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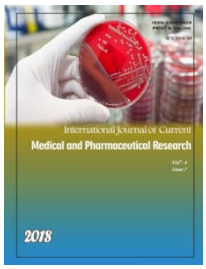

OCCURRENCE OF CUTANEOUS ADVERSE DRUG REACTIONS AMONG PATIENTS ATTENDING A TERTIARY CARE HOSPITAL - A PROSPECTIVE OBSERVATIONAL STUDY

Bincy Varghese[1]*., Jayakrishnan S.S[1] and Bindu R.S[2]

[1]Department of Pharmacy Practice, College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram, Kerala, India-695011
[2]Department of Dermatology and Venereology, Govt. Medical College, Thiruvananthapuram, Kerala, India-695011

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ABSTRACT

Cutaneous adverse drugs reactions (CADRs) are very common among ADRs. They account for patient's suffering, hospitalization and economic burden. Majority of CADRs are diagnosed clinically. The common offending drugs are antimicrobials, nonsteroidal anti-inflammatory drugs (NSAIDs), anti-epileptic drugs and anti-gout agents. The purpose of this study is to evaluate the occurrence of CADRs, clinical patterns associated, along with causality, severity and effect on quality of life. A Prospective observational study was undertaken over a period of six months in dermatology OPD, Govt. Medical College, Thiruvananthapuram, Kerala. A total of 58 patients, who met the inclusion criteria were enrolled in the study. The majority of the patients were found to be under the age of 50 years and female subjects were more than males. In this study, most of the reactions were caused by Phenytoin (19%), followed by Amoxicillin (13.8%). Commonest CADR in our study was Exanthematous (maculopapular) rash that is about 24.1%, followed by 19% Acuteurticaria. Causality assessment was done using Naranjo's algorithmic scale, majority of the cases were of probable score (69%). Severity assessment using modified Hartwig and Siegel scale shows majority of cases (56.9%) of grading. Quality of life assessment using Dermatological life quality index (DLQI) questionnaire shows majority of patients (46.6%) had a very large effect of CADRs in their QOL. Every drug must be regarded as potentially hazardous and the risk due to drug reaction must be weighed against the expected therapeutic benefit for each patient, so that the occurrence of CADRs can be minimized.

INTRODUCTION

Drugs can be remarkably beneficial, lengthen life and improve its quality by reducing symptoms and improving well-being, but all drugs have adverse effects and carry the potential for causing injury, even if used properly. According to WHO Adverse Drug Reaction can be defined as "A response to a drug which is noxious and unintended, which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modifications of physiological function". These drug reactions are undesirable and typically unanticipated reactions independent of the intended therapeutic purpose of a medication[1] that may burden the health system by not only increasing the morbidity and mortality but also the expenses. Science of Pharmacovigilance is accountable to identify, appraise, comprehend and avert ADRs with the eventual mean to develop secure and coherent utilization of medication.

Drug reactions can be classified into immunologic and non-immunologic etiologies. The majority (75-80%) of adverse drug reactions are caused by predictable, non-immunologic effects and the remaining 20-25% of adverse drug events is caused by unpredictable effects that may or may not be immune-mediated. Immune-mediated reactions account for 5-10% of all drug reactions and constitute drug allergies falling into this category[1]. Drug reactions are more common in women, increase with age and the number of medications used [2].

Cutaneous reactions are the most common form of ADRs. An adverse cutaneous reaction caused by a drug is 'any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompass all adverse events related to drug eruption, regardless of the etiology'. It should be suspected in any patient who develops a rash during a course of drug therapy. The reaction may be due to any medicine the patient is currently taking or has recently

Corresponding author:* **Bincy Varghese
Department of Pharmacy Practice, College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram, Kerala, India-695011

been exposed to, including prescribed and over-the-counter medicines, herbal or homoeopathic preparations, vaccines or contrast media. Also the non-drug components of a medicine, i.e. the pharmaceutical excipients may cause hypersensitivity reactions in some patients.

