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RESEARCH ARTICLE

Study of Adverse Cutaneous Drug Reactions Reported in Outpatient and Inpatient Departments of a South Indian Tertiary Care Teaching Hospital

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ABSTRACT

The objective of this prospective observational study is to study and report the pharmacoepidemiology and clinical patterns of adverse cutaneous drug reactions in patients and to identify the causative drugs associated with various adverse cutaneous drug reactions.

KEYWORDS

Adverse Cutaneous Drug Reactions, Outpatient, Inpatient, Teaching Hospital.

INTRODUCTION

A drug may be defined as a chemical substance, or a combination of substances, administered for the investigation, prevention or treatment of diseases or symptoms, real or imagined.

An adverse drug reaction (ADR) may be defined as an undesirable clinical manifestation resulting from administration of a particular drug; this includes reactions due to overdose, predictable side effects, and unanticipated adverse signs.

Another definition of ADR is 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.' It has been proposed that therapeutic ineffectiveness should also be regarded as an ADR.[25]

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Adverse drug reactions (ADRs) are undesirable and typically unanticipated responses independent of the intended therapeutic purpose of a medication that may result in significant morbidity and even mortality.[26]

Drugs, no matter how safe and efficacious, are always coupled with the inescapable risk of adverse reactions. ADRs are a cause of significant morbidity and mortality in patients with all areas of healthcare today. It has been estimated, that from one-third to as high as one-half of ADRs, are believed to be preventable. The other important risk factors associated with adverse drug reactions are gender, increased number of drug exposures, advanced age, length of hospital stay, and function of excreting organs.[9]

Adverse cutaneous drug reactions (ACDR) form an important clinical entity in dermatology practice, and the list of drugs implicated in the causation of cutaneous adverse severity of such reactions vary from mild to fatal ones. Although such cutaneous reactions are common, comprehensive information about their incidence, severity and ultimate health effects are often not available.

The frequency of ACDR in developed countries ranges from 1-3% among inpatients whereas in developing countries like India some studies peg it to 2-5% of the inpatients, but there is a lack of comprehensive data amongst outpatients. The inadequacy of data could be attributed to reasons like diagnostic dilemmas and lack of awareness to report.[27]

Cutaneous drug reactions are the most common adverse effects attributed to drugs. Any skin disorder can be imitated, induced or aggravated by drugs. The present study was carried out to determine the age, sex, incidence and clinical pattern of drug eruptions, to recognize offending drugs (self-medication or prescribed) and to evaluate mortality and morbidity associated with drugs.[2]

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 encompasses all adverse events related to drug eruption, regardless of the etiology. Cutaneous adverse drug reactions (CADR) are the most frequent of all manifestations of drug sensitivity. They manifest with varied and diverse morphological pattern ranging from trivial urticaria to severe form of vasculitis or toxic epidermal necrolysis and cutaneous necrosis or gangrene. Fatal reactions to drugs are uncommon, but reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS-TEN) and exfoliative dermatitis may result in death even if the eruption is the only manifestation. As innovation in medicine occurs and new drugs continue to be developed, there is potential for the occurrence of an increasing number of cutaneous drug reactions. However, the actual incidence of drug eruptions is difficult to determine, primarily because many mild and transitory reactions are not recorded. Commonly used drugs that are implicated in causing CADR are penicillins, sulfonamides, anticonvulsants, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDS), angiotensin converting enzyme (ACE) inhibitors, fluoroquinolones, etc. There are also chances of unexpected adverse outcomes to newly introduced drugs, causing inconvenience to both patients and physicians. 3Therefore, not only the dermatologists, but all practicing physicians should be familiar with these to diagnose them early and to be prepared to handle them adequately. However, we all know it is most challenging and practically difficult when the patient is on many medicines because of the relative paucity of laboratory testing that is available for any definitive and confirmatory drug-specific testing. Therefore, in practice, the diagnosis of ACDR is purely based on clinical judgment.[12]

Different types of immune effector mechanism can produce diverse clinical patterns of hypersensitivity reaction, for example, penicillins, as the classic drugs acting as happens, are reported to cause type 1 IgE-mediated (immediate-type) hypersensitivity reactions, as well as non-IgE, mediated reactions, including morbilliform eruptions (Rashs), erythema multiforme and Stevens–Johnson syndrome.[28]

The timing of skin reactions is often a useful diagnostic tool. In general, the onset occurs within a few weeks of the introduction of the causative drug. If a medicine has been taken for many years without a problem, then it is less likely to be responsible. When examining a list of medications taken by a patient with a rash, new drugs are made within the previous month are the probable cause. There are some notable exceptions to this rule. Hypersensitivity reactions to penicillins can occur several weeks after the drug has been discontinued, and the typical psoriasiform skin eruption was seen with the beta blocker practolol (withdrawn in the 1970s) took place after many months of treatment. Gold can also cause very delayed reactions.

Drugs suspected of causing skin reactions should usually be withdrawn and not used again in that patient, although the risk–benefit potential needs to be considered before discontinuing any necessary medicines. Symptomatic treatment may be required.

