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Cutaneous Drug Reactions Reported In a Dermatology Outpatient Clinic of a Tertiary Care Hospital

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Abstract
Background:*Cutaneous adverse drug reactions (CADR) are the most frequent serious adverse reactions reported in outpatient department of dermatology.*
Objective:*The aim of the study to assess the prevalence and clinical spectrum of CADR among patients and to assess causality and identify the offending drugs.*
Materials and Methods:*An observational study was undertaken over12month'speriod (Dec 2013- Dec 2014) in Dermatology OPD of tertiary care teaching hospital in GOVT. GENERAL HOSPITAL, KAKINADA, ANDHRA PRADESH by ADR card reporting. Drug history was recorded in a format specified in Indian National Pharmacovigilance Program and causality assessment carried out as per WHO-UMC criteria.*
Results:*Study showed that, ADR reported among 522 total, 217 (41.5%) were CADRs. These CADR are mostly seen in gender female & age group between 18-45 years. Group of drugs leading to above manifestations are Antimicrobials-48.3%, NSAIDS -19.3%, Steroids- 5.5%, Others -26.7%. CADR manifestations: Maculopapular rash- 26.3%, Photosensitivity- 21.2%, Urticaria- 17.5%, Bullous eruptions –12.0%, Severe Mucositis-10.1%, Pruritis – 5.1%, Fixed drug eruption –2.8 %, Stevens–Johnson Syndrome (SJS)- 1.8%, Toxic Epidermal Necrolysis (TEN)- 1.8%, Erythema multiformae-1.4%. Causality assessment was Certain 33.6%, Probable 16.1% and Possible 50.2% of the reactions.*
Conclusion: *CADRs are utmost necessity for a physician to have understanding, as well as knowledge of the drugs essential for diagnosis and prevention.*
Key Words:*Cutaneous adverse drug reactions,causality assessment, Pharmacovigilance.*

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I. Introduction

Adverse drug reactions (ADRs) are negative consequences of drug therapy andcan be a major setback in clinical practice. ADRs are unwanted and unintended effects ofdrug therapy, which may be responsible for significant morbidity and mortality and canincrease the cost of healthcare for the individual patient, healthcare delivery institutionsand the community at large. They are also responsible for a significant number of hospital admissions and frequent reasons for patients visiting the hospital and / or the physician. Drugs are almost always coupled with inherent risk of adverse reactions nomatter how safe and efficacious they are during clinical trials and subsequent wide spread therapeutic use. The incidence of ADRs varies from 6-7% of all hospitalizations andcould be observed in 10-20% of patients receiving drug therapy.[1]

Cutaneous adverse drug reactions (CADRs) are the commonest manifestations ofADRs occurring in 2-3% of patients receiving drug therapy for various reasons. The clinical spectrum and pattern of CADRs may vary from mild and transient maculopapularrash to severe and potentially fatal Stevens-Johnson syndrome (SJS) and toxic epidermalnecrolysis(TEN). Cutaneous manifestations of adverse drug reactions may be part of systemic manifestation with other organ system involvement or could be the onlymanifestation of the ADR. Drugs may also worsen preexisting skin disorders.The pattern of CADRs and the drugs responsible for them keep changing fromtime to time because of new drugs being made available for therapy, changing prescription pattern, increased use of drugs for treatment of diseases, drug interactions due to multiple drug therapy and also due to a growing tendency for self-medication inthe population.[1]

CADRs, like any other ADRs, are influenced by various factors like age, sex,underlying diseases, immune status, genetic factors, environmental factors, and history ofallergy. The incidence and prevalence of CADRs may vary in different geographical regions due to difference in disease prevalence, pattern of drug use, and Genetic andEnvironmental factors.[1]

Effective monitoring of CADRs, both hospital-based and population-based, formsan integral part of ADR monitoring programs as well as part of pharmacovigilance,not only to generate valid data but also to

identify and assess predisposing / underlyingrisk factors and to evaluate treatment outcome. However, reporting and documentation of CADRs is not being effectively organized and implemented in Indian population, andsystematic epidemiological studies for the same seem to be inadequate. Population-based epidemiological studies are cumbersome and time consuming and hence difficult to organize compared to hospital-based studies. However, in the last few years, a few studies in the Indian population have been reported mainly from major hospitals. Sincethe existing data regarding CADRs is rather limited, inconsistent and even conflicting, morestudies may be required to generate valid data and hence the present study was taken up.In the present study, the clinical pattern and spectrum of CADRs, the causative drugs, predisposing and underlying risk factors were assessed and the treatment outcomewas evaluated.