Cutaneous reactions are the most common form of ADRs occurring in 2%-3% of inpatient and in approximately 2% of outpatient patients referred for dermatologic evaluation. Approximately 2% of ADRs are considered severe or fatal [3,4].Any medicine can induce skin reactions and certain drug classes such as non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics and antiepileptics, have drug eruption rates approaching 1-5%[5]. Even though most drug-related skin eruptions are not serious, some are severe and potentially life-threatening. Serious reactions include angio-oedema, erythroderma, Stevens-Johnson syndrome and toxic epidermal necrolysis. Drug eruptions can also occur as part of a spectrum of multiorgan involvement, as in drug-induced systemic lupus erythematosus.

The skin and the mucosa are the common sites for initial presentation of many ADRs. Although the rate of acute severe adverse cutaneous reactions to medication is low, these reactions can affect any one who takes medicines and can result in death or disability. Proper data about the adverse effects of drugs helps physicians to use drugs balancing the benefits and hazards. It is important that skin reactions are identified and documented in the patient record so that their recurrence can be avoided.

The purpose of this study is to evaluate the occurrence of adverse cutaneous drug reactions and clinical patterns associated with it. During the study period various drug reactions, their causality and severity using valid scales were also determined. By this study an attempt has been also made to assess the extent to which the dermatologic problem affected patient's life using DLQI Questionnaire.

METHODOLOGY

Period of study: Data collection was done from January 2016 to June 2016, at Department of Dermatology and Venereology, Govt. Medical College, Thiruvananthapuram.

Study Design*:* Prospective observational study

Study Population: All patients reported to the OPD, Department of Dermatology; Medical College Hospital, Thiruvananthapuram, Kerala for undergoing treatment for adverse cutaneous drug reactions.

Sample Size*:* All patients reported to the OPD with CADR to the Department of Dermatology; Medical College Hospital, Thiruvananthapuram, Kerala for undergoing treatment for adverse cutaneous drug reactions.

Inclusion Criteria

- Both male & female.
- Patients who are willing to participate in the study.
- Patients reporting to OPD with drug induced cutaneous reaction for undergoing treatment.
- Be capable of speaking & reading English or Malayalam.

Exclusion Criteria

- Patient who are not willing to participate in the study.

Study Procedure

A written consent was obtained from the patient in the prescribed format. Patients who met the inclusion criteria were enrolled in the study. All information relevant to the study was collected from case records and direct interview with the patients with the help of Physician. The collected information was recorded in the data collection pro forma. The baseline assessment including patient demographics were recorded. The causality and severity was assessed using Naranjo's algorithmic scale and Modified Hartwig and Siegel Scale. The quality of life was calculated using validated DLQI Questionnaire.

Finally the results obtained were assessed and interpreted using statistical software, towards the accomplishment of the aim.

Plan of Analysis: Analysis of data was done using SPSS version 17.0 statistical software.

RESULTS

A total of 8431 patients were reported to the OPD out of which 58 patients were diagnosed with CADR.

Table 1 Distribution of the sample according to age

Age	Count	Percent
<=30	17	29.3
31 - 40	5	8.6
41 - 50	15	25.9
51 - 60	10	17.2
>60	11	19.0
Mean ± SD	43.5 ± 17.7	

From this study, majority of patients were found to be under the age of 30 years (29.3). The mean age was found to be 43.5 yrs.

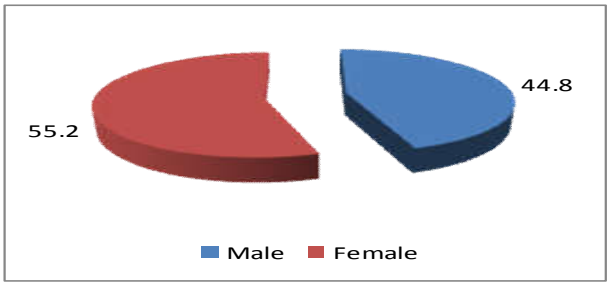

Figure 1 Percentage distribution of the sample according to gender

In this study, out of 58 patients, 44.8% were males and 55.2% were females.

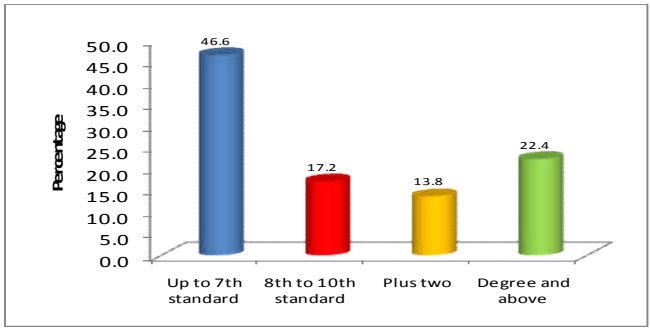

Figure 2 Percentage distribution of the sample according to level of education

In this study, majority of the patients (46.6%) had primary school level of education followed by 22.4% with degree level

of education. 13.8% had completed plus two and 17.2% had high school level of educational qualification.