Calamine lotion or systemic antihistamines may relieve pruritus, and topical corticosteroids may help inflammation and itch. For more severe reactions, systemic corticosteroids may be indicated. The main clinical features that are suggestive of a severe reaction include mucous membrane involvement, blisters or skin detachment, high fever, Angioedema or tongue swelling, facial edema, skin necrosis, lymphadenopathy or dyspnoea. In most cases, drug eruptions are reversible, resolving gradually after the causative drug is withdrawn. Knowledge of the half-lives of the implicated medicines can be necessary; for medications with long half-lives, the time to resolution may be several weeks or more.

Although skin-prick or blood tests may be used in the diagnosis of some reactions (e.g. Those dependent on IgE, such as immediate-type reactions to penicillin), they are not usually helpful in skin manifestations of an allergy.

The diagnosis of cutaneous drug reactions is also based on the detailed history and correlation between drug intake and the onset of adverse reaction.[28]

OBJECTIVES

- To study and report the pharmacoepidemiology and clinical patterns of adverse cutaneous drug reactions in patients.
- To identify the causative drugs associated with various Adverse cutaneous drug reactions.

MATERIAL AND METHOD

Study site: Patients attending the outpatient and inpatient departments of Dermatology and other departments such as Emergency (MED), MICU and Medicine, Pediatric and Surgery wards in the Shamanur Shivashankarappa Institute of Medical Sciences & Research Centre, Davangere, Karnataka

Study Duration: The study was carried out for for a period of six months.

Study design: It is a prospective observational study.

Study criteria: The study will be carried out by considering the following inclusion and exclusion criteria:

Inclusion criteria: All patients of either sex having Adverse cutaneous drug reactions

Exclusion criteria: Therapeutic failure, Overdosage, Abuse of medicines, Error in administering, Reactions where the drug taken were not certain and all types of poisoning

Source of data: The patient's profile sheet will be accessed, as well as the personal interview, will be conducted with the patient.

Ethical approval: Ethical clearance was obtained from the Institutional Ethical Committee of Bapuji Pharmacy College, Davangere, Karnataka.

Phases of study

A data collection form was prepared which contains details such as patient demographics (age, sex, weight, DOA, etc.), meticulous history, diagnosis, details of suspected drugs, type of CADR and severity of the reaction.

Data will be collected from the patient profile of the suspected CADR reported patient as well as a personal interview with the patient.

The collected data will be analyzed for the following parameters

1. Identifying the suspected drug
2. Assessment of reported ADR
3. Causality of reported ADR
4. Severity of seriousness of reported ADR
5. Management and outcome of ADR
6. Reporting of suspected ADR by using CDSCO's ADR reporting form to the Pharmacovigilance Centre.

Study procedure

The data were collected by using a data collection form with demographic details such a patient's age, sex, weight, DOA, etc.. The patient's meticulous history, diagnosis, details of suspected drugs, type of CADR's and

severity of the reaction were observed and recorded. These data were collected from the patient profile of the suspected CADR reported patient as well as a personal interview with the patient. The collected data were analyzed to identify the suspected drug, assessment of reported ADR, severity, and seriousness of the reported ADR, the causality of the reported ADR and its management and outcome of ADR. In the final phase of the study, the suspected ADR's were reported by using CDSCO's ADR reporting form to the Pharmacovigilance Centre.

Development of documentation forms: Three types of forms were used in the study namely Informed consent form for patients: Prepared in both English and regional language, Kannada.

Patient profile form: Provisions for entering patient demographics and drugs prescribed along with separate columns for identifying interactions.

Interaction notification and therapy modification form: Form for the physician with provisions for the severity of the interaction and proposed recommendations/changes as well as physician's treatment modification apart from proposed recommendations.

RESULT AND DISCUSSION

Details of a patient enrolled: The prospective observational study was conducted for 6 months to study of adverse cutaneous drug reactions reported in the outpatient and inpatient departments of a South Indian tertiary care teaching hospital in Davangere.

Table 1: Distribution of patients, according to gender

Sl.No.	Gender	No. of cases	Percentage
1	Male	80	53.3
2	Female	70	46.67
3	Total	150	100

A total of158 CADR's were reported during this period, of which 150 were confirmed by certain CADR's caused due to drugs.

A total of 150 patients were analyzed during the study period out of which, 53.4% were male and the rest 46.6% were female.

