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[1]Department of Dermatology, Nobel Medical College, Biratnagar, Morang, Nepal.
[2]Department of Dermatology, Purbanchal University Teaching Hospital, Morang, Nepal.

***Corresponding Author:**
Dr. Sunita Karki,
Email ID:
dr.sunitakarki@gmail.com.
ORCID iD: https://orcid.org/0000-0001-7468-8192

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Prevalence of Cutaneous Adverse Drug Reaction at a Tertiary Care Centre of Eastern Nepal: A Descriptive Cross-sectional Study

Sunita Karki[1*], Manish Pradhan[1], Anjan Rai[1], Rajiv Yadav[1], Niraj Khadka[2]

Abstract

Introduction: An adverse cutaneous drug reaction is defined as any unwanted alteration in the structure or function of the skin, its appendages, or mucous membranes resulting from drug exposure ranging from transient maculopapular rashes to life-threatening conditions such as toxic epidermal necrolysis. This study was aimed to find the prevalence of cutaneous adverse drug reaction in patients who visited the department of Dermatology at a tertiary care centre.

Method: A descriptive cross-sectional study was conducted at Nobel Medical College from January 2021 to February 2023. Participants were enrolled using convenience sampling. A comprehensive clinical history was recorded, encompassing the morphological pattern, progression, and duration of lesions. Adverse drug reactions (ADRs) were classified into four categories—definite, probable, possible, and unlikely based on Naranjo's causality assessment scale. Point estimates along with 95% confidence intervals were calculated for data analysis.

Result: Out of 4802 patients, 73 (1.52%) patients had cutaneous adverse drug reaction (1.18-1.86, 95% Confidence Interval). The most common morphological pattern of cutaneous adverse drug reaction (CADR) in current study was exanthematous (47.9%) followed by Steven- Johnson Syndrome (12.3%), fixed drug eruptions (12.3%) and urticaria (12.3%). The most common morphological pattern of CADR in current study was exanthematous(47.9%) followed by SJS (12.3%), FDE (12.3%) and urticaria (12.3%). As per Naranjo ADR probability scale, 42 cases (57.5%) were certain and 21 cases (28.8%) were probable

Conclusion: This study assessed the prevalence of cutaneous adverse drug reaction in tertiary care center of Eastern Nepal. It also established the most common type of morphological patterns of cutaneous drug reaction and the most common groups of drugs involved.

Keywords: Cutaneous adverse drug reaction; Exanthematous eruption; Naranjo's causality assessment score

Introduction

A Cutaneous Adverse Drug Reaction (CADR) is defined as any abnormal or harmful alteration in the structure or function of the skin, its appendages, or mucous membranes resulting from drug exposure. It includes all drug-induced cutaneous events, irrespective of their underlying cause.[1]

The skin is one of the primary target organs affected by adverse drug reactions (ADRs). The incidence of cutaneous adverse drug reactions (CADRs) among hospitalized patients is estimated to range from 1–3% in developed countries and 2–5% in India.[2] The development of ADRs is influenced by a complex interplay of patient-related, pharmacological, and socio-environmental factors. Notable risk factors include extremes of age (infancy and old age), alcohol consumption, sex, ethnicity, pregnancy, lactation, renal and hepatic dysfunction, as well as the dosage and frequency of drug administration.[3] Additional determinants such as atopy, genetic polymorphisms in drug-metabolizing enzymes, variations in human leukocyte antigen (HLA) alleles, coexisting medical conditions, active viral infections, immune status, and polypharmacy further influence the incidence, clinical presentation, progression, and outcomes of CADRs.[4]

The objective of this study was to find out the prevalence of cutaneous adverse drug reactions among patients who visited the department of Dermatology of a tertiary care centre in Eastern Nepal as very limited data is available in our country.

Method

A descriptive cross-sectional study was carried out in the Dermatology Outpatient Department (OPD) of Nobel Medical College and Teaching Hospital, Biratnagar, from January 2021 to February 2023. Ethical approval was obtained from the Institutional Review Committee (IRC) of Nobel Medical College and Teaching Hospital (IRC-NMCTH 586/2021). All consecutive patients presenting with suspected cutaneous adverse drug reactions (CADRs), or those with a history of similar eruptions following re-exposure to the same drug, were included in the study. Patients were excluded if the offending drug was unknown, if the reaction represented an exacerbation of a pre-existing chronic dermatological condition, or if the drug reaction followed the use of ayurvedic, homeopathic, or other indigenous medicines. Individuals unwilling to participate were also excluded. A convenience sampling technique was employed.

