Original Research Article

Cutaneous adverse drug reactions: A three years tertiary care hospital based retrospective study

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Abstract

Background: Cutaneous drug reactions(CADRs) are the commonest manifestation of adverse drug reactions. They may manifest in a wide range of clinical patterns. They may either be confined only to skin or may be a part of multisystemic disorder.**Aims**: To study the demographic profile of patients with CADRs, to study type of CADRs and identify the offending drugs.**Methodology**: It was a retrospective tertiary care hospital based study. Retrospective analysis of data of patients admitted with a diagnosis of 'cutaneous adverse drug reaction' between October 2016 to September 2019 was done.**Results**: Records of 205 patients were analyzed. Male: female ratio was 1:0.69. Most common age group 21-40 years accounting for 78 Pts (38%).Period of latency ranged from <2 hrs to 150 days (mean 24.10 ± 26.14). Co morbidities included Diabetes mellitus - 18 (8.78%),Chronic kidney disease - 3 (1.46%), Malignancy - 3 (1.46%) and HIV - 2 (1%). Risk factors observed werePoly-pharmacy - 69 (33.65%, Smoking - 51 (24.87%) and alcohol intake - 48 (23.41%). Most common drug rash was fixed drug eruption and most common drug group implicated was antimicrobials.**Conclusion**: A wide range of morphological patterns was observed. The results were in concordance with other studies.

Keywords: Cutaneous adverse drug reaction, morphological pattern, retrospective analysis

Introduction

An adverse drug reaction is defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medical product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawl of the product[1]. Adverse drug reactions are quite common in day to day medical practice. Dermatologists very commonly encounter drug reactions in their practice as cutaneous adverse drug reactions (CADRs) are the most frequent of all manifestations of drug sensitivity. They manifest with varied and diverse morphological patterns ranging from urticaria to severe forms like Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS-TEN) and exfoliative dermatitis. Fatal reactions to drugs are uncommon, but reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS-TEN) and exfoliative dermatitis may result even in death if not managed promptly. The pattern of cutaneous drug rash and the drugs responsible for that keep changing because of different prescribing patterns, use of newer drugs, self medication and referral bias.[2]The present study was conducted in the department of Dermatology, Venereology and Leprosy at Indira Ganghi Medical College, Shimla.

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Methods and materials

Ours was a tertiary care hospital based retrospective study done with the objectives:
To study the demographic profile of patients with CADRs.
To study type of CADRs and to identify the offending drug.
We retrieved data of patients admitted with a diagnosis of cutaneous drug rash in the department of dermatology between October 2016 to September 2019. A total number of 205 patients were admitted with cutaneous drug rash during this period.For every patient recorded parameters included: demographic profile of patient (age, sex), period of latency, duration of hospital stay, history of previous drug

allergies, medical history and associated co morbidity, pattern of drug rash, offending drugs.In addition to the above parameters, laboratory investigations like Complete haemogram with eosinophilic counts,biochemistry including liver function tests (LFTs), renal function tests (RFTs), chest radiography and immune status were also recorded.

Results

A total no. of 205 patients were admitted with a diagnosis of 'Cutaneous adverse drug reaction' during the study period. Out of these,121(59%) were males and 84(41%) were female patients. Male to female ratio was 1:0.69 (fig. 1).

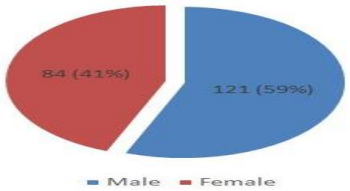

Fig 1: Gender distribution

Most common age group was 21-40 years with 78 (38%) patients falling into this group followed by 41-60 years, which comprised of 66 (32.19%) patients (fig. 2).