Table 2: Distribution of patients of age (N=150)

Age group (In years)	No of cases	Percentage
0-10	23	15.3
11-20	13	8.6
21-30	29	19.3
31-40	18	12
41-50	22	14.6
51-60	30	20
61-70	07	4.6
71-80	07	4.6
81-90	01	0.6
Total	150	100

Table 3: Distribution of cases on drug eruptions

Types of drug eruptions	No.of cases	Frequency (%)
Rash	80	53.3
Urticaria	18	12
FDE	8	5.3
Itching	6	4
Hypersensitivity	6	4
Angioedema	5	3.3
Alopecia	5	3.3
SJS	3	2
Psoriasis	3	2
Pruritis	3	2
Acne vulgaris	2	1.3
Anaphylaxis	2	1.3
Hyperpigmentation	2	1.3
TEN	1	0.6
Others	6	4
Total	150	100

The majority of the patients belonged to the age group of 51-60 years old, followed by 21-30

years old and 0-10 years old groups. The youngest victim was one and half months old, and the oldest was 81 years old. The period of development of lesions after drug intake varied from 1-30 days.

Among the various known patterns of CADR, the most commonly reported dermatological ADRs were rashes (53.3%), followed by urticaria (12%), fixed drug eruption (5.3), itching and hypersensitivity (4%), alopecia and angioedema (3.3%), SJS, psoriasis and pruritus (2%).

Table 4: Commonly incriminated drugs in drug eruption

Drugs	No.of ADRs	Percentage
Antibiotics	60	40
NSAIDS	22	14.6
Vaccines	11	7.3
Anti-epileptics	11	7.3
Anti-TB	5	3.3
Anti-Hypertensive	5	3.3
PPI	4	2.6
Anti-neoplastic	4	2.6
Steroids	4	2.6
Antidepressants	3	2
Anti-fungal	3	2
Statins	2	1.3
Sulphonylureas	2	1.3
Others	14	9.3

Table 5: Causality category-wise distribution of cutaneous adverse drug reaction

WHO-UMC causality criteria	No. of CADR's	Percentage
Certain	5	3.3
Probable	89	59.3
Possible	43	28.6
Unlikely	6	4
Conditional/unclassified	5	3.3
Unaccessable/unclassifiable	2	1.3

Out of 150 dermatological ADRs reported, the 5 number of cases found to be Certain, 89 cases were designated as probable, 43 cases were as possible, 6 cases were as unlikely, 5 cases were as conditional, and 2 cases were as un-assessable.

Table 6: Causality category-wise distribution of cutaneous adverse drug reaction

Naranjo algorithm	No. of CADR's	Percentage
Definite	5	3.3
Probable	89	59.3
Possible	43	28.6
Unlikely	13	8.6

According to Naranjo causality scale, out of 150 cases, 5 ADRs were definite, 89 ADRs were probable, 43 ADRs were possible, and 13 ADRs were unlikely. It was emphasized that most of the reported ADRs were caused by the accused drug and not otherwise.

Drugs suspected to cause CADR in the study population could be classified broadly into 18 groups, namely NSAIDS, sulphonylureas, macrolides, cephalosporins, penicillin, quinolones, tetracyclines, aminoglycosides, vaccines, anti-TB, anti-epileptics, etc. based on these data antibiotics causes most of the ADR, especially cephalosporin category (24.6%) followed by NSAIDs(14.66%).

Rashes are caused most commonly due to antibiotics (37 of 80 cases, 46.25%) and vaccines (6 cases, 7.5%). Urticaria is mainly caused due to NSAIDs (7 of 18 cases, 63.63%). Levetiracetam, Pyrazinamide, and gentamycin were the three most important causative drugs of SJS syndrome, and levofloxacin causes TEN, NSAIDs were the main culprit drugs for FDE also.

In a period of 6 months, the total number of CADRs reported was 150. Active surveillance along with spontaneous reporting contributed to getting this many ADRs. OPD based reports comprised 36% and ADR reported from indoor patients were 64% of the total ADR reports. Department of Medicine (33.3%) followed by pediatrics (15.3%), surgery (10%), emergency (1.3%), ICU (2.6%) and psychiatry (1.3%).

Table 7: Drug categories associated with different clinical types of cutaneous drug Reactions

Drug group	Rash	Urticaria	FDE	Angioedema	Pruritis	Hypersensitivity	Hyperpigmentation	Anaphylaxis	Itching	SJS	Alopecia	Acne vulgaris	Psoriasis	Others	Overall
NSAIDS	8	7	4	2	1	0	0	0	0	0	0	0	0	0	22
Sulphonylureas	0	1	0	0	1	0	0	0	0	0	0	0	0	0	2
Macrolides	3	0	0	0	0	0	0	0	0	0	0	0	0	0	3
Cephalosporins	25	3	2	1	0	0	0	1	5	0	0	0	0	0	37
Penicillin	2	2	0	0	0	2	0	1	0	0	0	0	0	0	7
Quinolones	6	0	0	0	0	0	0	0	0	0	0	0	0	2	8
Tetracycline	3	0	0	0	0	0	0	0	0	0	0	0	0	0	3
Aminoglycosides	1	0	0	0	0	0	0	0	0	1	0	0	0	0	2
Vaccines	11	0	0	0	0	0	0	0	0	0	0	0	0	0	11

