ejpmr, 2015,2(5), 448-457.

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 3294-3211

EJPMR

ADVERSE CUTANEOUS DRUG REACTION: STUDY OF 200 CASES FROM TERTIARY CARE HOSPITAL

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Article Received on 28/06/2015 **Article Revised on 19/07/2015** **Article Accepted on 10/08/2015**

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ABSTRACT

Background: Adverse cutaneous drug reactions (ACDRs) are caused by a wide variety of agents and in different forms. Aims: Our objective was to assess the clinical spectrum of ACDRs and to find out the causative drugs in patients of tertiary care hospital. Methods: 200 patients with ACDR presenting in skin OPD between 2005 – 2011 were included in this study. Type of drug reaction and offending drugs were noted. Routine hematological and biochemical investigations were done in all patients. S. VDRL and S. HIV tests were done as when indicated. Histopathology was done in cases which required confirmation. Results: The Mean age of patients with ACDR was 38.26 years. Highest number of patients (26.5%) were reported in 41-50 years of age. The male to female ratio was 1.4:1. The most common pattern of ACRD was urticaria and/or angioedema (33.5%) . Co-trimoxazole and Diclofenac were most common culprit drugs. Many rare and severe type of ACDR like acute generalized exanthematous pustulosis and drug induced rash with eosinophilia and systemic symptoms were found in our series. Conclusion: Identifying drug reaction at early stage and finding out culprit drug is essential for physician for preventing disability arising out of ACDR and also to morbidity and mortality due to complications of ACDR.

KEYWORDS: Adverse cutaneous drug reaction, drug rash, drug reaction

INTRODUCTION

Adverse cutaneous drug reactions (ACDR) are a commonly encountered disability in dermatology OPD. Their incidence is approximately 2.2% and higher incidence is seen in

general in female and hospitalized patients.[1] Various forms of benign and temporary drug reactions are common but incidence of severe and fatal drug reaction is increasing in setting of increasing number of patients with immune suppression like HIV infection and increasing use of medicines.

This study was undertaken to find out incidence of various types of adverse cutaneous drug reaction (ACDR) encountered in dermatology out-patient department and to find out causative agents for various kind of drug reactions. The diagnosis of drug reaction was based upon detailed clinical history, clinical findings and correlation between drug taken and appearance of skin lesions. Detailed history taking in suspected drug reaction case requires lots of patience and skillfulness to elicit positive history and eliminate negative findings.

MATERIALS AND METHODS

A prospective study was carried out on 200 cutaneous drug reaction patients presenting in skin department between 2005 to 2011 including referrals from indoor patients from various departments. Detailed history and clinical findings of each patient were noted including age, sex, onset of drug rash, time of suspected drug taken, route of administration, dosage used, past history of similar or other kind of drug reaction, type and severity of drug rash, any supporting investigations if available etc. Drug history was particularly inquired in each suspected patient in terms of allopathic, ayruvedic, homeopathic or any other indigenous drug taken. Only those patients in whom definite causal relationship with drug taken was evident clinically were enrolled in the study. Details regarding existing or past skin conditions like atopic dermatitis, contact/irritant dermatitis, any other skin condition were also noted. Family history of drug reaction was inquired. Systemic examination was carried out and thorough clinical examination of skin including hair, nail, mucosa was done in each patient. Investigations including complete blood count, urine and stool examination, liver and renal function tests were done in each patient. Other investigations like tests for HIV infection, S.VDRL, ANA tests, sonography, X-ray chest etc were done as and when required.

The severity of the ACDR was graded according to the University of Virginia Health System Adverse Drug Reaction Reporting Program criteria as follows [2]

1. Mild: A reaction that does not require treatment or prolongation of hospital stay
2. Moderate: A reaction that requires treatment and/or prolongs hospitalization by at least one day

3. Severe: A reaction that is potentially life-threatening or contributes to the death of the patient, is permanently disabling, requires intensive medical care (including extended hospitalization), or results in a congenital anomaly, cancer, or unintentional overdose.

