www.jmscr.igmpublication.org
Impact Factor 5.84
Index Copernicus Value: 83.27
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v5i2.94

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Original Article

Cutaneous Adverse Drug Reactions: A Two Years Retrospective Study From A Tertiary Care Hospital In Sub Himalayan Region

Authors
Dr Saru Thakur[1], Dr Mudita Gupta[2], Dr Gr Tegta[3], Dr Samriti Sood[4], Dr Kuldeep Verma[5]
[1,4,5]Postgraduate Student, [2]Assistant Professor, [3]Professor and Head, Department of Dermatology, Dept of Dermatology, Venereology and Leprosy, Indira Gandhi Medical College, Shimla, Himachal Pradesh
Corresponding Author
Dr Mudita Gupta
Dept of Dermatology, Venereology and Leprosy, Indira Gandhi Medical College, Shimla, Himachal Pradesh
Email: *muditadrgupta@yahoo.com*, Ph no. 9418495747

ABSTRACT
A wide spectrum of cutaneous manifestations can be produced by drugs.
Aim: *To determine the clinicoepidemiological pattern of drug eruptions and their causative agents in indoor patients.*
Methods: *Sixty patients who were admitted indermatology ward with cutaneous adverse reactions were included in this study from January 2015 to December 2016. Demographic characteristics, drug suspected, duration between drug intake and onset of reaction, route, medical history, physical examination, laboratory investigations were recorded.*
Results: *Male to female ratio was 1.22: 1. The mean age group of patients was 45±3.4 years. Interval between the drug intake by both oral and intravenous routes had a mean of 25.6± 4.94 days. Most common presentation was maculopapular rash seen in 21 patients (35%) followed by exfoliative dermatitis. Overall, the most common offending drugs were antibiotics as a whole seen in 27 patients (45%) followed by antiepileptic group in 13 patients (21.6%). Abnormal eosinophil counts were seen in 17 patients (28.3%). Liver function abnormalities were seen in 15 patients (25%). Rare presentations were anaphylaxis to paracetamol, photosensitivity to erlotinib and Acute Generalized exanthematous pustulosis to anti tubercular drugs. Outcome was favourable in 95% patients.*
Conclusion: *Detailed warnings should be issued to patients prohibiting future use of same or related drugs. In case of generalized severe drug rash early institution of steroids reduces morbidity and mortality*
Key words: *adverse cutaneous drug reaction, clinico epidemiological pattern.*

INTRODUCTION

An adverse cutaneous drug reaction is an undesirable change in the structure or function of the skin, its appendages or mucous membranes and it encompasses all adverse events related to drug eruption, regardless of the etiology[(1)].Drug reactions are classified into immunological and non – immunological etiologies. Gell and Coombs classification describes predominant immune mechanisms leading to clinical features of drug

hypersensitivity. However, certain reactions such as maculopapular, erythroderma, exfoliative dermatitis and fixed drug reactions are difficult to classify because of lack of evidence supporting a predominant immunological mechanisms[1]. Different classes of drugs can produce a wide spectrum of cutaneous manifestations varying from urticaria to toxic epidermal necrolysis (TEN). The overall incidence of cutaneous adverse reactions in developed countries is 1-3%, while developing countries have an incidence of 2-5%[2]. Cutaneous drug eruptions are not associated with high morbidity but seek attention as they are frequently common and require further discontinuation of the drug[3].

AIMS

To determine the clinicoepidemiological pattern of drug eruptions and their causative agents in dermatology indoor patients in a tertiary care centre.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Dermatology, Venereology and Leprosy, Indira Gandhi Medical College, Shimla. All indoor patients admitted with the diagnosis of drug eruptions were included in this study from January 2015 to December 2016. Patient's files were analysed from hospital records for data regarding demographic characteristics including age, sex, drug suspected, duration between drug intake and onset of reaction, route of drug administration, previous drug allergies, medical history, physical examination for pattern of drug eruption and sites of involvement. Laboratory investigations such as complete blood counts, renal functions and liver functions were also analysed.