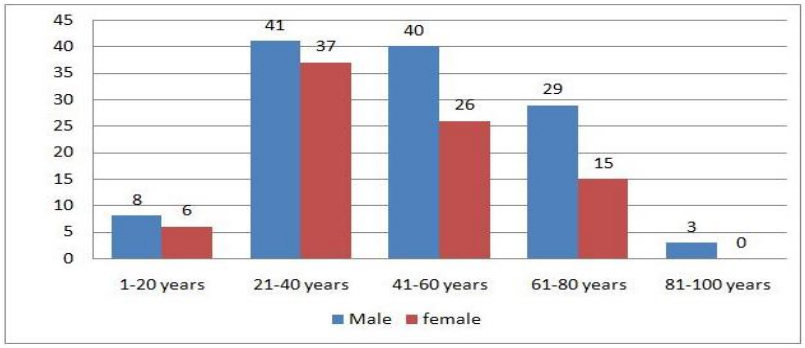

Fig 2: Age distribution

Period of latency i.e., time taken between intake of drug and appearance of rash varied between less than 2 hours to 150 days with a mean of 24.10 ± 26.14. Minimum latent period was seen in fixed drug eruption and maximum latent period was observed in lichenoid drug rash. 150 (73%) patients had a period of latency of less than 15 days whereas in 11 (5.4%) patients, it was found to be more than 60 days.Duration of hospital stay ranged from 1 to 120 days with a mean of 16.84 ± 14.23.Most common co-morbidity observed in our patients was diabetes mellitus i.e. in 18 (8.78%) followed by chronic kidney disease and malignancy, each seen in 3(1.46%) patients. HIV positive state was present in 2 (1%) patients.

Among various risk factors described for development of CADRs, we observed polypharmacy to be the most common in our patients, which was present in 69(33.65%) of the patients. Second most common risk factor observed was smoking, seen in 51(24.87%) patients, further followed by consumption of alcohol in 48(23.41%) patients.We found fixed drug eruption (FDE) to be the most common clinical pattern observed in 90(44%) study subjects, followed by maculo-papular drug rash in 38(18.5%), further followed by lichenoid drug rash in 15(7.3%) patients. Least common clinical patterns observed were purpuric rash, pityriasis rosea like rash, Fuch's syndrome and SJS-TEN overlap; each seen in 1% of the patients) (fig-3).

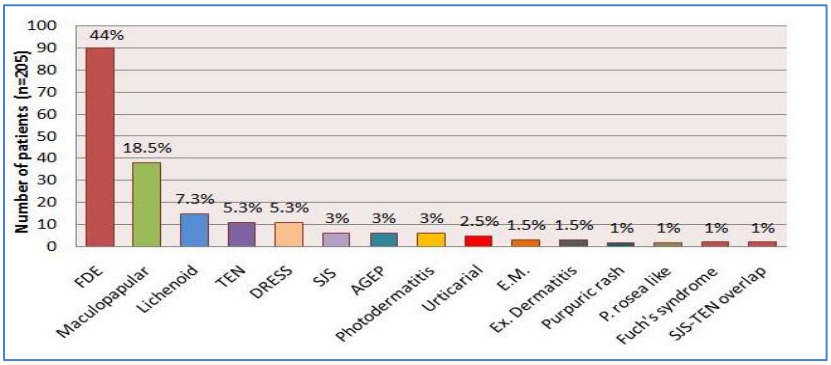

Fig 3: Clinical patterns of drug rash

Most common culprit drug group responsible for CADRs in our study was antimicrobials, seen in 68 (33.2%) patients followed by anti tubercular drugs in 43 (20.97%) of the patients. In 9 (4.39%) patients, the responsible drug remained unidentified (Table-1).

Table 1: Responsible class of drugs for CADRs

Class of offending drugs	No. of patients	Percentage
Antimicrobials	68	33.2
Antitubercular drugs	43	20.97
NSAIDS	36	17.56
Anticonvulsants	28	13.65
Chemotherapeutics	5	2.43
Hypouricaemic drugs	4	1.95
Fibrinolytics	3	1.46
Antifungals	3	1.46
Antiretrovirals	2	0.97
Antihistamines	2	0.97
Antileprosy	1	0.48
Antihypertensive drugs	1	0.48
Unknown	9	4.39
Total	205	100%

Various drugs and the number of patients in whom they were found to be as an offending agent, are shown in Table-2.

