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ANALYSIS OF CUTANEOUS ADVERSE DRUG REACTIONS PRESENTING TO THE DERMATOLOGY DEPARTMENT OF A TERTIARY CARE TEACHING HOSPITAL: A PROSPECTIVE, OBSERVATIONAL STUDY

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ABSTRACT: Background: Cutaneous adverse drug reactions (CADRs), having a wide range in terms of its spectrum, are an important cause of morbidity and mortality. They comprise 2-3% of all ADRs. This study was conducted to analyze various parameters of CADRs at our setup. **Methodology:** This prospective, observational study was carried out for 1 year at our setup after ethical approval. Those diagnosed as CADRs by the Dermatologist were included. Data was collected in suspected ADR reporting form and analyzed for various parameters like suspected drug and drug class for CADRs, spectrum as well as its type, severity, preventability, causality assessment, seriousness, and outcome. The lag period for the development of CADRs was also analyzed. This data collection was also uploaded *via* Vigiflow under Pharmacovigilance Programme of India (PvPI). **Results:** Total of 125 cases were recorded with 134 CADRs. These 134 cases included a wide range comprising of 27.61% rashes to 5.97% Stevens-Johnson syndrome (SJS). For these CADRs, most common suspected drug classes were anti-infectives (34.32%) followed by NSAIDs (29.10%) whereas most common suspected drugs were Diclofenac (17), Paracetamol (12), Amoxicillin (10), *etc*. 83.58% CADRs were type B hyper-sensitivity reactions. Causality assessment according to WHO-UMC criteria showed 61.94% CADRs had probable causality. The lag period for the majority of CADRs was 1 day. **Conclusion:** CADRs were frequent with drugs commonly prescribed in day to day clinical practice. Thus, the meticulous use of drugs is inevitable. Strict rules and regulations for judicious drug use, workshops on pharmacovigilance for health care professionals, adequate reporting of ADRs, *etc*. can all lead to increased general vigilance.

INTRODUCTION: The famous quote, "two sides of a coin," fits perfectly in case of a drug. While the better side cures diseases in the majority, the bitter side may produce adverse reactions in a few. WHO has defined adverse drug reaction (ADR) as, "Any response to a drug which is noxious, unintended and which occurs at a dose normally used in man for a prophylactic, diagnostic or therapeutic purpose or the modifications of physiological function" [1].

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Among all the body systems that get affected by ADRs, skin is one of the most commonly involved systems. They comprise approximately 2-3% of all ADRs [2]. Studies have found the incidence of cutaneous (CADRs) in developed countries as 1-3%, while in developing countries it is supposed to be higher between 2 and 5% [3]. CADRs are mainly hypersensitivity reactions having a wide spectrum ranging from simple macular rash or urticaria to as severe and fatal as Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN). Thus, CADRs are an important cause of morbidity, hospitalization, increased health expenditure and even death [3]. They ultimately affect the quality of life of patients. Thus, clinicians need to prescribe drugs meticulously to prevent further occurrences of ADRs in the same patients.

This also points towards the fact that CADRs should be reported, monitored and solved thoroughly as the safety of human health stands above all. Reporting of CADRs is a baby step in this direction on a global basis. It leads to increased general vigilance and may influence the recommendations for drug use through regulatory authorities [3]. Various studies on CADRs differ in their results based on diversities and variations in age, gender, pharmacology of causative drugs. Hence, the main purpose of this study was to analyze CADRs concerning various parameters.

Objectives of the study were to analyze the spectrum of CADRs presenting to the Dermatology Department at our setup; to analyze the suspected drug and drug class causing CADRs as well as its causal association with CADRs; to analyze the severity, preventability, and seriousness of CADRs.

MATERIALS AND METHODS: This was a prospective, observational study which began once the Institutional Review Board approved the study protocol. This study was carried out at the Department of Dermatology of a Tertiary Care Teaching Hospital in Ahmedabad, for a duration of 12 months from December 2016 to December 2017. The sample size was duration based. Once collected, data was recorded on Suspected ADR Reporting Form (PvPI - NCC IPC) [4].

The data was collected from those patients who were diagnosed as cases of CADR by the Dermatologist. These patients should be visiting the OPD (Outdoor Patient Department) or admitted in the Dermatology ward due to CADR. Those are developing CADR after getting admitted for other etiology were also included. These CADR patients were included in the study only if they gave a voluntary written informed consent willingly. For those aged, less than 18 years, written informed consent of parent/guardian was taken into consideration. Patients not willing to give their written informed consent, pregnant and lactating females, those suffering from comorbid conditions were excluded from the study.

