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A CLINICAL STUDY OF CUTANEOUS ADVERSE DRUG REACTIONS IN TERTIARY CARE HOSPITAL

Dermatology

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ABSTRACT

The patterns of cutaneous eruption and the offending agent vary amongst the different population previously studied. This study aims to determine the different clinical patterns of cutaneous adverse drug reactions (CADRs) in our population and recognize the common drug implicated. A prospective observational study was conducted over a period of two years recording various CADRs.

Out of the 630 patients, common reactions observed were Fixed drug eruption (25.71%), Urticaria / Angioedema (21.27%), Exanthematous rash(15.87%), Erythema multiforme(3.81%), Steven-Johnson Syndrome (4.13%) and Toxic epidermal necrolysis (2.07 %). The most common pharmacological group was Antimicrobials (37.01%), NSAIDS (16.64%), Anticonvulsants (7.61%) and Antiretroviral therapy (12.52%). Cotrimoxazole was the culprit in 11.11%, Nevirapine in 9.36%, Amoxycillin in 7.61% and Phenytoin in 5.23% of patients. 10 patients of TEN proved to be fatal. Among 15.56% HIV reactive patients, the most common pattern was exanthematous rash (45.91%) with Nevirapine(59.20%) as the most common culprit drug.

KEYWORDS

cutaneous adverse drug reactions, Fixed drug eruption

INTRODUCTION

Adverse drug reactions are one of the major preventable public health problems.[1] Although cutaneous reactions are common, they are often under-reported and under-recognized.[2] Except for studies in hospitalized populations and those focusing on the most severe reactions, data regarding the incidence of cutaneous drug reactions in the general population are minimal. This inadequacy of data could be attributed to the reasons such as diagnostic dilemmas, lack of awareness to report and in part due to the absence of post-marketing surveillance.

Polypharmacy, easy availability of over the counter medications and unsupervised medications in the Indian subcontinent are some of the causes for increased prevalence of drug reactions.[3] Skin is one of the most common organ systems affected in drug reactions. Distinctive morphological pattern aid in early recognition of cutaneous adverse drug reactions (CADR) and prompt discontinuation of the offending drug thus decreases morbidity. These clinical patterns and their causative drugs vary greatly among the different populations previously studied.[4]

In our study, we aim to determine the clinical patterns of CADRs in our population and recognize the common drug implicated. The purpose is also to study its relationship with age and gender, the incidence of CADRs in HIV reactive patients and to evaluate the morbidity and mortality in patients having severe cutaneous adverse reactions.

MATERIAL AND METHODS

This prospective, observational study was conducted from September 2013 to August 2015 in Department of Dermatology, Venereology and Leprology at our institute after obtaining clearance from the Institutional Ethical Committee. Patients were clinically evaluated and those suspected of having drug reactions were included in the study. The WHO causality definitions were used to assess the suspected offending drug. Patients who developed drug reactions following intake of traditional medicines and who were not willing for the study were excluded.

Detailed history was taken in all the patients and thorough clinical examination as mentioned in the pre-set proforma was done. Information regarding the intake of drugs, their indications, duration of drug intake, and the date of onset of eruptions, morphology, as well as the past and family history of any drug eruption were recorded. Mucous membrane examination was done in all cases. Any change in hair and nails was also noted. Appropriate haematological Indices, liver function tests, renal function tests, Chest radiography and biopsy were done. In the patients receiving more than one drug, the most likely offending agent was identified based on the clinical pattern and incubation period and this was confirmed by remission on withdrawal of the same.

Patients were treated in out-patient department. Those with severe drug reactions were hospitalized for intensive care and management of drug reactions. Patients were advised to avoid offending drugs and drugs which cause cross sensitivity. All the patients of drug reactions were followed up regularly after the treatment.