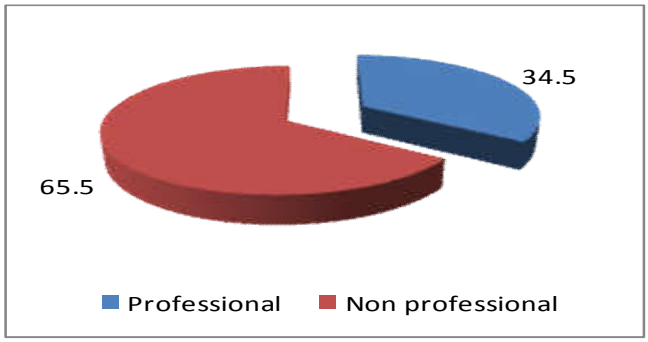

Figure 3 Percentage distribution of the sample according to occupation

From this study it was observed that 65.5% of patients in the study population were non-professionals and 34.5% were professionals.

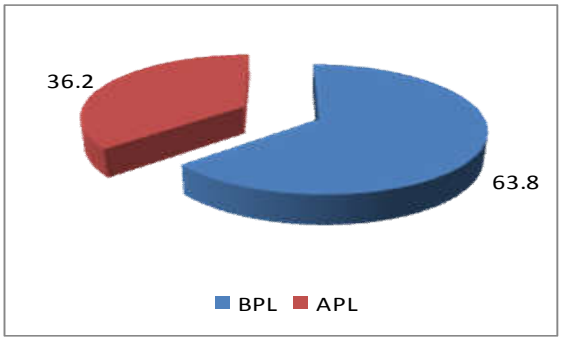

Figure 4 Percentage distribution of the sample according to economic status

From this study, based on their economic status majority of the patients were from BPL (Below Poverty Line) category (63.8%) and the remaining 36.2% were from APL (Above Poverty Line) category.

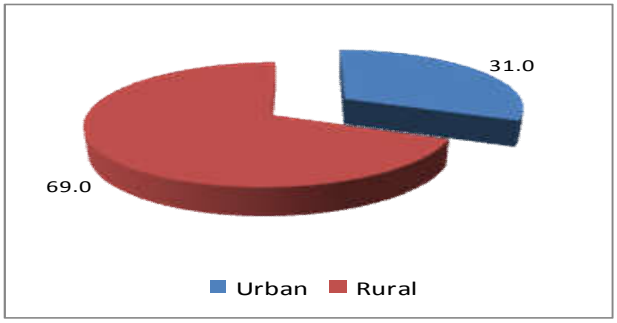

Figure 5 Percentage distribution of the sample according to residing area

It was observed that majority of patients in the study population were from rural areas (69%) and only (31%) were from urban area.

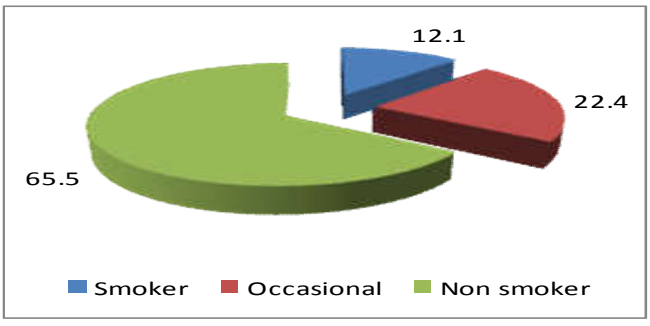

Figure 6 Percentage distribution of the sample according to smoking habit

In this study, majority of the study population (65.5%) did not have this habit. 12.1% patients were smokers and 22.4 % were occasional smokers.

