Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 6, 2021

Original Research Article

A STUDY OF CLINICAL MANIFESTATIONS OF CUTANEOUS ADVERSE DRUG REACTIONS

Rachakonda Ramesh [1], Bandhavi Karri [2]

1. **Associate Professor, Department of Dermatology, Prathima Institute of Medical Sciences, Nagunur, Karimnagar, Telangana State.**
2. **Assistant Professor, Department of Dermatology, Prathima Institute of Medical Sciences, Nagunur, Karimnagar, Telangana State.**

Corresponding Author: Dr. Bandhavi Karri, Email: drbandhavi@gmail.com

Abstract

Background: Adverse cutaneous drug reactions span from minor maculopapular rashes to severe conditions like toxic epidermal necrolysis, which can be life-threatening. Currently, there are no specific laboratory tests or confirmatory drug screenings to identify the causative drug. Therefore, diagnosis largely relies on clinical judgment in most cases.

Methods: Conducted at the Department of Dermatology of Prathima Institute of Medical Sciences, Naganur Karimnagar. The study included patients presenting to the Dermatology Outpatient Department and those admitted with suspected cutaneous adverse drug reactions to systemic medications. Detailed clinical histories, including drug intake, were recorded for each patient. Causality assessment followed WHO definitions, and data were analyzed using SPSS software.

Results: A total of 65 patients were included in the study and the mean age of the cohort was 29.55 ± 6.25 years. *A slight peak in young adults***:** The 21-30 age group has the highest frequency (20 individuals, 30.77%) and the 41-50 age group follows closely (16 individuals, 24.61%). Antibiotics: The leading cause in both genders, with 19 cases (29.23%) in females and 13 (20.00%) in males, totaling 32 (49.23%). Nonsteroidal anti-inflammatory drugs (NSAIDs): 7 cases (10.77%) in females and 6 (9.23%) in males, totaling 13 (20.00%). Less common categories: Anticonvulsants: 5 cases (7.69%), primarily in females (3). Disease-modifying antirheumatic drugs (DMARADs): 5 cases (7.69%), only observed in females. Other categories: Antidepressants, diuretics, antipsychotics, mood stabilizers, antitubercular therapy (ATT), proton pump inhibitors (PPIs), antifungals, and allopurinol each had 1-2 cases, with some limited to one specific gender.

Conclusion: Exanthematous eruptions and fixed drug eruptions were the most common, followed by photosensitivity and urticaria. Less frequent reactions included Steven Johnson syndrome and pigmentation changes. Antibiotics and NSAIDs emerged as the leading culprits, potentially due to their widespread use and known risk profiles. Anticonvulsants, DMARADs, and other categories contributed to a smaller proportion of cases. The itching was the most prevalent symptom, followed by burning sensations/pain and no associated symptoms.

Keywords: Cutaneous drug eruptions, Antibiotics, NSAIDs, Disease-modifying antirheumatic drugs (DMARADs)

Introduction

An adverse cutaneous drug reaction (ACDR), commonly known as "Drug eruption," refers to any undesired alteration in the skin, its appendages, or mucous membranes, encompassing all adverse events associated with drug eruptions, regardless of their cause [1]. ACDRs represent the most frequent type of adverse drug reactions, accounting for approximately 24% in one study and 29% in another [2, 3]. The incidence of drug eruptions is often underestimated, as many mild and transient eruptions go

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 6, 2021

unrecorded, and skin disorders are sometimes incorrectly attributed to drugs. In developed countries, the incidence of ACDRs among inpatients ranges from 1 to 3% [4, 5], while in developing nations like India, some studies estimate it to affect 2 - 5% of inpatients [6-9]. According to the World Health Organization (WHO), about 2% of all ACDRs are deemed "serious," and only a small fraction are fatal [10]. The relative incidence rate of ACDR among new patients visiting dermatology outpatient departments was found to be 2.05 per 1000 in a study by Abanti S et al [11].