Objective: The aim of the study to assess the prevalence and clinical spectrum of CADR among patients and to assess causality and identify the offending drugs**.**

II. Materials And Methods

The study was approved by the Institutional Ethics Committee of Rangaraya Medical College, Kakinada to conduct the study. Patients of both sexes attending medical out-patient department in the Government General Hospital, Kakinada were selected for this study.

- ❖ STUDY DESIGN: Prospective Observational study
- ❖ STUDY SITE: Hospital/ Institutional based study
- ❖ STUDY PERIOD: The study was carried out between 1st December, 2013 and 30th November 2014 (12months).
- ❖ SAMPLE SIZE CALCULATION:Basing on available number of patients reporting to OP unit of dermatology department,a total of 522 patients reported ADR; out of this only 217 patients were CADR enrolled as per the selection criteria.A total of 217 patients were enrolled in the study.
- ❖ INCLUSION CRITERIA:

Patients of all age groups and both sexes with or suspected CADRs.

- ❖ EXCLUSION CRITERIA:

Patients with reactionswhere the drugs takenwere not known or unclear drug history.
Patients not willing to comply with the study procedure.

STUDY PROCEDURE:

- ❖ Patients were evaluated for the pattern, duration and severity of the reactions.
- ❖ Dechallenge test is done.
- ❖ Rechallenge test to confirm the causative drug was not done due to ethical considerations.
- ❖ When more than one drug was used, the drugs with the high suspicion for causation were withdrawn in the order of suspicion and response to withdrawal was assessed and causality established.
- ❖ Drug history was recorded in a format specified in Indian National Pharmacovigilance Program and Causality assessment carried out as per WHO-UMC criteria[2].

LAB INVESTIGATIONS:

- Hemogram (Hb%, RBC, WBC)
- Absolute eosinophil count (AEC)
- Serum electrolytes
- Random Blood sugar (RBS)
- Liver functions tests (SGOT, SGPT)
- Renal functions test (serum creatinine)
- HIV (ELISA)

STATISTICAL ANALYSIS:

At the end of the study all data is compiled and statistically analysed using SPSS software version 21.Descriptive data was presented as mean±SD, wherever necessary, the results were depicted in the form of percentages with tables and graphs.

III. Results

Table 1: Distribution of study subjects according to their age.

Age (years)	Frequency
0 to10	8(3.7%)
11 to 20	26 (11.9%)
21 to 30	31 (14.3%)
31 to 40	37 (17.0%)
41 to 50	18 (8.3%)
51 to 60	29 (13.4%)
61 to 70	46 (21.2%)
>71	22 (10.2%)
Total	217 (100%)