The data collected was analyzed for parameters like age group and gender distribution; the spectrum of CADRs; suspected drug and drug class for CADRs. Also, type; causality assessment; severity and preventability of CADRs were analyzed according to Rawlins and Thompson Classification; WHO-UMC Criteria; Modified Hartwig and Siegel scale; Modified Schumock and Thornton scale respectively [5]. Other few parameters like seriousness and outcome of CADRs were based on WHO definition for serious adverse event and UMC criteria for Outcome respectively. No. of days between drug exposure and the development of CADR were also calculated. Patients were asked to come for a follow-up visit after 7 days. The statistical analysis of all the parameters in the data was done using Microsoft Excel Office 365.

This data was also uploaded to the WHO Uppsala Monitoring Centre *via* Vigiflow under the Pharmacovigilance Programme of India (PvPI) by the ADR Monitoring Centre (AMC) at our institute.

RESULTS: A total of 125 cases, diagnosed by the Dermatologist were analyzed for 12 months. Among these 125 cases, CADRs reported were 134.

Socio-demographic Profile: In the age range of 3-80 years, the most commonly affected age group was 21-40 years which constituted 43.2% (54/125). Mean age of the sample was 34.84 years. Male: Female ratio of 1.27:1. Age group wise gender distribution is given in **Table 1.**

TABLE 1: AGE GROUP WISE GENDER DISTRIBUTION

	Gender		
Age group (years)	**Male**	**Female**	**Total (n=125)**
≤20	14	12	26
21-40	30	24	54
41-60	19	14	33
61 – 80	7	5	12
Total	70	55	125

Suspected Drug and Drug Class: Among the various drug classes suspected, most common were Anti-infectives and NSAIDs constituting 46 (34.32%) and 39 (29.10%) respectively followed by Corticosteroids, Anti-epileptics, Miscellaneous and Anti-hypertensives (see **Table 2**). Among Anti-infectives, Amoxicillin (10/46) whereas in NSAIDs, Diclofenac (17/39) and Paracetamol (12/39) were the topmost culprit drugs. Corticosteroids induced CADRs were 27 which were mainly due to Clobetasol (11/27), Betamethasone (06/27), Mometasone (04) and few others.

Anti-epileptics like Phenytoin alone were responsible for 8 CADRs. Cyclosporine, Allopurinol, Levodopa + Carbidopa, Iron sucrose and Povidone-iodine had also resulted in singular cases of CADRs each. For suspected drug class wise CADRs, refer to **Table 3**.

TABLE 2: SUSPECTED DRUG CLASSES AND DRUGS

Suspected Drug Class	Suspected Drugs (n)	Total (n=134) (%)
Anti-infectives	Anti-bacterial: Amoxicillin (10), Ceftriaxone (01), Levofloxacin (04), Ofloxacin (02), Ciprofloxacin (01), Norfloxacin (01), Doxycycline (02), Tetracycline (01), AKT (05), Dapsone (01), Azithromycin (02), Anti-protozoal: Metronidazole (06). Anti-viral: Efavirenz (03), Nevirapine (02). Anti-fungal: Terbinafine (03), Itraconazole (01) Anti-parasitic: Permethrin (01)	46 (34.32%)
NSAIDs	Diclofenac (17), Paracetamol (12), Ibuprofen (06), Aspirin (02), Etoricoxib (01), Tramadol (01)	39 (29.10%)
Corticosteroids	Clobetasol (11), Betamethasone (06), Mometasone (04), Beclomethasone (03), Halobetasol (02), Methyl Prednisolone (01)	27 (20.14%)
Anti-epileptics	Phenytoin (08), Valproate (03), Lamotrigine (01), Phenobarbitone (01)	13 (17.16%)
Miscellaneous	Iron Sucrose (01), Povidone Iodine (01), Allopurinol (01),Levodopa (01), Cyclosporine (01),Cetirizine(01)	06 (4.47%)
Anti-hypertensives	Atenolol (02), Losartan (01)	03 (2.23%)

TABLE 3: SUSPECTED DRUG CLASS WISE CADRS

	Suspected Drug Classes (n=134)						
CADRs (n=134)	Anti-infectives	NSAIDS	Corticosteroids	Anti-epileptics	Miscellaneous	Anti-hypertensives	Total (n=134)
Rash	18	11	3	4	1	0	37
Urticaria	14	11	0	0	0	0	25
Miscellaneous	2	0	10	1	3	2	18
Fixed eruptions	2	10	0	2	1	0	15
Angioedema	7	4	1	0	1	1	14
Tinea incognito	0	0	13	0	0	0	13
Stevens-Johnson syndrome	1	2	0	5	0	0	8
Erythema multiforme	1	1	0	1	0	0	3
Drug hypersensitivity syndrome	1	0	0	0	0	0	1
Total	46	39	27	13	6	3	134

The Spectrum of CADRs: In our study, a wide spectrum of CADRs included rashes, urticaria, fixed eruptions (FE) to SJS, erythema multiforme (EM) and DHS (see **Fig. 1**).