Anti-epileptics	7	0	0	0	0	3	0	0	0	0	0	0	0	1	11
PPI	4	0	0	0	0	0	0	0	0	0	0	0	0	0	4
Anti-Tb	1	2	0	0	0	0	0	0	1	1	0	0	0	0	5
Anti-hypertensive	3	0	0	0	0	0	0	0	0	0	0	0	1	1	5
Anti-fungal	1	0	2	0	0	0	0	0	0	0	0	0	0	0	3
Statins	0	2	0	0	0	0	0	0	0	0	0	0	0	0	2
Anti-neoplastic	0	0	0	0	0	0	1	0	0	0	3	0	0	0	4
Antidepressants	0	0	0	1	0	0	0	0	0	0	2	0	0	0	3
Steroids	0	0	0	1	0	1	0	0	0	0	0	1	1	0	4
Others	5	1	0	0	1	0	1	0	0	1	1	1	1	2	14

Table 8: Frequency of drugs implicated by cutaneous adverse reactions

Adverse Reactions	Culprit drug	No. of patients
Rashes	Ceftriaxone	19
	Cefapirazone	4
	Cefotaxime	2
	Amoxicillin	2
	Ciprofloxacin	3
	Levofloxacin	2
	NSAIDS	8
	Doxycycline	3
	Azithromycin	2
	Pentavac	6
	Hepatitis b	3
	Phenytoin	3
	Pantoprazole	4
	Others	19
Urticaria	Cefpodoxime	3
	Isoniazid	2
	NSAIDS	7
	Rosuvastatin	2
	Others	4
FDE	NSAIDS	4
	Fluconazole	2
	Ceftriaxone	2
SJS	Levetiracetam	1
	Gentamycin	1
	Pyrazinamide	1
TEN	Ofloxacin	1
Acneiform eruption	Lithium	1
	Prednisolone	1
Pruritis	Tramadol	1
	Hydroxychloroquine	1
	Glimipride	1
Angioedema	Diclofenac	2
	Cefixime	1
	Others	2
Hyperpigmentation	Zidovudine	1
	Doxybucin	1
Others (9) (anaphylaxis, itching, alopecia, purple toe syndrome, dress syndrome, eczema, etc.)		19 (one each)

However, few departments like ophthalmology, ENT, Orthopedics did not contribute any ADR.

Table 9: ADR reports contributed by the various health departments

Health departments	No.of ADR reported	Percentage
OPD/Dermatology	54	36
Medicine	50	33.3
Pediatrics	23	15.3
Emergency	2	1.3
ICU	4	2.6
Psychiatry/special ward	2	1.3
Surgery	15	10

Table 10: Seriousness Assessment

Seriousness	Serious	Non-Serious
No.of ADRs	11	139
Percentage of ADRs	7.3	92.6

On the evaluation of the seriousness of CADRs, 11 (7.3%) cases showed severe reactions, and the rest 139 (92.6) cases were non-serious.

Table 11: Severity assessment

Severity level	Non-severe (mild and moderate)	Severe
No.of ADR's	144	6
Percentage of ADRs	96	4

For the purpose of analysis, the patient was divided into two groups based on severity, i.e. severe and non-severe. The non-severe group included both mild and moderately severe cases of drug eruption. A total number of 144 (96%) ADRs were non-severe and 6 (4%) ADRs were serious, these were mostly skin reactions like SJS, TEN, and urticaria.

Table 12: Predictability

Predictability	Predictable	Non-predictable
No.of ADRs	72	78
Percentage	48	52

An evaluation of the chances of predictability of ADRs, 72 (48%) was predictable, and 78 (52%) were non-predictable

Table 13: Preventability

Preventability	Definitely preventable	Probably preventable	Not preventable
No. of ADRs	122	12	16
Percentage	81.3	8	10.6

An evaluation of the chances of the preventability of ADRs, 122 (81.3%) was preventable, were as 16 cases (10.6%) were not preventable, and 12 (8%) were probably preventable.

Table 14: Action taken against suspected drug

Action was taken against suspected drug	No. of cases	Frequency (%)
Drug withdrawal	108	72
Drug altered/ Repalcement	32	21.3
No change	10	6.6
Medication was given for ADR	83	55.3

There were four different actions taken against the suspected drug which was, the drug withdrawal 108 (72%), drug altered 32 (21.3%), no change was done in 10 (6.6%) cases, and the total number of medications given for the management of ADRs were 83 (55.3%).

Drugs are used for treatment and prophylaxis of various disease conditions and are considered as safer drugs when used rationally. Drugs show some Adverse Drug Reactions in different

patient conditions. ADRs monitoring is an essential aspect of therapeutics. However, most of the time it is overlooked and not considered significant. Even when observed, many would not document and report voluntarily. Establishing Pharmacovigilance units in the hospital has facilitated this activity to a great extent. [15]

This study focused on the pattern of Dermatological Adverse Drug Reactions of class in the post-marketing surveillance studies to find out the effects in a large, diverse population. The suspected ADRs were also notified in the National Pharmacovigilance Program of India as the site where a study conducted is one of the ADR monitoring centers (AMC) at SSIMS & RC, Davangere. The direct reporting is also helpful for suspecting ADRs.

