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Evaluation of Adverse Drug Reactions in Outpatients and Inpatients in Department of Dermatology at Tertiary Care Hospital

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Abstract

Objective: The study aims to evaluate the clinical spectrum, morphology, and causative drugs responsible for CADRs in inpatients and outpatients attending the dermatology department of a tertiary care center. It also emphasizes the necessity of an effective pharmacovigilance system to improve drug safety and minimize CADR-related morbidity and mortality.

Methods: A cross-sectional observational study was conducted at a tertiary care center in Jamnagar, Gujarat, from January 2023 to June 2024. A total of 150 patients presenting with CADRs at the dermatology outpatient department were included. Detailed clinical history, physical examination, and relevant laboratory investigations were performed. Causality was assessed using WHO-UMC and Naranjo criteria, while severity and preventability were evaluated using standard classification systems.

Results: Out of 150 patients, 54% were male and 46% female, with the majority in the 25-44 age group. The most common CADRs were maculopapular rash (28%), urticaria (25%), and fixed drug eruptions (16%). Antimicrobials (45%), NSAIDs (32%), and antiepileptics (10%) were the most implicated drug classes. According to WHO-UMC criteria, 65% of reactions were probable, 28% possible, and 6.66% definite. Most reactions (90%) were mild to moderate, while 10% were severe and required hospitalization.

Conclusion: Mild-to-moderate CADRs were more prevalent than severe reactions. Antimicrobials and NSAIDs were the most common culprits. Severe ADRs were mainly linked to antiepileptics. Physicians should exercise caution in prescribing drugs with known CADR risks and promote awareness to reduce self-medication and polypharmacy. Implementing a strong pharmacovigilance system is crucial for improving patient safety.

Keywords: Cutaneous adverse drug reactions, Pharmacovigilance, Antimicrobials, NSAIDs, Stevens-Johnson syndrome, Toxic epidermal necrolysis.

Introduction

There are no really 'safe' biologically active drugs. There are only safe physicians (Harold A. Kaminetzsky). In the course of their regular clinical work, doctors come across a variety of potential cutaneous adverse drug reactions (CADRs). According to WHO an Adverse drug reaction (ADR) is defined as "a response to a drug which is noxious & unintended, which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function excluding failure to accomplish the intended purpose." [1,2] The most common sites for the early manifestation of many adverse medication responses are the skin and mucosa [3]. CADRs affect between 2% and 3% of hospitalized patients [4]. There are two categories for cutaneous adverse medication reactions: mild and severe. The great majority of adverse cutaneous drug reactions are benign, but up to 2% of all such reactions are severe and potentially lethal [5].

Drug eruptions can present clinically as anything from moderate maculopapular exanthema to severe cutaneous adverse drug responses (SCARs), which include the rare but sometimes lethal toxic epidermal necrosis (TEN) and Stevens-Johnson syndrome (SJS). Drugs are double-edged weapons. Drugs, no matter how safe and efficacious, are always coupled with the inescapable risk of adverse reactions. When a drug is marketed, little is known about its safety in clinical use because only a few thousand patients are likely to have been exposed to it. However, during post-marketing surveillance, when the drug is used extensively in a large number of populations, many new adverse events are unearthed. Thus, drug safety assessment should be considered an integral part of day-to-day clinical practice. [4,5]

The concept of drug safety, first reported in Ayurveda and detailed in Charak Samhita, has been a cause of concern throughout the entire period of the history of medicine. ADRs are now more numerous because

- The number of drugs prescribed is high.
- The ever-increasing number of new drugs on the market.
- Lack of formal system for monitoring adverse drug reactions [6]

The incidence of ACDR in developing countries like India is some studies peg it to 2-5% of the inpatients, but there is a lack of comprehensive data amongst outpatients. [7,8,9] Inadequacy of data could be attributed to reasons like diagnostic dilemmas and lack of awareness to report.