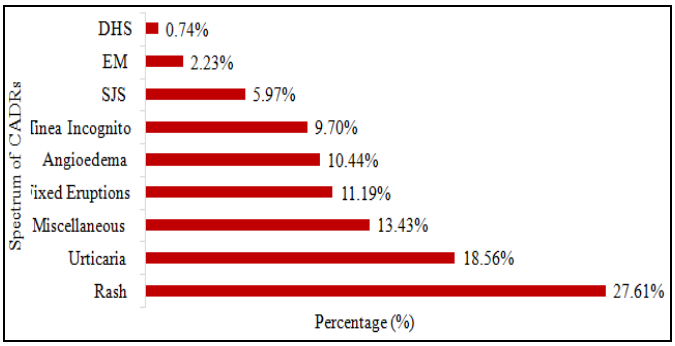

FIG. 1: SPECTRUM OF CADRs (n=134)

Among 134 CADRs, majority were rashes and urticaria which constituted 37 (27.61%) and 25 (18.56%) respectively followed by miscellaneous 18 (13.43%), fixed eruptions 15 (11.19%), angioedema 14 (10.44%), tinea incognito 13 (9.7%), SJS 08 (5.97%), erythema multiforme 03 (2.23%) and DHS 01 (0.74%). Miscellaneous included skin atrophy, skin hypopigmentation, hypertrichosis, irritant contact dermatitis, *etc*. Subtypes of rashes areas shown in **Fig. 2**.

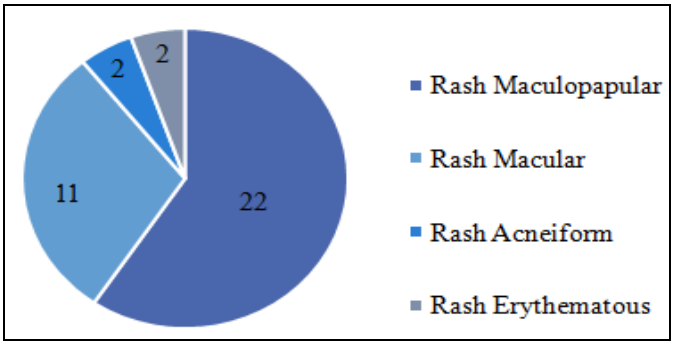

FIG. 2: NO. OF TYPES OF RASHES (n=37)

Type of CADRs (Rawlins and Thompson Classification of ADRs): Majority CADRs belonged to type B (bizarre/hypersensitivity), *i.e*. 112 (83.58%) while the rest fell in type A

(Augmented), *i.e.* 22 (16.41%). Among 112 cases of type B CADRs; type 1, 2, 3, 4 hypersensitivity reactions were 88, 16, 03 and 04 in number respectively.

The seriousness of CADRs: Out of 134 CADRs, 110 (82.09%) were non-serious while 24 (17.91%) were serious as shown in **Fig. 3**. These CADRs were classified based on the WHO definition of serious adverse event (SAE).

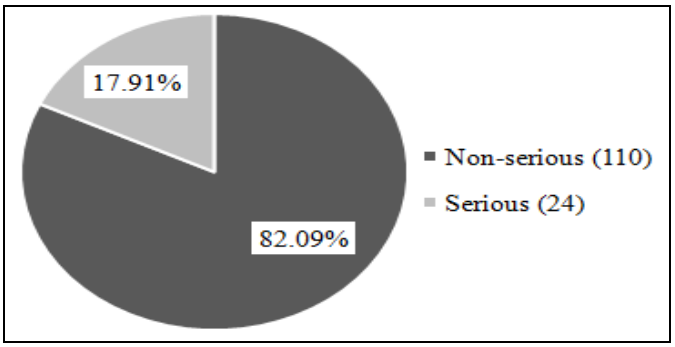

FIG. 3: SERIOUSNESS OF CADRs (n=134)

The Outcome of CADRs: Approximately, 95 (70.89%) CADRs were still recovering, whereas only 39 (29.10%) CADRs had recovered within 1 week of their incidence. This was done based on UMC criteria for the outcome of ADRs.