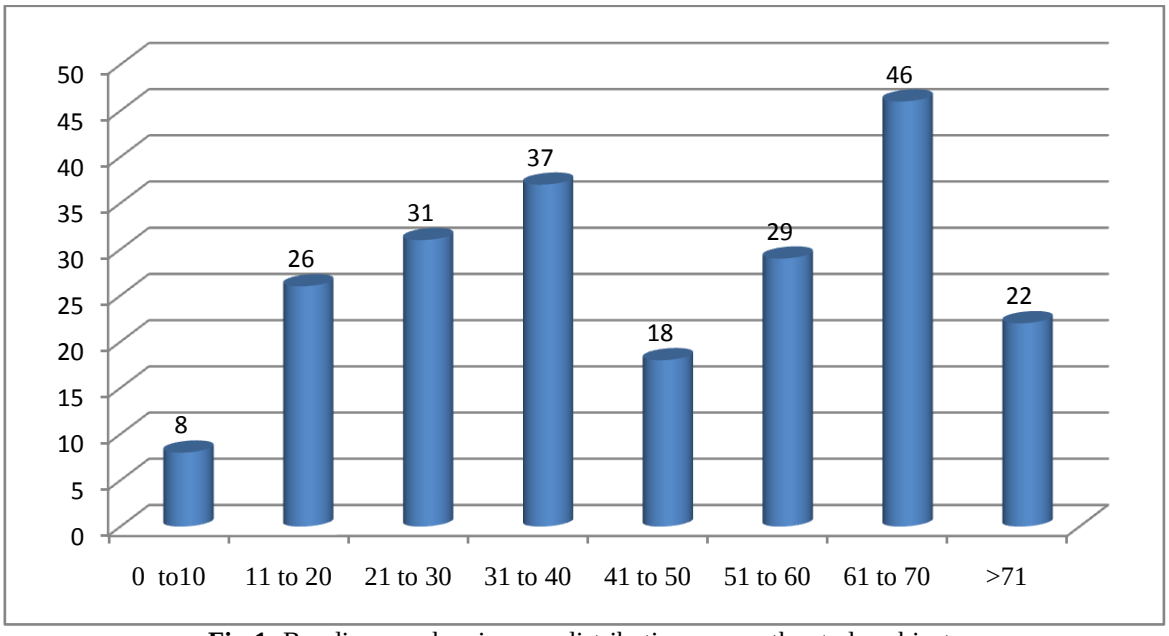

Fig-1: Bar diagram showing age distribution among the study subjects

TABLE 2: Distribution of study subjects according to their gender.

Gender	No. Of patients (%)
Females	123 (56.6)
Males	94 (43.3)
Total	217 (100)

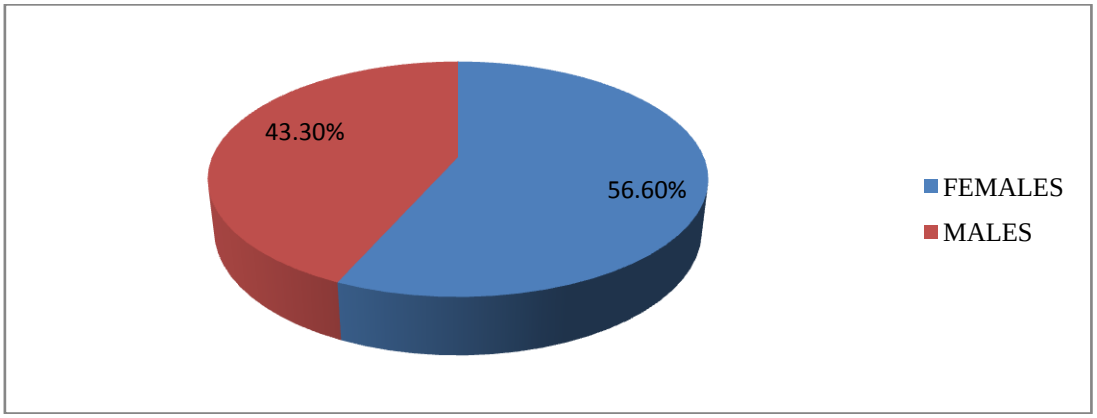

Fig 2: Pie diagram showing gender distribution among the study subjects

Male: Female Ratio = 1: 1.3

Table 3:Distribution of study subjects according to their laboratory abnormalities

Laboratory tests	No. of patients
Hb% ↓	27
RBC ↓	29
WBC ↑	22
AEC (>500/mm3) ↑	64
RBS ↑	18
SGOT ↑	20
SGPT ↑	20
Serum creatinine ↑	23

- There is a significant deviation from the normal range
- None of the patients were positive with HIV test