The sample size was calculated using the following formula:

$$n = \frac{Z^2 \times p \times q}{e^2}$$

$$= \frac{1.96^2 \times 0.50 \times 0.50}{0.02^2}$$

$$= 2401$$

Where,

n = minimum required sample size

Z = 1.96 at 95% confidence interval (CI)

p = the prevalence of cutaneous drug reactions was 50% assumed in our population

q = (1-p)

e = margin of error, 2%

The calculated sample size was 2401. Since the convenience sampling method was done, the sample size was doubled and the final sample size was 4802.

The clinically diagnosed patients with cutaneous adverse drug reaction attending the dermatology outpatient department and the patients admitted in the wards with suspected cutaneous adverse drug reactions to systemic drugs were enrolled in the study as case.

Data collected from the participants included age, sex, implicated drug class(es), indication for use, time interval between drug intake and onset of skin eruption, history of similar reactions with the same or different group of drugs, and improvement of the cutaneous reaction upon drug withdrawal. Additional demographic details such as ethnicity, occupation, and address were also recorded. A comprehensive drug history was obtained, covering all prescription and non-prescription medications taken within the past month, including the date of administration, dosage, duration of use, any interruptions in treatment, route of administration, and any underlying disease states or injuries that could have contributed to or triggered the cutaneous eruption.

A thorough general, cutaneous and mucosal examination regarding clinical pattern of lesion were performed and recorded. Adverse drug reactions (ADRs) were classified into four categories—definite (score ≥9), probable (score 5 to 8), possible (score 1 to 4), and unlikely (score ≤ 0) based on Naranjo's causality assessment scale[5]. It has a total of 10 items with options yes, no and don't know.

We performed all the necessary laboratory investigations for supporting evidence and to rule out

infectious cause of skin eruption. We also conducted skin biopsies in few patients.
Cases were diagnosed as cutaneous adverse drug reactions based on a thorough medical history and detailed clinical examination.
Data were analyzed using IBM SPSS Statistics 22.0. Point estimate and 95% Confidence Interval was calculated.

Result

Among 4802 patients, 73 (1.52%) had CADRs (1.18-1.86, 95% Confidence Interval). In this study maximum number of cases of CADR were found in age group 20-29 years (20 cases, 27.4%) and least number of patient of CADR were found in age group 60-69 years (2 cases, 2.7%). The mean age were 33.34 years with youngest age being 1 years and eldest being 74 years.Out of 73 patients, 33(45.2%) were male and 40(54.8%) were female in a ratio of male to female 1:1.2.
The most common morphological pattern of CADRs observed in the current study was exanthematous rash (47.9%), followed by Stevens - Johnson syndrome (12.3%), fixed drug eruption (12.3%), and urticaria (12.3%), as shown in table 1.

Table 1: Morphological Pattern of CADR (n=73)

Morphological pattern	n (%)
Exanthematous	5 (47.9)
Leucocytoclastic Vasculitis (LCV)	1 (1.4)
Fixed Drug Eruptions(FDE)	9 (12.3)
Urticarial	9 (12.3)
Urticarial vasculitis	4 (5.5)
Steven Johnson Syndrome(SJS)	9 (12.3)
SJS-Toxic Epidermal Necrolysis overlap	1 (1.4)
Toxic Epidermal Necrolysis (TEN)	1 (1.4)
Acute Generalised Exanthematous pustulosis (AGEP)	2 (2.7)
Erytherma Multiforme (EM)	2 (2.7)

The most commonly implicated group of drugs in CADRs were antimicrobials, which were identified as the causative agents in 35 cases (47.9%), followed by non-steroidal anti-inflammatory drugs (NSAIDs), responsible for 27 cases (37%).Among all the drugs implicated in CADRs in this study, the most common was the combination of paracetamol and ibuprofen, accounting for 11 cases (15.1%). Ceftriaxone was the second most frequently implicated drug, observed in 8 patients (11%), followed by nimesulide in 6 patients (8.2%), paracetamol alone in 5 patients (6.8%), and cefixime in 5 patients (6.8%), as presented in table 2.