RESULTS

A total of 60 patients with cutaneous adverse reactions were included in this study which comprised of 33 males and 27 females. The male to female ratio was 1.22 : 1. The mean age group of patients was 45±3.4 years. Maximum patients 17 out of 60 (28.3%) belonged to the age group of 31-40 years followed by 9 (15%) each in age groups 21-30 and 61-70 years (Table 1). The youngest patient was 15 years old boy and oldest was 80 years old male in this study.

Table 1: Age and sex distribution of our cases

Age group (In years)	Males n	Females N	Total N	Percentage %
1-10	0	0	0	0
11-20	3	2	5	8.3
21-30	3	6	9	15
31-40	5	12	17	28.3
41-50	5	3	8	13.3
51-60	5	1	6	10
61-70	6	3	9	15
71-80	6	0	6	10
Total	33	27	60	100

The interval between the drug intake by both oral and intravenous routes had a mean of 25.6± 4.94 days. The range was from 40 minutes to 203 days. Most of the patients developed rash while they were taking the incriminated drug. Two patients (3%) were administered the drug by intravenous route, while the rest 58 took the drug orally.

There were 8 patients (13.3%) who had similar episodes in the past to same as well as different drugs. Patients had associated comorbidities such as carcinoma with brain metastasis, immunocompromised state due to HIV /AIDS, deranged renal functions, hepatitis, depression, mental retardation, seizures, hypertension, diabetes, thyroid disorders (hypo and hyperthyroidism), paraplegia, cerebral contusions, head injuries, cranial haemorrhaghes and leprosy.

Various patterns of drug eruptions observed in our study were maculopapular rash, drug rash with eosinophilia and systemic systems (DRESS), erythroderma, urticaria, bullous fixed drug eruption, erythema multiforme major, Steven Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), SJS-TEN Overlap, mucosal erosions, Acute Generalised Exanthematous Pustulosis (AGEP), Dapsone hypersensitivity syndrome (DHS), anaphylaxis and vasculitis (Figure 1). The most common presentation was maculopapular seen in 21 patients (35%) followed by erythroderma.