Thus, the present study was undertaken to evaluate the clinical spectrum of all cutaneous ADRs in the outpatients attending the Dept of Dermatology. It also emphasizes the need and importance of an effective pharmacovigilance program.

Materials and Methods

In this cross-sectional observational study conducted at a tertiary care center in Jamnagar, Gujarat, the participants' exposure and results were assessed

simultaneously. All age groups and both sexes with clinical characteristics suspected of CADRs who presented to the dermatology, venerology, and leprosy outpatient department or were referred from other departments at G.G. Hospital between January 2023 and June 2024 were included after given their written consent. Cases where probable/possible offending drugs could not be detected due to insufficient data and cases that were unlikely, conditional, or unassessable under WHO-UMC causality criteria were excluded from the study.

The study comprised 150 patients who had reported experiencing varied cutaneous medication responses. The most crucial drugs were examined in light of the common skin conditions and their significance for CADR. The patient's clinical history was meticulously documented, encompassing the primary complaints, such as symptoms, onset site, dosage, duration, indication, drug class, latency time between drug administration, and the emergence of cutaneous lesions; family history; related illnesses; lesion morphology; progression sites; mucosal examination; and related systemic symptoms. Improvements in systemic characteristics and cutaneous lesions after stopping the medication were also noted. Details on associated allergies, comorbidities, and severity were recorded in addition to the drug use history.

A comprehensive physical examination was performed, which included a dermatological examination and a systemic assessment to determine the level of involvement, morphology, and place of the lesion, and mucosal examination. Digital images were captured. Haematological, biochemical, and viral indicators were investigated. When the underlying risk factors were present, the venereal disease research laboratory (VDRL) test was conducted.

In cases where the diagnosis was unclear, the biopsy was examined histopathologically. Laboratory results, clinicopathologic characteristics, and dermatologic treatment outcomes were analyzed when in doubt. After excluding other aetiologies and illnesses with similar symptomatology, such as responses to certain foods, infections, and environmental variables, the diagnosis of CADR was made. All the information was carefully recorded in the CDSCO Suspected ADR reporting form. The causation of CADRs was assessed using the Naranjo Adverse Drug Reaction Probability Scale, which assigned ratings of extremely probable (definite), possible, and probable. All of the patients received information about CDRs and a list of drugs that may induce reactions in order to avoid any such mishaps. Finally, all the data was compiled and subjected to descriptive statistical analysis.

Result

A total of 166 cases of suspected adverse cutaneous drug reactions were recorded during the period of study. Out of these 16 cases were excluded either because the offending drug was not identified or the data was insufficient to make any analysis. The remaining 150 cases were analyzed. Out of 150 patients, 81 (54%) were male and 69 (46%) were female (Figure 1). Maximum patients (41%) belonged to the age group of 25-44, followed by 45-64 (31%) and 15-24 (11%). Mean age of patients with ACDR, Range and M: F ratio were 36.81±17.26, 14 months-70 years and 1.17:1 respectively.

Individual types of cutaneous ADRs (based on morphology)

The most common morphological varieties of drug reaction were maculopapular rash (28%), followed by urticaria (25%) and fixed drug eruptions (16%). Together they accounted for 69% of all cases. Other types of cutaneous adverse drug reactions that were seen in our study included 12 cases of Stevens-Johnson syndrome (SJS), 8 cases of toxic epidermal necrolysis (TEN), 2 cases of red man syndrome, 5 cases of palmar-plantar erythrodysesthesia, 4 cases of erythema multiforme, 4 cases of photosensitivity, 1 case of erythematous rash, 2 cases of discoid lupus erythematosus (DLE), and 7 other cases were seen. (Figure 2)

Responsible drugs group and individual drug reactions

Most frequently reported adverse drug reactions were for antimicrobial agents in 67 cases (45%), followed by NSAIDs—48 cases (32%) and antiepileptics—15 cases (10%) (Table 2). NSAIDs and antimicrobials are drugs that were found to be responsible for urticaria, 27% and 54%, respectively. Antimicrobial drugs were found to be responsible for maculopapular rash (57.5%) and FDE (61.55%), respectively. NSAIDs were responsible for 70% of cases of FDE (Table 2).

