Research Article

Cutaneous Adverse Drug Reactions (CADRs) at a Quaternary Care Hospital in South India: Focus on Reaction Time and Treatment Cost

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ABSTRACT

Background: Cutaneous Adverse Drug Reactions (CADRs) are a major problem in drug therapy and is one of the leading causes of morbidity and mortality in health care. The purpose of the study was to evaluate the Mean Reaction Time, Causality, Severity and Preventability of CADRs and Treatment cost associated with CADRs. **Methods:** A prospective, observational study of patients diagnosed with CADR was carried out over a period of one year in the Department of Dermatology and Department of Clinical Pharmacy at a quaternary care hospital in South India. Diagnosis of CADRs was confirmed by the dermatologist and Clinical Pharmacist evaluated the suspected CADRs for Causality by WHO-UMC and Naranjo's scale, Severity by Hartwig and Siegel scale and Preventability by Schumock and Thornton criteria. **Results:** 42 CADRs were reported during the study period. Most commonly manifested CADR was Acneiform Eruption (23.8 %) followed by Maculopapular Rash (19.0%) and drugs used for the management of CADRs accounted for INR 5807.93. Most common offending drug group was Anti-infectives (33.3%) followed by Oral Steroids (23.8%). WHO and Naranjo scale rated 95.2% of CADR as probable and 4.7% as certain/ possible (Naranjo scale). Hartwig and Siegel scale marked 64.20% as moderate, 30.90% as mild and 4.70% as severe CADRs. According to Schumock and Thornton criteria 95.2% of CADR were not preventable and 4.7 % were definitely preventable. **Conclusion:** Awareness about CADRs is essential for early detection and prevention. The healthcare system should promote mandatory reporting of CADRs for ensuring safe drug use and patient care.

Key words: Cutaneous Adverse Drug Reactions, Reaction Time, Causality, Severity, Preventability.

INTRODUCTION

CADRs (Cutaneous adverse Drug Reactions) are defined as undesirable changes in either structure or function of skin, the appendages or the mucous membranes due to a drug. CADR accounts for 2-5% of all Inpatients and 2.6% of outpatients in India. Female sex, increasing age, more number of drugs, immunosuppressed patients and autoimmune disorders are the most common risk factors that may lead to CADRs. Among the CADRs, Toxic Epidermal Necrolysis (TEN), Erythroderma, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalised Exanthemata's Pustulosis (AGEP) and Drug Induced Vasculitis are the common Severe Cutaneous Drug Reactions which can have severe morbidity and even mortality.[1] Severe CADRs are mostly idiosyncratic and unpredictable hypersensitivity reactions with a heterogeneous clinical presentation, so a high index of suspicion is required for their early recognition.[2]

There is a potential for the occurrence of an increasing number of CADRs in the future, as innovation in medicine occurs and new drugs continue to be developed. As many mild and transitory reactions are not recorded, the true incidence of drug eruptions is difficult to determine. The incidence and pattern of CADRs differs among various drugs. Hence, understanding the precise nature of CADRs and knowledge about the drugs that can cause CADR may help to narrow down the search for the offending agent and help physicians in choosing safer drugs.[3]

DOI: 10.5530/ijopp.13.3.36

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Cost of disease treatment associated with Adverse drug Reactions (ADRs) requires a huge amount of financial resources and many countries spend 15% to 20% of hospital budgets to treat drug complications and it affects the patients by prolonging or requiring hospitalization, systemic complications and mortality.[4] 5-9% of all hospital costs are related to ADRs and therefore prior to administration of any drug, risk and benefit factors should be evaluated.

Keeping these observations in the background, the study was undertaken to assess the suspected CADRs in patients diagnosed through dermatology consultation in our hospital.

MATERIALS AND METHODS

This one-year prospective, observational study was conducted from January 2017 to December 2017 in the department of Dermatology in collaboration with Clinical Pharmacists. Study was approved by the Institutional Ethics committee (Ref. No. Institutional Ethical Committee/cert/28) and all information related to patients were kept confidential.

