Study of adverse cutaneous drug reactions as a part of pharmacovigilance from a tertiary care teaching hospital of Madhya Pradesh

Dr. Simran Sharma[1], Dr. Chetan Singh[2], Dr. Rakesh Das[3*], Dr. Rajesh Ranjan[4]

[1,2,3]Department of Pharmacology, Index Medical College, Indore, Madhya Pradesh
[4]Department of Community Medicine, MGM Medical College, Indore, Madhya Pradesh

***Corresponding Author:** Dr. Rakesh Das, Department of Pharmacology, Index Medical College, Indore, Madhya Pradesh. E-mail: dr.dasrakesh@gmail.com

Cite this paper: Sharma S, Singh C, Das R, Ranjan R. Study of adverse cutaneous drug reactions as a part of pharmacovigilance from a tertiary care teaching hospital of Madhya Pradesh. J Med Res Pub Health 2023 July-Sep;1(1):4-11. DOI: 10.5281/zenodo.8340537

Received on: 10-06-2023 Accepted on: 11-08-2023 Published on: 01-09-2023

ABSTRACT

Background & objectives: Gaining a comprehensive understanding of the characteristics and mechanisms underlying Adverse Cutaneous Drug Reactions (ACDR) might facilitate the process of identifying the specific causative agent. The study aimed to evaluate incidence, assessment of causality, severity and preventability of Adverse Cutaneous Drug Reactions as a part of Pharmacovigilance from a central Indian medical college. **Methods:** The study employed several methods for data collection and analysis, including the CDSCO ADR Reporting Form, the WHO causality assessment scale, the Hartwig and Siegel's Assessment scale, and the Modified Schomock and Thronton's preventability assessment scale. **Results:** The findings of this study revealed that out of the total sample size of 23 patients, a small proportion of 0.3% were identified as having either one or both types of adverse cutaneous drug reactions (ACDRs). The most prevalent type of adverse cutaneous drug reactions (ACDRs) observed among the study patients was fixed drug eruption, accounting for 34.8% of cases. This was followed by acneform eruption, which accounted for 21.7% of cases, and urticaria, which accounted for 13% of cases. **Conclusions:** The implementation of pharmacovigilance activities has been found to have a considerable impact on the enhancement of adverse drug reaction (ADR) reporting.

Key words: adverse cutaneous drug reactions, medicine, skin, pharmacovigilance

INTRODUCTION

Drug eruptions are a prevalent category of skin disorders frequently encountered by dermatologists. These Adverse Cutaneous Drug Reactions (ACDRs) encompass a broad range of manifestations, ranging from temporary maculopapular rashes to severe and potentially life-threatening conditions such as toxic epidermal necrolysis and acneform eruptions.[1] An Adverse Cutaneous Drug Reaction (ACDR) refers to any unpleasant alteration in the structure or functionality of the skin, its appendages, or mucous membranes.

This term incorporates all negative occurrences associated with drug eruptions, irrespective of their underlying causes. Pharmacovigilance can be defined as the scientific field that encompasses the identification, evaluation,

Access this article online

Quick Response Code:

www.jmrph.in

DOI: 10.5281/zenodo.8340537

comprehension, and mitigation of undesirable effects associated with medications, with a particular focus on both immediate and prolonged adverse reactions.[2]

The prevalence and variety of cutaneous drug reactions have been amplified due to the extensive and non-selective use of medications.[3] Gaining insight into the characteristics of adverse cutaneous drug reactions (ACDRs) can aid in focusing the investigation on identifying the responsible substance. There is a scarcity of data and literature pertaining to the specific component of the out-patient department. The insufficiency of data can be attributed to a lack of awareness regarding the reporting of Adverse Drug Reactions (ADRs). Hence, the purpose of this study was to investigate the occurrence, causality assessment, severity, and preventability of Adverse Cutaneous Drug Reactions within the context of Pharmacovigilance, specifically focusing on a medical school located in a rural region of northern India.