Causality Assessment of CADRs (WHO-UMC Criteria): For majority CADRs, causality was probable (61.94%) followed by possible (29.10%) and certain (8.95%) causality (refer **Fig. 4**).

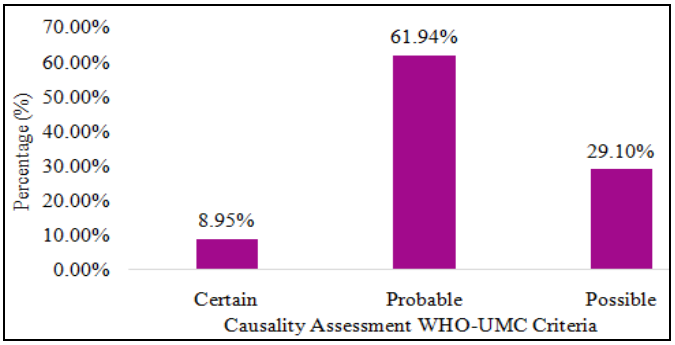

FIG. 4: CAUSALITY ASSESSMENT OF CADRs ACC. TO WHO-UMC CRITERIA (n=134)

Severity of CADRs (Modified Hartwig and Siegel Severity Scale): 7.46% CADRs were mildly severe, 84.32% were moderately severe, and 8.2% were severe (see **Table 4**).

Preventability of CADRs (Modified Schumock and Thornton Preventability Scale): Out of 134 CADRs, 100 CADRs were not preventable while only 34 CADRs were preventable as shown in **Table 5**.

TABLE 4: SEVERITY OF CADRs

Level of Severity	Total n=134 (%)
Mild	10 (7.46%)
Moderate	113 (84.32%)
Severe	11 (8.2%)

TABLE 5: PREVENTABILITY OF CADRs

Preventability	Total n=134 (%)
Not preventable	100 (74.62%)
Preventable	34 (25.37%)

Lag Period: For 34 CADRs, the period between drug exposure and the onset of CADR was 1 day followed by 2 days for 24 CADRs. For remaining CADRs, it varied in the range of 3-150 days. A lag period of 150 days was observed in 1 case of Phenytoin-induced maculopapular rash.

DISCUSSION: This prospective observational study focused on the cutaneous involvement of ADRs for 12 months. These hypersensitivity reactions have a wide range in terms of severity and distinctiveness. Each study performed till date has shown varying results owing to the diversities among the population. In our study, the incidence of CADRs was 0.21%. It is similar with an observed incidence of 0.45% by Thakkar S *et al.*, [6] but differs with various other studies which have stated its incidence in developing countries as 2-5% [3]. This might be related to the no. of drugs since it is supposed that incidence is directly proportional to no. of drugs being ingested. However, it's hard to comment on whether this is a true incidence rate due to the few limitations mentioned below.

Socio-demographic characteristics of the affected population were studied. Age group correlation of CADRs is known with the elderly. But here, adults of 21-40 years were commonly encountered with CADRs. Might be because this particular age group was active and precautions. Gender distribution showed a higher male preponderance. Both these results coincide with results from Sharma R *et al.*, and Patel *et al.* [7, 8] Analysis of suspected drug class showed Anti-infectives and NSAIDs as first and second leading drug classes respectively followed by Corticosteroids and Anti-epileptics at third and fourth place. Amrinder *et al.*, and Patel T *et al.*, also had similar results for suspected drug classes [8, 9]. The most common causative drugs for majority

CADRs in our study were Diclofenac followed by Paracetamol, Amoxicillin, Fluoro-quinolones, and Phenytoin.

These are commonly prescribed in day-to-day practices. Thus, CADRs can be linked with a similar prescribing pattern of these drugs. These results were identical with Ghosh *et al*., stating drugs causing maximal undesired effects were Paracetamol, Amoxicillin [10]. Few studies had different results such as by Nandha *et al*., and Sharma *et al*., that demonstrated Cotrimoxazole and Tinidazole as the most offending drug respectively [3, 7]. These suspected anti-infectives, NSAIDs as well as iron sucrose have been reported to cause angioedema. In our study, SJS has been encountered majorly with Phenytoin, an anti-epileptic. This is a common finding with other Indian studies too. Among the rare CADRs, Pyrazinamide-induced EM was one. Topical steroid preparations of Clobetasol, Mometasone, Betamethasone lead to tinea incognito and other CADRs like skin atrophy, skin hypopigmentation. Sheth *et al*. has also mentioned a case series on topical steroid induced tinea incognito [11]. This shows that corticosteroids should be used judiciously to avoid preventable CADRs. A case of Cyclosporine-induced hypertrichosis was also noted.