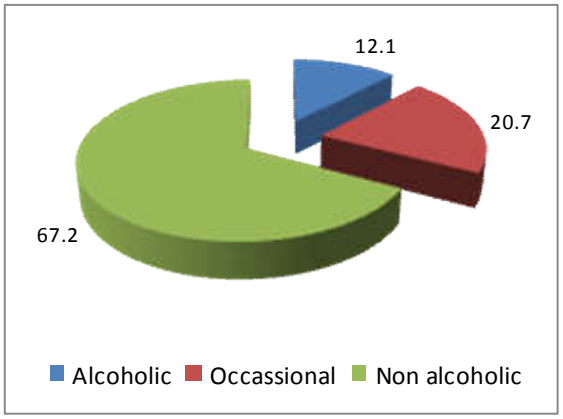

Figure 7 Percentage distribution of the sample according to alcohol abuse

In the study population, majority of patients (67.2%) did not have this habit. Only patients (12.1%) were alcoholic and 20.7% were occasional alcoholics.

Table 2 Distribution of patients according to the occurrence of ACDR

ACDR	Count	Percent	95% CI
Present	58	0.7	
Absent	8373	99.3	0.5 - 0.9
Total	8431	100	

From this study it was found that out of 8431 patients, 58 patients were presented with cutaneous adverse drug reaction. The percentage distribution was found to be 0.7% (95% confidence interval 0.5-0.9%).

Table 3 Distribution and ranking of most offending drugs causing ACDR

Drugs	Count	Percent	Rank
Phenytoin	11	19.0	1
Amoxicillin	8	13.8	2
Sodium valproate	4	6.9	3
Ayurvedic preparations	3	5.2	5.5
Ciprofloxacin	3	5.2	5.5
Doxycycline	3	5.2	5.5
OHA	3	5.2	5.5
Anti-TB	2	3.4	11.5
Carbamazepine	2	3.4	11.5
Clavulanic acid	2	3.4	11.5
Cefixime	2	3.4	11.5
IDRV	2	3.4	11.5
Indigenous preparations	2	3.4	11.5
Paracetamol	2	3.4	11.5
Prednisolone	2	3.4	11.5
Azithromycin	1	1.7	25
Ambroxol	1	1.7	25
Acyclovir	1	1.7	25
Levosalbutamol	1	1.7	25
Guaiphenesin	1	1.7	25
Betamethasone	1	1.7	25
Dexamethasone	1	1.7	25
Diclofenac	1	1.7	25
Fluconazole	1	1.7	25
Fluoxetine	1	1.7	25
Homoeopathic preparations	1	1.7	25
Levetiracetam	1	1.7	25
Piroxicam	1	1.7	25
Phenobarbitone	1	1.7	25
Promethazine	1	1.7	25
Tramadol	1	1.7	25
Trifluoperazine	1	1.7	25
Trihexylphenidyl	1	1.7	25
Tinidazole	1	1.7	25

In this study, majority of the reactions were caused by Phenytoin (19%), followed by Amoxicillin (13.8%) and Sodium valproate (6.9%). Azithromycin, Ambroxol, Aciclovir, Levosalbutamol, Guaphenesin, Betamethasone, Dexamethazone, Deflazacort, Diclofenac, Fluconazole, Fluoxetine, Homoeopathic, Levetiracetam, Methotrexate, Piroxicam, Phenobarbitate, Promethazine, Tramadol, Trifluoperazine, Trihexylphenidyl, Tinidazoleetc shared 1.7% of the total reactions respectively.

Table 4 Percentage distribution of the sample according to the signs and symptoms of ACDR

Clinical pattern	Count	Percent
Pruritus	24	41.4
Pruritic raised lesions all over the body	29	50.0
Rash (all over body)	28	48.3
Facial edema	16	27.6
Oral erosions	11	19.0
Eye discharge	10	17.2
Swelling of lips	9	15.5
Involving mucous membranes	5	8.6
External genitals	1	1.7
Pruritic fluid filled lesions	1	1.7
Rash face	2	3.4

In this study about 50% of the total population showed pruritic raised lesions all over the body. 48.3% cases showed rashes all over the body. 3.4% exhibited rash face and 1.7% experienced reactions involving external genital areas and 1.7% had pruritic fluid filled lesions.