MATERIALS AND METHODS

The present survey was conducted by the Department of Pharmacology in conjunction with the Department of Dermatology at Index Medical College, Madhya Pradesh. The survey targeted patients who were attending the Dermatology Outpatient Department (OPD). The focus of this study was the Out Patient Department of Dermatology at Index Medical College in Madhya Pradesh. The study population consisted of individuals who were receiving medical care at the outpatient department of a dermatology clinic. The chosen research methodology is a prospective study. The designated time frame for conducting research and analysis is from March to December of 2021. The study was conducted with a sample size of 7692 participants.

Exclusion criteria encompassed individuals who solely reported symptoms without observable cutaneous manifestations, participants who were unable to recall the specific medications they had ingested, and individuals whose lesions were shown to be associated with an underlying medical condition upon further evaluation. Several participants who reported using traditional medicines, specifically ayurveda and homeopathic remedies, were also eliminated from the study.

Tools for the study

The CDSCO ADR Reporting Form[4] collects information pertaining to drug history, including data about the start and type of the reaction, any linked drugs, and the individual's past history of similar or other adverse reactions. The incidence rate was computed, and then, the age, sex, and primary drug responsible for the adverse drug reactions (ADRs) were used as criteria for classification.

The causation assessment of adverse drug reactions (ADR) was conducted using the WHO causality assessment scale[5], which categorizes ADRs into specific levels of certainty, including certain, probable, possible, unlikely, unclassified, and unassessable. The study incorporated ACDRs that were reported under the categories of certain, probable, and potential.

The severity assessment in this study was conducted using a modified version of the Hartwig and Siegel's scale.[6] This scale categorizes the severity of adverse drug reactions (ADRs) as mild, moderate, or severe, taking into account many aspects

such as the need for treatment modification, prolonged hospitalization, and the level of disability caused by the ADR.

The assessment of preventability was conducted using a modified version of the Schomock and Thornton scale[7] (Schomock & Thornton, 1992). The scale utilized in this study classified the identified ACDRs into three categories: definitely preventable, maybe preventable, and not preventable.

Study strategy

All medical professionals, including doctors, residents, interns, and students, were encouraged to promptly report any suspected adverse cutaneous drug reactions (ACDRs) by closely monitoring patients attending the Dermatology Outpatient Department. This reporting may be done either by direct telephone communication or by notifying the Department of Pharmacology. Participants were subjected to a screening process and subsequently enrolled in the study if they exhibited observable skin lesions that were considered to be caused by drug usage. Additionally, their participation was contingent upon providing written consent that demonstrated their informed understanding and agreement to be included in the study. The reporting of adverse drug reactions was required to be conducted on a daily basis throughout the duration of the trial, adhering closely to the 'CDSCO ADR Reporting Form'.

Prior to the initiation of the study, all individuals participating in this research were provided with detailed information regarding the factors outlined in the CDSCO ADR Reporting Form. To provide quality assurance, the findings were simultaneously cross-verified by a senior faculty member from the Dermatology department. The Department of Pharmacology and the Department of Dermatology were actively engaged in collaborative efforts, consistently exchanging observations and reports on a regular basis. Prior to the initiation of the trial, approval was obtained from the Institutional Ethics Committee (IEC). The researchers got informed consent from the participants of the study.

The acquired data was inputted into Microsoft Excel 7, and afterwards analyzed using SPSS (Statistical Package for Social Sciences) 22.0 software. Categorical variables have been represented using numerical counts and corresponding percentages. The statistical tests employed in this study were the Independent T test and the Chi Square test. A p-value of less than 0.05 was used as the threshold for determining statistical significance.

RESULTS

Among the 7,692 patients who visited the dermatology outpatient department (OPD) throughout the designated study period, a total of 23 individuals (0.3%) were identified as having experienced various forms of Adverse Cutaneous Drug Reactions. The age group most frequently impacted by this phenomenon was individuals between the ages of 20 and 35, with a higher prevalence observed among males.

