

A clinical study of cutaneous adverse drug reactions**Riddhi Shah, Sakshi Agrawal*, Neela Bhuptani**

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ABSTRACT

Background: Adverse cutaneous drug reactions pose a diagnostic challenge due to a myriad of clinical manifestations and wide variety of causative agents. Present study aims to record various clinical patterns of adverse drug reactions, their causative agents and to study the pattern of morbidity and mortality in patients with severe cutaneous adverse drug reactions.

Methods: 150 patients with adverse cutaneous drug reactions were included who came to Department of Dermatology, Venereology and Leprosy at PDU Govt. Medical College and Hospital, Rajkot, Gujarat from September 2009 to September 2011. Thorough history with all routine haematological and biochemical investigations, septic screening were done. HIV testing was done in severe reactions. Appropriate specific treatment was given with counselling regarding the offending drug.

Results: The most common age group was 21-30 years (26.67%) with male to female ratio being 0.92:1. Morbilliform rash was the most common clinical type (42.67%) in both HIV reactive and non-reactive patients. Antimicrobials were the most common group (29.33%) and nevirapine was the most common offending drug (27.33%). Mortality rate was 2% (3 out of 150 cases) and all the patients were of toxic epidermal necrolysis.

Conclusions: The pattern of cutaneous adverse drug reactions and the causative drugs are remarkably different in our study. Knowledge of the pattern and the causative agent helps in better management and reduced consequences in these patients particularly in severe adverse cutaneous drug reactions.

Keywords: Adverse cutaneous drug reactions**INTRODUCTION**

With the addition of a multitude of drugs to the physician's armamentarium, almost every day a new drug enters the market. This wide and indiscriminate use of drugs has increased the incidence and the modes of presentation of drug reactions.¹ An adverse drug reaction (ADR) may be defined as an undesirable clinical manifestation resulting from administration of a particular drug; this includes reactions due to overdose, predictable side effects and unanticipated adverse manifestations.² A cutaneous adverse drug reaction is termed severe if it results in death, requires hospitalisation or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening.³ Cutaneous drug reactions are the most frequently reported adverse reactions to drugs, partly

because the eruptions are visible and hence easily diagnosed. These reactions may vary from pruritus and rash to life threatening skin conditions like Stevens Johnson Syndrome and Toxic Epidermal Necrolysis. These severe reactions, although rare have significant mortality, morbidity and long term consequences. Drugs have an increased chance of causing reaction in immunocompromised patients including AIDS patients.¹ Diagnostic challenge arises in the patients when multiple medications have been taken prior to drug eruption and here comes the importance of meticulous and accurate history taking.

METHODS

The present study is a prospective, open, observational study, carried out in the Department of Dermatology,

Venereology and Leprosy at PDU Government Medical College and Hospital, Rajkot, Gujarat during a period of 2 years from September 2009 to September 2011. All patients attending the Dermatology OPD with active lesions of cutaneous adverse drug reactions due to systemic drugs were included in the study. Thorough clinical history of all the patients was taken and recorded according to preformed proforma. Precise history of drug intake including allopathic, homeopathic, ayurvedic medicines along with its temporal correlation with initiation of the symptoms was elicited with an emphasis on whether it was prescribed or self-administered.

Careful history regarding relevant skin or systemic diseases, atopy, past and family history of drug eruption was noted. Final diagnosis was made after excluding other possible causes of similar clinical picture. Morphology of the eruption, duration of the rash, associated mucosal and systemic involvement and improvement on drug withdrawal was established. Rechallenge was not attempted in any of the patients. In case of more than one drug suspected, the most likely offending drug was noted and the impression was confirmed by subsidence of the rash on withdrawing the drug.

All routine investigations including complete blood count, urine routine and microscopic examination, renal function tests, liver function tests, serum protein and blood sugar, septic screening were done in all patients. HIV testing was done in cases of severe adverse drug reactions and in those with risk factors. CD4 count was recorded in all HIV reactive patients. Appropriate specific treatment was given to each patient. All patients were counselled and educated to avoid self-administration of the offending drugs. Each patient was given a list of drugs to be avoided in future.