Identification of CADRs

The definition of CADR "any desirable 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" was considered.[5] All patients attended to dermatology outpatient unit as well as referred to dermatology unit diagnosed with CADRs were included in the study (Figure 1) and assessed for causality, severity and preventability by the Clinical Pharmacists. Dermatologists identified and confirmed the CADRs with patient interview, medical and medication history before the development of CADRs, clinical examination and review of past case records.

Data Collection

A pro forma was used to collect data of demography, diagnosis, investigations, adverse reactions, their clinical morphology, causative drugs with dosage, route, frequency and duration of administration, outcome, severity, concomitant medications, reaction time to develop the event, general and dermatological examination details and Laboratory investigations. Pharmacological classification was used to code the causative drugs.

Assessment of CADRs

The WHO causality assessment scale was used to assess drug–CADR pair. It classifies ADRs into "certain," "probable," "possible," "unlikely," "unclassified," or "unclassifiable" based on the time sequence of events, dechallenge, rechallenge and alternative explanation to reactions provided by other concomitant drugs or underlying disease. The preventability of CADRs was assessed according to Schumock and Thornton's criteria modified by Lau *et al.* were ADRs were categorized into definitely preventable, probably preventable and not preventable based on the presence or absence of one or more of the predisposing factors.[6] Severity of CADRs were assessed with Hartwig and Siegel scale where ADRs were categorized into seven levels according to their severity. Level 1 and 2 represents mild category whereas level 3 and 4 under moderate and level 5, 6 and 7 represents severe category.[7]

Statistics

Statistical analysis was done using Minitab, Version 16. Categorical and continuous variables are presented as numbers and percentages. Variables were statistically evaluated using chi square test. P value <0.05 was considered statistically significant.

RESULTS

Total number of 9,721 patients consulted Dermatologist and reported 42 CADRs during the study period, yielding an incidence rate of 0.43%. CADRs accounted for prolongation of hospital stay in 9 (21.4%) patients with an average length of stay of 2.2 days and among them 4 (9.5%) patient's required emergency observation with an average length of stay of 1.75 days in the casualty. 24.4% (N: 9) comprised of potentially life threatening Severe CADRs.

Characteristics of Patients

Patients were distributed as per the age group. The youngest patient was 10 year old and the oldest was 71 years. (Table 1). Males accounted for 47.6% (N: 20) and females accounted for 52.3 % (N: 22) of CADRs. The mean age of patients developed CADRs was 41.4 and majority of them were in the age group 20-40 years followed by 41-59 years.

Reaction Time of CADRs

Acneiform eruption (23.8%), Maculopapular rash (19.0%) and DRESS (14.2%) were the commonly reported CADRs. Mean time period for the appearance of cutaneous reaction after suspected drug intake (Reaction Mean Time Period) varied from 3 days to 50.33 days in different type of CADRs with more than one incidence (Table 2). Reaction time of CADRs with single

incidence varied from 2 days to 46 days (Table 3). Drugs suspected to cause CADRs were categorized according to their pharmacological classification (Table 4) and among those, the most implicated group was found to be Anti-infectives followed by Oral steroids. Antibiotics, Antiepileptics, Antigout agents, Disease modifying Antirheumatoid Drugs (DMARDs) and Antibacterial combinations were accounted for serious CADRs.

Causality, Severity and Preventability of CADRs

The causality, Severity and Preventability of CADR in our study population was categorized as per WHO-UMC and Naranjo causality assessment criteria, Hart wig Severity assessment scale and Schumock and Thornton scales respectively. Majority of the reactions were assessed as probable and not preventable (95.2%) (Table 5).

Treatment of CADR

Drugs used for the management of CADR's accounted for INR 5807.93. They were categorized according to the CIMS classification and observed that oral steroids, Topical Emollients and Antihistamines constitutes 60.8% of treatment group with drug cost of INR 2517.85. Among the treatment groups Acne Treatment preparations and Antifungals were used for longer duration period (Table 6).

