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Original Research Article

Patterns of Cutaneous Adverse Drug Reaction at a Tertiary Care Hospital, Central India, MP

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Abstract: Aim of this prospective, hospital based study is to determine the pattern of cutaneous adverse drug reactions (ADRs) and their causative drugs. The study was conducted in the department of Pharmacology and department of Medicine, at SS Medical College and associated SGM Hospital, Rewa, MP between Oct 2014 to Sept 2015; a total 130 cases were enrolled with suspected ADRs after taking written informed consent. In this study maximum (25%) patients were belonged to 18-25 years of age group, of these 55% were males and 45% females. Mean (± SD) age of these patients was 34.84 ± 20.99 years. The skin and mucous membrane are most commonly (52.29%) affected organ system with the suspected ADRs followed by central nervous system (9.19%) and gastrointestinal system (8.62%). Among the cutaneous ADRs; maximum 51.64% were skin rashes followed by 29.67% pruritus, 5.49% oral ulcers, 3.29% Stevens-Johnson syndrome (SJS), 2.19% bullous eruption, 2.19% swelling lips, 2.19% TEN, 1.09% oral candidiasis, 1.09% red man syndrome and 1.09% hair changes. Of these ADRs; most were associated with use of antimicrobials (82.41%) followed by NSAIDs (14.28%). Amongst AMAs maximum 20.97% were associated with fluoroquinolones followed by 18.68% cephalosporin, 10.98% penicillin and 5.49% sulphonamide. In this study skin and mucous membrane are most commonly (52.29%) affected organ system; skin rashes and pruritus are the most common cutaneous ADRs and majority of cases were associated with use of antimicrobials include fluoroquinolones and cephalosporins. The major drawback of this study is it's under reporting of ADRs; hence our study does not yield the exact incidence of suspected ADRs.
Keywords: Cutaneous adverse drug reactions (CADR); Skin rashes; Toxic epidermal necrolysis (TEN); Stevens-Johnson syndrome (SJS).

INTRODUCTION:

An adverse drug reaction as defined by WHO is a "response to a medicinal product which is noxious, unintended and occurs at dosage normally used in men for the prophylaxis, diagnosis or treatment of disease or for the restoration, correction or modification of physiological function [1]. According to center for health policy research, more than 50% of the approved drugs in the United States were associated with some type of adverse effects not detected prior to the approval [2]. At least one ADR has been reported to occur in 10 to 20% of hospitalized patient [3]. Recent epidemiological studies estimated that ADRs are fourth to sixth leading cause of death, [4] though some researcher implicated as they are 7th common cause of death [5].

Although many of the ADRs are relatively mild and disappear when drug is stopped or dose is reduced, others are more serious and last longer [6, 7]. The commonest organ system involved in occurrence of suspected ADRs was skin and mucous membrane as reported by several studies [8-12]. A cutaneous adverse reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompass all adverse events related to drug eruption, regardless of the etiology. Drug reactions can be classified into immunologic and non-immunologic etiologies. The majority (75-80%) of

adverse drug reactions are predictable, non-immunologic and the remaining 20-25% are unpredictable that may or may not be immune-mediated [13]. Immune-mediated reactions account for 5-10% of all drug reactions and constitute drug allergies falling into this category [14, 15].

Cutaneous adverse drug reactions (ADR) can be caused by a wide variety of agents. They are responsible for approximately 3% of all disabling injuries during hospitalization and complications of drug therapy are the most common type of adverse event in hospitalized patients. Many of the commonly used drugs have reaction rates above one percent [16]. There is a wide spectrum of cutaneous ADR ranging from a transient maculopapular rash to fatal toxic epidermal necrolysis (TEN) [17]. The pattern of cutaneous ADR and the drugs responsible for them is changing every year. The reported percentage of cutaneous ADR that are potentially serious are varies greatly but is probably about 2 percent. Hence, we had tried to assess the clinical pattern, spectrum, frequency and severity of suspected cutaneous ADRs and their co-relation with specific drug group in ICU and ward admitted patients in Department of Medicine of Sanjay Gandhi Memorial Hospital, Rewa (M.P.).