The most prevalent type of adverse cutaneous drug reactions (ACDRs) observed among the study participants was fixed drug eruption, accounting for 34.8% of cases. This was followed by acneform eruption and urticaria, which accounted for 21.7% and 13% of cases, respectively. The predominant medicines implicated in adverse cutaneous drug reactions (ACDRs) associated with fixed

drug eruption were prednisolone, betamethasone, and isoniazid. Conversely, metronidazole, cotrimoxazole, and paracetamol were shown to be the primary culprits in ACDRs characterized by acneform eruptions. Antimicrobials, along with other steroids and non-steroidal anti-inflammatory drugs (NSAIDs), have been implicated in the occurrence of a wide range of adverse cutaneous drug reactions (ACDRs). The provided information is presented in Table 1. (Table 1)

Table 1: Profile of Adverse Cutaneous Drug Reactions detected among study subjects

Type of Adverse Cutaneous Drug Reactions*	**Number of patients**	**Drugs Responsible**
Fixed drug eruption	8	Prednisolone, Betamethasone, Chlorpromazine, Clobetasol, Isoniazid, tinidazole
Acneform eruption	5	Cotrimoxazole, Diclofenac, Metronidazole, Mefenemic acid, Paracetamol, Quinine, Levofloxacin
Urticaria	3	Aceclofenac, Cephalosporin, Paracetamol, Propofol, Multivitamin, ramipril
SJ syndrome	2	Ciprofloxacin, Septran, Ofloxacin, Allopurinol
Bullous eruption	2	Carbamazepine, Furosemide, Ibuprofen, Diclofenac
Maculopapular rash	2	Ofloxacin, Isoniazid, Levofloxacin
Eczematous drug eruption	1	Indomethacin, Sparfloxacin, Betamethasone
Hypertrichosis	1	Betamethasone
Swelling of lips	2	Ceftriaxone, Carbamazepine
Acne rosacea	1	Clobetasol
Vesicular eruption	1	Azithromycin, Levofloxacin
Hypo-pigmentation	2	Betamethasone, Chlorpromazine
Pellagrous dermatitis	1	Isoniazid
*More than one type of Adverse Cutaneous Drug Reactions were noted		

The examination of the causality of adverse cutaneous drug reactions revealed that a majority of these reactions (52.2%) were classified as likely. A specific set of annualized compound daily returns (ACDRs) exhibited a value of 30.4%. The next table, labeled as Table 2, presents the relevant data. (Table 2)

Table 2: Assessment of Causality of ACDRs detected using 'WHO causality assessment scale' among study subjects

Assessment	**Category**	**No. of ADRs**	**Percentage**
Causality	Certain	7	30.4%

	Probable	12	52.2%
	Possible	4	17.4%

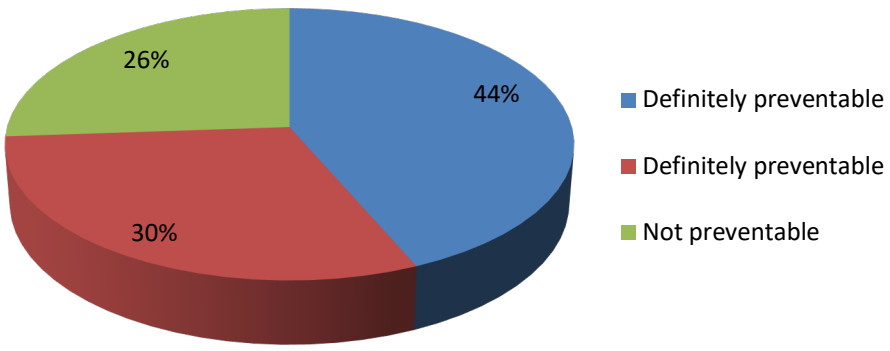
The findings of the study on the severity assessment of Adverse Cutaneous Drug Reactions indicate that a significant proportion (65.3%) of these reactions were classified as moderate in severity. The following table, labeled as Table 3, provides relevant data and information. (Table 3)