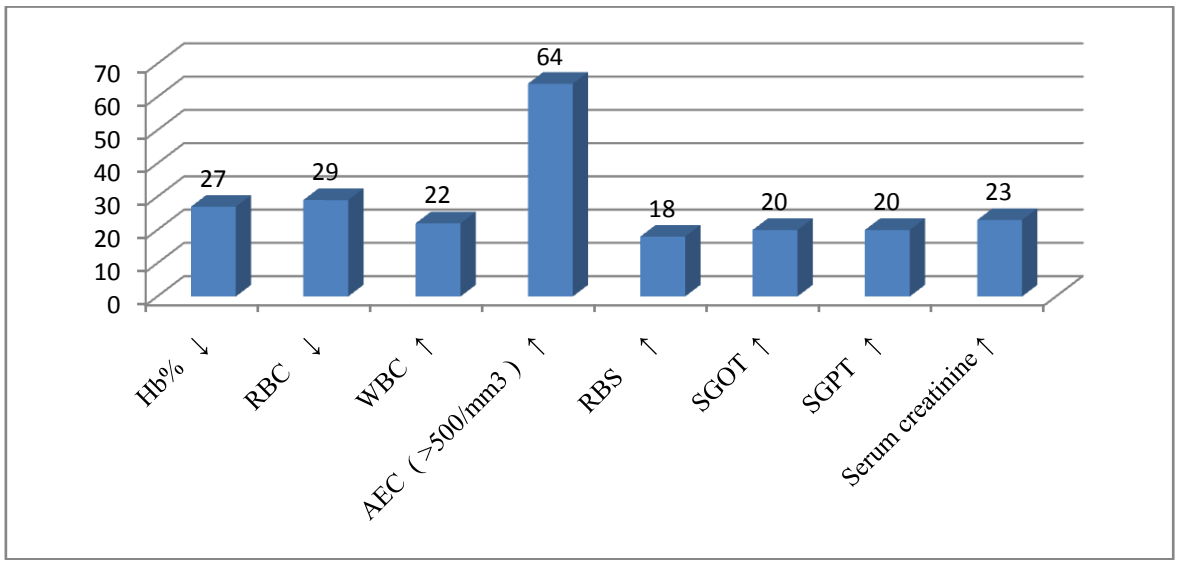

Fig 3: Bar diagram showing laboratory abnormalities among the study subjects

Table 4 :Distribution of study subjects according to their clinical pattern of reactions.

Reactions	No. of patients (%)
Maculopapular Rash	57 (26.3)
Photosensitivity	46 (21.2)
Urticaria	38 (17.5)
Bullous Eruptions	26 (12)
Severe Mucosities	22 (10.1)
Fixed Drug Eruptions (FDE)	6 (2.8)
Stevens Johnson Syndrome (SJS)	4 (1.8)
Toxic Epidermal Necrolysis (TEN)	4 (1.8)
Erythema Multiformae	3 (1.4)
Pruritis	11 (5.1)
Total	217 (100)