MATERIAL & METHODS:

This study was carried out in the Department of Pharmacology, after getting approval from institutional ethical committee. The data of suspected ADRs were recorded in a specially designed proforma (CDSCO ADR reporting form) from October 2014 to September 2015; in ICU and ward admitted patients at the department of Medicine of SGM Hospital, Rewa (M.P.). Total 130 patients were enrolled in study that was presented with suspected ADRs. For each patient with suspected ADR, a detailed history including drug history, personal history, family history, present and past medical history and history of previous drug allergy were documented after taking written informed consent. The any untoward event was labeled as adverse drug reaction after discussion with the treating physician. To establish the etiologic agent for a particular type of reaction, attention was paid to the drug history, temporal correlation with the drug, duration of the rash, approximate incubation period, morphology of the eruption, associated mucosal or systemic involvement, improvement of lesions on withdrawal of drug and recurrence of lesion on rechallenge. In case of more than one drug was thought to be responsible, the most likely offending agent was noted and the impression was confirmed by subsidence of the rash on withdrawing the drug. Clinical evaluations were done to assess the clinical pattern, frequency and severity of suspected cutaneous ADRs and involvement of therapeutic drug classes. The data were analyzed by using Microsoft Office Excel sheet 2007 and expressed in form of number and percentage.

RESULTS:

In this study total 130 patients were enrolled, of these maximum (25%) patients were belonged to the 18-25 years of age group, in which 55% were males and 45% were females. Among males maximum 26% were belonged to 18-25 years and 41-60 years of age group. In females maximum 35% were belonged to 26-40 years of age. The mean (± SD) age of these patients was 34.84 ± 20.99 years. (Figure-1)

Among the affected organ system**, s**kin and mucous membrane were most commonly (52.29%) involved in development of ADRs followed by central nervous system (9.19%), gastrointestinal system (8.62%), respiratory system (4.59%), hepatobiliary system (1.72%) and others (17.24%) which includes – tinnitus, visual disturbances, fever, rigor, weight gain and dryness of mouth. (Figure-2) Among the suspected cutaneous ADRs reported in this study; maximum 51.64% was skin rashes, followed by 29.67% pruritus, 5.49% oral ulcers, 3.29% Stevens-Johnson syndrome (SJS), 2.19% bullous eruption, 2.19% swelling lips, 2.19% toxic epidermal necrolysis (TEN), 1.09% oral candidiasis, 1.09% red man syndrome and 1.09% hair changes. (Table-1) Among the total suspected ADRs; most of these were associated with use of antimicrobials (68%) followed by NSAIDs (10.0%), haematinics (10.0%), antihypertensive (3.12%), antianginal, anti-epileptics, oral hypoglycemics, corticosteroids (1.8%) and ionotrops were associated with 1.25% of ADRs. (Table-2) Among the cutaneous ADRs only; maximum (82.42%) were related with use of antimicrobials followed by 14.28% with NSAIDS, 2.19% steroids and 1.09% were seen with anticonvulsant drugs.(Table-2)/(Figure-3) Amongst AMAs maximum 20.97% of cutaneous ADRs were associated with the use of fluoroquinolones followed by 18.68% cephalosporin, 10.98% penicillin, 5.49% sulphonamide, 4.39% antimalarial, 4.39% antiamoebic, minimum with 1.09% antifungal and 15.38% with other drugs which includes doxycycline, tetracycline, meropenem, vancomycin, nevirapine and albendazole.(Table-3)

OBSERVATIONS:

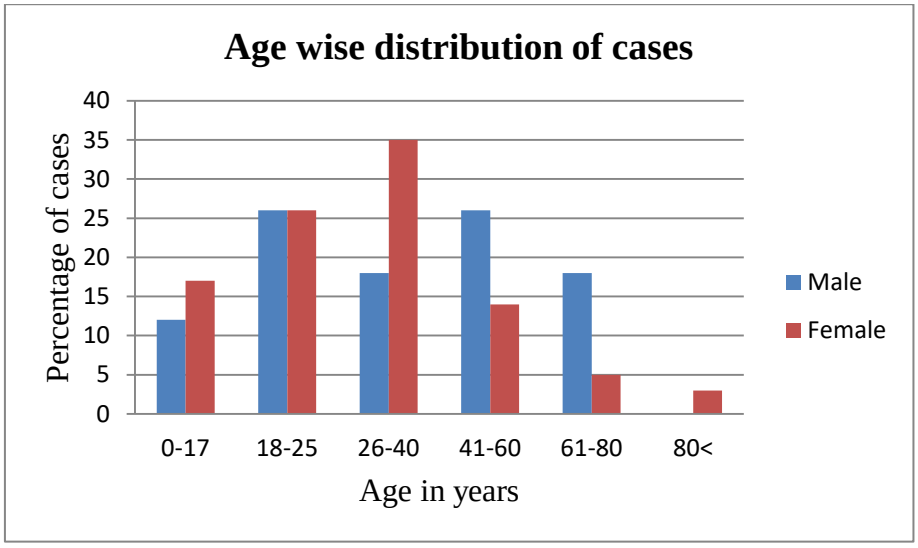

Fig 1: Age wise distribution of cases.

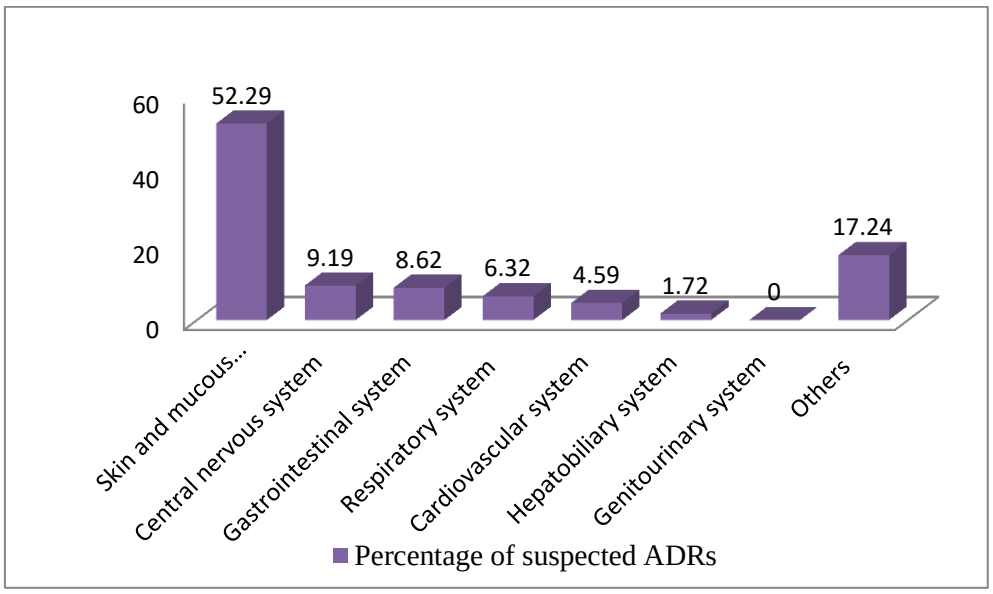

Fig 2: Percentage distribution of suspected ADRs according to the affected organ system.

Table 1: Frequency distribution of suspected cutaneous ADRs during study period

Suspected ADRs	Frequency of suspected cutaneous ADRs					
	Male		Female		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Skin rashes	31	49.20%	16	57.14%	47	51.64%
Pruritus	20	31.74%	07	25.0%	27	29.67%
Oral ulcers	04	6.34%	01	3.57%	05	5.49%
SJS*	02	3.17%	01	3.57%	03	3.29%
Bullous eruption	02	3.17%	00	00%	02	2.19%
Swelling lips	01	1.58%	01	3.57%	02	2.19%
TEN**	01	1.58%	01	3.57%	02	2.19%
Red man syndrome	01	1.58%	00	00%	01	1.09%
Oral candidiasis	01	1.58%	00	00%	01	1.09%
Hair changes	00	00%	01	3.57%	01	1.09%
Total	63	69.23%	28	30.76%	91	100

* SJS =Stevens-Johnson syndrome ** TEN= toxic epidermal necrolysis

Table 2: Comparison of distribution of total and cutaneous suspected ADRs according to drug classes.