Table 5 Percentage distribution of the sample according to common class of drugs causing ACDRS

Common class of drugs causing ACDRS	Count	Percent
Analgesics	3	5.2
Antibiotics	19	32.8
Anticonvulsants	19	32.8
Antifungals	1	1.7
Antihistamines	1	1.7
Antipsychotic	3	5.2
Antiamoebics	1	1.7
Antitubercular	2	3.4
Antivirals	1	1.7
Bronchodialators	1	1.7
Mucolitics	2	3.4
NSAIDs	2	3.4
Oral Hypoglycaemic Agents	3	5.2
Others	6	10.3
Steroids	4	6.9
Vaccines	2	3.4

In this study the most common class of drugs responsible for ACDR are found to be antibiotics and anticonvulsants which is about 32.8% each. The class of drugs such as Antifungals, Antihistamines, Anti-amoebic, Antivirals and Bronchodilators shared equal distribution of 1.7% each.

Table 5 Percentage distribution of patients according to the clinical pattern of ACDR

ACDR	Count	Percent	Rank
Exanthematous(maculopapular) rash	14	24.1	1
Acute urticarial	11	19.0	2
DHS	6	10.3	3
Angioedema	5	8.6	4.5
Exfoliative dermatitis	5	8.6	4.5
Erythema multiforme	4	6.9	6
FDE	3	5.2	7.5
Drug induced mucositis	3	5.2	7.5
Drug induced liver injury	2	3.4	11
SJS	2	3.4	11
TEN	2	3.4	11
SJS-TEN overlap	2	3.4	11
Steroid acne	2	3.4	11
Allergic contact dermatitis	1	1.7	14.5
Chronic urticarial	1	1.7	14.5

In this study the majority of ACDR comprises of Exanthematous (maculopapular) rash that is about 24.1%, followed by 19% Acute urticarial. 1.7% was each of Allergic contact dermatitis and Chronicurticaria.

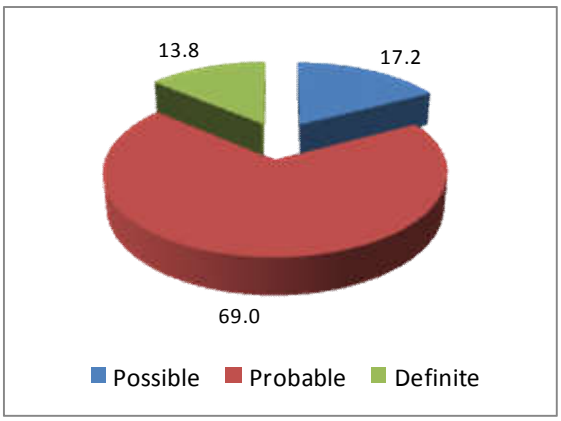

Figure 9 Percentage distribution of the sample according to Naranjo's Scale

In this study a total of 58 cases of cutaneous ADRs were analysed for causality. After assessment, 8 cases (13.8%) scored definite, 40 cases (69%) were of probable score whereas 10 cases (17.2%) were in possible score category. Unlikely, conditional or unassessible cases were excluded from the study.

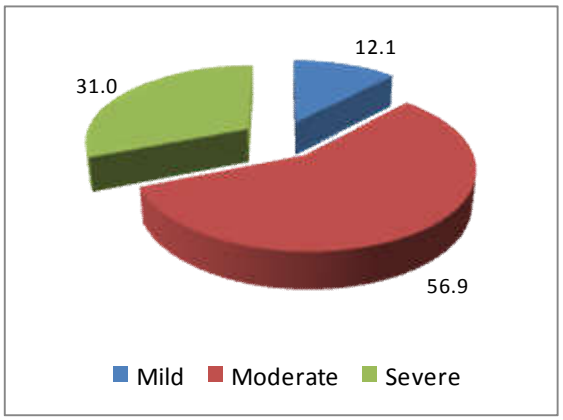

Figure 10 Percentage distribution of the sample according to severity

In our study the Severity assessment shows that out of 58 patients, 7 (12.1%) cases of mild grading, 33 (56.9%) of moderate and 18 (31%) case of severe grading.