Table 2: Offending drugs

Offending drugs	No. (%age)	Other Offending drugs	No (%age)
Tinidazole	22 (9.09)	Levofloxacin	5 (2.06)
Ethambutol	19 (7.85)	Norfloxacin	5 (2.06)
Paracetamol	16 (6.61)	Ofloxacin	5 (2.06)
Phenytoin	15 (6.19)	Aceclofenac	5 (2.06)
Ciprofloxacin	14 (5.78)	Allopurinol	4 (1.65)
Isoniazid	12 (4.95)	Ibuprofen	4 (1.65)
Rifampicin	10 (4.13)	Diclofenac	4 (1.65)
Pyrazinamide	10 (4.13)	Others	58 (23.96)
Carbamezapine	8 (3.30)	Total	242 (100%)
Ornidazole	8 (3.30)		
Doxycycline	7 (2.89)		
Septran	6 (2.47)		

The result of analysis of correlation between pattern of rash and the culprit drug is illustrated in Table-3.

Table 3- Co relation between pattern of drug rash and offending drug

Drug rash	Common drugs	No. (%age)	Less common drugs	No (%age)
FDE	Tinidazole Ciprofloxacin Paracetamol	22 (9.09) 12 (4.95) 8 (3.30)	Doxycycline Ornidazole Norfloxacin Others	7 (2.89) 5 (2.06) 5 (2.06) 42 (17.35)
Maculopapular rash	**Rifampicin** **Phenytoin** **Pyrazinamide** Carbamezapine Ethambutol Isoniazid	**7 (2.89)** **6 (2.47)** **6 (2.47)** 5 (2.06) 5 (2.06) 5 (2.06)	Nimesulide Aceclofenac Streptomycin Levofloxacin Others drugs	2 (0.82) 2 (0.82) 2 (0.82) 2 (0.82) 15 (6.19)
Lichenoid rash	**Ethambutol** **Isoniazid**	**7 (2.89)** **5 (2.06)**	Pyrazinamide Levofloxacin Metoprolol	2 (0.82) 2 (0.82) 1 (0.41)
TEN	**Etoricoxib** Aceclofenac	**2 (0.82)** **2 (0.82)**	**Voriconazole** Allopurinol	1 (0.41) 1 (0.41)

	Phenytoin	2 (0.82)	Others	4 (1.65)
DRESS	**Phenytoin** **Allopurinol** **Rifampicin** **Streptomycin**	**3 (1.23)** **2 (0.82)** **2 (0.82)** **2 (0.82)**	**Carbamezapine** **Pyrazinamide** **Ethambutol** **Isoniazid** **Levofloxacin** **Dapsone**	1 (0.41) 1 (0.41) 1 (0.41) 1 (0.41) 1 (0.41) 1 (0.41)
Urticarial rash	**Ethambutol Pyrazinamide**	**3 (1.23)** **2 (0.82)**	**Isoniazid** **Rifampicin**	1 (0.41) 1 (0.41)
AGEP	**Ethambutol** **Griseofulvin**	**3 (1.23)** **1 (0.41)**	**Isoniazid** **Trebinafine**	1 (0.41) 1 (0.41)
SJS	**Paracetamol** **Phenytoin** **Capecitabine**	**2 (0.82)** **1 (0.41)** **1 (0.41)**	**Phenobarbitone** **Oxcarbazepine**	1 (0.41) 1 (0.41)
Photodermatitis	**Perfenidone** **Nitrofurantoin**	**3 (1.23)** **1 (0.41)**	**Carbamezapine** **Cefixime**	1 (0.41) 1 (0.41)
Exfoliative dermatitis	**Phenytoin** **Pyrazinamide**	**2 (0.82)** **2 (0.82)**	**Oxcarbazepine**	1 (0.41)
Erythema multiforme	**Paracetamol** **Naproxen**	**1 (0.41)** **1 (0.41)**	**Ornidazole**	1 (0.41)
Purpuric rash	**Phenytoin**	**1 (0.41)**	**Aceclofenac**	1 (0.41)
Pityriasis rosea like	**Paracetamol**	**1 (0.41)**	**Sodium valproate**	1 (0.41)
Fuch's syndrme	**Paracetamol**	**1 (0.41)**	**Diclofenac**	1 (0.41)
SJS-TEN overlap	**Aceclofenac**	**1 (0.41)**		