Causality assessment using WHO-UMC criteria

Cases that were unlikely, conditional, or unassessible under WHO-UMC criteria were excluded from the study. Causality assessment of suspected ADRs shows that out of 150 reported CADRs, 42 (28%) were assessed to be possible and 98 (65%) as probable (Table 3).

Assessment of severity and preventability

Reported reactions were found to be mild-moderate (135, 90%) followed by severe (15, 10%). 10% of reactions (15/150) were considered serious as per the WHO definition of serious adverse drug reaction (Table 4). Preventability of adverse cutaneous drug reaction was assessed by Schumock and Thornton criteria.

Discussion

There was a slight male preponderance in the study, with a male-to-female ratio of 1.17:1. While Pudukadan & Thapa's study [11], which reveals a female majority, does not correspond with this, it does with Patel & Marfatia's study [12], Rajendran et al. [13], and Jha et al. [14]. In this study, the average age range for both genders were 31 to 40 years, followed by 41 to 50 years. This is in line with research by Sharma et al. [15], where the majority of patients were in the 20–39 age range. In the study conducted by Rajendran et al. [13], the most common age group was 40 to 60 years.

In previous studies, the most common morphologic patterns were exanthematous rash, urticaria and/or angioedema, fixed drug eruption, and erythema multiforme. 129 Of the various types of adverse cutaneous drug reactions seen. The most common morphological varieties of drug reaction, maculopapular rash (28%), were the most common, followed by urticaria (25%) and fixed drug eruptions (16%) (Figure 2). These observations are in conformity with studies carried out by Chatterjee et al. [17], Padukadan et al. [11], and Noel MV et al. [16]. Others have noted exanthematous eruption (maculopapular rash) to be the most common type of drug reaction. A study also found maculopapular rash to be the most common type of ACDR [15]. Pudukadan & Thapa [11] and Patel & Marfatia [12] found fixed drug eruptions as the most common drug eruption, followed by maculopapular rash & urticaria.

The majority of adverse drug reactions (139, 93%) were of Type B, since these reactions were totally aberrant

effects that are not to be expected from the known pharmacological actions of a drug when given in the usual therapeutic doses to a patient whose body handles the drug in the normal way. The remaining 11 (7%) ADRs belonged to Type A, since these reactions were the result of an exaggerated, but otherwise normal, pharmacological action, of a drug given in usual therapeutic doses. Ghosh et al. [18] recorded 96% Type B reactions and only 4% Type A in their study, which is quite similar to our result. Most frequently reported adverse drug reactions were for antimicrobial agents in 67 cases (45%), followed by NSAIDs—48 cases (32%) and antiepileptics—15 cases (10%). Patel & Marfatia [12] and Pudukadan & Thapa [11] found similar results in their study. Sharma et al. [15] and Chatterjee et al. [17] reported antimicrobials as the major group, followed by antiepileptics & NSAIDs.

In the present study, among antimicrobials Penicillins (Ampicillin/Amoxycillin) and Fluoroquinolones (Ofloxacin /Norfloxacin/ Ciprofloxacin) were the most commonly implicated drugs together accounting for almost 60.42% of all cases due to antimicrobials. Among NSAIDs, 83.33% of reactions were due to paracetamol and ibuprofen. Phenytoin was responsible for 50% of cases due to antiepileptics, followed by carbamazepine (Figure 3). A drug-induced reaction cannot be confirmed by a gold standard inquiry. According to Shear et al. [19], diagnosing and evaluating a drug's cause instead entails analysing a variety of characteristics, including the timing of drug exposure and reaction time, the course of the reaction with drug withdrawal or discontinuation, the timing and nature of a recurrent eruption on rechallenge, a history of similar reactions to the suspected drug, and prior reports of similar reactions to the same drug.