RESULTS

A total of 150 patients of Adverse Cutaneous Drug Reactions were studied spanning over a period of 2 years. The male to female ratio was 0.92:1 with most common age group being 21-30 years (26.67%). Drug was prescribed by a medical person in 139 cases (92.67%), while self-administered in 11 cases (7.33%). Most common route of administration was found to be oral (98.67%). The incubation period for clinical manifestations varied from 1 day to 5 years.

History of some cutaneous drug reaction in the past was present in 45 patients (30%). Lesions were generalised in 98 cases (65.33%) and localised in 52 cases (34.67%). Morbilliform rash was the most common clinical type of drug reaction (42.67%) followed by fixed drug eruption (20%), urticaria (12%) and toxic epidermal necrolysis (7.33%). Other types were erythema multiforme, SJ Syndrome, photosensitivity reaction, DRESS syndrome, dapsone syndrome, lichenoid drug rash and exfoliative dermatitis. Among the offending drugs for cutaneous

drug reactions, antimicrobial drugs were the most were the most common group (29.33%). Among the individual drugs, nevirapine was the most common culprit drug (27.33%) overall as well as for morbilliform rash (Table 1).

Table 1: Comparison of drugs causing cutaneous adverse drug reactions with other study.

Drugs	Present Study		Sharma VK et al	
	No of Cases	%	No of Cases	%
ART				
Nevirapine	41	27.33		
Efavirenz	02	1.33		
Antimicrobials				
Sulphonamides	21	14	18	19.6
Ampicillin/Amoxycillin	08	5.33	48	9.6
Fluoroquinolones	06	04	18	3.6
AKT(H/E/S)	05 (3/1/1)	3.33	21	4.2
Tetracycline	04	2.67		
Macrolides (Erythromycin)			06	1.2
Others			30	4.4
Anti Malarials	07	4.67	08	1.6
			90	18
NSAIDS				
Paracetamol	11	7.33		
Diclofenac	06	04		
Ibuprofen	05	3.33		
Dicyclomine	02	1.33		
Nimesulide	02	1.33		
Aspirin	02	1.33		
Lornoxicam	01	0.67		
Unknown				
Antipyretic	09	06		
Anti convulsants				
Phenytoin	06	04	58	11.6
Carbamazepine	04	2.67	46	9.2
Phenobarbitone			07	1.4
Miscellaneous				
Fluconazole	01	0.67		
Beta Blocker	01	0.67	05	1
Others	06	4.02	65	14.6
Total	150	100	500	100

For fixed drug reaction, antimicrobial group (50.03%) was the most common culprit with sulphonamide being the most common individual drug (26.7%). Urticaria/angioedema was mainly caused by NSAIDS (77.78%). Out of 150 patients, 52 (34.67%) were HIV reactive and morbilliform rash was the commonest pattern of drug reaction in them (71.1%). Altered renal function was the commonest complication observed among the patients with Toxic Epidermal Necrolysis (54.5%). Among the study patients, 3 cases of TEN proved to be fatal, while the outcome was satisfactory in all other cases.

DISCUSSION

Adverse cutaneous drug reactions vary in their patterns of morphology and distribution. In Indian studies the most common morphologic patterns are exanthematous, urticarial and/or angioedema, fixed drug eruption and erythema multiforme.⁴ Most common clinical pattern in our study was morbilliform rash (Figure 1) (42.67%) followed by fixed drug eruption (20%) and urticaria (12%).



Figure 1: Morbilliform rash due to Nevirapine in HIV reactive patient.

This is in contrast with studies done by Marfatia et al and Pudukadan et al where most common finding was fixed drug eruption in 30.5% and 31.1% cases respectively.^{5,6}

The incidence of cutaneous drug reactions was nearly equal in males and females with a slight preponderance of female sex (52%) in our study with male: female sex ratio being 0.92:1 which is comparable with 0.87:1 as observed by Pudukadan et al.⁶ The mean age group of our patient was 21-30 years (26.67%) followed by 31-40 years (21.33%) as was also observed by Pudukadan et al where maximum patients were in the group of 20-39 years.⁶ The youngest and oldest patients in our study were of 6 months and 75 years respectively however in both the studies the drug reactions are more common in the middle age group.