RESULTS

In the present study, 630 cases of drug reactions were studied. There were 336 male (53.33%) and 294 (46.67%) female ratio being 1.14:1. The highest percentage of patients belonged to 21-30 years age group with 23.80% (n=150) patients, followed by 31-40 years which included 23.17 % (n=146) patients. Age of the patients ranged from 5 months to 80 years (Mean age 40.20 years).

A total of 35 different patterns of CADRS were noted.

Table 1 shows different clinical patterns of CADRs.

Table 1 : Different clinical patterns of CADRs

Sr. No.	Pattern of reaction	No. of cases	Percentage
1	Fixed drug eruption	162	25.71 %
2	Exanthematous rash	100	15.87 %
3	Urticaria	85	13.49 %
4	Urticaria+angioedema	31	4.92 %
5	S.J.Syndrome	26	4.13 %
6	Erythema Multiforme	24	3.81%
7	Drug induced pigmentation	19	3.06 %
8	Angioedema	18	2.86 %
9	Acneiform eruptions	18	2.86 %
10	Toxic epidermal Necrolysis	17	2.70 %
11	EM Major	13	2.06%
12	Drug induced hypertrichosis	10	1.59 %
13	Nail pigmentation	10	1.59 %
14	Photosensitivity	9	1.43 %
15	Diffuse hair loss	8	1.27 %
16	Striae	8	1.27 %

17	DRESS	8	1.27 %
18	Contact dermatitis	7	1.11 %
19	Exfoliative dermatitis	6	0.95 %
20	Lichenoid drug eruption	6	0.95%
21	Lipodystrophy	5	0.79 %
22	Drug induced icthyosis	5	0.79%
23	Anagen effluvium	4	0.63 %
24	Cutaneous atrophy	4	0.63%
25	Papulopustular eruptions	4	0.63%
26	Oral ulceration	3	0.48%
27	Drug induced purpura	3	0.48%
28	Acute generalized exanthematous pustulosis	3	0.48%
29	Hand foot syndrome	3	0.48%
30	Nicholau syndrome	2	0.32%
31	Telengectasia	2	0.32%
32	Lichen planus	2	0.32%
33	Flagellate dermatitis	2	0.32%
34	Methotrexate toxicity	2	0.32%
35	Gingivial hyperplasia	1	0.16%

The most common was fixed drug eruption (FDE) (Figure 1) in 25.71% patients followed by urticaria / angioedema in 21.27% patients and then exanthematous rash in 15.87% patients.

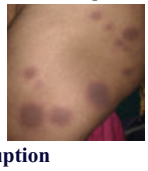

Figure 1 Fixed drug eruption

Table 2 shows commonest drugs causing CADR.

Table 2 : Commonest drugs causing CADRs			
Sr.No.	**Offending drug**	**No. of cases**	**Percentage**
1	Cotrimoxazole	70	11.11%
2	Nevirapine	59	9.36%
3	Amoxicillin	48	7.61%
4	Phenytoin	33	5.23%
5	Ibuprofen	33	5.23%
6	Diclofenac	27	4.29%
7	Levofloxacin	26	4.12%
8	Paracetamol	25	3.96%
9	Ofloxacin	24	3.80%
10	Corticosteroids	19	3.01%
11	Ciprofloxacin	19	3.01%
12	Clofazimine	16	2.53%
13	Isoniazid	15	2.38%
14	Chloroquine	15	2.38%
15	Carbamazepine	15	2.38%
16	Aspirin	11	1.74%
17	Zidovudine	11	1.74%
18	Efavirenz	09	1.42%
19	Nimesulide	09	1.42%
20	Norfloxacin	09	1.42%
21	Topical Steroids	08	1.26%

Antimicrobials and NSAIDS were the common causative pharmacological group observed.

Table 3 determines the association between CADR and the common implicated drug.