DISCUSSION

In this study, the frequency of CADRs was maximum in patients with age group of 20-40. This is in conformity with other two studies conducted in India with the most common age group affected by CADRs was 20-39 years.[8,9] However high prevalence of ADRs has been found in elderly than in various systematic reviews.[10,11] Different age groups had shown significant impact of CADRs in this study but the study conducted in Malaysia and India observed that different age groups and sex has no significance on the incidence of CADRs.[12] An average length of stay of 2.2 days were observed for CADRs in the present study. Study conducted by Lee HY *et al.* reported an average length of stay of 9 days for patients admitted with CADR.[13]

Pattern of cutaneous adverse drug reactions and incriminated drug classes observed in this study are not similar with other CADRs studies in India. In our study incidence of Acneiform eruption was found to be high (23.3%) and major causative agent was found to be Anti-infectives followed by Oral Steroids. Study by Patel TK, Thakkar SH and Sharma D reported maculopapular rash (32.39%), fixed drug eruptions (20.13%), urticarial (17.49%) and Steven Johnson Syndrome/ Toxic Epidermal Necrolysis (SJS/TEN) (6.84%) and the major causative drug groups were found to be Antimicrobials (45.46%), NSAIDs (20.87%) and Anti-Epileptic drugs (14.57%).[14] Study conducted by Sejal a Thakkar *et al.* in an Indian hospital reported 171 CADRs and commonly observed CADRs were maculopapular rash (23.98%), Urticaria (21.64%) and Fixed drug eruptions (18.13%). Causative agents includes Antimicrobials (35.18%) and NSAIDs.[6] Study conducted by Babu L.N *et al.* also observed 62.4% (n:183) were related to Antimicrobials followed by NSAID's (12.9%) and Antacids (5.8%) . They also reported Urticaria/ Angioedema as the most common 109(37.2%) followed by Generalised Pruritis 57(19.5%) and Fixed Drug Eruption 37(12.6%).[15] Observational study by Abanti Saha *et al.* in an Eastern Indian tertiary care outpatient setting reported Morbilliform Eruption (30.18%) as the commonest CADR and drugs implicated were Sulphonamides (17%) followed by fixed dose combination of Fluoroquinolones with Nitroimidazoles (11.30%).[3]

Total drug cost for the treatment of CADRs in the study was estimated to be 5807.93. Study conducted by S P Shah *et al.* reported cost incurred by the hospital in

Table 1: Demographics of study Population.

Age Group Distribution				
Age Group	**CADR N (%)**	***P* Value**	**SCADR N (%)**	***P* Value**
1-19	3 (7.14%)	0.001	0 (0)	0.392
20-40	15 (35.7)		3 (7.14)	
41-59	13 (30.9)		3 (7.14)	
≥ 60 years	2 (4.7)		3 (7.14)	
Sex Distribution				
Sex	**CADR N (%)**	***P* Value**	**SCADR N (%)**	***P* Value**
Male	15 (35.7)	0.602	5 (11.9)	0.739
Female	18 (42.8)		4 (9.5)	

*Different age groups had shown significance in incidence of non-serious type of CADRs. Sex has no significance on both serious and non-serious type of CADRs.

Table 2: Reaction Mean time of CADRs.

Cutaneous Reactions	Total No (%)	Reaction Mean Time Period in Days (95% CI) %
Bullous Fixed Drug Eruption	5 (11.9)	7.4 (2.2-3.2)
Maculopapular Rash	8 (19.0)	6 (3.4-8.7)
DRESS	6 (14.2)	10.66 (8.7-16.4)
Acneiform Eruption	10 (23.8)	14 (13.0-14.9)
AGEP	2 (4.7)	2.5 (2.2-2.7)

Indian national rupees (INR) 374,255, i.e., SD 8241 and average cost incurred by outpatients was INR 99 (USD 2.18) and that of hospitalized patients was INR 264 (USD 5.81).[16] Study in Korea reported total healthcare cost of 752,067 USD over a period of 6 years for serious adverse reactions with major portion of the cost spent on Inpatient care (703832 USD).[17]