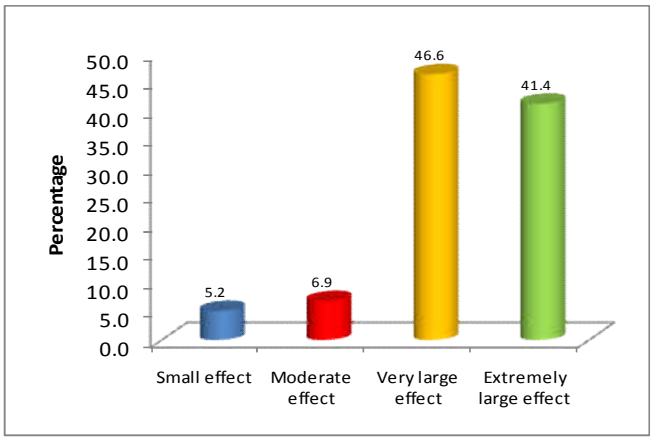

Figure 11 Percentage distribution of the sample according to quality of life

In this study, out of 58 total cases, majority of population 46.6% had a very large effect by the ACDR followed by

41.4% of population were had an extremely large effect in their QOL. 6.9% showed a moderate effect. Only 5.2% of the total showed a small effect in their QOL.

DISCUSSION

In the study, Majority of patients were found to be under the age of 30 yrs. Only 8.6% of patients belonged to the age group of 31-40yrs. The mean age was found to be 43.5 yrs. This study findings correlates with the study by *Hadi A et al*[6]. These results were contrary to the studies conducted by *Campos-FernandezMdel M et al*[7] and *Borch et al*[8] who reported the mean age of patients to be above 50 years.

In this study, 44.8% of patients were males and 55.2% were females. Mild predominance of CADRs was seen in females as compared to males in concordance with other studies such as *S Chatterjee et al*[9]*and Saha A et al*[10]. This difference may be attributed to the fact that the females may be more conscious of any cutaneous reactions and report it, while males tend to ignore or not notice minor cutaneous reactions. *Naldi et al*[11] attributed this gender difference to the consumption of multiple drugs and high elderly populations in females. In contrast to this study male preponderance has been seen in some other studies by *Patel RM et*al[12] and *SharmaVK et al*[13]. Majority of patients (46.6%) were having primary school level of education rest have higher educational background. This reflects the high literacy rate of people in Kerala. The poor economic background may be the reason for the low level of education of the majority.

Majority of patients in the study population were non-professionals (65.5%) and 34.5% were professionals. This may be due to the low financial status of the patients so they cannot afford the high cost associated with the treatment at private sector hospital.

Based on the economic status the study population was classified into BPL and APL. 37 patients (63.8%) belong to BPL group and 21 patients (36.2%) belong to APL group. Thus from this study it was inferred that most of the study population seeking treatment from this Government tertiary care hospital was from BPL category since they were not able to afford the higher cost of medication and other allied expenses at private sector hospital.

In this study, majority of patients 69% belongs to rural area and 31% of patients are residing in urban area. The majority of patient belongs to low economic background hence they reside in rural areas.

Majority of patients in the study population (65.5%) did not have smoking habit, this is because majority of the patients were female. 22.4% patients were occasional smokers and 12.1% were regular smokers.

Only 12.1% of patients in the study population were alcoholic and majority (67.2%) of the patients were not alcoholic. Majority of the population were females, hence shows higher number of non-alcoholics.

From the study, out of 8433 patients, 58 patients were presented with cutaneous adverse drug reaction. The percentage distribution was found to be 0.7% (95% confidence interval 0.5-0.9%). This result was supported by a studies conducted by *Naldi et al*[11] and *Von Elm E et al*[14]. Inpatients have high rates of CADRs compared to outpatients because they have severe ailments and are prescribed with more number of drugs. The rate in the present study is lower than the figures reported in other studies such as those by *SChatterjee et al*[9] (26 per 1000) and *Ghosh et al*[15] (285 per 1000). The reason for this low incidence rate was that the study was conducted in a tertiary centre, so that patients with mild drug reactions may not come to the Dermatology OPD or could have been treated by Physicians in other disciplines.

In this study, majority of the reactions were caused by Phenytoin (19%). This result is consistent with other studies by *Patel TK et al*[16] and *Choon SE et al*[17]. Azithromycin, Ambroxol, Acyclovir, Levosalbutamol, Guaiphenesin, Betamethasone, Dexamethasone, Diclofenac, Fluconazole, Fluoxetine, Homoeopathic preparations, Levetiracetam, Piroxicam, Phenobarbitone, Promethazine, Tramadol, Trifluoperazine, Trihexylphenidyl, Tinidazole each shared 1.7% of the total reactions respectively and showed the less occurrence.