Table 3: Association between CADRs and the common implicated drug					
FDE	**Urticaria and/or angioedema**	**Exanthematous rash**	**Erythema multiforme**	**SJS**	**TEN**
Cotrimoxazole 32.72%	Amoxicillin 24.14%	Nevirapine 38.00%	Nevirapine 26.47%	Phenytoin 38.46%	Phenytoin 17.64%
Paracetamol 8.97%	Diclofenac 16.38%	Phenytoin 12.00%	Amoxicillin 5.88%	Nevirapine 26.92%	Cotrimoxazole 17.64%
Ciprofloxacin 8.02%	Ibuprofen 16.38%	Amoxicillin 9.00%	Carbamazepine 5.88%	Carbamazepine 11.54%	Carbamazepine 17.64%
Ofloxacin 7.41%	Cotrimoxazole 6.90%	Efavirenz 7.00%	Chloroquine 5.88%	Cotrimoxazole 7.69%	Nevirapine 17.64%
Levofloxacin 7.69%	Dicyclomine 6.03%	Metronidazole 4.00%	Cotrimoxazole 5.88%	Aceclofenac 3.85%	Amoxicillin 5.88%

All the patients of Steven Johnson Syndrome (S.J.S) (n=26) were treated as indoor patients. No mortality was reported. Out of 17 patients of Toxic epidermal necrolysis (TEN), 10 patients having higher SCORTEN died due to acute respiratory distress and electrolyte imbalance. Eight patients of Drug reaction with eosinophilia and systemic symptoms (DRESS) were reported during the study period. Phenytoin was the causative agent in 4 patients followed by carbamazepine. No mortality was detected. Three patients of Acute generalized exanthematous pustulosis (AGEP) **(FIGURE 2)** were reported in our study with diclofenac and ampicillin as the offending drug. Six patients developed the generalized exfoliation of the skin. Isoniazid was the offending drug in 3 patients, while carbamazepine, chloroquine and sunitinib were the cause in one patient each. Two patients suffered from methotrexate toxicity presenting with oral ulceration and ulceration over psoriatic plaque after taking methotrexate 7.5 mg daily for 3 days.

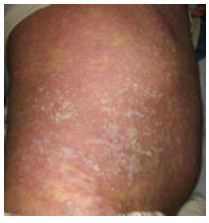

Figure 2: Acute generalized exanthematous pustulosis (AGEP)

In 18 patients with acneiform eruptions, oral corticosteroid and isoniazid was the offending drug. Oral corticosteroids were also the most common cause of hypertrichosis in 7 patients followed by Cyclosporin and phenytoin in the remaining. Nine patients developed photosensitivity to Fluoroquinolones. In other cases doxycycline and furosemide were responsible.

Clofazimine caused the characteristic mahogany pigmentation in 15 patients of leprosy. Five patients developed icthyoses over lower limbs due to clofazimine and isoniazid. Three patients developed melasma due to oral contraceptive pills and one patient developed hyperpigmentation over acne scars with minocycline therapy.

Five out of six patients developed lichenoid drug eruption with Antihypertensive drugs. Patients were treated with moderate potency topical steroids. One patient developed nicolau syndrome after deep intramuscular injection of dexamethasone and injection pheniramin and another patient developed after deep intramuscular injection of diclofenac sodium.

Chemotherapeutic agents particularly cytarabine and cyclophosphamide were responsible for anagen effluvium in all the 4 cancer patients. Erlotinib, gefitinib and cetuximab were the culprit drugs for the papulo-pustular eruption over the trunk. In the three patients presenting with oral ulceration, cisplatin and carboplatin were the offending drug. Three patients developed hand foot syndrome after starting chemotherapy with capecitabine. Two patients of chronic myeloid leukemia who were on imatinib for one year developed lichen planus. 2 patients developed flagellate dermatitis over trunk to the bleomycin injection.

