Section: General Medicine

Original Research Article

CLINICO-EPIDEMIOLOGICAL STUDY OF ADVERSE CUTANEOUS DRUG REACTION IN A TERTIARY CARE CENTRE

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Received : 18/11/2024
Received in revised form : 27/01/2025
Accepted : 11/02/2025

Keywords:
Adverse drug reaction, Adverse Cutaneous drug reaction, ACDR

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DOI: 10.47009/jamp.2025.7.1.137

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2025; 7 (1); 693-701

Abstract

Background: Adverse drug reaction constitute a major clinical problem in terms of human sufferings and increased health care costs. The aim is to determine the age, sex incidence and clinical pattern of drug eruptions and to evaluate the mortality associated with drug reactions. **Materials and Methods:** Eighty nine patients with adverse cutaneous drug reactions were recruited for this study during the year 2013 in the Department of Dermatology at Government Medical College Kozhikode, after satisfying the WHO causality grading "probable" **Result:** The mean age of patients with cutaneous drug eruptions was 40.77yrs.Most of them (22.47) were in the age group of 31-40.The male to female ratio was 1.47:1.The most common eruptions observed were maculopapular rash(22.5%), SJS(22.5%), and DHS(14.6%) and the most common causes were phenytoin(16.85%) and diclofenac(7.86%), ayurvedic (7.86%).The limitations of the study are that drug reactions reported in Departments other than Dermatology were not included. Patients with minor drug reaction would not have taken medical help. **Conclusion:** Maculopapular rash and SJS were the common type of cutaneous adverse drug reactions. Antimicrobials and anticonvulsants were the most common cause of cutaneous adverse drug reaction. Most common cause of SJS and TEN were antimicrobials and anticonvulsants respectively. Ciprofloxacin was the most common antimicrobial causing SJS. Among the anticonvulsants phenytoin and carbamazepine were most commonly incriminated for SJS and TEN respectively. Quinolones induced SJS are on the increase. Majority of erythrodermas were due to anti tuberculous treatment. Ayurvedic drugs can cause severe cutaneous adverse reactions like SJS and DHS. Newer antiepileptics like lamotrigine caused significant number of drug reaction. The pattern of ACDRs and the drugs causing them is changing. Knowledge of these drug eruptions and the causative drugs is very essential for the clinician in the present scenario.

INTRODUCTION

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 manifestation.[1]

Adverse cutaneous reaction to drugs are frequently seen in 2-3% of hospitalized patients.[1] There is a wide spectrum of cutaneous adverse drug reaction varying from transient maculopapular rash to toxic epidermal necrolysis. It is for this reason that an awareness of possible adverse cutaneous effect of drugs and the drugs most frequently associated with it is essential. The pattern of cutaneous adverse drug eruption and the drugs responsible for them keep changing every year. Incidence increases in proportion to the number of drugs prescribed.

Adverse drug reaction constitute a major clinical problem in terms of human suffering and increased health care costs. This study was therefore conducted to evaluate the clinical spectrum of all cutaneous adverse drug reaction, mortality associated with it and to establish the causal link between the suspected drug and the reaction by using the WHO causality definitions.

Objectives

To determine the age, sex incidence and clinical pattern of drug eruptions.

To evaluate the mortality associated with the drug reactions.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

MATERIALS AND METHODS

Study Design: Descriptive study
Study Setting: OP and IP patients in the Department of Dermatology, Government Medical College Kozhikode during the year 2013.
Sample Size: 89. All patients who satisfied the inclusion criteria and exclusion criteria were included in the study.
Study Duration: 1year
Inclusion Criteria

- Both OP and IP patients with no age limits with features of cutaneous drug reaction were included. Only cases with a WHO causality grading of "probable" were included in the study.
- A "probable" causal association is considered to be one where there is a reasonable time sequence, the event is unlikely to be attributable to concurrent disease or other medicines and a reasonable response is observed on de challenge
- According to WHO – UMC causality assessment system, causality of an adverse drug reaction can be classified as

1. **Certain**

- Event or laboratory test abnormality, with plausible time relationship to drug intake.
- Cannot be explained by disease or other drugs.
- Response to withdrawal plausible (pharmacologically, pathologically).
- Event definitive pharmacologically or phenomenologically.
- Re challenge satisfactory, if necessary.

2. **Probable**

- Event or laboratory test abnormality, with reasonable time relationship to drug intake.
- Unlikely to be attributed to disease or other drugs.
- Response to withdrawal clinically reasonable.
- Re challenge not required.

3. **Possible**

- Event or laboratory test abnormality, with reasonable time relationship to drug intake.
- Could also be explained by disease or other drugs.
- Information on drug withdrawal may be lacking or unclear.

4. **Unlikely**

- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible).
- Disease or other drugs provide plausible explanations.

5. **Conditional/ Unclassified**

- Event or laboratory test abnormality.
- More data for proper assessment needed or
- Additional data under examination.