Clinically, ACDRs may present as pruritus, urticaria, laryngeal edema, bronchospasm, and even anaphylactic shock with hypotension and, in severe cases, potentially death. Immediate reactions occur within minutes of drug administration, while accelerated reactions occur within hours or days and typically manifest as urticarial but may include laryngeal edema. Penicillins are the most common cause of IgE-dependent drug eruptions. [12] Regular monitoring and reporting of adverse drug reactions (ADRs) are crucial for maintaining patient safety and quality of life. It also contributes to cost-saving for both patients and healthcare institutions. By reporting known or suspected ADRs, pharmacists, healthcare practitioners, and patients can assist in identifying patterns and trends, potentially leading to increased regulatory scrutiny or even the withdrawal of drugs with unfavorable risk-benefit ratios. Various reporting agencies worldwide are engaged in monitoring ADRs. This prospective study aimed to explore the clinical spectrum of cutaneous adverse drug reactions, identify the responsible drugs, and assess their preventability.

Material and Methods

This prospective study was done in the Department of Dermatology with the utilization of the services of the Department of Microbiology for the identification of the fungal strains in Prathima Institute of Medical Sciences, Naganoor, Karimnagar, Telangana state. Institutional ethical approval was obtained for the study. Written consent was obtained from all the participants of the study after explaining the nature of the study in vernacular language.

Inclusion criteria

1. Patients with skin and mucosal lesions following exposure to medications
2. Aged 18 years and above
3. Males and females
4. Willing to participate in the study voluntarily

Exclusion criteria

1. Cutaneous reactions due to topical medications
2. Not as per the inclusion criteria

Data collection utilized a predefined form containing demographic information and a comprehensive clinical history. This history encompassed details such as drug intake, onset of reaction, prior history of drug reactions, duration of reaction, type of cutaneous reaction, and response to dechallenge. To exclude infectious causes, relevant investigations were conducted. A reaction was deemed preventable if previous exposure to the suspected causative drug(s) or a related medication had led to a skin eruption. Each case underwent causality assessment according to WHO definitions, categorized as ‘certain’, ‘probable’, ‘possible’, ‘unlikely’, ‘conditional/ unclassified’, or ‘unassessable/unclassifiable’2. Only cases classified as ‘certain’ or ‘probable’ were included in the analysis.

Statistical analysis: All the available data was analyzed and uploaded to an MS Excel spreadsheet and analyzed by SPSS version 19 in Windows format. The continuous variables were represented as mean, standard deviations, and percentages. The categorical variables were represented as p values obtained by application of Fischer’s Exact test and values of (<0.05) were considered as significant.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 6, 2021

Results

A total of n=65 cases were found and included in the study. Out of n=65 cases, n=40 (61.54%) were females and n=25(38.46%) were males. Table 1 shows the distribution of patients with adverse cutaneous drug reactions (ACDRs) across different age groups in a study of 65 participants. The distribution seems relatively even across different age groups, with no single group dominating the mean age of the cohort was 29.55 ± 6.25 years. *A slight peak in young adults***:** The 21-30 age group has the highest frequency (20 individuals, 30.77%) and the 41-50 age group follows closely (16 individuals, 24.61%). *Gradual decline with increasing age:* The frequency of cases gradually decreases in older age groups, with the lowest occurring in the 61-70 age group (4 individuals, 6.15%). Younger individuals might use more medications overall, including those with higher risks of ACDRs. Age-related changes in the immune system could influence susceptibility to drug reactions. Older adults might be less likely to seek healthcare for mild ACDRs, leading to underrepresentation in the study.