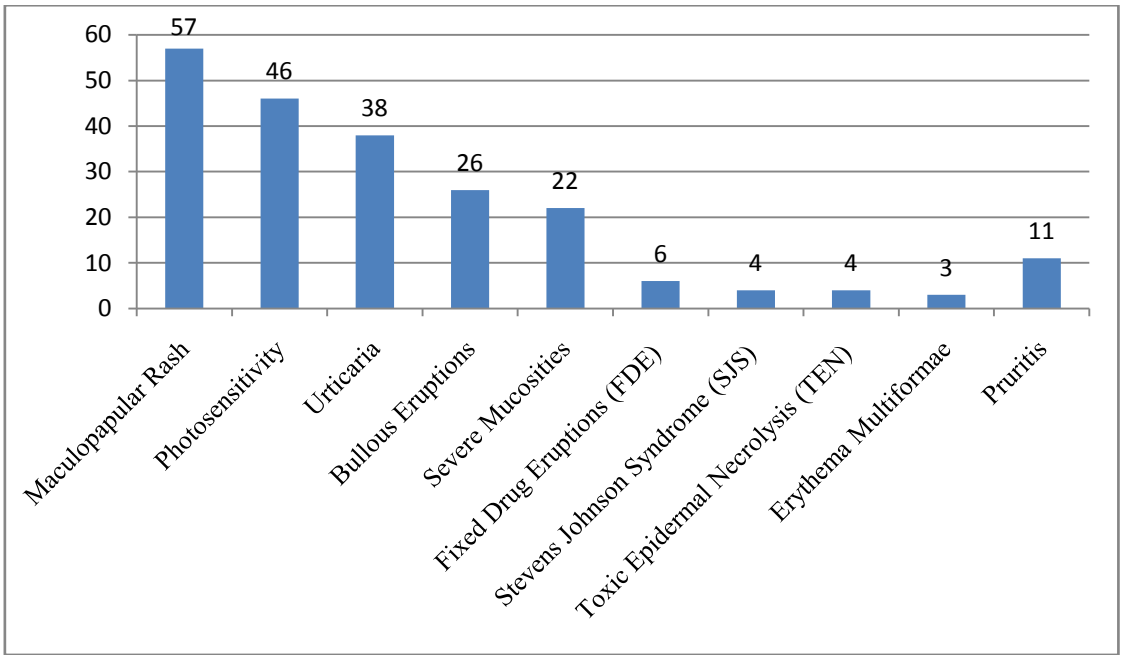

Fig 4: Bar diagram showing clinical pattern of reactions among the study subjects

Table 5: Distribution of study subjects according to their causative drugs

Drug	No. of patients (%)
Cotrimoxazole	28(12.9)
Ibuprofen	14(6.4)
Betamethasone	12 (5.5)
Ampicillin	11(5.0)
Carbamazepine	9 (4.1)
Phenytoin	9(4.1)
Ciprofloxacin	6(2.7)
Ofloxacin	7(3.2)
Cephalexin	9(4.1)
Chloroquine	9(4.1)
Paracetamol	13(5.9)
Diclofenac	15(6.9)
Quinolone+Nitroimidazole	9(4.1)
Sulfonamides	11(5.0)
Norfloxacin	9(4.1)
Tetracyclins	6(2.7)
Valproic Acid	4(1.8)
Others	36 (16.5)
Total	217 (100)