6. **Un assessable/Unclassifiable**

- Report suggesting an adverse reaction.
- Cannot be judged because information is insufficient or contradictory.
- Data cannot be supplemented or verified

Exclusion Criteria

- Drug reactions where the drugs taken were not known are excluded from the study. Patients with a systemic cause for the cutaneous finding were excluded.

Method of Study
Diagnosis of Cutaneous drug reaction was based on history of drug ingestion, clinical findings and exclusion of other similar disorders. Diagnosis was confirmed by observing the disappearance of signs and symptoms after discontinuation of the suspected offending drug. Complete blood count, LFT, RFT, Serum electrolytes, RBS, Urine R/E &Microscopy, Absolute Eosinophil count were carried out in all patients. HBSAg, Anti HCV, HIV Screening, ANA, Tzanck Smear, Peripheral Smear, Chest X ray, USG Abdomen done in selected patients.
Statistical Analysis
Data were entered in Microsoft Excel spread sheet and analysed statistically using SPSS software for windows. Significance of association was analysed by calculating p value (which was considered significant when less than .05 with the help of Chi square test.

RESULTS

A total of 89 cases of cutaneous adverse drug reactions (CADRs) to 37 drugs have been included. The total number of new patients registered in Dermatology in the year 2013 were 14,126.
The incidence of CADRs in the patients seen at the Dermatology department was 6.3 per 1000 patients. The most common age group of the patients classified with CADRs was 31-40 yrs (with 20 patients) and the mean age was 40.77yrs, with the youngest being 6months old and the oldest being 77 years old. Extremes of age showed least number of patients with 7 and 4 patients in the age group 0-10 and >70 years age group respectively.
Male to Female ratio was 1.47 in this study, with 53 males (60%) and 36(40%) females.
The most common cutaneous adverse drug reaction seen in our patients were maculopapular rash and SJS each comprising about 22.5%(20/89), followed by DHS14.6(13/89), FDE 9(8/89), TEN 9(8/89), Urticaria 7.9(7/89), Erythroderma 4.5(4/89), SDRFE 2.2 (2/89). Bullous, Eczema, Angioedema, EM, Pustular, AGEP, Purpuric, each comprising 1.1(1/89).
Among the various rashes seen in males and females, sex predominance was not statistically significant. Antimicrobials and anticonvulsants contributed 25 cases (28%) each.
Phenytoin was the most common drug causing cutaneous adverse drug reaction (16.85%) followed by diclofenac and ayurvedic medication each comprising (7.86%).NSAIDS constitute(15.7%).Among the individual drugs diclofenac contributed 7 cases, ciprofloxacin 5, Lamotrigine 5 and carbamazepine 4 cases.
Fixed drug eruptions were encountered in 8 patients (8.9%) in this study. NSAIDS constituted the major

ISSN (O): 2687-5365; ISSN (P): 2753-6556

causative drugs (62.5%). Commonest causative agent was paracetamol (25%).

Among the 20 cases of Stevens Johnson syndrome, antimicrobials were most commonly incriminated, followed by anticonvulsants. Ciprofloxacin was the most common antimicrobial agent causing SJS. One patient died of SJS due to ATT.

Anticonvulsants were the most common cause of maculopapular rash (35%) with phenytoin contributing (30%) of the cases.

Anticonvulsants were the most common cause of DHS (61.53%) in which phenytoin and Lamotrigine contributes (30.7%) each. Anticonvulsants contribute 62.5% of the TEN cases of which carbamazepine predominates (25%).One patient died of TEN due to dapsone.

Antimicrobials were the most common cause of urticaria comprising about (57.14%). Antituberculous drugs were the most common cause of erythroderma comprising (75%).