43(20.97%) of our patients had drug rash secondary to ATT. These patients had taken multiple drugs. All the patients who had drug rash secondary to ATT were rechallenged with anti tubercular drugs one by one and out of these, 15 patients (7.31% of the total) showed sensitivity to multiple drugs. Three patients (1.46% of the total) were found to be sensitive to three anti tubercular drugs, 2 patients (0.97% of the total) were found to be sensitive to four anti tubercular drugs.

Also,we analyzed systemic involvement with various types of drug rash. Haematological involvement was observed in 46(22.43%) and it was most commonly seen with macoulopapular drug rash (5.31%), followed by drug reaction with eosinophilia and systemic symptoms (DRESS) (4.39%) and further followed by exfoliative dermatitis (2.43%) (fig- 4).

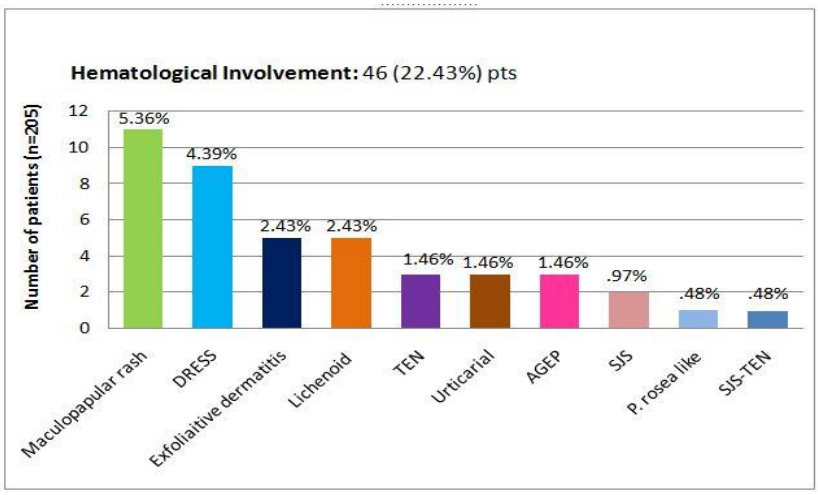

Fig 4: Systemic involvement (Hematological involvement)

Similarly, hepatotoxicity was most commonly observed with DRESS (4.39%), followed by maculopapular and TEN (3.9% in each) (fig- 5).

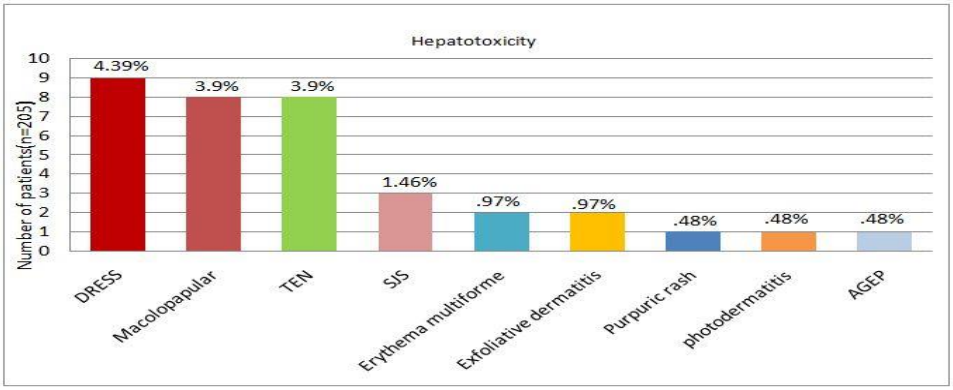

Fig 5: Systemic involvement (Hepatotoxicity)