Class of drugs causing suspected ADRs	Total and Cutaneous ADRs reported during study			
	All total ADRs		Cutaneous ADRs	
	Number	Percentage	Number	Percentage
Anti-microbials	109	68.12%	75	82.41%
NSAIDS	16	10.00%	13	14.28%
Hematinics	16	10.00%	00	00%
Antihypertensive	5	3.12%	00	00%
Antianginal	3	1.87%	00	00%
Antiepileptics	3	1.87%	01	1.09%
Hypoglycemic drugs	3	1.87%	00	00%
Corticosteroids	3	1.87%	02	2.19%
Inotrops (Digitalis)	2	1.25%	00	00%
Total	160	100	91	100

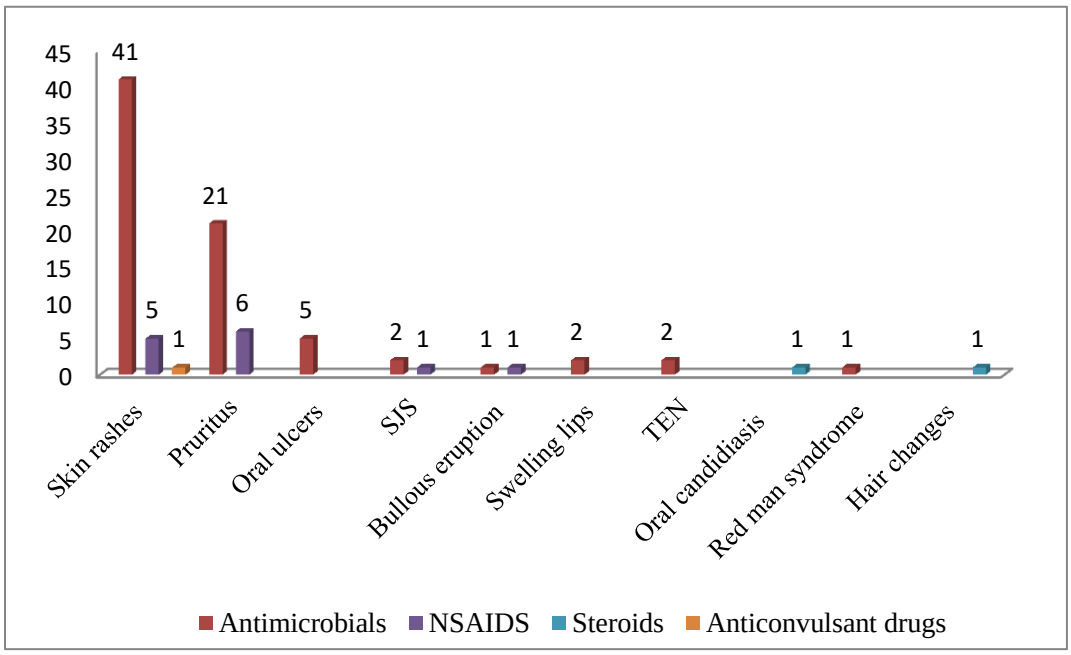

Fig 3: Frequency of total suspected cutaneous ADRs (in numbers) produced by different class of drugs.

Table 3: Distribution of suspected Cutaneous ADRs according to drug classes

SN	Drug Groups / Classes	Number	Percentage
Antimicrobials (75) 82.42%	Fluoroquinolones	20	20.97%
	Cephalosporins	17	18.68%
	Penicillins	10	10.98%
	Sulphonamide	05	5.49%
	Antimalarial drugs	04	4.39%
	Antifungal drugs	01	1.09%
	Antiamoebic drugs	04	4.39%
	**Others	14	15.38%
NSAIDS (13) 14.28%	Nimesulide/Paracetamol/Ibuprofen/ Aceclofenac/ Combination.	13	14.28%
Steroids (02) 2.19%	Beclomethasone	02	2.19%
Anticonvulsant drugs (01) 1.09%	Phenytoin	01	1.09%
	Total	91	100

**Others includes doxycycline, tetracycline, meropenem, vancomycin, nevirapine and albendazole

DISCUSSION:

In every day of clinical practice, almost all physicians come across many instances of suspected adverse cutaneous drug reactions (ACDR) in different forms. Although such cutaneous reactions are common, but their comprehensive information regarding their incidence, severity and ultimate health effects are often not available. It is also a fact that in the present world, almost every day a new drug enters in market; therefore, a chance of a new drug reaction manifesting somewhere in some form in any corner of world is unknown or unreported.