Table 1: Showing the age-wise distribution of Adverse cutaneous drug reactions included in the study

Age group	*Frequency*	*Percentage*
18 – 20	4	6.15
21 – 30	20	30.77
31 – 40	15	23.07
41 – 50	16	24.61
51 – 60	6	9.23
61 – 70	4	6.15
Total	65	100

Table 2 shows the distribution of different types of cutaneous drug reactions (CDRs) observed in 65 study participants. Exanthematous was seen in (32 cases, 49.23%). Fixed drug eruption occurs in (13 cases, 20.00%). Photosensitivity was seen in (5 cases, 7.69%). Urticaria: Hives characterized by raised, itchy welts (5 cases, 7.69%). Steven Johnson syndrome (SJS) was in (2 cases, 3.08%). Pigmentation was seen (2 cases, 3.08%). Other: Pruritus (itching), purpura (bruising), aciniform pustulosis (pustules), urticarial vasculitis (inflammation of blood vessels with hives), lichenoid (scaly papules), and erythroderma (widespread reddening) each occurred in only one case (1.54%).

Table 2: Clinical pattern of cutaneous drug reactions in n=65 cases of study

Type of drug reaction	*Frequency*	*Percentage*
Exanthematous	32	49.23
Fixed drug eruption	13	20.00
Photosensitivity	5	7.69
Urticaria	5	7.69
Steven Johnson syndrome	2	3.08
Pigmentation	2	3.08
Pruritus	1	1.54
Purpura	1	1.54
Acneiform eruptions	1	1.54
Urticarial vasculitis	1	1.54
Lichenoid	1	1.54
Erythroderma	1	1.54
Total	65	100.0

This table shows the distribution of different medications responsible for cutaneous adverse drug reactions (CADRs) in 65 study participants. Antibiotics: The leading cause in both genders, with 19 cases (29.23%) in females and 13 (20.00%) in males, totaling 32 (49.23%). Nonsteroidal anti-inflammatory drugs (NSAIDs): 7 cases (10.77%) in females and 6 (9.23%) in males, totaling 13 (20.00%). Less common categories: Anticonvulsants: 5 cases (7.69%), primarily in females (3).

Disease-modifying antirheumatic drugs (DMARADs): 5 cases (7.69%), only observed in females. Other categories: Antidepressants, diuretics, antipsychotics, mood stabilizers, antitubercular therapy (ATT), proton pump inhibitors (PPIs), antifungals, and allopurinol each had 1-2 cases, with some limited to one specific gender. Women might generally use more medications, including those with higher risks of CADRs, or be more likely to report them. Certain medications or drug interactions might be more likely to cause CADRs in females due to hormonal factors. Different drug classes have varying risks of CADRs, with antibiotics and NSAIDs known to be frequent culprits.

Table 3: Drugs causing cutaneous adverse drug reactions

	Females	*Males*	*Total (%)*
Antibiotics	19	13	32
NSAIDs	7	6	13
Anticonvulsant	3	2	5
DMRAD	5	0	5
Antidepressant	1	1	2
Diuretics	2	0	2
Antipsychotic	1	0	1
Mood stabilizer	1	0	1
ATT	0	1	1
PPI	1	0	1
Antifungal	0	1	1
Allopurinol	0	1	1
Total	40	25	65