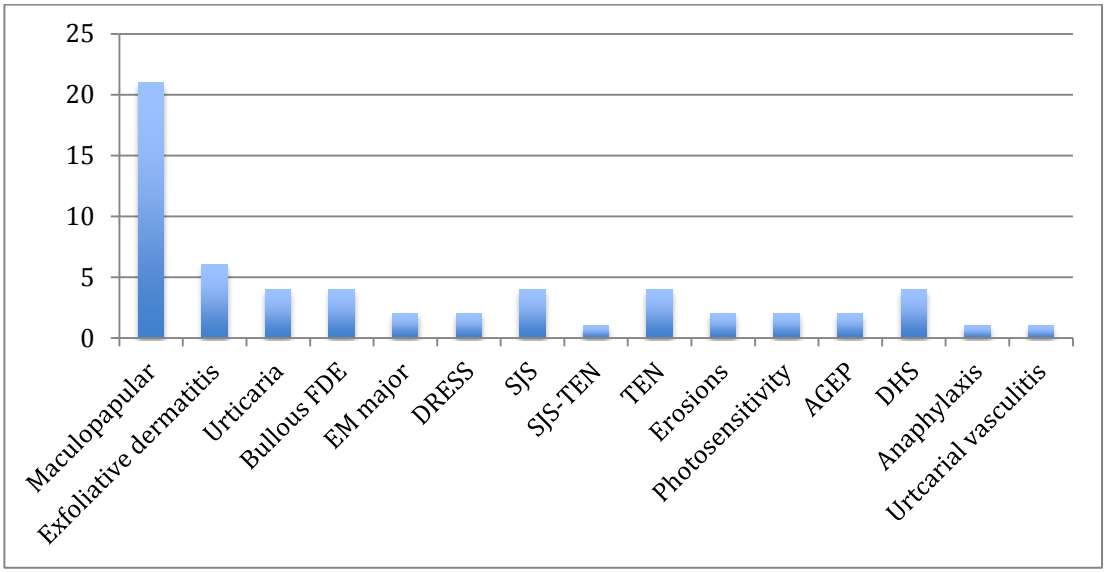

Figure 1: Pattern of drug rash as observed in our study

On physical examination, generalized body involvement was more commonly seenas compared to localized involvement. Generalized involvement was seen in 34 patients (56.67%) in whom, the pattern of rash observed was maculop-apular rash, exfoliative dermatitis, DRESS, Dapsone hypersensitivity syndrome and TEN. Mucosal involvement was observed in 27 of patients.The site of onset was acrals (hands, feet, palms) in 24 patients (40%), followed by face and neck in 17(28.3%) and trunk in 13 (21.6%). There were 6 patients (10%) who developed mucosal lesions (oral) prior to onset of skin lesions.

Among the laboratory parametres, abnormal eosinophil counts (>500/mm^3)were seen in 17 patients (28,3%). Liver function abnormalities in the form of more than two fold rise in the level of aminotransferases was seen in 15 patients (25%). Renal function were abnormal in 4 patients (6%). ICTC and VDRL were done when indicated. ICTC was found to be reactive in 3 patients (5%).

Overall, the most common offending drugs were antibiotics as a whole seen in 27 patients (45%). These included antitubercular drugs (ATT) causing rash in 9 patients (15%), antileprosy drug dapsone implicated in 4 patients (6%) and other antibiotics in 14 patients (23.3%). Antimicrobial group was followed by antiepileptic group in 14 patients (23.3%), out of which phenytoin was the most common causative agent in 12 patients (20%) followed by carbamazepine and oxcarbamazepine in one patient each. These were followed by NSAIDS as observed in 8 patients (13.3%). Among NSAIDS, the commonest drugs werenimesulide in 4 patients, followed by diclofenac in three patients and paracetamol in 1 patient.Other drugs implicated were antiretroviral drugs, erlotinib, fluconazole, levocetrizine, allopurinol, propranolol and artemether. In one patients the causative drug could no be found (Table 2).

Table 2 : Distribution of drugs implicated for causing eruptions

Drug implicated	Number	Percentage
ANTIBIOTICS	14	23.3
Amoxicillin	2	3.3
Amoxicillin + clavulanic	1	1.6
Septran	2	3.3
Ofloxacin	1	1.6
Oflaxicin + ornidazole	3	5
Tinidazole	1	1.6
Levofloxacin	1	1.6
Cephalosporins	2	3.3
Nitrofurantoin	1	1.6
ANTITUBERCULAR DRUGS	9	15
ANTILEPROSY		
Dapsone	4	6.6
ANTIEPILEPTICS	14	23.3
Phenytoin	12	20
Carbamazepine	1	1.6
Oxcarbamazepine	1	1.6
NSAIDS	8	13.3
Paracetamol	1	1.6
Diclofenac	3	5
Nimesulide	4	6.6
ANTIRETROVIRAL	2	3.3
ALLOPURINOL	2	3.3
IMMUNOSUPPRESSIVE		
Erlotonib	2	3.3
OTHERS		
Levocetrizine	1	1.6
Propranolol	1	1.6
Artemether	1	1.6
fluconazole	1	1.6
Unknown	1	1.6
TOTAL	60	

The drugs implicated for causing maculopapular rash ,which was most commonly observed in our study were antiepileptics, followed by antimicrobials including antitubercular drugs, NSAIDS and antiretroviral drugs (Table 3)

Table 3: Drugs implicated for maculopapular rash

Drug	Number	Percentage
ANTIEPILEPTICS		
Phenytoin	9	15
Carbamazepine	1	1.6
ANTIBIOTICS		
Septran	1	1.6
Ceftriaxone	1	1.6
Nitrofurantoin	1	1.6
ATT	2	3.3
NSAIDS		
Diclofenac	3	5
Nimesulide	1	1.6
Antiretroviral drugs	2	3.3
TOTAL	21	35

SJS and TEN were caused by antibiotics, phenytoin, allopurinol and nimesulide. (figure 2)