In the present study, findings showed that higher numbers of cases found in males. However, there was not the much significant difference between the two genders on the rate of CADR (male: 53.3%, female: 46.67%). The same outcome found in some studied having a higher male preponderance. [1,15] Moreover, many studies showed a female preponderance. There is no significant difference in the numbers of male and female. The reason of higher incidence in the present study could be that males are more conscious about any dermatological reaction and treatment of ADR before it get severe.

Our study showed that men and women are not equally vulnerable, which is similar to the study done in Chandigarh by Sharma, et al. Where male preponderance was seen. [29] As all these studies were institution based, this difference in demographic profile can be accounted by the difference in the demography of the patients attending the clinics.

Age range in our study was the age of 'one and half' months to 81 years, which is similar to other studies [2,29] and shown that no age is exempted for CADR.[1] In our study showed that the older group(20 and above)had significantly higher rate compared with the younger group(15%); and patients under the age of 10 were significantly less likely to have a CADR compared to the age group of 20 and above years old, adults(between 20-59years old) in that younger adult group(21-30 years old)were showing 19.3% ; of the total CADR and the older adult group(51-60years old) were showing the higher rate of 20%; of the total CADRs analyzed.

Cutaneous adverse drug reactions was found to be caused more commonly by prescribed drugs than over-the-counter (OTC) drugs. This can reflect a changing trend that more patients were buying medication after visiting doctors. Understandably the patients reported early to the treating physician and a vigilant doctor can thus detect a CADR before it turns serious. This fact can be utilized for early detection if the prescribing physician is having high index of suspicion for CADR. Similar finding was noted in a study from Goa,[30] which reported that 75.45% of dispenced drugs were prescribed drugs and the reminder 24.55% was OTC prescriptions.

In a period of 6 months total number of CADRs reported was 150. Active surveillance along with spontaneous reporting contributed for getting this many ADRs. OPD based reports comprised 36% and ADR reported from indoor patients were 64% of the total ADR reports. Department of medicine (33.3%) followed by pediatrics (15.3%), surgery (10%), emergency (1.3%), ICU (2.6%) and psychiatry (1.3%). However, few departments like ophthalmology, ENT, Orthopedics did not contribute any ADR. Our study results shows no similarity with other study which also had same categorisation, it differs from the studies done in Jammu by Tandon et.al.[6] in that study OPD based reports comprised 76.05% and ADR reported from indoor patients was 23.94% of total ADR reports.

The results of this study are in accordance to a recent study by World Health Organization

(WHO), where it has been shown that high-income countries had the highest ADR reporting rates. There is, therefore, a need to strengthen ADR reporting, especially in low-income countries by suitably modifying the organizational structure, training and economic resources of national PV centers.[31] Active surveillance contributed to the majority of the total pool of ADRs, suggesting UR of ADR.

However, there is a concern that such a compulsion can lead to false reporting thus compromising the quality of reports. Regulators in United Kingdom, France, European Union, the United States and Canada are developing suitable approaches to enhance passive ADR reporting systems.[32]In the current study, the reports received from OPD were lower than ADRs among inpatient departments. The lower reporting from OPD patients can be overcome by encouraging and educating patients to report or by developing a system of active screening of all medical records of outpatients for ADRs.

Similar studies like ours suggest positive complementary contribution of patients to PV and drug safety.[33] These studies have shown that direct reporting of ADRs by patients have proven useful in intensifying ADR reporting. The present study suggests that the human resource, that is, Pharmacology residents can be utilized effectively to strengthen reporting and for educating the health professionals, providing feedback and personal communications with prescribers. Doctors (Interns, House officers), nurses, pharmacist and residents also need to be more actively involved in reporting ADRs, to widen the reporter base.

In present work, the most suspected ADR were rashes in 80 (53.3%) cases followed by urticaria in 18 (12%), Fixed Drug Eruption (FDE) in 8 (5.03%) cases. Highly occurring ADR in present study was rashes, which is similar to results obtained in other studies.[15] There were studies conducted in past showing that most common suspected ADR was rash followed by urticaria and/or FDE which are were also observed in the present study.[29,15] More number of ADRs was suspected for patients due to the more number of drugs prescribed. It is obvious that the dermatological ADR patterns and the drugs causing various reactions are changing every year which may be due to the emergence of newer molecules and changing trends in the use of drugs. The current study showed 139 non-serious and 11 serious dermatological ADRs. The study conducted by Gohel et al at Ahmedabad, showed 72 non-serious and 2 serious dermatological ADRs.[1]

The most common offending drug classes were antimicrobial agents 60 (**43.30%)** followed by 22 (26.80%) NSAIDs, 11(26.80%) were of vaccines and anti-epileptic. Chatterjee et al. showed the same higher incidence of suspected drug class which were antimicrobial agents (34.10%), antiepileptic (32.88%) and NSAIDs (21.51%).[27]This is quite consistent with present study that most offended drug class was antimicrobials followed by NSAIDs and then antiepileptic.In study at Karmasad by Suthar showed NSAIDs, antibiotics & antiepileptic, were reported to produce higher incidence rate, in which two thirds of the patients developing ADRs were due to NSAIDs and antibiotics.[42]