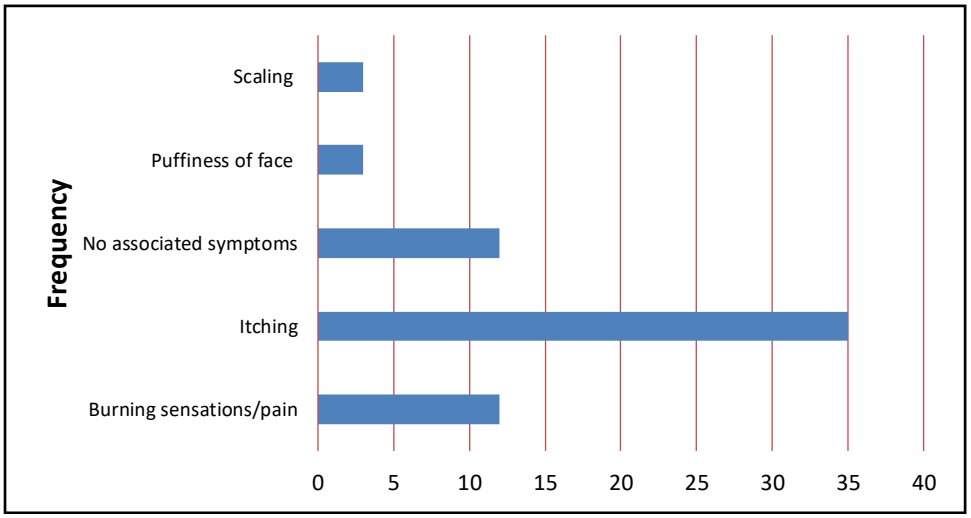

Figure 1: Associated symptoms of n=65 cases of ADRS reported in the study

Figure 1 displays the distribution of associated symptoms experienced by participants in a study of adverse drug reactions (ADRs). ***Most common symptoms:*** Itching is the most prevalent symptom, affecting over half (53.84%) of the participants. Burning sensations/pain and no associated symptoms are equally common, occurring in around 18.46% of cases each. ***Less common symptoms:*** Puffiness of the face and scaling are less frequent, affecting only 4.61% of participants each. The high prevalence of itching suggests allergic or irritant reactions as potential mechanisms for many ADRs. Burning sensations/pain could indicate inflammation

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 6, 2021

or nerve-related side effects of certain medications. The presence of no associated symptoms in some cases highlights the diverse presentations of ADRS, where not everyone experiences noticeable symptoms. Less common symptoms like puffiness of the face and scaling might be associated with specific drug classes or individual susceptibilities.

Table 4: Showing the Elevated Absolute eosinophil count in n=28 out of n=65 cases of ADRs

Clinical presentation	*AEC > 440*	*Percentage*
Acneiform eruptions (n=1)	1	100.0
Erythroderma (n=1)	1	100.0
Exanthematous (n=32)	16	50.00
Fixed drug eruption (n=13)	6	46.15
Urticaria (n=5)	2	40.00
Steven Johnson syndrome (n=2)	2	100.0

Table 4 shows the association between specific clinical presentations of adverse drug reactions (ADRs) and elevated absolute eosinophil count (AEC > 440) in a study of 65 participants. *Elevated AEC:* A total of 28 out of 65 cases (43.08%) had elevated AEC. All cases of aceniform eruptions and erythroderma had elevated AEC (100%). Over half of the cases with exanthematous eruptions (50%) and Steven Johnson syndrome (100%) had elevated AEC. Around 46% of fixed drug eruption cases and 40% of urticaria cases had elevated AEC. Presentations like acneiform eruptions, erythroderma, and Steven Johnson syndrome are known to be associated with eosinophilic involvement, explaining the high association with elevated AEC.

Discussion

Adverse drug reactions can be categorized into immunologic and non-immunologic causes, with the majority resulting from predictable, non-immunologic effects. Early diagnosis of cutaneous adverse drug reactions (CADRs) is crucial to mitigate morbidity and mortality associated with these reactions, as severe cases can occasionally be fatal. We utilized the WHO causality definitions to classify CADRs, as this method is straightforward and widely recognized. The average age of our patients was 29.55 ± 6.25 years, which aligns with the results of a study conducted in Malaysia [13], although it was younger compared to findings from studies conducted in France [14] and Italy [15]. Our study showed a higher proportion of female patients. In contrast, several other studies have reported a higher involvement of males [14, 16, 17]. The majority of our patients fell within the 21 to 40 age group, which is consistent with findings from other studies [16, 18]. This observation is in line with the results reported by Dimri D et al. [18] and Gonzalez Martin G et al. [19]. However, some studies have suggested that CADRs are more common in younger children and older adults due to immune system dysfunction and decreased drug metabolism [20]. Older patients often consume a larger number of medications, leading to an increased incidence of drug reactions. Approximately seven percent of our patients were aged over 60 years.