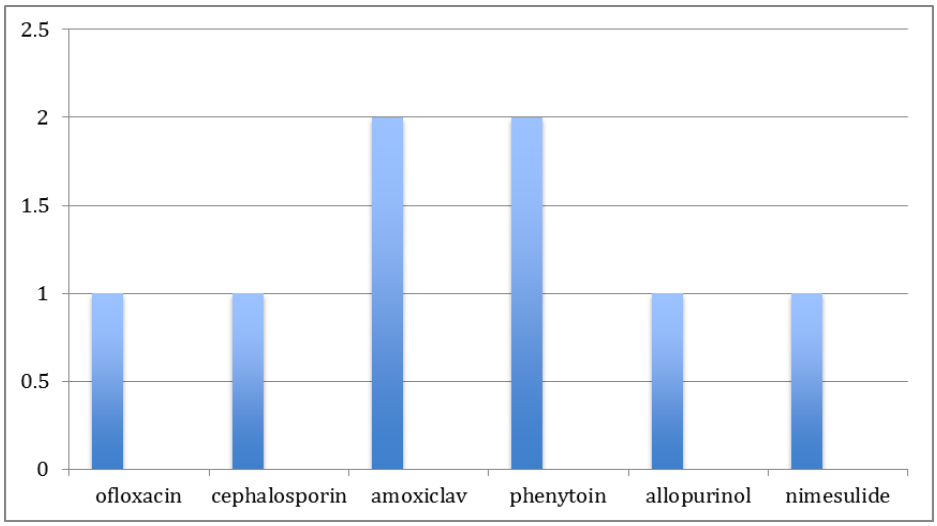

Figure 2 : Drugs implicated in SJS-TEN.

Drug rash due to ATT

There were 9 patients who developed rash due to antitubercular drugs. The interval between the onset of rash and development of cutaneous lesions had a mean of 40 ± 13.4days.The interval varied from 2 days to 75 days. The pattern of rash was exfoliative dermatitis in 5 patients, maculopapular in 3 patients and AGEP in 1 patient with mucosal involvement seen in 7 patients. Liver functions and renal functions were

deranged in 2 patients each. Eosinophilia was observed in 5 patients. ATT was withdrawn in all cases and patients were initiated on oral steroids. Clinical response appeared in 7-14 days with total duration of steroids ranging from 10- 45 days. Out of total 7 Patients were rechallenged with ATT. The culprit drug was found to be ethambutol and rifampicin in 2 patients each. And surprisingly, two of our patients tested positive for 2 drugs each i.e. rifampicin and ethambutol in 1 patient with isoniazid and ethambutol in the other patient. In one patient who had completed intensive phase of ATT, we rechallenged with isoniazid and rifampicin only, which the patient tolerated well. Rechallenge could not done in 2 patients as one was sick and the other left against medical advice.

The outcome was favourable in all except 3 patients (5%), who collapsed during hospital stay. These were 2 patients of TEN secondary to Phenytoin and one patient of anaphylaxis.

DISCUSSION

Adverse drug reaction as defined by WHO is " a response to a drug that is noxious and unintended and occurs at doses normally used in human for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function"[4].In this present study, males outnumbered the females ratio was 1.22 :1.. This is in concordance with another study by Sharma et al[2], Suthar et al[5] and Patel et al[6] . However female preponderance has been observed by David et al[7].The reason for male preponderance could be the fact that males are more aware of their illness and more likely to seek medical care. The age group of patients with maximum cases occurred between 31-40years, similar to previous studies[8]. However in our study, we also had 15% cases in the age group 61-70 years. Adverse reactions tend to increase with age [9].These patients are usually on multiple drugs and have associated co-morbities, which predisposes them to drug eruptions and increased morbidity and mortality as compared to younger patients.

Maculopapular rash was the commonest as seen in other studies by Nadimpalli et al[10]. However, some studies report fixed drug eruption (FDE) as the most commonly observed eruption[2,6,11]. This may be due to the fact that our study is based entirely on indoor patients and FDE patients unless severe or extensive are usually not admitted. Secondly, the most commonly implicated drugs in our study cause more of maculopapular rash than FDE.