Observations and Results: Out of 200 patients there were 117 male and 83 female patients. Mean age in present study was 38.26 years. Maximum number of patients were in age group of 41 -50 years (n= 53 , 26.5 %), followed by 21 -30 years, patients below 20 years of age and those above 60 years of age were less than 10% each. (Table 1) The youngest patient was 10 month old female and the oldest was 77 year old male.

Most of the patients developed cutaneous drug reaction while they were taking medicines. The duration of development of rash and drug intake was few hours to upto 2 months. Among 200 patients 79 (39.5%) had history of drug reaction in past.

Various types of cutaneous drug eruptions seen during present study are summarized in Table 2. Maximum number of patients presented for Urticaria/angioedema (n=67, 33.5%) and Fixed drug eruption (FDE) (n=31, 15.5%).) (Figure 1,2,3) Dermographism (fFIgure 4), generalized pruritus, xerosis & acneiform eruption were other common drug reactions seen. Erythema multiforme (figure 5) (EM) and Steven Johnson Syndrome (SJS)/ toxic epidermal necrolysis (TEN) (figure 6,7), exfoliative dermatitis, Drug induced rash with eosinophilia and systemic symptoms (DRESS) (Figure 8) and Acute generalized exanthematous pustulosis (AGEP) were serious types of drug reaction forming significant group of patients (n=20, 10%). ADRs related to hair and nail were seen in 3 patients each. Pruritus (generalized or palmo-plantar) without significant skin lesions were seen in 16 patients (8%). Acneiform eruptions were seen in 18 patients (9%), most of them were male (n=15, 7.5%). Morbilliform rash (Figure 9), urticarial vasculitis, lichenoid eruption (figure 10), photodermatitis (Figure 11), pigmentation were observed in very few number of patients. Oral ulcers were seen in 4% patients. One female patient on AKT developed rash of lupus erythematosus (LE) with positive S. ANA and negative anti-dsDNA which subsided on discontinuation of drug.

Most common drugs causing urticaria and/or angioedema were diclofenac and co-trimoxazole followed by chloroquine and other NSAIDs. (Table 3) Most common drugs causing FDE were co-trimoxazole and quinolone group of antibiotics.(Table 4) Isoniazide and oral steroids were most common cause for acneiform drug eruption. Statins were most common drug to cause xerosis while isotretinoin produced most cases of xerosis and cheilitis

(retinoid dermatitis) Chloroquin was consistent cause for palmo-plantar pruritus while antiepileptics were sole cause for development of DRESS. (Table 5) Antiretroviral drug Nevirapine produced morbilliform rash in one male HIV reactive patient on HAART, two HIV reactive patients developed SJS/TEN due to co-trimoxazole, while nail pigmentation was seen in one patient on zidovudine. Hair loss seen in 3 patients in this series was found to be associated with isotretinoin, methotrexate and CHOP chemotherapy, one each. Out of 200 patients significant biochemical abnormalities were seen in patients with DRESS, exfoliative dermatitis, AGEP and HIV reactive patients. Patients with DRESS had reversible hepatic enzyme abnormality and eosinophilia in all patients. None of the patient showed atypical cells on peripheral blood smear. In patient with exfoliative dermatitis induced by dapsone and AGEP induced by terbinafine peripheral blood neutrophilic leucocytosis were seen. We found four patients who were HIV reactive. HIV reactive patients with ADR showed Variable leucopenic lymphopenia, hepatic enzyme abnormalities, and anemia but none of them could be directly attributed to ADR. Mild eosinophilia were seen in 29 patients with other types of ADR.

Biopsies were done in all patients with DRESS, exfoliative dermatitis, AGEP, urticarial vasculitis and few of SJS/TEN for confirmation of diagnosis. Findings on biopsy in all patients were consistent with clinical diagnosis.

As far as severity of drug reaction was concerned 23 (11.5%) patients had severe drug reaction which required prolong hospitalization out of which 1 HIV reactive patient of TEN died of severe drug reaction and related metabolic disturbances. (Table 6).