In majority of the cases the offending drug was being prescribed (92.67%) and administered by oral route (98.67%). A past history suggestive of some cutaneous drug reaction was found in 45 patients (30%) among which 14 patients (31.1%) developed reaction due to the same drug. Most common clinical pattern in our study was morbilliform rash (42.67%) followed by fixed drug eruption (20%) and urticaria (12%). This was in cofirmity with Sharma VK et al, however Marfatia et al reported fixed drug eruption to be the most common pattern followed by urticaria, morbilliform rash and pruritus.^{5,7} Similar observation was also made by Pudukadan et al where fixed drug eruption was the most common presentation (31.1%) followed by maculopapular rash, SJS-TEN and urticaria (Table 2).⁶

Antimicrobial group of drugs were found to be the most common culprit (29.33%) in our study as opposed to Marfatia et al where NSAIDS formed the major group (21%).⁵ However, our findings were similar to that as observed by Sharma VK et al and Pudukadan et al.^{6,7}

Table 2: Comparison of clinical patterns with other 2 studies.

Type	Present study		Sharma VK et al		Marfatiya et al	
	No. of cases	%	No. of cases	%	No. of cases	%
Morbilliform Rash	64	42.67	173	34.6	36	18
Fixed Drug Reaction	30	20	150	30	61	30.5
Urticaria	18	12	70	14	37	18.5
Toxic Epidermal Necrolysis	11	7.33	33	6.6	02	01
Erythema Multiforme	9	06	22	4.4	02	01
Stevens Johnson Syndrome	7	4.67	24	4.8	06	03
Photosensitivity	4	2.67	04	0.8	05	2.5
DRESS	2	1.33				
Lichenoid Drug Rash	2	1.33	04	0.8		
Dapsone Syndrome	2	1.33			01	0.5
Exfoliative Dermatitis	1	0.67	09	1.8	05	2.5
Bullous Drug Reaction			07	1.4	01	0.5
Pruritus					25	12.5
Others			04	0.8	19	9.5
Total	150	100	500	100	200	100

Nevirapine was the most common individual culprit drug found in our study (27.33%) followed by sulphonamides

(14%) as opposed to cotrimoxazoles being the most common drug implicated by Pudukadan et al (22.2%) and

Marfatia et al (29.5%) respectively (Table 2).^{5,6} This difference can be attributed to the higher prevalence of HIV reactive patients (34.67%) in our study, increasing prevalence of HIV/AIDS, the easy and free availability of ART, well-functioning ART centre at our institute and increased awareness regarding drug reactions among general population and prompt referral for the same.



Figure 2: Patient of toxic epidermal necrolysis due to unknown antipyretic who died of septicaemia.

Morbilloform rash, in our study, was most commonly caused by nevirapine (46.88%) in contrast to Marfatia et al and Sharma VK et al where fluoroquinolones and phenytoin were the commonest culprits respectively.^{5,7} Antimicrobials were the most common drugs causing fixed drug eruptions (50.03%), sulphonamides being the most common among them (26.7%). This is in concordance with other studies Marfatia et al and Sharma VK et al, where sulphonamides were the commonest causative drugs followed by NSAIDs.^{5,7} NSAIDs were the most common offending drug for urticaria/angioedema (77.78%) which was in concordance with the study of Marfatia et al and Sharma VK et al.^{5,7}

In present study, unknown antipyretic (54.54%) was the most common culprit drug causing TEN as opposed to phenytoin (16.13%) in the study by Barvalia et al and Sharma VK et al.^{7,8} The most common complication in these patients was altered renal function tests with raised urea and creatinine (54.5%) which was reversible on treatment. Other complications observed were septicaemia (45.5%), altered liver function tests (36.4%), altered renal function tests (54.5%) leucocytosis (36.4%), leucopenia (36.4%) and hyponatremia (36.4%). Dry eye was the most common sequelae seen in 3 patients all of which were females. 3 cases proved to be fatal, the cause of death being septicaemia in 2 patients and Acute respiratory distress syndrome (ARDS) in one patient. Out of the 2 patients of septicaemia, one patient developed diabetic ketoacidosis (Figure 2), while the other developed respiratory and metabolic acidosis leading to multiorgan failure. This is in concordance with study by Marfatia et al where also septicaemia was found to be the most common complication in patients with SJS-TEN.⁵ Post inflammatory hyperpigmentation was seen in all the

survivors, with nail shedding seen in most of the cases. A female patient had significant telogen effluvium in follow up (Figure 3).