13 (6.34%) of our patients had acute kidney injury and it was most commonly observed with maculopapular drug rash and TEN and was least commonly encountered in purpuric rash, photodermatitis and acute generalized exanthematous pustulosis (AGEP) (fig- 5).

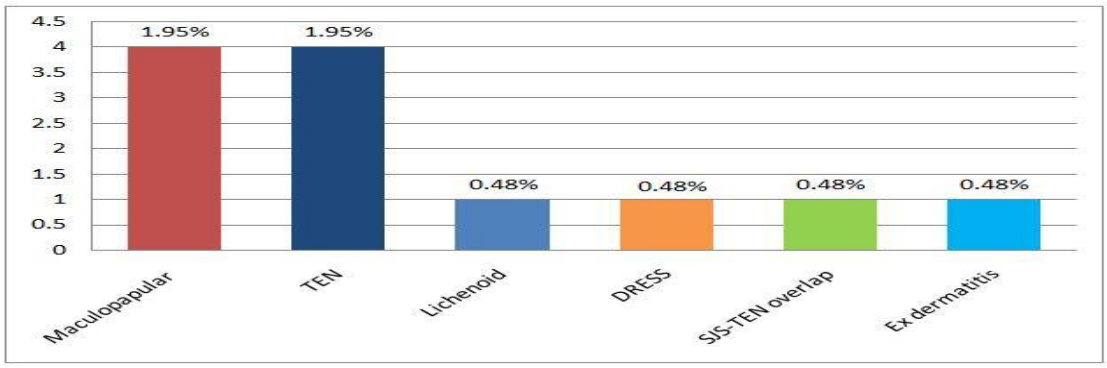

Fig 6: Systemic involvement (Acute kidney injury)

We further analyzed the culprit drugs involved in haematological involvement, hepatotoxicity and acute renal injury and the results are shown in Table-4.

- **Hematological**: Phenytoin - 8 (3.9%)

  Ethambutol - 7 (3.41%)

  Isoniazid - 6 (2.92%)

  Rifampicin/pyrazinamide/PCM - 4(1.95%) patients each

- **Hepatotoxicity**: Phenytoin - 8 (3.9%)
  Carbamezapine – 5 (2.43%)

  Ethambutol - 4 (1.95%)

  Isoniazid/PCM/Allopurinol - 3(1.46%) pts each

- **Acute kidney injury:** Phenytoin - 3(1.46%)

- Ethambutol/ pyazinamide - 2(0.97%) patients each

Fig 7: Most common drugs causing systemic involvement

Discussion

Any drug can cause drug reaction and cutaneous reactions are one of the most common types of adverse drug reactions.[3] Cutaneous adverse reactions have a wide range of clinical manifestations. They may vary from pruritus, urticaria, angioedema, maculopapular rash, erythema multiforme, fixed drug eruption to Steven Johnson syndrome and TEN.We analyzed the demographic profile of patients with CADRs as well as pattern, causative drugs and other characteristics of CADRs. In our study males outnumbered female patients which was similar to the studies done by James Jet al. and Sharma VK et al.[4,5] However, female preponderance has been observed in some studies.[2,3,6] Variation in demographic profile in different studies can be related to the difference in the demography of patients attending different clinics.The most common age group in our study was 21-40 years, accounting for 38% of the total patients. This was in concordance with previous studies.[6,7] However, Mahatme et al., Leape LL et al. and Hafner JW et al. observed that cutaneous drug reactions were more commonly seen in comparatively elder age group i.e. 51-60 years. [8, 9, 10]This difference can be explained by the variation in health care seeking behaviour of people in different regions.In the present study, minimum period of latency was observed in fixed drug reaction i.e. <2 hours and maximum latent period was observed in lichenoid drug reaction i.e. > 60 days. Earlier observers have also reported minimum latent period for fixed drug eruption.[11]69 (33.65%) of our patients had a history of multiple drugs intake. In these patients, the most likely culprit agent was considered based on review of literature and was confirmed by subsidence of rash on withdrawl of drug or rechallenge with smaller doses in case of ATT.. Polypharmacy can cause drug interactions, thereby leading to increased incidence of adverse drug reactions.