Table 3: Assessment of Severity of ACDRs detected using 'Hartwig and Siegel's Assessment scale' among study subjects

Assessment	Category	No. of ADRs	Percentage
Severity	Mild	7	30.4%
	Moderate	15	65.3%
	Severe	1	4.3%

According to the Modified Schumock and Thornton Scale, a significant proportion of Adverse Cutaneous Drug Reactions, namely 43.5%, were categorized as 'Definitely preventable'. This was followed by 'Probably preventable' at 30.4%, and 'Not preventable' at 26.1%. The provided diagram, labeled as Figure 1, is presented for reference. (Figure 1)

Figure 1: Pie diagram showing Preventability of ACDRs by Modified Schumock and Thornton Scale (n=23)



DISCUSSION

The present study was designed to investigate the patterns of Adverse Drug Reaction (ADRs) occurrence while simultaneously assessing the impact of Pharmacovigilance activities at our tertiary care center. The reported prevalence of adverse cutaneous drug

reactions (ACDRs) was found to be 0.3%. The reported values in prior Indian research, such as those conducted by Chatterjee et al. (26 per 1000) and Ghosh et al. (285 per 1000), are higher than the current findings.[8,9]

One potential explanation for the decreased incidence rate may be attributed to an improved drug prescribing methodology, or alternatively, a continued lack of awareness surrounding adverse drug reaction (ADR) reporting. An other potential explanation for the observed low incidence rate could be that the study was done in a tertiary facility, which may have resulted in underrepresentation of mild rashes as patients may not have sought dermatology outpatient department (OPD) care or may have received treatment from specialists in other specialties. Moreover, a subset of patients exhibiting clear symptoms of CADR were omitted from the final assessment due to their inability to provide specific details regarding the implicated medications. Additionally, some patients reported using traditional remedies containing undisclosed or unidentifiable active components, which further hindered their inclusion in the study. Another notable contributing factor to the decreased incidence rate was the absence of patients experiencing adverse cutaneous drug reactions (ACDRs) induced by antiretroviral medications. This can be attributed to the fact that the department responsible for administering antiretroviral therapy autonomously controlled skin responses, without necessitating referral to the dermatology department.

A separate study conducted in southern India[10] found that the age group most commonly affected was 20-39 years, followed by 40-59 years, with a higher incidence observed among females (M:F = 0.87:1). In our study, we also observed the most common age group to be 20-35 years, but with a higher prevalence among males. However, a study conducted in Chandigarh reported a higher male-to-female ratio.[11]

In relation to the clinical spectrum of adverse cutaneous drug reactions (ACDRs), it was found that the most prevalent type was fixed drug eruption, accounting for 34.8% of cases. This was followed by acneform eruption and urticaria, which accounted for 21.7% and 13% of cases, respectively. Previous studies have identified maculopapular rash and fixed drug eruption (FDE) as the prevailing adverse cutaneous drug reactions (ACDRs)[8,9]. Specifically, FDE has been reported to be primarily caused by antimalarials and fluoroquinolones.[12] A comprehensive analysis conducted in Pakistan has revealed sulfonamides and tetracycline as the principal agents responsible for such reactions.[13]

The present investigation revealed that the occurrence of acneform eruption can be attributed to the use of steroids and anti-tubercular medicines. The antipsychotics were identified as the causative agents for Stevens-Johnson syndrome in the investigation. The findings of this study are consistent with the earlier research conducted by Noel MV and Nayak S.[14] Additionally, this analysis identified antimicrobials, steroids, and NSAIDs as other potential causes of ACDRs, which aligns with the results of other studies.[15,16]

The analysis of causality indicated that 30.4% of the cases were categorized as certain, 52.2% as probable, and 17.4% as possible, which aligns with the findings of Chatterjee et al.[8] Additionally, the severity assessment conducted by Hartwig found

that 4.3% of all reported adverse cutaneous drug reactions (ACDRs) were classified as severe. Significantly, the present study employed the modified Schomock and Thronton scale to assess preventability, a crucial aspect that had been overlooked in previous investigations on adverse drug reactions in ambulatory care settings.