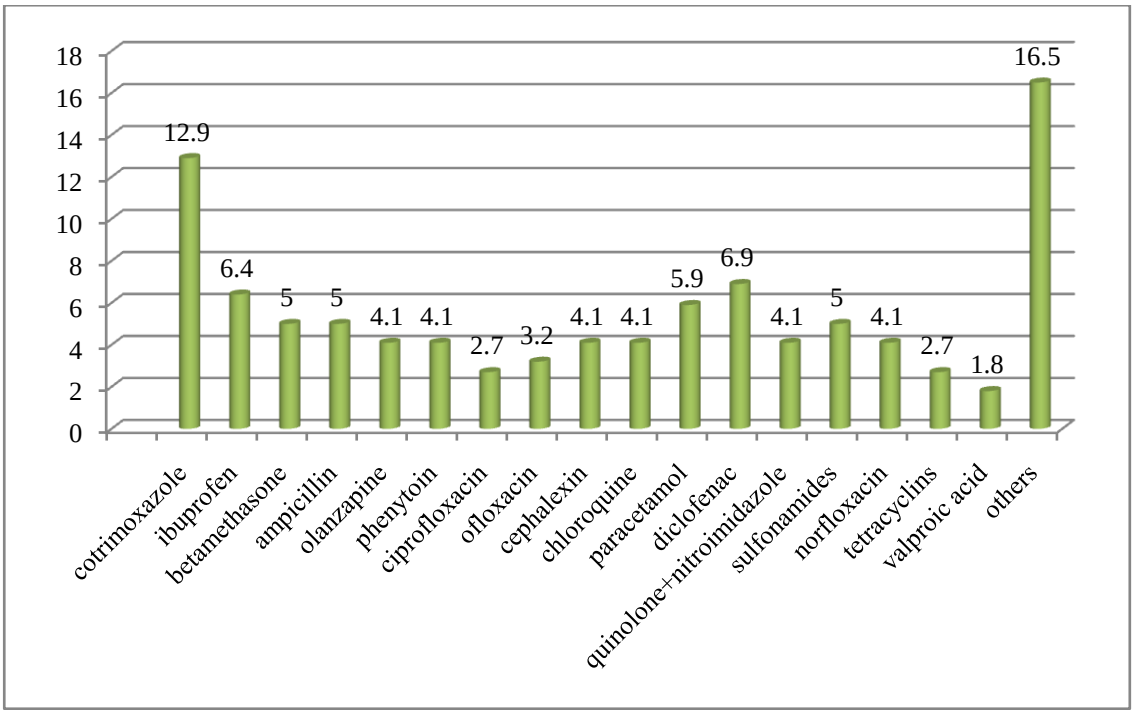

Fig 5: Bar diagram showing distribution of causative drugs among the study subjects

Table 6: Distribution of study subjects according to their pattern of drug consumption

Drug category	On prescription	self medication	Supervised administration	Total (%)
Antimicrobials	67	16	22	105 (48.3)
NSAIDS	27	15	0	42 (19.3)
Steroids	7	2	3	12(5.5)
Others*	21	28	9	58 (26.7)
Total (%)	122 (56.2)	61 (28.1)	34 (15.7)	217 (100)

Table 7: Distribution of study subjects according to the route of drug administration**

Drug category	**Oral**	**Parental Route**		**Topically**
		IM	IV	
Antimicrobials	89	-	13	18
NSAIDS	66	32	-	-
Steroids	27	-	-	22
Others*	16	7	-	6
TOTAL	198	39	13	46
		52		

Note : ** Some patients used more than one drug category, so the total cannot be rounded to 100%.

Table 8: Distribution of study subjects according to their probability of reactions[3]

Drug Category	Probability			
	Possible	Probable	Certain	Total
Antimicrobials	50	13	42	105 (48.3)
NSAIDS	23	7	12	42 (19.3)
Steroids	7	2	3	12 (5.5)
Others*	29	13	16	58 (26.7)
Total (%)	109 (50.2%)	35 (16.1%)	73 (33.6%)	217 (100%)

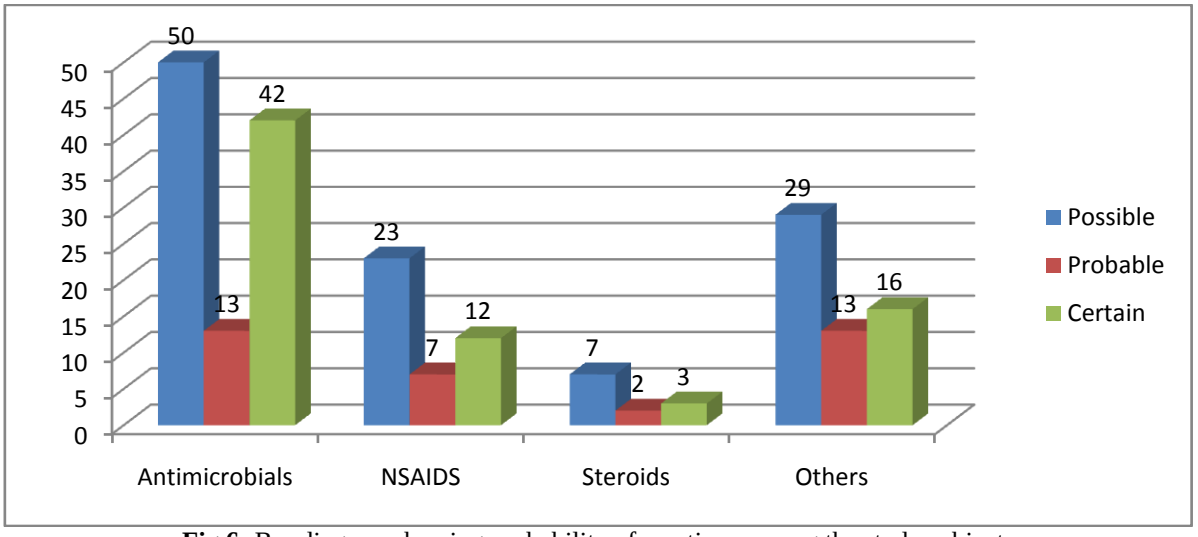

Fig 6: Bar diagram showing probability of reactions among the study subjects

Note: * includes other causative drugs and antiepileptic drugs

IV. Discussion

In the present study we found that CADRs, was one of the most common types of ADRs, which contributes 41.5% of total ADRs.Various studies suggest that the contribution of CADRs is 2-40% in total adverse drug reactions.[4-6]

The present study constituted of 56.6% female's patients and 43.3% male's patients with CADRs.

