular adhesion molecule-1 (ICAM-1). ICAM-1 stimulates the CD8+ effector/memory T-cells. Whenever the culprit drug is re-introduced in the body, these CD8+ effector/memory T-cells produce a large amount of interferon-gamma and TNF-alpha, causing tissue damage and reactivation of the

lesions.^{13,14} FDR can occur at any age. In our study, majority of patients belonged to 21–30 years age group, which correlates with other studies. In this study, antimicrobials (31 [39.74%]) were the most common group of drugs causing FDR, followed by NSAIDs (28 [35.90%]), antifungals drugs (12 [15.38%]), antiepileptics (2 [2.56]) and antitubercular drugs (3 [3.85%] each), and antiretroviral drugs and antispasmodics ([1.28%] each). In study by Ghosh et al. antibiotics were found to be the most frequent cause of adverse cutaneous reactions, thus showing similar results, although antiepileptics were second common cause.¹⁵ In a study by Raksha et al., NSAIDs caused 21% of the FDR followed by sulfa drugs with 14%.¹⁶ In our study, diclofenac was found to be most commonly associated with FDR (16 [20.51%]) followed by metronidazole (6 [7.69%] cases), and then cotrimoxazole, fluconazole and ciprofloxacin 5 (6.41%) each. In studies by Singh et al. and Shrivastava et al, cotrimoxazole was found to be the most common antimicrobial as the cause of FDR.^{17,18} A study by Pudukadan and Thappa showed that the most common culprit drugs were cotrimoxazole in 22.25% of patients followed by dapson in 17.7% of patients.¹⁹ In our study, when two or more drugs were thought to have caused the FDR, the most likely drug was noted and it was confirmed when the symptoms reduced on withdrawing the drug. There are many methods to find out the offending drug such as intradermal tests, provocation tests or skin prick tests but they are of limited use as they need expertise, time

consuming and may even cause life-threatening ADRs that may raise ethical issues. Fortunately, there is an in vivo challenge test called the drug patch test, which is easy to perform and can be used to detect ACDRs.²⁰ Patch testing was first used by Alanko et al. for determining the causative drugs in FDR.²¹ In ACDRs, patch testing is the investigation of choice and it is useful in FDRs caused by NSAIDs.²⁰ Patch testing for contact dermatitis and drug test has the same basic principle and methodology. Patch testing is usually performed on a previously affected skin to avoid false-negative result.²² For patch testing, petrolatum, water, or alcohol can be used as vehicles in which 1-10% of pure drug form should be used. Drugs causing most of the reactions are anticonvulsants (carbamazepine, phenobarbitone, phenytoin or lamotrigine), betalactam antibiotics (amoxicillin and ampicillin), NSAIDs and sulfonamides. If the patch test results are negative, oral provocation test has been found to be the only reliable method to spot the offending drug. In our study, the only limitation is that no objective test was conducted to confirm the culprit drug and instead of mentioning all the drugs taken by the patient, only that drug which was most likely to cause drug reaction was recorded.

Conclusion

Among all ACDRs, FDR is an important type, which is seen very often nowadays because a wide array of drugs is available. The primary factor responsible for drug reactions are unmonitored selling of over the counter (OTC) medications. The main drugs causing FDR include antibiotics, analgesics, and antiepileptics. In order to reduce the cases of ACDR, we must focus on reporting of maximum cases and their monitoring. Patients should also be counseled about drug reactions and should be given drug list of that respective ACDR to avoid recurrence. Hence, this study highlights the importance of a sustained combined effort needed on part of the pharmacists, physicians as well as the public to effectively monitor the rampant use of over the counter medication as well as prescribed drugs to curtail the drug reactions which can potentially occur, and prevent them at a grassroot level.

Conflict of Interest: None.

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