Our study revealed a broad clinical spectrum of cutaneous adverse drug reactions, of different types. The most frequently observed reaction type was exanthematous, consistent with findings reported by several other authors [4,8,12,15-17]. Following exanthematous reactions, fixed drug eruption emerged as the second most common type, which aligns with the findings of Patel RM et al. [18]. Notably, Pudukadan D et al. have similarly identified fixed drug eruption as the most prevalent type [19]. Antimicrobials emerged as the most frequently

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 6, 2021

implicated drug category in cutaneous adverse drug reactions (CADRs), a finding consistent with observations made by several authors [17, 21]. Among antimicrobials, antibiotics stood out as the primary cause of CADRs in our study, a trend similarly reported by other researchers. [22]. Specifically, cefixime was identified as the most common culprit in CADRs within our study cohort. Contrastingly, cotrimoxazole has been identified as the primary causative agent in other investigations. [23, 24]. Notably, antibiotics in our study were associated with both non-serious and serious CADRs, including Stevens-Johnson Syndrome (SJS). In a study by Kacalak-Rzepka et al., NSAIDs were found to induce adverse events most frequently [25]. Conversely, anticonvulsants were identified as the primary culprits in the majority of cutaneous adverse drug reactions (CADRs) in a study by Botelho LF et al., accounting for approximately 24% of cases [26]. Within our investigation, antibiotics were predominantly linked to exanthematous drug reactions, representing 69% of cases. This aligns with findings by Sharma VK et al., who noted anticonvulsants as the most common group of drugs implicated in exanthematous reactions [17]. Furthermore, in our study, fixed drug eruption (FDE) was most frequently caused by NSAIDs, whereas sulfonamides emerged as the predominant drug group implicated in FDE according to observations by Sharma VK et al. [17]. In our study, the overall incidence of cutaneous adverse drug reactions (ADRs) was determined to be 0.43%. This finding closely resembled that of a survey conducted in France [14]. However, a higher incidence rate was reported in a study conducted in India [16]. Notably, the reported incidence of CADR in Mid-Western Nepal was notably higher at 1.6% [27]. Serious CADRs were identified in approximately 9% of our cases, compared to 24% in Mid-Western Nepal [27] and 16.5% observed by Tuchinda P et al. [22]. Higher incidence rates of serious CADRs have been documented by other authors as well [14, 16]. Within our study, Stevens-Johnson syndrome (SJS) emerged as the most common type of serious CADR, a trend consistent with observations by other authors [27]. Notably, anticonvulsants were identified as the commonest drug group involved in serious CADR in our study, a pattern similarly observed in other studies [17, 26].

Conclusion

This study found that young adults (21-30) showed a slight peak in ADR prevalence, possibly due to higher medication use or age-related immune system changes. Exanthematous eruptions and fixed drug eruptions were the most common, followed by photosensitivity and urticaria. Less frequent reactions included Steven Johnson syndrome and pigmentation changes. Antibiotics and NSAIDs emerged as the leading culprits, potentially due to their widespread use and known risk profiles. Anticonvulsants, DMARADs, and other categories contributed to a smaller proportion of cases. The itching was the most prevalent symptom, followed by burning sensations/pain and no associated symptoms. Puffiness of the face and scaling were less common. A significant association was observed between elevated AEC and specific presentations like acneiform eruptions, erythroderma, and Steven Johnson syndrome, suggesting a potential role of eosinophils in these reactions.

References

1. Surajit Nayak, Basanti Acharjya. Adverse cutaneous drug reaction. Indian J Dermatol 2008:53(1):2 – 8
2. Bordet R, Gautier S, Le Louet H et al. Analysis of the direct cost of adverse drug reactions in hospitalized patients. Eur J Clin Pharmacol 2001; 56: 935 - 41.
3. Thiessard F, Roux E, Miremont-Salamé G et al. Trends in spontaneous adverse drug reaction reports to the French pharmacovigilance system (1986–2001). Drug Saf 2005; 28: 731 – 40.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 6, 2021