In present study, ceftriaxone was highly suspected drug followed by diclofenac. Probability of the higher incidence of ADR due to these two drugs could be due to self-medication of such medication without physician consult as it is common among local population or common prescribing pattern. In present study, one case of clopidogrel induced psoriasis and one case of telmisarten induced psoriasis was found out. One of the study also proved that long term use of these medications can produce the psoriasis.[43]

And also one each case of phenytoin induced Dress syndrom, terbinafen induced purple-toe syndrome, telmisartan induced Eczema and lithium induced Acne.

In our study, 1 case of Toxic Epidermal Necrosis (TEN) and 3case of Steven Johnson

Syndrome (SJS) were reported. In study conducted by Lihiteet al.[44] 2 cases of TEN and 1 case of SJS were reported whereas Sharma et al. [27] has shown 11.4% fatal cases of TEN and SJS.

After suspecting ADR, suspected drugs were discontinued or replaced or dose was reduced or medications given for management of ADR. Drug suspected of causing skin reactions should usually be withdrawn and not used again in patients, although risk- benefit potential need to be considered before discounting any medicine.

Most of the ADRs were managed by the withdrawal of the drug in 108(72%) cases. The remaining 32 (21.03%) patients drugs were altered and 10 (6.06%) patients continued on the same drug, without any major changes. The total number of medication given for management of ADRs were 83(55.3%).

Withdrawal of the suspected drug and antidote such as the use of systemic and topical steroids, antipruritic agents and oral antihistamines were given most commonly for ADR management. Calamine lotion or systemic antihistamines may relieve pruritus and topical corticosteroids may help inflammation and itch. For more serious reactions, systemic corticosteroids may be indicated. The similar finding also presented in studies where drug were being discontinued[9,42] and higher incidence same class of antidote were given.[45]

It was the dermatologist's discretion, whether the benefit of the drug overweighed the existing ADR and give line of treatment for ADR.

In present study, most of the ADRs in our study were designated as probable (59.03%) or possible (28.06%) in WHO-UMC causality assessment which is quite consistent with Few studies showed higher cases of probable 73.2%, 80.35% respectively.**[27,42]** The percentage of dermatological ADRs falling in category of definite (certain) is very low (3.3%) comparing to other category which is also found low in few studies (11.42%, 1.7% respectively).**[9,46]** In our study according to WHO-UMC causality assessment, NSAIDs and anti-epileptics caused "certain" type of ADR compared to other type of ADR.

In present study according to Naranjo's causality scale, 5 ADRs were definite, 89 ADRs were probable, 43 ADRs were possible. The study at Guwahati by Lihite et al showed higher cases of probable ADRs similar to the present study.**[47]** Comparison of strength of agreement between different scales of causality assessment (WHO-UMC causality assessment and Naranjo's causality scale) is done by using Cohen's kappa test. It showed that full agreement was not found between any of two scales of causality assessment. Positive but poor agreement based on kappa values was seen between WHO and Naranjo's causality comparison. This was due to different definitions of causality criteria for assessing adverse drug reactions.

In present study, only 6 ADRs were of high severity and the rest of all 144 ADRs were of moderate severity. A majority of ADRs were categorized as moderately severe while few cases of severe in nature, and similar findings are reported in other studies.[9,48]

Result of present study showed most of ADRs were "Definitely Preventable" (89.3%). On evaluation of chances of preventability of ADRs, all the ADRs may have been preventable, if proper precaution were taken like patients should carry drug list indicating which drugs they are allergic to at time of hospital visit to avoid reactions again. The predictability of reactions which are reported, Non-predictable were 52% and predictable where 48%.

The limitations of the study were the exact incidence of dermatological ADRs which may be difficult to obtain owning to fact that the researcher must rely on patient for reporting of ADR and drug details. In our study, reports from dermatology OPD and also dermatological ADRs reported from other departments of

hospital were considered, even though UR, small sample size, confined to the Outpatient Department of Dermatology for a short period of 6 months. Due to lack of follow up, exact outcome of ADR was not obtained in all patients. Moreover, ADRs of recently introduced drugs could also not be generated.

Dechallenge and rechallenge were not done in many cases after identification of ADRs until happened naturally. A number of20 cases were reported previous history of skin reactions after re-exposure to a drug and exacerbation of eruption.

There are a few recommendations for work in this area is for determination of exact incidence, study may carry out for longer duration of time with large patient populations. Further studies are required to determine the prevalence, predictors and risk factors of the dermatological ADRs in order to improve the drug safety. For patients who don't come back for follow up, some steps should be taken to consider them and give more attention to better patient care. Patients' awareness regarding OTC drugs and self-medications should also be strengthened.