Upon analyzing the CADRs in our study, cases of rashes and urticaria exceeded those of fixed eruptions, angioedema, tinea incognito, *etc*. however, some rashes, urticaria, fixed eruptions have shown fluctuations in various Indian studies [3, 7, 10, 12]. Genetic variations in the affected population can be considered as a factor here. No. of cases of SJS, EM, DHS was fewer. Studies by Thakkar *et al*., Ghosh *et al*., also showed that SJS was relatively lesser in number [6, 10].

CADRs are known to be hypersensitivity reactions in majority cases. Thus, mainly all belonged to type B except for few induced by corticosteroids that were included in type A. Causality assessment using WHO-UMC criteria showed probable causality for majority CADRs followed by possible causality. Certain causality in cases of fixed eruptions can be attributed to information of accidental rechallenge. For Pyrazinamide-induced erythema multiforme, rechallenge was positive due to the reintroduction of AKT one by one after dechallenge positive. Causality assessment by Patel *et al*. showed probable followed by certain and possible causality [8]. Variations in causality can happen to depend upon availability of information on history, dechallenge, rechallenge, *etc*.

Non-serious CADRs were more in no. they are compared to serious ones. Non-serious cases were mainly OPD cases and did not require any hospitalization or intervention other than medical treatment. They didn't fall in any of the categories mentioned in WHO definition for serious ADR. Of all, hospitalization was required only in a few. Also, no deaths had been reported during the study period. This was contradictory to study by Patel T *et al*., which stated that CADRs are the main causes of mortality in dermatology patients [8]. More than half no. of cases was recovering. Even if they had recovered, data could not be recorded since the patients were lost on follow-up. This was one limitation consistent with many studies.

In the present study, corticosteroids-induced CADRs and those with certain causality were preventable. All the other hypersensitivity reactions were not preventable unless the patient had a history of similar CADR. Severity wise, majority CADRs were moderately severe. This is because only a few CADRs could be resolved with the withdrawal of the offending drug. A larger number was given basic treatment with topical or oral antihistamines and corticosteroids after withdrawing the causative drug. SJS, EM, DHS were considered as severe.

Majority of CADRs developed within a single day of drug intake. Nandha *et al*., has mentioned that the appearance of CADRs was maximum between 2-14 days [3]. This states that all the patients should be closely watched during the initial few days of drug ingestion. Those with a history of any ADR should be given instructions well in advance. This can have an impact on the statistics of morbidity and mortality. During these 12 months, we also came across CADRs due to lose medications quite frequently. However, such CADRs could not be documented due to lack of information on suspected drugs. This was one of the biggest limitations of our study. They also lead to an increased ADR burden. A study by Shah *et al*. has

mentioned about CADRs being induced by these loose or unknown medications [12]. The decrease in their number can also be useful for reducing CADRs induced morbidity and mortality.

In 2010, the Pharmacovigilance Programme of India (PvPI) was launched and initiated with the sole objective of safeguarding the health of Indian Population in coordination with global ADR Monitoring Centre (AMC), *i.e*. WHO-UMC. Our setup is also one such regional AMC under PvPI. Here, ADRs are reported and uploaded *via* Vigiflow. But in spite of the online availability of global database, detailed and adequate information on ADRs is still lacking at some point. Also, its incidence is directly linked with the physical, mental, social and economic burden to the society. Thus, with this study being carried out for 12 months, we could perform a survey of the pattern of CADRs and the suspected drugs inducing them. Limitations were under-reporting of CADRs, CADRs due to losing medications, patients lost on follow-up, unwillingness to give written informed consent in a few, self-prescription of drugs, *etc*. Strength is that it will be continuing at our regional AMC under PvPI.

CONCLUSION: These results show that CADRs were frequent with drugs commonly prescribed in day to day clinical practice. Hence, their meticulous use should be promoted to prevent unnecessary exposure of drugs to the patients. Rules and regulations for the judicious use of drugs should be implemented to create a general vigilance. Results of studies from all parts of the country can also be combined, and steps can be taken for formulating a proper protocol to lower the incidence. Drug lists given to all fresh cases of CADRs for future reference can be advantageous.

Reporting of ADRs should be made mandatory at all healthcare facilities. Workshops should be conducted under PvPI to create awareness among healthcare professionals. Awareness related to E-reporting of ADRs (ADR app), Nikshay is also necessary. Sensitization of prescribers, as well as chemists for safety profile of over the counter drugs, can prove beneficial.

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CONFLICT OF INTEREST: None

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