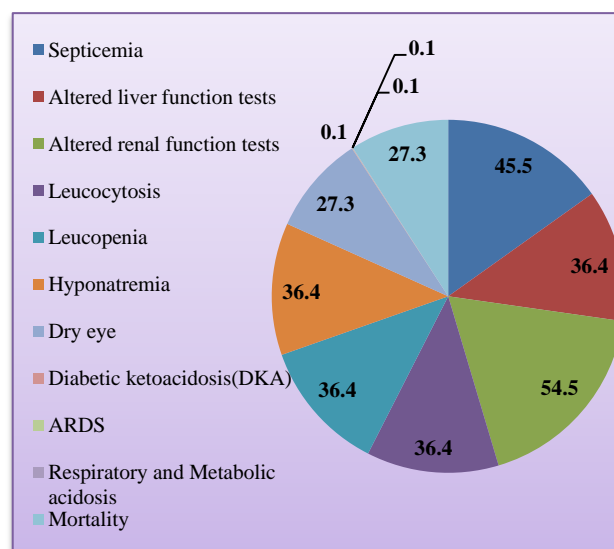


Figure 3: Percent of complications in patients of toxic epidermal necrolysis.

There were 7 cases of SJ Syndrome, out of which 5 cases were HIV Reactive and the culprit drug was nevirapine. All the cases recovered completely without any serious complications.

Table 3: Morphological types of cutaneous ADR and the suspected drugs In HIV reactive patients.

Type of cutaneous ADR	Offending drug with frequency of occurrence	Total no. of cases	%
Morbilloform Rash	Nevirapine (30)	37	71.1
	Isoniazid (2)		
	Ethambutol (1)		
	Efavirenz (2)		
	Sulfonamide (2)		
Erythema Multiforme	Nevirapine (4) Sulfonamide (1)	05	9.6
Sj Syndrome	Nevirapine (5)	05	9.6
Ten	Nevirapine (2) Sulfonamide (1)	03	5.8
Photosensitivity	Norfloxacin (1)	01	1.9
Angioedema	Chloroquine (1)	01	1.9
Total		52	100

There were 2 cases of DRESS syndrome, both due to carbamazepine. They were treated with tapering doses of corticosteroids. The rash subsided with significant desquamation. 2 cases of dapsone syndrome were observed, where the drug was being given for tuberculoid leprosy and recurrent aphthous ulcers. Dapsone syndrome was observed in 10 out of 604 patients in a study by Prasad et al.⁹

The culprit in two cases of lichenoid rash was beta blockers. Interestingly one patient developed rash only on taking colored tablets, the coloring agent being titanium dioxide. Exfoliative dermatitis was seen in one patient and the culprit drug was streptomycin. Among the HIV reactive patients (34.67%), morbilliform rash was the most common clinical pattern (71.1%) followed by erythema multiforme and SJ Syndrome (9.6% cases each) and nevirapine was the most common culprit drug. This is in contrast to the study conducted by Sharma et al in HIV positive patients where nevirapine induced rash was observed in only 11.8% cases (Table 3).¹⁰

CONCLUSION

The pattern of cutaneous adverse drug reactions and the causative drugs are remarkably different in our study. Knowledge of the pattern and the causative agents helps in prompt and early diagnosis of the condition, better management and reduced morbidity, mortality and consequences in these patients. Also as each drug has the potential to cause cutaneous adverse drug reaction, so risk benefit ratio should be weighed in each patient. Also proper counselling is required regarding further avoidance of the culprit and the related drugs so as to prevent further episodes of drug reactions.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Shah R, Agrawal S, Bhuptani N. A clinical study of cutaneous adverse drug reactions. Int J Basic Clin Pharmacol 2017;6:919-23.