Finally; cutaneous drug reactions should be reported to the manufacturer and the regulator agency, especially if the skin eruption is rare, serious or unexpected.

Adverse cutaneous drug reactions are distressing to both the patient and physician; when they are more effective and potent drugs are being developed, it is inevitable in modern day practice. However, it is incumbent on us as physicians to weigh the benefits and risks of each and every therapeutic decision carefully. We must be alert to potential adverse events and to recognize them early. However, it is better if we can prevent them from happening. Drugs are used for treatment and prophylaxis of various disease conditions and are considered as safer drugs when used rationally. Drugs show some Adverse Drug Reactions in different patient conditions. ADRs monitoring is an essential aspect of therapeutics. However, most of the time it is overlooked and not considered significant. Even when observed, many would not document and report voluntarily. Establishing Pharmacovigilance units in the hospital has facilitated this activity to a great extent. [15]

This study focused on the pattern of Dermatological Adverse Drug Reactions of class in the post-marketing surveillance studies to find out the effects in a large, diverse population. The suspected ADRs were also notified in the National Pharmacovigilance Program of India as the site where a study conducted is one of the ADR monitoring centers (AMC) at SSIMS & RC, Davangere. The direct reporting is also helpful for suspecting ADRs.

In the present study, findings showed that higher numbers of cases found in males. However, there was not the much significant difference between the two genders on the rate of CADR (male: 53.3%, female: 46.67%). The same outcome found in some studied having a higher male preponderance.[1,15] Moreover, many studies showed a female preponderance. There is no significant difference in the numbers of male and female. The reason of higher incidence in the present study could be that males are more conscious about any dermatological reaction and treatment of ADR before it get severe.

Our study showed that men and women are not equally vulnerable, which is similar to the study done in Chandigarh by Sharma, et al. Where male preponderance was seen. [29] As all these studies were institution based, this difference in demographic profile can be accounted by the difference in the demography of the patients attending the clinics.

Age range in our study was the age of 'one and half' months to 81 years, which is similar to other studies[2,29] and shown that no age is exempted for CADR.1 In our study showed that the older group (20 and above)had significantly higher rate compared with the younger group (15%); and patients under the age of 10 were

significantly less likely to have a CADR compared to the age group of 20 and above years old, adults (between 20-59years old) in that younger adult group (21-30 years old)were showing 19.3% ; of the total CADR and the older adult group (51-60years old) were showing the higher rate of 20%; of the total CADRs analyzed.

Cutaneous adverse drug reactions was found to be caused more commonly by prescribed drugs than over-the-counter (OTC) drugs. This can reflect a changing trend that more patients were buying medication after visiting doctors. Understandably the patients reported early to the treating physician and a vigilant doctor can thus detect a CADR before it turns serious. This fact can be utilized for early detection if the prescribing physician is having high index of suspicion for CADR. Similar finding was noted in a study from Goa,[30] which reported that 75.45% of dispensed drugs were prescribed drugs and the reminder 24.55% was OTC prescriptions.

In a period of 6 months total number of CADRs reported was 150. Active surveillance along with spontaneous reporting contributed for getting this many ADRs. OPD based reports comprised 36% and ADR reported from indoor patients were 64% of the total ADR reports. Department of medicine (33.3%) followed by pediatrics (15.3%), surgery (10%), emergency (1.3%), ICU (2.6%) and psychiatry (1.3%). However, few departments like ophthalmology, ENT, Orthopedics did not contribute any ADR. Our study results shows no similarity with other study which also had same categorization, it differs from the studies done in Jammu by Tandon et.al.6 in that study OPD based reports comprised 76.05% and ADR reported from indoor patients was 23.94% of total ADR reports.

The results of this study are in accordance to a recent study by World Health Organization (WHO), where it has been shown that high-income countries had the highest ADR reporting rates. There is, therefore, a need to strengthen ADR reporting, especially in low-income countries by suitably modifying the organizational structure, training and economic resources of national PV centers.[31] Active surveillance contributed to the majority of the total pool of ADRs, suggesting UR of ADR.

However, there is a concern that such a compulsion can lead to false reporting thus compromising the quality of reports. Regulators in United Kingdom, France, European Union, the United States and Canada are developing suitable approaches to enhance passive ADR reporting systems.[32] In the current study, the reports received from OPD were lower than ADRs among inpatient departments. The lower reporting from OPD patients can be overcome by encouraging and educating patients to report or by developing a system of active screening of all medical records of outpatients for ADRs.

Similar studies like ours suggest positive complementary contribution of patients to PV and drug safety.[33] These studies have shown that direct reporting of ADRs by patients have proven useful in intensifying ADR reporting. The present study suggests that the human resource, that is, Pharmacology residents can be utilized effectively to strengthen reporting and for educating the health professionals, providing feedback and personal communications with prescribers. Doctors (Interns, House officers), nurses, pharmacist and residents also need to be more actively involved in reporting ADRs, to widen the reporter base.