In this study, WHO causality definitions were used to categorize the ADRs into definite, probable, and possible categories, as it is a very simple and widely accepted method to assess causality. According to WHO-UMC criteria, 10 (6.66%) were definite, and 98 cases (65.33%) were probable. 42 cases (28%) were considered possible because dechallenge data was either negative or doubtful and the reaction could be attributed to existing clinical condition. According to Naranjo's scale, 5% definite, 55% probable, and 40% possible ACDR. [20] In a study carried out at Manipal College of Pharmaceutical Sciences [18] reported 5% definite, 55% probable, and 40% possible ACDR according to WHO UMC criteria. However, the study included inpatients as well, and it utilized Naranjo's scale for causality assessment. Noel et al. [16] have reported 2% definite, 80% probable, and 18% possible reactions.

The differences in various studies may be due to different scales used for causality assessment or because of individual differences in the interpretation of data.135 patients (90%) had mild to moderate adverse cutaneous drug reactions as they didn't require any specific therapy. They were simply managed by withdrawal of the suspected drug & supportive treatment. 15 patients (10%) suffered severe adverse drug reactions and required immediate cessation of the suspected drug, hospitalization, and intensive medical care. The results comply with earlier studies [11, 12].

Limitations

A drug rechallenge was not performed. Underreporting, inability to find incidence rate, lack of follow-up data (in many cases).

Implications: This study focuses on the need to establish a reporting culture amongst prescribers in our country. Besides identification of ADRs, adequate measures to

prevent them should be undertaken to reduce the patient's pain, suffering, and economic burden to the healthcare facility.

Conclusion

In our study, mild-moderate CADRs were commonly seen compared to severe CADRs. Patients with a history of severe ADRs must be advised to avoid the drug completely in the future due to systemic involvement leading to morbidity and mortality. Awareness about CADRs in the general population is also required to stop polypharmacy, which hinders the identification of the culprit drug, since drug rechallenge may lead to complications and limited availability of in vitro tests.

Physicians should assess drug and family histories before prescribing medications, closely monitor new prescriptions, and discourage self-medication. Drug cards that list the offending drug along with any cross-reacting medications need to be prepared for the patient. Early detection of certain morphological features is essential for locating the offending substance and immediately halting it to prevent iatrogenic morbidity and mortality.