Table 2: Frequency distribution of drugs implicated in CADR (n=73)

Drug Group (n, %)	Culprit drugs	
	Drug Name	n (%)
Antimicrobials (35, 47.9%)	Ceftriaxone	8 (11)
	Meropenem	2(2.7)
	Cefepime	1(1.4)
	Levofloxacin	1(1.4)
	Azithromycin	1(1.4)
	Piperacillin	1(1.4)
	Cefoperazone	1(1.4)
	Flucloxacillin	2(2.7)
	Cefpodoxime	2(2.7)
NSAIDs (27, 37%)	Nimesulide	6(8.2)
	(Paracetamol +Ibuprofen)	11(15.1)
	Paracetamol	5(6.8)
	Naproxen	3(4.1)
	Mefenamic acid	1(1.4)
	Ketorolac	1(1.4)
	Febuxostat	2(2.7)
	Dapsone	3(4.1)
Anticonvulsants (5, 6.8%)	Sodium valproate	2(2.7)
	Carbamazepine	2(2.7)
	Phenytoin	1(1.4)
Sulfa drugs (4, 5.5%)	Sulfasalazine	1(1.4)
Hypouricemic (2, 2.7%)	Febuxostat	2(2.7)

Out of the 73 cases analyzed, 55 patients (75.3%) received the drug through oral administration, while the remaining 18 patients (24.7%) were administered the drug intravenously. The mean duration of onset of cutaneous adverse drug reactions (CADRs) following drug administration was 3.27 days. Most patients developed CADRs within 1 to 2 days after receiving the drug, ranging from 1 to 26 days. The mean time to appearance of rash varied depending on the type of reaction. For exanthematous eruptions, the average onset time was 4 days, while it was 2 days for fixed drug eruptions (FDE), urticarial vasculitis, and acute generalized exanthematous pustulosis (AGEP). Stevens–Johnson syndrome (SJS) and erythema multiforme (EM) showed a longer mean onset time of 6 days, whereas patients with SJS-TEN overlap and urticaria developed symptoms after an average of 3 days. The shortest mean onset time—just 1 day—was observed in cases of toxic epidermal necrolysis (TEN) and leukocytoclastic vasculitis (LCV).

Table 3: Case distribution according to Naranjo's ADR probability score (n=73)

Naranjo ADR probability scale	n(%)
Unlikely	2(2.7)
Possible	8(11)
Probable	21(28.8)
Certain	42(57.5)

According to the Naranjo Adverse Drug Reaction (ADR) Causality Assessment Scale, 42 cases (57.5%) were classified as "certain," while 21 cases (28.8%) were considered "probable" for having experienced ADRs (Table 3).

Discussion

Out of 4,802 patients, the prevalence of cutaneous adverse drug reactions (CADRs) in our study was 1.52%, which is consistent with the findings reported by Bigby in a systematic review, where the incidence of CADRs across nine studies was found to range from 0% to 8%. [6]

In the current study, the mean age of patients presenting with cutaneous adverse drug reactions (CADRs) was 33.34 years, which is comparable to findings by Sharma et al.[7] (33.26 years) and Neupane et al.[8] (32 ± 15.7 years). In our study, the highest number of CADR cases occurred in the 20–29-year age group (20 cases, 27.4%), while the lowest number was in the 60–69-year age group (2 cases, 2.7%). These findings are consistent with those of Sharma et al.[7] who reported the highest incidence in the 21–30-year age group (30.6%), followed by the 31–40-year group (26%). Similarly, Neupane et al.[8] also found the majority of cases of CADR were in the 21–30-year age group. The trend observed across these studies suggests that CADRs are more common in individuals in their 20s to early 40s, likely due to the higher representation of this demographic in the general population, as reflected in the population pyramid.

The present study found that out of 73 patients with CADRs, 33 (45.2%) were male and 40 (54.8%) were female, with a male-to-female ratio of 1:1.2. A similar pattern was observed in a study by Anant K. et al.[9] where out of 70 CADR cases, 23 (32.8%) were male and 47 (67.1%) were female, indicating a higher prevalence among females in both studies. The women experiencing higher risk of drug reactions may be linked to alteration of pharmacokinetics of drugs in females during menarche, pregnancy, lactation and menopause.

The most common morphological pattern of CADR in the current study was exanthematous eruption, observed in 35 cases (47.9%), followed by the SJS/TEN spectrum in 11 cases (15.1%) and fixed drug eruption (FDE) in 9 cases (12.3%). This finding is consistent with several other studies that also identified exanthematous or maculopapular eruptions as the most prevalent pattern. [2,8,10,11,12] A relatively higher proportion of SJS/TEN cases was noted in our study, which may be attributed to referral bias, as the study was conducted at a tertiary care center, where more severe, life-threatening CADRs are likely to be referred, while milder cases such as FDE or urticaria may be managed at primary or secondary care levels. In contrast, some other studies have reported FDE as the most common morphological presentation.[7,13,14,15]Since FDE is usually asymptomatic, patients with FDE tend to seek medical attention less often or may not be referred, which could explain why our study did not identify FDE as the most common reaction pattern, unlike the aforementioned studies.