Complications were seen in 9 patients in the form of septicemia (n=2), post-inflammatory depigmenation and hypopigmentation(n=4), post-ACDR synechie formation in eyes in one patient of SJS which required surgical management, oral candidiasis (n=1), balanoposthitis (n=1).

DISCUSSION

The morphology and severity of drug reaction vary widely as per prevalent disease and common drugs used in particular center. In present study we found urticaria and /or angioedema (33.5%) to be the most prevalent type of drug reactions seen, followed by FDE (15.5%). Pudukadan D *et al*, reported the commonest pattern to be FDE (31.1%), followed by maculopapular rash (12.2%).[3] Patel RM et al reported FDE (30.5%) to be the most common

ACDR followed by urticaria (18.5%) and morbilliform rash (18%)[4]. Wang et al reported highest incidence of EM (27.4%) followed by exanthematous rash (25%) in their series[5]. Various other studies have reported different prevalence rate of different types of ACDR. [6,7]

Most common age group was 41-50 years. Patel RM et al have also reported 41-50 years of age as the commonest group involved with 21-30 years and 31-40 years age group showing almost similar incidence. Pudukadan D et al have shown 20-39 years as most commonly affected age group in their study. Various studies have reported various age group predominance in their study from younger age group 20-39 years to elderly patients. [8,9,10]

Male out number female in our study (M:F 1.4:1) probably due to social set up where more male come forward for the treatment and also self-medication which was commonly seen with male patients. Similar incidence has been reported by Patel RM et al; while M:F ratio is 0.87:1 in Pudukadan et al study.

Most common offending drugs in our patients were co-trimoxazole followed by diclofenac. Pudukadan *et al.* reported cotrimoxazole (22.25%), followed by dapsone (17.7%), as the commonest culprit drugs. In a study by Inbaraj SD et al the drugs which commonly produced Cutaneous Drug Reactions were NSAIDs (39.1%), followed by Quinolones (22.1%).[11]

Drug rash with eosinophilia and systemic symptoms (DRESS) which was seen in 3 (1.5%) of our patients is relatively newly described severe type of ACDR due to antiepileptics chiefly. DRESS was noted to occur from 10 – 60 days of drug intake so it is difficult to apply causal relationship to culprit drug but careful observation and prompt diagnosis in such cases is necessary as early treatment and stoppage of drug is essential for uneventful outcome in this cutaneous drug reaction with systemic involvement. Study by Wang et al have reported 1% incidence of DRESS in their study. [5]

Acute generalized exanthematous pustulosis (AGEP) is another rare type of drug reaction occurring following intake of various antibiotics, NSAIDs and other group of drugs.[12] We came across one patient of AGEP induced by oral antifungal Terbinafine.

DRESS and AGEP are types of ACDR not described previously in many studies though individual case reports in literature are many.

Patients with SJS/TEN are another group of patients who require constant monitoring and multidisciplinary management to prevent complications and fatality. In our study we came across 9 patients (4.5%) of SJS/TEN. Out of which one was 6 year old female child with severe TEN due to antiepileptic phenytoin. Two of our patients with SJS/TEN developed septicemia and one patient of TEN with HIV infection died of severe ADR. Ocular complications are also commonly seen in patients with SJS who have ocular involvement and proper care is not delivered early. One of our patient who came with severe ocular involvement had synechiae formation and required surgical management for the same. Wang et al have reported 15.4% indcidence of SJS/TEN in their patients while Patel RM et al have reported 4% incidence of the same in their series. [4,5] SJS/TEN in our series was mainly due to co-trimoxazole in comparison to SJS/TEN induced by ibuprofen by Patel RM et al.[4]

Statin induced xerosis was seen in 5 patients in our study and has also been reported by Inbaraj SD et al. [11] AKT was culprit in 7 out of 15 cases of generalized pruritus. Patel RM et al has also reported AKT as common cause of generalized pruritus. The incidence of acneiform eruptions induced by Isoniazide (INH) was 4.5% in our study while Patel RM et al reported 1% of acneiform eruptions due to INH. We found one case of FDE induced by cetrizine which was confirmed by oral challenge test. (In none of the other cases rechallange was done in our patients.) Single case of urticarial vasculitis due to ampicillin, cloxacillin combination was found in our series.