Among various morphological patterns of cutaneous adverse drug reactions, we found fixed drug eruption to be the most common which was seen in 33% of our patients. This was in concordance with two earlier studies.[6, 12] However, Mahatme et al. reported urticaria to be the most common pattern.[8] Some researchers have observed maculopapular or morbiliform eruption as most common morphological pattern.[5,7,13,14] SJS and TEN, the severe forms of CADRs were seen only in 3% and 1% respectively of our patients. In literature, higher incidence of SJS/ TEN has been reported in Indian studies.[5,12,15] Western studies have observed SJS/ TEN as a rarity.[16] Easy availability of over the counter drugs in Indian set up might be responsible for this higher incidence.In the present study, the most common responsible group for CADRs was antimicrobials, which accounted for 33.2% of the patients. Some of the previous studies have also reported antimicrobials to be the most common culprit group. Naldi L et al. found antimicrobials to be responsible in 38.6% of cases in their study.Pudukadan et al. and Jhaj R et al. observed the incidence of antimicrobials as a causative factor in 56.9% and 55.8% respectively in their studies.[3,6,17]

On subanalysis of culprit antimicrobial drugs, Tinidazole was found to be the most common implicated drug (in 9.09% of the patients). A six years study from Chandigarh, India, and another multicentric hospital study from Italy reported sulphonamides to be the predominant drug group causing CADRs.[3,5] Second commonest implicated drug group found in our study was antitubercular drugs (ATT) in 20.97% patients followed by non steroidal anti inflammatory drugs (NSAIDs) in 17.56% of the patients. Ruchika et al. reported NSAIDs to be the second leading group responsible in 21.90% whereas Sharma et al. observed NSAIDs being causative in 18% of the patients .[2,5] Variations in prescribing patterns in different regions may explain this.In our study, raised eosinophil counts were observed in patients with maculopapular drug rash, lichenoid drug rash, DRESS, SJS /TEN , AGEP, urticarial drug rash and exfoliative dermatitis. Some authors in literature have described peripheral eosinophil count to be of little diagnostic value in CADRs.[15] Since raised eosinophil counts were observed in various serious drug reactions in our study, we consider that it may be helpful in early stages to establish the diagnosis. We observed hepatotoxicity in 18.53% and acute kidney injury in 6.34% of our patients. Hepatotoxicity was most commonly seen with DRESS (4.39%), followed by maculopapular drug rash and TEN (3.9% each) and acute renal injury was more common in maculopapular drug rash and TEN (6.34% each). In literature, altered liver function tests have been described as an independent indicator of severity of CADRs.[18,19]

Conclusion

Cutaneous drug reactions are quite commonly encountered by dermatologists in their day to day practice. At present, there is no gold standard investigation available for diagnosing drug rash. Taking proper history such as which drug was taken prior to the eruption, for how long it was taken, whether the rash improved on withdrawl of the drug and if there was similar history of rash in the past helps in establishing the diagnosis. Rechallenge with smaller doses helps in confirming the causative agent. Morbidity and mortality can be reduced if CADRs are identified early. Patients should be sensitized and councelled to avoid readministration of the offending drugs as well as to avoid self administration of drugs. Education and counseling of patients can prevent morbidity and mortality due to cutaneous adverse drug reactions.

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