In the present study the morphological varieties of CADRs commonly reported were maculopapular rash 26.3%.Various studies and literatures have already concluded that maculopapular rash is the most common CADRs.[4]

In our study commonest offending drug group for CADRs was antimicrobials (48.3%). The second most common offending drug group NSAIDS being (19.3%) while steroids was third most common group (5.5%). A study performed by Ghosh, et al. in Manipal found that antimicrobials (30%) were the most common group causing CADRs[4]. Another study done by Jhajet al., found that maculopapular rashes (50%) and urticaria (21.5%) were common morphological CADRs and antimicrobials (56.9%) were the most common culprits[5].Also, Noel et al., found that maculopapular rash was (35%) the most common CADR in the hospitalized patients.[6]Hiware S, et al., have found out among 2693 total ADRs reported, 872 (33.04%) were CDRs and Antimicrobials (55.5%) were the main drugs involved followed by NSAIDs (18.56%) and steroids (12.61%)[7]. Chatterjee, et al., in their study also found that antimicrobials were topmost in causation of CADRs (34.10%) followed by anticonvulsants (32.88%) and NSAIDS (21.51%).[8] Results of our study were comparably similar to above mentioned studies with mild variations in the percentages but the overall group of drugs causing the most CADRs were Antimicrobials fallowed by NSAIDS and Steroids.

The common offending drugs causing CADRs Cotrimoxazole (12.9%) showed highest CADRs followed by diclofenac sodium (6.9%), ibuprofen (6.4%), paracetamol (5.9%), betamethasone (5.5%) and sulfonamides (5.0%).[7-9]

In our study most of the offending drugs were taken orally (198), followed by parenteral route (52) and topically (46).In our study causality analysis was done by using WHO assessment scale and it was found to have (76 - 33.6%) certain, (33 - 16.1%) probable and (108 - 50.2%) possible CADRs.

V. Conclusion

Once a cutaneous drug reaction is diagnosed and treated, the patient must be completely educated regarding the nature of his/her drug reaction. The patient should carry an emergency identification card containing the list of allergic drugs. The names of the medication, potentially cross-reacting drugs and drugs that can be safely taken are important aspects of the card. In case of genetic predisposition, counseling to the family members is a must. This can be important especially in SJS, TEN, drug hypersensitivity syndromes and SSLRs.[10]

A wide clinical spectrum of CADRs ranging from mild to severe i.e., erythema multiformae to SJS/TEN was observed.The commonest causative drugs are antimicrobials, NSAIDS, Steroids.Cotrimoxazole were the leading causative drugs among the antimicrobials, diclofenac among NSAIDS and phenytoin among the antiepileptics.The common causative agents for SJS / TEN were carbamazepine and phenytoin.

Most of the CADRs were certain as predisposing risk factors were not clearly known and demarcated.Mild to moderate reactions were managed by drug withdrawal and appropriate rescue measures. CADRs are utmost necessity for a physician to have understanding, as well as knowledge of the drugs essential for diagnosis and prevention.Hence, there is necessity for awareness about this data on ADRs in order to avoid irrational drug use by the clinicians. Besides, drug reactions are a common reason for litigation. Not warning a patient about potential adverse effects, prescribing a medicine to a previously sensitized patient or prescribing a related medication with cross-reactivity are the most common medico legal pitfalls; therefore, should not be ignored or taken lightly.[10]Finally; cutaneous drug reactions should be reported both to the manufacturer and the regulator agency especially in the cases of CADRs that are unexpected, rare or life threatening.

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