4. Bigby M. Rates of cutaneous reactions to drugs. Arch Dermatol 2001;137:765 - 70.
5. Craig KS, Edward WC, Anthony AG. Cutaneous drug reactions. Pharmacol Rev 2001; 53:357 - 79.
6. Noel MV, Sushma M, Guido S. Cutaneous adverse drug reactions in hospitalized patients in a tertiary care center. Indian J Pharmacol 2004; 36:292 - 95.
7. Uppal R, Jhaj R, Malhotra S. Adverse drug reactions among in patients in a North Indian referral hospital. Natl Med J India 2000; 13:16 - 18.
8. Jhaj R, Uppal R, Malhotra S, Bhargava VK. Cutaneous adverse reactions in inpatients in a tertiary care hospital. Indian J Dermatol Venereol Leprol 1999; 65:14 - 17.
9. Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care center in South India. Indian J Dermatol Venereal Leprol 2004; 70:20 - 24.
10. Wiffen P, Gill M, Edwards J, Moore A. Adverse drug reactions in hospital patients: A systematic review of the prospective and retrospective studies. Bandolier Extra 2002:1 - 16.
11. Abanti S, Das NK, Hazra A, Gharami RC, Chowdhury SN, Datta PK. Cutaneous adverse drug reaction profile in a tertiary care outpatient setting in Eastern India. Indian J Pharmacol 2012; 44:792 - 77.
12. Bhattacharya S. The facts about penicillin allergy: a review. J Adv Pharm Technol Res. 2010 Jan;1(1):11-7.
13. Ding WY, Lee CK, Choon SE. Cutaneous adverse drug reactions were seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2010; 49: 834–41.
14. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stucco C, Crickx B, et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. Brit J Dermatol. 2003; 149: 1018-22.
15. Naldi L, Conforti A, Venegoni M, Grazia Tronco M., Caputi, A, Ghiotto E, et al. Cutaneous reactions to drug: An analysis of spontaneous reports in four Italian regions. Br J Clin Pharmacol. 1999; 48: 839–46.
16. Sushma M, Noel MV, Ritika MC, James J, Guido S. Cutaneous adverse drug reactions: A 9-year study from a South Indian Hospital. Pharmacoepidemiol Drug Saf. 2005; 14(8): 567-70.
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): 95-99.
18. Dimri D, Raina RS, Thapliyal S, Thawani V. Retrospective analysis of pattern of cutaneous adverse drug reactions in Tertiary Hospital of Pauri Garhwal. J Clin Diagn Res. 2016; 10(5): FC01-06.
19. Gonzalez-Martin G, Caroca CM, Paris E. Adverse drug reactions (ADRs) in hospitalized pediatric patients. A prospective study. Int J Clin Pharmacol Ther. 1998; 36(10): 530–33.
20. Schmitt LC. Drug reactions in the elderly. Cutis 1988; 41: 58e60.
21. Chattopadhyay C, Chakrabarti N. A cross-sectional study of cutaneous drug reactions in a private Dental College and Government Medical College in Eastern India. Niger J Clin Pract. 2012; 15(2): 194-98.
22. Tuchinda P, Chularojanamontri L, Sukakul T, Thanomkitti K, Nitayavardhana S, Jongjarearnprasert K, et al. Cutaneous adverse drug reactions in the elderly: A retrospective analysis in Thailand. Drugs Aging. 2014; 31(11): 815-24.
23. Patel RM, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol. 2008; 74(4): 430.
24. 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(1): 20-24.
25. Kacalak-Rzepka A, Klimowicz A, Bielecka-Grzela S, Załuga E, Maleszka R, Fabiańczyk H. Retrospective analysis of adverse cutaneous drug reactions in patients hospitalized in Department of Dermatology and Venereology of Pomeranian Medical University in 1996-2006. Ann Acad Med Stetin. 2008; 54(2): 52-8.

ISSN: 0975-3583, 0976-2833 VOL 12, ISSUE 6, 2021

26. Botelho LF, Porro AM, Enokihara MM, Tomimori J. Adverse cutaneous drug reactions in a single quaternary referral Hospital. Int J Dermatol. 2016; 55(4): e198-203.
27. Neupane S, Sharma SR. Cutaneous adverse drug reactions: A 6-month Teaching Hospital based study from mid-Western Nepal. J Clin Diagn Res. 2012 May (Suppl-1); 6(3): 445-448.