The present study found that antimicrobials were the most frequently implicated drug group in cutaneous adverse drug reactions (CADRs), accounting for 35 cases (47.9%), followed by non-steroidal anti-inflammatory drugs (NSAIDs) with 27 cases (37%) and anticonvulsants with 5 cases (6.8%). In contrast, studies by Peyrière H et al.[16] and Sharma et al.[17] identified anticonvulsants as the most common causative agents. Similarly, Babu N et al.[12] reported that the most frequently implicated drugs in CADRs were amoxicillin (30%), diclofenac (23.3%), carbamazepine (20%), and phenytoin (16.7%).The higher incidence of CADRs associated with antimicrobials and NSAIDs in our study may be attributed to their over-the-counter availability, widespread use, and a lack of stringent regulation in dispensary practices. Among antimicrobial agents, cephalosporins were the leading subgroup, responsible for 20 cases (27.4%), followed by penicillins (8 cases, 11%) and fluoroquinolones (4 cases, 5.5%). Within the NSAID group, the most commonly implicated drugs were a combination of paracetamol and ibuprofen (11 cases, 15.1%), followed by nimesulide (6 cases, 8.2%).Ceftriaxone was more frequently implicated in CADRs than amoxicillin in our study, likely due to its broader spectrum of antimicrobial activity and its common empirical use.

In our study, the mean duration for the onset of cutaneous adverse drug reactions following drug administration was 3.27 days. Most patients developed CADRs within 1 to 2 days, with the overall onset range from 1 to 26 days. These findings are consistent with those of Beniwal et al.[13], who reported a typical onset of CADRs was 1 to 2 days, and Patel RM et al.[14], who observed the lesions appeared between 1 and 45 days after drug intake.

According to the Naranjo Adverse Drug Reaction (ADR) Causality Assessment Scale, the current study found that 42 cases (57.5%) had a definite (certain) association with the suspected drug, 21 cases (28.8%) were classified as probable, 8 cases (11%) as possible, and 2 cases (2.7%) as unlikely. In contrast, Sharma R et al.[17] evaluated 150 patients and reported that 116 cases (77.3%) had a probable ADR association, 19 cases (12.6%) had a definite (highly probable) association, and 15 cases (10%) had a possible association. Similarly, Hasan R et al.[11] found that 82.5% of cases were classified as probable, 12.5% as definite, and 5% as possible. The differences in Naranjo scale assessments between our study and previous research may be attributed to factors such as variations in responses to the questionnaire, the prevalence of polypharmacy, self-medication practices, and differences in the accuracy of patients' recall.

When comparing our findings with both recent and earlier studies, we observe a diverse range of morphological patterns in cutaneous adverse drug reactions (CADRs). As therapeutic indications evolve and new pharmacological agents are introduced, the spectrum of drugs associated with adverse reactions continues to shift over time.

Difficulty in identifying the culprit drug when patients were under multiple medications and availability of limited definitive laboratory tests was some of the limitations we faced in calculating the prevalence of acute drug reactions and identifying the culprit drug and type of lesion.

Conclusion

Cutaneous adverse drug reactions (CADRs) observed in our study demonstrated a wide clinical spectrum, ranging from self-limiting maculopapular eruptions to life-threatening conditions such as toxic epidermal necrolysis (TEN) and acneiform eruptions. The most frequently observed morphological pattern was exanthematous eruption, followed by Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), urticarial eruptions, and fixed drug eruptions (FDE). Antimicrobials were the most commonly implicated drug class, followed by non-steroidal anti-inflammatory drugs (NSAIDs), with both categories associated with reactions ranging from mild to severe. These findings highlight the critical need for judicious and evidence-based prescribing practices, especially when using high-risk medications.

Recommendation: Adverse cutaneous drug reactions (ACDRs) may occur in any patient and are commonly associated with frequently prescribed medications. These reactions exhibit a broad spectrum of clinical manifestations. In our clinical setting, the diagnosis of ACDRs relies primarily on careful clinical evaluation. Recognition of cutaneous drug eruptions plays a critical role in both the diagnosis and management of drug-induced adverse events. Since early detection and prompt identification of the offending agent are pivotal for effective treatment and prevention of severe reactions, it is essential that clinicians possess a thorough understanding of ACDRs and their diverse presentations to ensure timely and optimal patient care.