In present work, the most suspected ADR were rashes in 80 (53.3%) cases followed by urticaria in 18 (12%), Fixed Drug Eruption (FDE) in 8 (5.03%) cases. Highly occurring ADR in present study was rashes, which is similar to results obtained in other studies.[15] There were studies conducted in past showing that most common suspected ADR was rash followed by urticaria and/or FDE which are were also observed in the present study.[29,15] More number of ADRs was suspected for patients due to the more number of drugs prescribed. It is obvious that the dermatological ADR patterns and the drugs causing various reactions are changing

every year which may be due to the emergence of newer molecules and changing trends in the use of drugs. The current study showed 139 non-serious and 11 serious dermatological ADRs. The study conducted by Gohel et al at Ahmedabad, showed 72 non-serious and 2 serious dermatological ADRs.[1]

The most common offending drug classes were antimicrobial agents 60 (43.30%) followed by 22 (26.80%) NSAIDs, 11(26.80%) were of vaccines and anti-epileptic. Chatterjee et al. showed the same higher incidence of suspected drug class which were antimicrobial agents (34.10%), antiepileptic (32.88%) and NSAIDs (21.51%).27This is quite consistent with present study that most offended drug class was antimicrobials followed by NSAIDs and then antiepileptic.In study at Karmasad by Suthar showed NSAIDs, antibiotics & antiepileptic, were reported to produce higher incidence rate, in which two thirds of the patients developing ADRs were due to NSAIDs and antibiotics.[42]

In present study, ceftriaxone was highly suspected drug followed by diclofenac. Probability of the higher incidence of ADR due to these two drugs could be due to self-medication of such medication without physician consult as it is common among local population or common prescribing pattern. In present study, one case of clopidogrel induced psoriasis and one case of telmisarten induced psoriasis was found out. One of the study also proved that long term use of these medications can produce the psoriasis.[43]

And also one each case of phenytoin induced Dress syndrom, terbinafen induced purple-toe syndrome, telmisartan induced Eczema and lithium induced Acne.

In our study, 1 case of Toxic Epidermal Necrosis (TEN) and 3case of Steven Johnson Syndrome (SJS) were reported. In study conducted by Lihiteet al.44 2 cases of TEN and 1 case of SJS were reported whereas Sharma et al. 27has shown 11.4% fatal cases of TEN and SJS.

After suspecting ADR, suspected drugs were discontinued or replaced or dose was reduced or medications given for management of ADR. Drug suspected of causing skin reactions should usually be withdrawn and not used again in patients, although risk- benefit potential need to be considered before discounting any medicine.

Most of the ADRs were managed by the withdrawal of the drug in 108(72%) cases. The remaining 32 (21.03%) patients drugs were altered and 10 (6.06%) patients continued on the same drug, without any major changes. The total number of medication given for management of ADRs were 83(55.3%).

Withdrawal of the suspected drug and antidote such as the use of systemic and topical steroids, antipruritic agents and oral antihistamines were given most commonly for ADR management. Calamine lotion or systemic antihistamines may relieve pruritus and topical corticosteroids may help inflammation and itch. For more serious reactions, systemic corticosteroids may be indicated. The similar finding also presented in studies where drug were being discontinued[9,42] and higher incidence same class of antidote were given.[45]

It was the dermatologist's discretion, whether the benefit of the drug overweighed the existing ADR and give line of treatment for ADR.

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CONCLUSION

Cutaneous adverse drug reaction profile in this study is similar in many ways to studies conducted earlier in India. Present study made an impact on other departments of this institution for ADR reporting and a functional system of reporting and assessment for ADRs was initiated by the department of pharmacology under Pharmacovigilance program. ADR reporting forms (CDSCO) were distributed to all the departments of the institution.

From the results revealed from this study it was concluded that dermatological Adverse Drug Reaction was a common occurrence and awareness of them is essential for diagnosis and prevention. The dermatological ADR varied in their appearance, duration, causality, severity, and preventability.

The study shows that ADRs attribute to a significant percentage of the hospital visit, the dermatological population. The mechanism behind most of the dermatological ADRs was hypersensitivity reactions, and analysis of the data shows that maculopapular rash and urticaria were the most common morphological reaction type. Antimicrobial agents and NSAIDs were most commonly implicated drug class. Most of the reactions were of moderate severity, and could be managed by the withdrawal of the drug. Depending upon the nature of ADR, actions against suspected drug, along with symptomatic treatments were given whenever found significant. UR is observed in spontaneous ADR reporting, a multipronged approach in necessary to overcome UR. Most of ADR gets unreported due to lack of interest in ADR monitoring and reporting at hospital settings.

By the present piece of work, pharmacist contributed patient safety and rational use of drug by assessing, reporting and treating CADRs. The health care system should promote the spontaneous reporting of dermatological adverse drug reaction to Pharmacovigilance centers for ensuring drug safety.

By implementing the ADR reporting and monitoring system, the pharmacist can promote drug safety and better patient care, among health care professionals. Involvement of pharmacist in patient care can help in prevention and early detection of ARDs.

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