Table I (Age and sex distribution)

Age group	Number of patients			%
	Male	female	Total	
0 -10 years	03	05	08	4%
11 – 20 years	06	05	11	5.5%
21 – 30 years	24	21	45	22.5%
31-40 years	27	14	41	20.5%
41-50 years	28	25	53	26.5%
51 -60 years	19	08	27	13.5%
61 – 70 years	07	04	11	5.5%
>70 years	03	01	04	2%
Total	117	83	200	

So to conclude; the pattern of ACDRs and the drugs causing them vary in different population and depend upon use of common drugs. No age group is exempt from ACDR, even serious ACDR are commonly seen in children. Thorough knowledge of ACDR due to various drugs is essential for dermatologists to identify drug reaction at early stage for better

management of patients. Each drug should be considered potentially able to produce ACDR. Percentage of ACDR produced by commonly used drugs like co-trimoxazole, diclofenac and other NSAIDs, various antibacterial drugs, common antiepileptics demand for watchful eye on patients prescribed these medicines.

Table II (Type of Adverse Cutaneous Drug Reaction)

Type of drug reaction	Male	female	Total (%)
Urticaria and/or angioedema	36	31	67 (33.5)
FDE	21	10	31(15.5)
Dermographism	4	2	6 (3)
Morbilliform rash	3	2	5 (2.5)
Urticarial vasculitis	0	1	1(0.5)
Generalized Pruritus	4	7	11(5.5)
Palmo-plantar pruritus	3	2	5 (2.5)
EM	2	4	6 (3)
SJS/TEN	6	3	9 (4.5)
DRESS	3	0	3 (1.5)
AGEP	1	0	1(0.5%)
Exfoliative dermatitis	0	1	1(0.5)
Acneiform eruption	15	3	18 (9)
Lichenoid eruption	0	1	1(0.5)
Oral ulcer	5	3	8 (4)
Xerosis &/or Cheilitis	9	6	15 (7.5)
Alopecia/ hair loss	0	3	3 (1.5)
Nail changes	2	1	3 (1.5)
pigmentation	1	2	3 (1.5)
photodermatitis	1	0	1 (0.5)
LE – like skin rash	0	1	1 (0.5)
	117	83	200

Table III (Drugs causing Urticaria and/or Angioedema)

Drugs	Number of patients (n=67)
Antipyretic, antiinflammatory	
Diclofenac	17
paracetamol	2
Aspirin	3
ibuprofen	6
Unknown NSAIDs – chiefly self medication	6
Antibiotics/ Antimicrobials	
Co-trimoxazole	9
Penicillin & group	4
Quinolones	4
Dapsone	1

Tetracycline	1
metronidazole	2
Chloroquine	4
others	4
Other drugs	
Loperamide	2
omeprazole	1
Alternative medicine	1

Table IV (Drugs causing FDE)

Drug	**Number of patients (n=31)**
ANTIBIOTICS/ ANTIMICROBIALS	
Co-trimoxazole	9
Quinolones	4
Doxycycline	1
Rifampicin	1
griseofulvin	1
metronidazole	2
Amoxycylline/ ampicillin	1
erythromycin	1
others	1
NSAIDs	
paracetamol	1
Diclofenac	2
ibuprofen	1
Other NSAIDs	1
Miscelleneous	
Cetrizine	2
loperamide	1
sulfonylureas	1
Unknown medicine (self use)	1

Table V (Most common drugs causing other types of ADR)

Drugs	**Type of ADR commonly seen**	**Number of patients**
Isoniazide	Acneiform eruption	9/18 (50%)
steroids	Acneiform eruption	6/18 (33.33%)
statins	xerosis	5/15 (33.33%)
isotretinoin	Xerosis & cheilitis	11/15 (73.33%)
chloroquin	Palmo-plantar pruritus	4/5 (80%)
AKT	Genreralised pruritus	7/11(63.6%)
DRESS	Phenytoin/carbamezapine	3/3 (100%)
SJS/TEN	Co-trimoxazole	4/9 (44.5%)