Mean reaction time of reported CADRs in the present study is varied from 3 days to 50.33 days with majority of CADRs developed during the time period of 0-5 days followed by 6-15 days. Incubation period for the onset of drug reaction was found be in the range of one day to maximum of 46 to 60 days in a Clinico demographic study conducted in India with majority of CADR (n: 32) developed during the time period of 2 -14 days followed by 25 number of CADR's with less than one day time period for onset.[18] Unlike other published prospective study reports of few hours to one week of incubation period for serious CADRs,[9] mean reaction time of Serious CADRs like DRESS and AGEP in the present study was varied from 2.5 days to 10.6 days and Toxic Epidermal Necrolysis (n:1) with the reaction time of 20 days. Study by VK Sharma *et al.* reported that the incubation period for maculopapular rash and Urticaria varied from 30 min to 3 weeks, range of two days to 2 months for Fixed Drug Eruption and few hours to one week for SJS and TEN.[19]

Oral steroids was used for 22.7% of patients with serious reactions in this study. Even though the management of CADR with systemic corticosteroids are controversial, patients of DRESS with altered liver function tests, Lymphadenopathy and atypical lymphocytes in peripheral blood film, It was seen that prompt withdrawal and early administration of systemic steroids resulted in marked improvement in patients.[20,21]Assessment of causality, severity and preventability of CADR in a tertiary care hospital reported 78%, 59% and 12% of CADRs under probable category, moderate level

Table 3: Reaction time of CADRs with single incidence.

Cutaneous Reactions	Total No (%)	Reaction Time Period in Days (95% CI) %
Photo allergic Drug Reaction	1 (2.3)	3
TEN	1 (2.3)	20
Urticaria	1 (2.3)	2
Angioedema	1 (2.3)	6
Stomatitis	1 (2.3)	8
Sweet's Syndrome	1 (2.3)	46
Pride Syndrome	1 (2.3)	2
Drug induced hypersensitivity	1 (2.3)	2
Flagellate Dermatitis accompanied with Nail Dystrophy	1 (2.3)	Unknown*
SDRIFE (Symmetric Drug Related Intertriginous and Flexural Erythema)	1 (2.3)	Unknown*
Fixed Drug Eruption	1 (2.3)	Unknown*

*Unknown: Patients were not able to recollect the time of reaction after suspected drug intake.

Table 4: Pharmacology category of drugs reported with CADRs.

Causative Agent	Percentage	CADR
Anticonvulsant	4 (9.5%)	DRESS (1), TEN (1), Stomatitis (1), Drug Induced Hypersensitivity (1)
Antigout and DMARDs	3 (7.1%)	DRESS (3)
Chemotherapy	4 (9.5%)	Flagellate Dermatitis with Nail Dystrophy (1), Angioedema (1), Bullous Eruption (1), PRIDE Syndrome (1)
NSAID's	4 (9.5%)	Photo allergic drug reaction (1), Bullous FDE (1), Maculopapular Rash (1), FDE (1)
Oral Steroid	10 (23.8%)	Acneiform Eruption (10)
Anti-Infectives	14 (33.3%)	Maculopapular Rash (4), DRESS (2), Sweet syndrome (1), AGEP (2), SDRIFE (1), Bullous FDE (3), Urticaria (1)
Others*	3 (7.1%)	Maculopapular Rash (3)

*Others comprised of Sulpha drugs, Cardiovascular agents and Antidepressant agents.

Table 5: Assessment of CADRs.

	WHO/ Naranjo		Hartwig Scale			Schumock and Thornton	
	Probable	Certain / Possible*	Mild	Moderate	Severe	Definitely Preventable	Not Preventable
Number	40	2	13	27	2	2	40
Percentage	95.20%	4.70%	30.90%	64.20%	4.70%	4.70%	95.20%

*Possible causality assessment was measured using Naranjo Scale

Table 6: Drug Cost for the management of CADRs.