In the present study, the mean age of subjects was 34.84±20.99 years for males and 29.98±19.58 years for females; the mean age difference between the gender was not statistically significant ($p>0.05$), the eldest being 85 years and the youngest subject being 1 year of age. According to affected organ system of suspected ADRs, the skin and mucous membrane is the commonest organ that involved in 52.29% of total suspected ADR, which is similar with previous studies in which dermatological manifestations were most common ADR [8-12]. This was followed by involvement of Central nervous system (9.19%), gastrointestinal system (8.62%), respiratory system (6.32%), cardiovascular system (4.59%) and hepatobiliary system (1.72%) and remaining 17.24% ADR as others**.**

Of total cutaneous ADRs; 69.23% were occur in males and 30.76% occurs in females, which is similar to *Gupta et al.;* [18] *and Chawla et al.;* [19] studies. *However* the incidence of cutaneous adverse reactions such as skin rashes, Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are more in females in our study this was similar to *Surajit Nayak et al.;* [13] *study i*n which cutaneous drug reactions have higher incidence in women than in men. In present study, cutaneous ADRs were most commonly (52.29%) reported ADR; this incidence is more variable to *Gruchalla et al.;* [20] study according to which cutaneous reactions comprise approximately 2-3% of all adverse drug reactions.

Amongst the cutaneous ADRs, skin rashes was most commonly (51.64%) reported cutaneous ADR which is similar to Chatterjee *et al.;* [21] study. Various other studies show that the exanthematous eruptions are the most common type of drug eruption [22-24]. Exanthematous drug eruptions, also known as maculopapular drug eruptions. It was 51.64% in our study which was dissimilar to *Thappa et al.; [25]* study in which fixed drug eruptions (31.1%) were observed most commonly and maculopapular rash (12.2%) are second most common. However another study [26] was reported that the incidence of skin eruptions is approximately 45% of all the cutaneous adverse drug reactions. Most of these rashes are mild, self-limited and usually resolve after the causative drug has been discontinued. Severe and potentially life-threatening reactions (e.g. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) occur 3.29% and 2.19% respectively) were also reported in this study.

In present study among the total suspected ADRs; most of these were associated with use of antimicrobials (68.12%) which is similar to various previous studies *Wester et al.; [27] Gor et al.; [28], Vora et al.; [29] Leape et al.; [30]* probably this may due to that, the AMAs are most commonly prescribed drug in our hospital followed by NSAIDs and haematinics. Among cutaneous ADRs only; maximum 82.42% cases were related with the use of antimicrobials followed by 14.28% with NSAIDS, this was similar to *V K Sharma et al.; [31]* study in which the drugs most commonly responsible for cutaneous ADRs were antimicrobials (42.6%), anticonvulsants (22.2%) and NSAIDs (18%). Amongst AMAs, maximum cutaneous ADRs were associated with fluoroquinolones (20.97%) followed by cephalosporin (18.68%), penicillin (10.98%) and sulphonamide (5.49%), this was differ to the study conducted by *Fiszenson-Albala et al.;* [32] *in which* penicillin is most common AMAs associated with cutaneous ADRs.

CONCLUSION:

In every day of clinical practice, almost all physicians come across many instances of suspected adverse cutaneous drug reactions (ACDR) in different forms. Cutaneous adverse drug reactions (ADRs) can be caused by a wide variety of agents. They are responsible for approximately 3% of all disabling injuries during hospitalization. In this study, males have higher incidence of suspected cutaneous ADRs, which have a ranged from common mild reactions like skin rashes, pruritus to severe reactions like SJS and TEN. The most common cutaneous ADRs were exanthematous skin rashes and pruritus. The commonest drug groups associated with suspected ADRs were antimicrobials and NSAIDs. Amongst AMAs fluoroquinolones is a major cause of cutaneous ADRs.

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