The interval between drug exposure and onset of rash was variable depending upon the type of rash and drug implicated. The patients who developed urticarial, anaphylaxis and bullous fixed drug eruptions developed rash within few hours (within one day), whereas those with DHS, DRESS and due to ATT or antiepileptics developed lesions within 3weeks to 3 months.

The most common drugs implicated in our study were antimicrobials including ATT(38.3%) followed by antiepileptics and then NSAIDS, ascompared to other studies which observed antimicrobials as most common rash followed by NSAIDS[2, 11]. Among the antimicrobials, ofloxacin-ornidazole was commonly implicated after ATT, versus tinidazole [2] and sulfonamides [7,8] in other studies.

We encountered some rare presentations also in our study. Anaphylaxis was reported which was secondary to paracetamol. There have been rare reports of such adverse reaction due to paracetamol[12]. Two immunosuppressed patients presented with photosensitive rash which was secondary to erlotinib, which is an epidermal growth factor inhibitor. Photosensitivity reaction is a rare toxicity in erlotinib treatment, which has been confirmed by a positive photo patch test [13].Another rare finding in our study was acute generalized exanthematous pustulosis which has been rarely reported secondary to antitubercular therapy[14]. Histopathological examination was done in our case to confirm the diagnosis.

Eosinophilia was seen in 28.3%patients in our study, which is higher as compared to previous studies by Sharma et al[2] and Romagosa et al [15].

However some authors say that eosinophil counts carry little diagnostic values in the setting of cutaneous adverse drug eruptins (CADRs), but higher levels may be useful in patients with severe reactions. Altered liver and renal functions may be due to toxic effects of drugs or their presence per se predisposes the individual to severe CADRs due to altered metabolism and clearance from the body.Patients on multiple drugs further increases risk of adverse reactions [16] .

Drug rash due to ATT was seen in 15% of our patients. Rechallenge was done in 7 patients. The safety of diagnostic rechallenge has been mentioned in more than 150 cases in literature with no long term morbidities or deaths due to direct rechallenge [17]. Positive rechallenge with 2 drugs has been rarely reported in literature, which was seen in 2 of our patients.

In our study, the overall mortality was 5 %, with TEN responsible for 3% and anaphylaxis for 1.6% as compared to overall mortality of 1.71%, SJS/TEN 16.39%, exfoliative dermatitis 3.57%, erythema multiforme 0.13% and maculopapular rash causing 0.45% mortality in previous studies [18]. Mortality in anaphylaxis has been reported in 12.96% cases in literature[19] .Hospitalization is required in 11.39% cases of cutaneous reactions. The overall mortality was higher in our study as the present study included only indoor patients. Also, these patients had associated comorbidities such as seizures, carcinoma breast with brain, pulmonary metastasis, hypertensive crisis, cardiac involvement and electrolyte imbalance.

In our severe cutaneous drug eruptions, mortality was only seen in 3% TEN patients, as compared to 16.39%, Anaphylaxis 1.6% versus 12.96% and no mortalities among DRESS, DHS, maculopapular rash, Erythema multiforme, SJS patients as early institution of steroids was done in all severe cases. It was in only one patient of severe reactions (TEN), that steroids were not instituted as she had presented after 7 days of onset of rash. In all others, oral or injectable steroids were initiated on admission. Hence, it was concluded in our study that early institution of steroids can in reducing the mortality associated with the severe adverse drug reactions.

Antiepiletics constituted the second largest group (23.3%) implicated in drug rash in our study. This included 12 patients on phenytoin leading to maculopapular rash, DRESS, exfoliative dermatitis and TEN. The mean duration of onset of rash was 39.71 ± 2.82 days. Among these 12 patients, 7 (58.3%) were prescribed phenytoin prophylactically in cases of head injury. The indication of using phenytoin in head injury is in cases of subcortical parenchymal injury or the presence of septic foci in brain. Also, antiepileptics are required in first 7 days of head injury[20], after which the risk of administering phenytoin should be weighed against the risk of severe cutaneous reactions. Even alternative antiepileptics may be prescribed instead of phenytoin, carbamazepine, lamotrigine and related drugs, which may be decrease the burden of severe adverse cutaneous reactions in such patients.