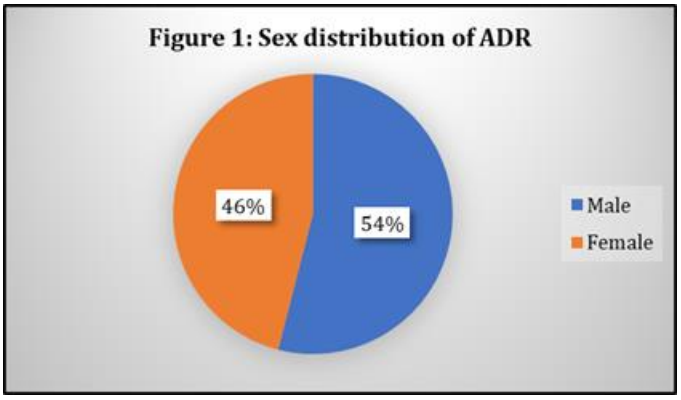

Figure 1: Sex distribution of ADR

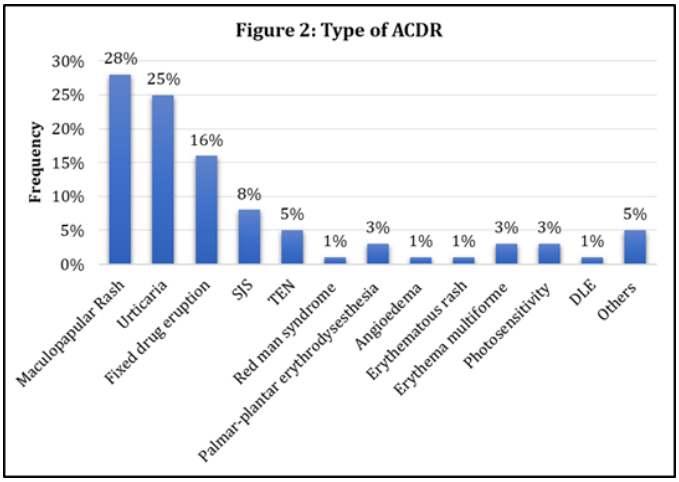

Figure 2: Type of ACDR

Table 1: Distribution of drugs responsible for ACDR

Drug Group	No. of Patients	%
Antimicrobials	**67**	**45**
Penicillins	21	14
Fluoroquinolones	19	12.66
Cephalosporins	7	4.6
Antimalaria	5	3.33
Antitubercular drugs	4	2.66
Antiamoebic drugs	3	2
Tetracyclines	3	2
Glycoproteins	3	2
Beta lactamase inhibitor	1	0.66

Antiviral drugs	1	0.66
NSAIDS	**48**	**32**
Paracetamol	25	16.66
Ibuprofen	15	10
Diclofenac	3	2
Aspirin	2	1.33
Naproxen	3	2
Antiepileptic	**15**	**10**
Phenytoin	7	4.66
Carbamazepine	6	4
Valproate	1	0.66
Lamotrigine	1	0.66
Antineoplastic	**5**	**3**
Capecitabine	3	2
Paclitaxel	2	1.33
Vitamins B12	**6**	**4**
Others	**9**	**6**
Bromhexine	2	1.33
Omeprazole	1	0.66
Enalapril	1	0.66
Contrast media	2	1.33
Hydroquinone	2	1.33
Antitoxin	1	0.66

Table 2: Individual drug reactions

Drug reactions	Maculopapular rash (n=40)	Urticaria (n=37)	Fixed drug eruption (n=24)
Antimicrobial	57.5%	54.1%	29.16%
NSAIDS	20%	27%	70.83%
Antiepileptics	17.5%	18.9%	0

Table 3: Causality assessment using WHO-UMC criteria

Causality type	Number of Cases	Present study (n=150) WHO-UMC criteria	Present study (n=150) Naranjo's scale	Noel et al (n=56) Naranjo's scale	Ghosh et al. (n=53) WHO- UMC criteria
Certain	10	7%	5%	2%	5%
Probable	98	65%	55%	80%	55%
Possible	42	28%	40%	18%	40%

Table 4: Assessment of severity and preventability

Severity of reaction	Number of cases	%
Mild – Moderate	135	90
Severe	15	10
Total	150	100
Preventability	Number of cases	%
Preventable	16	11
Probably Preventable	5	3
Not Preventable	129	86
Total	150	100

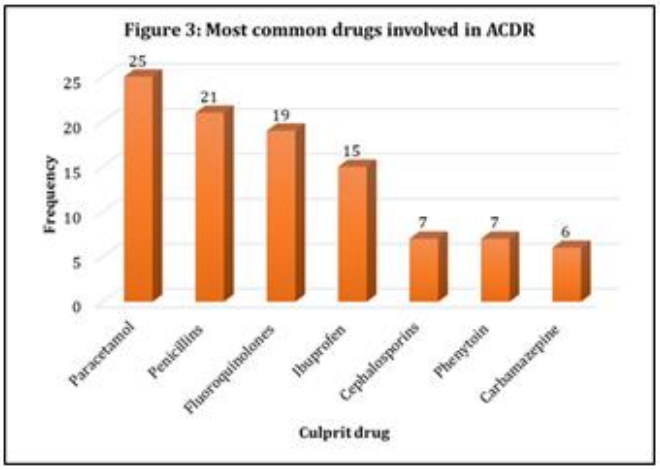

Figure 3: Most common drugs involved in ACDR

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