Treatment				
Treatment Group	**Number**	**Percentage**	**Mean Duration of Treatment (In Days)**	**Drug Cost**
Acne Treatment Preparations	6	6.2%	42.33	541.92
Antihistamines	14	14.4%	5.21	49.95
Emollients	23	23.7%	7.91	1889.34
Ophthalmic Lubricants	2	2.1%	5	395.73
Antifungals	7	7.2%	31.71	589.89
Oral Steroids	21	22.7%	6.3	628.85
Topical Antibiotics	5	5.2%	17.2	350
Topical steroids	10	11.3%	7.8	649.61
Others*	3	4.1%	30	712.64

*Others includes facial cleansers and wound debridement preparations

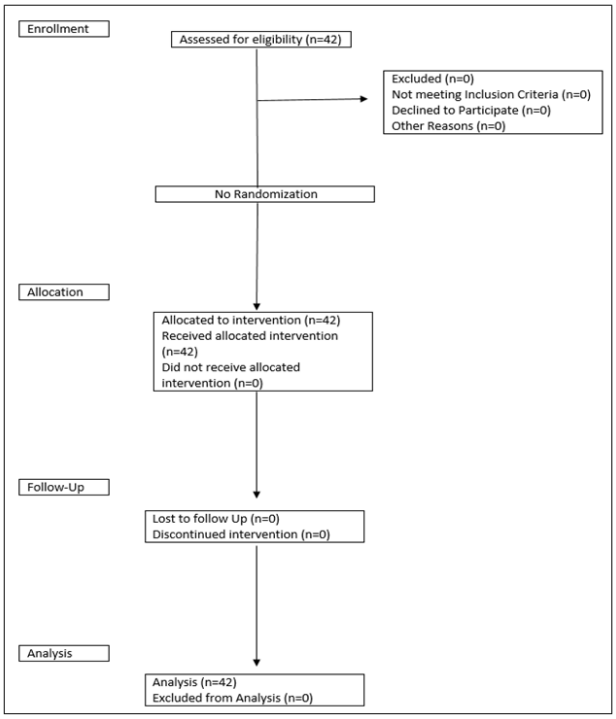

Figure 1: Consort Flow Chart of the study.

severity and definitely preventable respectively using Naranjo Algorithm, Hartwig severity assessment scale and Schumock and Thornton scale respectively.[22] This study reports 95.2%, 64.2% and 4.7% of CADRs under probable causality, moderately severe and definitely preventable reactions respectively.

Even though the study reports different type of CADRs, Study population were limited to judge the incidence pattern of CADRs. Also further studies on steroid induced Acneiform eruption are needed since its incidence pattern reported in the study was not similar to other published studies in India.

CONCLUSION

Healthcare professionals should have adequate knowledge about the CADRs of drugs that may help them in selecting safer drugs, early diagnosis, prompt treatment and thereby helpful to society at large. The pattern of CADRs and the drugs causing them is remarkably different in our population.

ACKNOWLEDGEMENT

Authors would like to thank all healthcare professionals in Aster Medcity Hospital for timely reporting of Adverse Drug Reactions

CONFLICT OF INTEREST

There are no conflicts of Interest

ABBREVIATIONS

CADRs: Cutaneous Adverse Drug Reactions; **SCADRs:** Severe CADRs; **TEN:** Toxic Epidermal Necrolysis; **DRESS:** Drug Rash with Eosinophilia and Systemic Symptoms; **AGEP:** Acute Generalized Exanthemata's Pustulosis; **DMARDs:** Disease modifying Antirheumatoid Drugs; **SDRIFE:** Symmetric Drug Related Intertriginous and Flexural Erythema; **NSAID's:** Non-Steroidal Anti-Inflammatory Drugs.

SUMMARY

Study reported 42 CADRs out of 9721 patients with higher incidence of Acneiform eruption (23.8%), Maculopapular rash (19.0%) and DRESS (14.2%) and the most implicated groups were Antiinfectives followed by Oral steroids. Reaction Mean Time Period were varied from 3 days to 50.33 days for CADRs with more than one incidence. Majority of the reactions were managed with Oral steroids, Topical Emollients and Antihistamines and overall cost for the treatment of CADRs was INR 5807.93. It is important for prescribing clinician to be aware of the toxic profile of drugs they prescribe and healthcare professionals be vigilant for the occurrence of

unexpected CADRs to avoid the burden of disease and treatment cost up to an extent.

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