CONCLUSION

Adverse cutaneous reactions can have varied presentations including rare presentations. Early suspicion and recognition of such event is important to decrease morbidity and mortality. Detailed warning should be issued to the patient in writing prohibiting future use of the same or related drug. Past history of drug allergies should be sought in every case. Prescribing medicines or related drug with cross sensitivity to previously sensitized individuals carry medicolegal, hence need to be dealt seriously.

Early institution of steroids can decrease the burden of mortality associated with severe drug reactions.

Sources of support nil

REFERENCES

1. Nayak S, Acharjya B. Adverse cutaneous drug reaction. Indian J Dermatol. 2008; 53(1) : 2-8.

2. Sharma R, Dogra D, Dogra N. A study of cutaneous adverse drug reactions at a tertiary centre in Jammu, India. Indian Dermatol Online J. 2015;6:168-71.
3. Akpinar F, Dervis E. Drug Eruptions : An 8-year study including 106 patients at a Dermatology Cinic in Turkey. Indian J Dermatol. 2012;57:194-8.
4. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. The Lancet. 2000; 356: 1255-9.
5. Suther JV, Desai SV. A study of adverse cutaneous drug reactions in outdoor patients attending to Skin and V.D. Department of Shree Krishna Hospital, Karamsad. Int J Res Pharm Biomed Sci 2011;2:2229-31.
6. Patel RM, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol. 2008; 74: 430-6.
7. Pudukadan D, Thapa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care centre in South India. Indian J Dermatol Venereol Leprol. 2004; 70: 20-24.
8. 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;47:95-9.
9. Sullivan JR, Shear NH. Drug eruptions and other adverse drug effects in aged skin. Clin Geriatr Med 2002;18:21-42.
10. Nadimpalli SKKV, Badabagni P, Dasika S, Bendapudi RV. A study of cutaneous adverse drug eruptions in dermatological practice. Indian J Clin Exp Dermatol. 2016; 2: 79-83.
11. Qayoom S, Bisati S, Manzoor S, Sameem F, Khan K. Adverse cutaneous drug reactions – A clinic-demographic study in a tertiary care teaching hospital of the Kashmir valley, India. Arch Iran Med. 2015; 18 : 228-33.
12. Bachmeyer C, Vermeulen C, Habki R, Blay F, Leynadier F. Acetaminophen (paracetamol)-induced anaphylactic shock. South Med J. 2002;95:759-60.
13. Tokimasa Y, Fujiwara K, Higo H, Kameyama N, Kayatani H, SatoK, Matsuo K et al. Photosensitivity reaction induced by erlotinib. Int Canc Conf J. 2012; 1: 173-5.
14. Cantisani C, Paradisi A, Richetta AG, Mattozzi C, Calvieri S. Acute generalized exanthematous pustulosis during antituberculosis therapy. Clin Ter 2013; 164: 137-8.
15. Romagosa R, Kapoor S, Sanders J, Berman B. Inpatient adverse cutaneous drug eruptions and eosinophilia. Arch Dermatolo 2001;137:511-2.
16. Hafner JW, Belknap SW, Squillante MD, Bucheit KA. Adverse drug events in emergency department patients. Ann Emerg Med 2002;39:258-67
17. Kakande B, Lehloenya RJ. Drug reactions associated with antituberculosis drugs. Curren allergy Clin Immunol. 2015; 28: 264-8.
18. Patel TK, Thakkar SH, Sharma DC. Cutaneous adverse drug reactions in Indian population: A systematic review. Indian Dematol Online J. 2014; 5 :76-86.
19. Patel TK, Patel PB, Barvaliya MJ, Tripathi CB. Drug-induced anaphylactic reactions in Indian population : A systematic review. Indian J Crit Care Med. 2014;18: 796-806.
20. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S,Winn HR. A randomized, Double-blind study of phenytoin for the prevention of post – traumatic seizures. N Engl J Med. 1990; 323: 497-502.