It was observed that about 50% of the total population showed pruritic raised lesions all over the body as clinical manifestation of the ACDR. Only 1.7% experienced pruritic fluid filled lesions and reactions involving external genital areas each.

In this study the most common class of drugs responsible for ACDR are found to be antibiotics and anticonvulsants which is about 32.8%. The class of drugs such as Antifungals, Antihistamines, Antiamoebic, Antivirals and Bronchodilators shared equal distribution of 1.7% shows less responsible for ACDRs. This result is similar to that of *Alanko K et al*[18] but differs from that of study conducted by *Hadi A et al*[6] in which NSAIDs were the most common class of offending drugs.

The drugs like Amoxicillin, Ciprofloxacin, Fluoxetine, IDRV, OHA, Paracetamol, Sodium valproate, Tramadol, Trifluoperazine, Trihexylphenidyl, Tinidazole plays major role in causing acute urticarial reactions. The Ayurvedic drugs are found to cause allergic contact dermatitis. It was found that chronic urticarial reaction was induced by certain homoeopathic preparation. It was found that Amoxicillin, Anti-TB, Betamethasone, Carbamazepine, Clavulanic acid, Doxycycline, IDRV, OHA, Phenytoin are the drugs causing maculopapular rash. Drugs like Aciclovir, Indigenous preparation, Levetiracetam, Phenytoin, Sodium valproate were resulted in erythema multiforme. It was observed that Amoxicillin, Carbamazepine, Clavulanic acid and Phenytoin caused Drug Hypersensitivity Syndrome. It was observed that Diclofenac, Fluconazole, Phenytoin and Piroxicam are associated with Fixed Drug Eruptions. It was observed that drugs Amoxicillin, Ambroxol, Levosalbutamol, Guaiphenesin, Ciprofloxacin, Clavulanic acid and Phenytoin are associated with drug induced mucositis. It was observed that Amoxicillin, Ciprofloxacin, Prednisolone, Tramadol and Tinidazole resulted in angioedema.

In this study, Ayurvedic drug, Cefixime and Indigenous preparation resulted in exfoliative dermatitis. Anti-tubercular drugs and sodium valproate resulted in causing drug induced liver injury.

The most common drugs causing SJS was found to be Anti-TB, Phenytoin and Sodium valproate. The common drugs causing TEN are Azithromycin, Cefixime and Promethazine. Both Phenytoin and Phenobarbitone resulted in SJS-TEN overlap. The common drugs causing steroid acne are Dexamethasone and Prednisolone.

In this study Exanthematous (maculopapular) rash was the most commonly observed ACDR comprises of 24.1% and this result is consistent with other studies by *Ding WY et al*[19] and *Zhong H et al*[20]. This result was contrast to studies by S *Chatterjee et al*[9] in which urticaria was the major morphological variety. In our study the second most common CADR was Acuteurticaria about 18.3%. Only 1.7% was each of Allergic contact dermatitis and Chronicurticaria.

In this study, a total of 58 cases of cutaneous ADRs were analysed for causality. 8 cases (13.8%) scored definite, 40 cases (69%) were of probable score whereas 10 cases (17.2%) were in possible score category. This results correlates with the study conducted by *Verma R et al*[23]. Another study conducted by *Noel MV et al*[21] shows variation from this results which may be due to various factors affecting drug usage, physician's drug preferences and different scales used for causality assessment.

In this study, Severity assessment shows out of 58 patients, 7 (12.1%) cases of mild grading, 33 (56.9%) of moderate and 18 (31%) cases of severe grading. This is in concordance with the results of other study conducted by *Thappa DM et al*[22] and is contrast to the study by *Verma R et al*[23] in which majority of the cases were mild.

In this study, out of 58 total cases, majority of population 46.6% had a very large effect by the ACDR followed by 41.4% of population were had an extremely large effect in their QOL. 6.9% showed a moderate effect. Only 5.2% of the total showed a small effect in their QOL.

CONCLUSION

Every drug must be regarded as potentially hazardous and the risk due to drug reaction must be weighed against the expected therapeutic benefit for each patient, so that the occurrence of ACDRs can be minimized.

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