Out of the 630 patients, 98 patients were HIV-reactive. Most of the patients were in the age group of 21-40 years. The most common pattern of adverse cutaneous reaction was exanthematous rash in 45.91% (n=45) patients. Most common drug was nevirapine in 59.2% (n=58) cases. Zidovudine was the causative agent in 12 cases out of which 10 developed nail pigmentation. Other causative agents were cotrimoxazole and Antitubercular therapy. 3 patients developed lipodystrophy due to stavudine while 2 patients developed due to zidovudine. All the patients developed loss of fat from cheeks and accumulation of fat over trunk and over nape of neck.

DISCUSSION

Adverse drug reactions range from common eruption to life-threatening drug-induced diseases. These may be solely limited to the skin, or they may be part of a systemic reaction, such as drug hypersensitivity syndrome or toxic epidermal necrolysis.

Previous studies showed variable results about the incidence of CADRs in different gender. Studies by sushma et al[5] and Sharma et al[6] reported a male preponderance while study by Padukon et al[7] showed a female preponderance with the ratio of 0.87:1. Male to female ratio in this study was 1.14:1. Difference in the body weight and composition, hormonal influence on drug metabolism may be the probable explanation for the effect of gender on the CADR.[8]

Majority of CADRS was in the age group 21-30 years with the mean age of 40.20 years. The age incidence was in conformity with Ruchita Nandha et al.[9] and Marfatia et al[10]. All these studies suggest that the middle aged group is the most commonly affected and is rare at the extremes of age. Another study by Kongkaew *et al*.[11] found more CADRs in the elderly. This may be due to increased use of medications and altered drug metabolism in them.

FDE was the most common pattern noted in 25.71% patients. This is in accordance to the most of the studies done previously.[7,10,12] Bullous eruption was observed in 50 patients. The most common individual drug causing FDE was cotrimoxazole, while the most common pharmacological group was fluoroquinolones. In contrast, Jhaj *et al*.[13] reported 50% cases of morbilliform rash, 21% cases of urticaria, 13.9% cases of SJ syndrome and 4.9% cases of TEN. Malhotra *et al*[14] reported morbilliform rash in 29.63%, SJ/TEN in 22.22% and urticaria in 9.26% cases as the common patterns of eruption. This variation could be due to different population characteristics and diverse pattern of drug usage.[7]

The most common group of drugs causing ADRs were antimicrobials (37.01%), NSAIDS (16.64%) and anticonvulsants (7.61%) and Antiretroviral therapy (12.52%). Cotrimoxazole was the culprit in 11.11%, Nevirapine in 9.36%, Amoxycillin in 7.61% and Phenytoin in 5.23% of patients. This is in accordance to the study by Agarwal et al[15] and Patel et al[16] who reported 37.5% and 45.6% of the total reactions to antimicrobials. Diclofenac followed by ibuprofen were the most common offending drug in the NSAID group. These were also the common causes of urticaria. The general reason for the administration of drug was fever, pain, seizures and infections.

Severe cutaneous adverse reactions accounted for 9.36% of the study group similar to Sharma R et al (6.6%).[17] Most common drugs causing S.J.S-TEN were phenytoin, nevirapin, cotrimoxazole and carbamazepine. This is in line with Sharma et al[6] where Anticonvulsants were responsible for 43.8% of life-threatening reactions.

The most common pattern of adverse cutaneous reactions in HIV reactive patients was exanthematous rash in 45.91% (n=45) patients, while acneiform eruptions, striae and DRESS were found to be less common. SCARs were more common in HIV reactive patients. Nevirapine was the most common drug implicated followed by zidovudine. ATT was responsible for the drug reactions in only two cases. However study by Jha AK et al[18] reported ATT causing maximum eruptions in 28.3% cases followed by zidovudine in 20.7% cases.

Drug eruptions are distinct disease entities with varying frequency and severity. A precise diagnosis of the reaction pattern can help narrow possible causes because different drugs are more commonly associated with different types of reactions. The pattern of CADRs and the drugs causing them vary among the different population. A sound knowledge of these drug eruptions may help the clinician to better manage their cases.

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