Table VI (Severity of ACDR)

Severity of ADR	Number of patients
Mild	48 (24%)
moderate	129 (64.5%)
severe	23 (11.5%)

Figures and legends

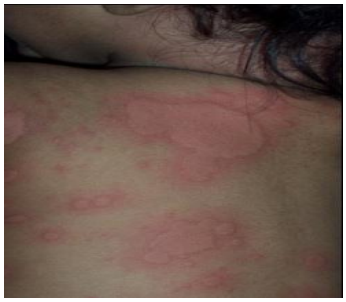

Figure1: Urticaria

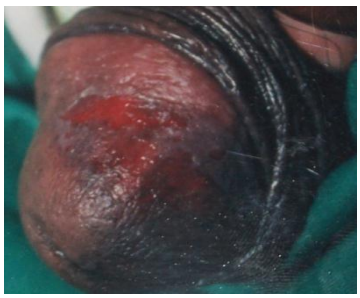

Figure 2: Bullous FDE

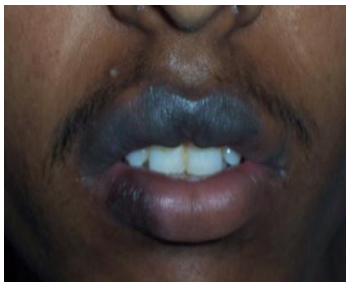

Figure 3: FDE

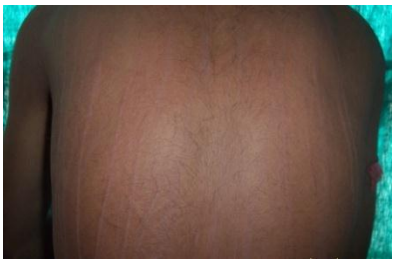

Figure 4: Dermographism

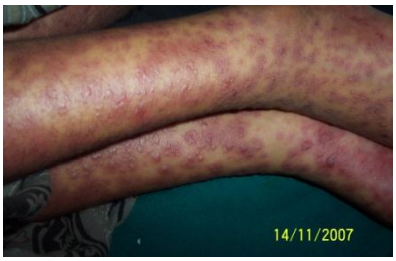

Figure 5:EM

Figure 6: TEN

Figure 7: SJS

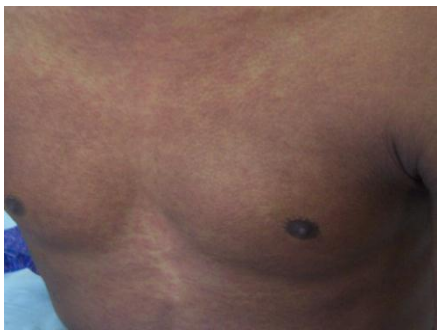

Figure 8: Rash of DRESS

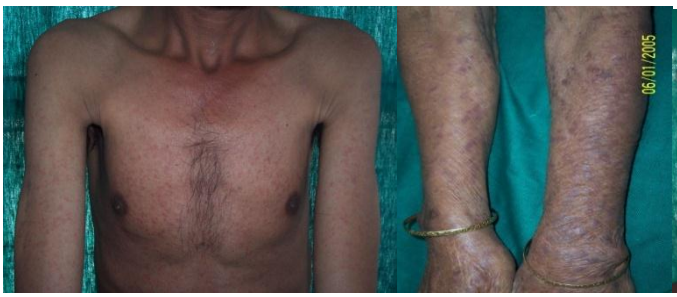

Figure 9:Morbilliform rash

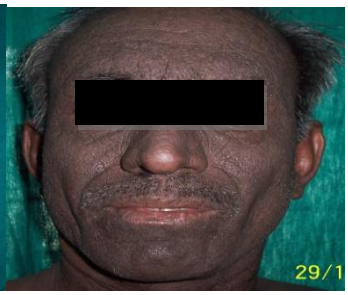

Figure 10:Lichenoid rash

Figure 11: Photodermatitis

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