Conflict of Interest: The authors declare no conflict of interest

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References

1. Nayak S, Acharjya B. Adverse cutaneous drug reaction Indian J Dermatol. 2008; 53:2–8. PMID: 19967009 DOI: 10.4103/0019-5154.39732
2. Modi A, Desai M, Shah S, Shah B. Analysis of cutaneous adverse drug reactions reported at the regional ADR monitoring center. Indian J Dermatol. 2019;64(3):250. PMID: 31148872 DOI: 10.4103/ijd.IJD_682_16.
3. Alomar MJ. Factors affecting the development of adverse drug reactions. Saudi Pharm J. 2014;22(2):83-94. PMID: 24648818 DOI: 10.1016/j.jsps.2013.02.003
4. Jha N, Alexander E, Kanish B, Badyal DK. A Study of Cutaneous Adverse Drug Reactions in a Tertiary Care Center in Punjab. Indian Dermatol Online J. 2018 Oct;9(5):299–303. PMID: 30258795 DOI: 10.4103/idoj.IDOJ_81_18.

5. Naranjo CA et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther Aug 1981; 30(2):239-45. PMID: 7249508.DOI: 10.1038/clpt.1981.154.
6. Bigby M. Rates of cutaneous reactions to drugs. Arch Dermatol. 2001;137(6):765–70. PMID: 11405768
7. Sharma R, Dogra D, Dogra N. A study of cutaneous adverse drug reactions at a tertiary center in Jammu, India. Indian Dermatol Online J. 2015;6(3):168. PMID: 26009710. DOI: 10.4103/2229-5178.156384
8. Neupane S, Basnet B. Cutaneous adverse drug reactions: a four-year study from western Nepal. J-GMC-N. 2017;10(2):21-6. DOI:10.3126/jgmcn.v10i2.20804
9. Anant K, Chaukimath SP, Ajit J, Leela H. A Study of Cutaneous Adverse Drug Reactions; Clinical/Morphological Pattern & Causative Agents Reported in an ADR Monitoring Centre in a Tertiary Care Hospital of North Karnataka. Biomed Pharmacol J. 2020;13(3):1549-54. DOI : https://dx.doi.org/10.13005/bpj/2029
10. Dubey AK, Prabhu S, Shankar PR, Subish P, Prabhu MM, Mishra P. Cutaneous adverse drug reactions to modern medicines and initial experiences from a spontaneous adverse drug reaction reporting program in a tertiary care teaching hospital of Western Nepal. J. Pakistan Assoc. Dermatologists. 2005;15(3):222-6.
11. Hasan R, Akhtar N, Begum M, Ali ME, Paul HK, Zakaria AS, et al. Cutaneous morphological patterns of adverse drug reactions: a study of 50 cases. J. Pakistan Assoc. Dermatologists. 2010;20(4):206-11.
12. Babu N, Mahantheswarappa Y, Thimmappa RM, Eshwarappa VH, Shankarbharathi A, Kundu P. A study of cutaneous morphological patterns of adverse drug reactions in tertiary care center, Chitradurga, Karnataka, India. Int J Res Dermatol 2020;6(4):499-501. DOI: http://dx.doi.org/10.18203/issn.2455-4529.IntJResDermatol20202654
13. Beniwal R, Gupta LK, Khare AK, Mittal A, Mehta S, Balai M. Clinical profile and comparison of causality assessment tools in cutaneous adverse drug reactions. Indian Dermatol Online J. 2019;10(1):27. PMID: 30775295 DOI: 10.4103/idoj.IDOJ_207_18
14. Patel RM, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol VenereolLeprol. 2008;74(4):430. PMID: 18810845 DOI: 10.4103/0378-6323.42883
15. David P, Devinder MT. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care center in South India. Indian J Dermatol Venereol-Leprol. 2004;70(1):20-4. PMID: 17642552.
16. Peyrière H, Dereure O, Breton H,et al. Network of the French Pharmacovigilance Centers. Variability in the clinical pattern of cutaneous side effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2006;155(2):422-8. PMID: 16882184 DOI: 10.1111/j.1365-2133.2006.07284.x
17. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents--a 6 year series from Chandigarh, India. J Postgrad Med. 2001;47(2):95-9. PMID: 11832597.