The strength of this study is in its evaluation of Adverse Cutaneous Drug Reactions within the context of Pharmacovigilance, conducted in a medical college located in a rural region in northern India. Another advantageous component of this survey is the continuous monitoring of quality reporting. However, it is important to note that the focus of our study center predominantly revolves on individuals from a lower socioeconomic background. Consequently, the scope of our study was constrained, resulting in restricted exposure to newer pharmaceutical substances within our study group. One of the most apparent limitations of the current survey is its evident nature.

CONCLUSION

The most commonly seen adverse cutaneous drug reactions (ACDRs) were fixed drug eruption and acneform eruption. The timely diagnosis of cutaneous reactions by physicians can contribute to limiting the extent of damage caused by such reactions. The implementation of pharmacovigilance measures has been found to have a substantial impact on the enhancement of adverse drug reaction (ADR) reporting.

ACKNOWLEDGMENT

We owe a debt of gratitude to the department for providing assistance during the course of the research.

AUTHORS' CONTRIBUTION

All the authors have contributed equally.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR'S FUNDING

The authors hereby state that they did not get any financial assistance for their research, writing, or publication of this paper.

REFERENCES

1. Nayak S, Acharjya B. Adverse cutaneous drug reaction. Indian J Dermatol 2008; 53:2-8.
2. Neupane S, Sharma S. Cutaneous adverse drug reactions. Journal of Clinical and Diagnostic Research 2012; 6:445-8.
3. Bilimoria FE, Shah BE, Drug reactions. In: Valia RG, Valia RR. IAVDL Textbook of Dermatology. 3rd ed. India: Blalani publication; 2008. p. 1633-68.
4. Central drugs standard control organization. Suspected adverse drug reaction reporting form; 2010. Available from URL: http://www.cdsco.nic.in/ADR_form_pvpi.pdf.
5. Gupta SK. Adverse drug reaction: classification, mechanism and interaction. Textbook of pharmacovigilance. 1st ed. New Delhi: Jaypee Brothers; 2011. p. 39-57.
6. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. AM J Hosp Pharm 1992; 49:2229-32.
7. Schomock GT, Thronton JP. Focusing on the preventability of

adverse drug reactions. Hosp Pharm 1992; 27:538.

8. Chatterjee S, Ghosh AP, Barbhuiya J, Dey SK. Adverse cutaneous drug reactions: A one year survey at a dermatology outpatient clinic of a tertiary care hospital. Indian J Pharmacol 2006;38:429-31.
9. Ghosh S, Acharya LD, Rao PG. Study and evaluation of various cutaneous adverse drug reaction in Kasturaba Hospital, Manipal. Indian J Pharm Sci 2006;68:212-5.
10. Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care center in South India. Indian J Dermatol Venereol Leprol 2004; 70:20-4.
11. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: Clinical pattern and causative agents- a 6 year series from Chandigarh, Indian J Postgrad Med 2001; 47:95-9.
12. Mahboob A, Harron T. Drugs causing fixed eruptions: a study of 450 cases. Int J Dermatol 1998; 37:833-8.
13. Dubey AK et al. Dermatological adverse drug reactions due to systemic medications – a review of literature. Journal of Pakistan Associations of Dermatologists 2006; 16:28-38.
14. Noel MV, Sushma M, Guido S. Cutaneous adverse drug reactions in hospitalized patients in a tertiary care center. Indian J Pharmacol 2004; 36:292-5.
15. Jhaj R, Uppal R, Malhotra S, Bhargava VK. Cutaneous adverse reactions in in-patients in a tertiary care hospital. Indian J Dermatol Venereol Leprol 1999;65:14-7.
16. Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of acute cutaneous drug reactions in a Scandinavian university hospital. Acta Derm Venereol 2006;86:518-22.