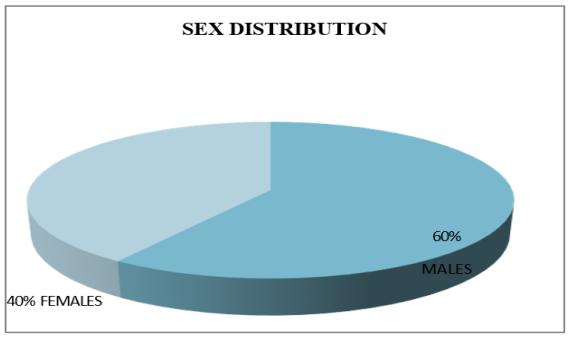

Figure 1: Sex distribution

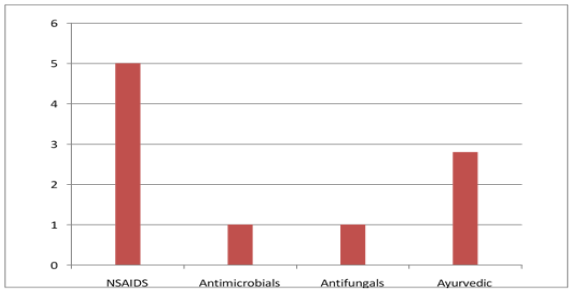

Figure 2: Fixed Drug Eruption

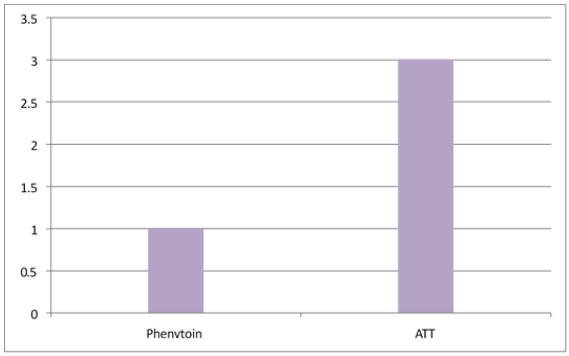

Figure 3: Erythroderma

The mean incubation period for maculopapular rash was 11 days, for Stevens Johnson syndrome it was 8 days, for TEN 23 days and for DHS 18 days. The incubation period for FDE ranged from 3hours to 4 days with mean incubation period of 2 days. The incubation period of urticaria ranged from 1hour to 2 weeks, with the median incubation period being 3 days.

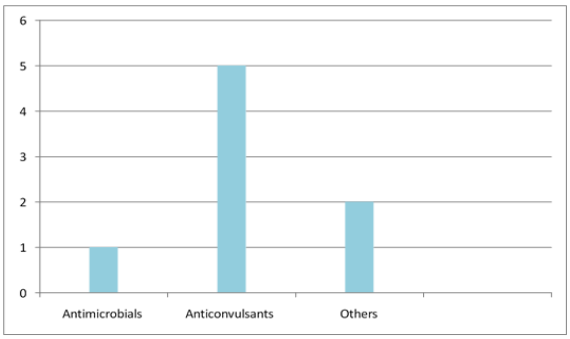

Figure 4: Toxic Epidermal Necrolysis

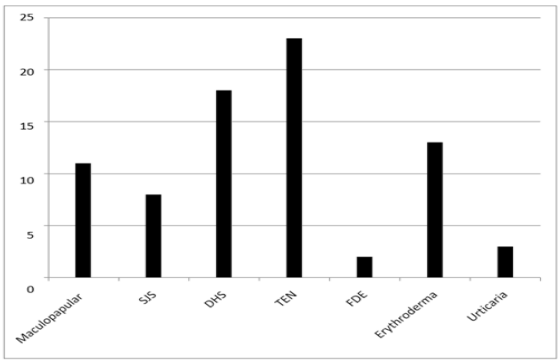

Figure 5: Relation of rash type with incubation period

Photo 1: Erythroderma due to ATT

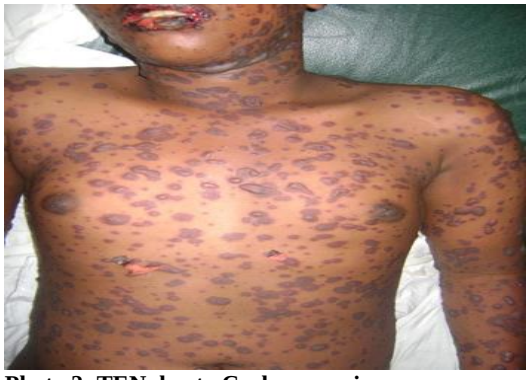

Photo 2: TEN due to Carbamazepine

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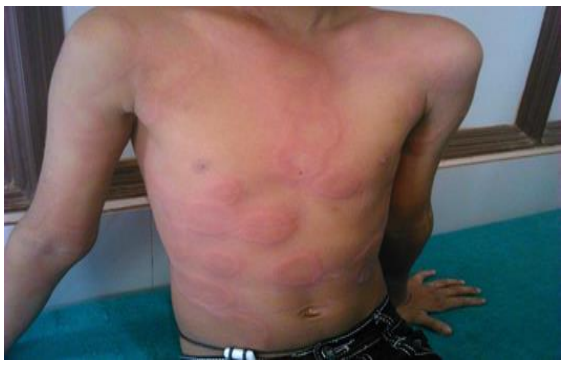

Photo 3: Urticaria due to Cefixime

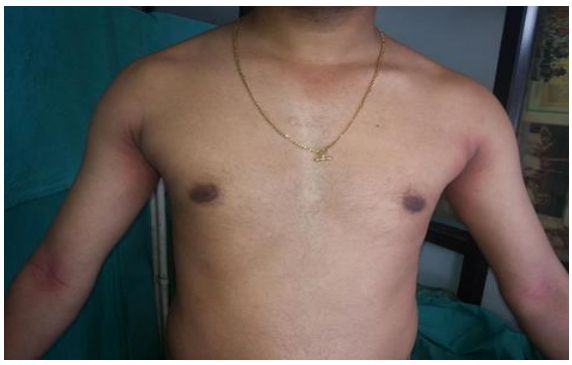

Photo 5: SDRIFE due to Diclofenac

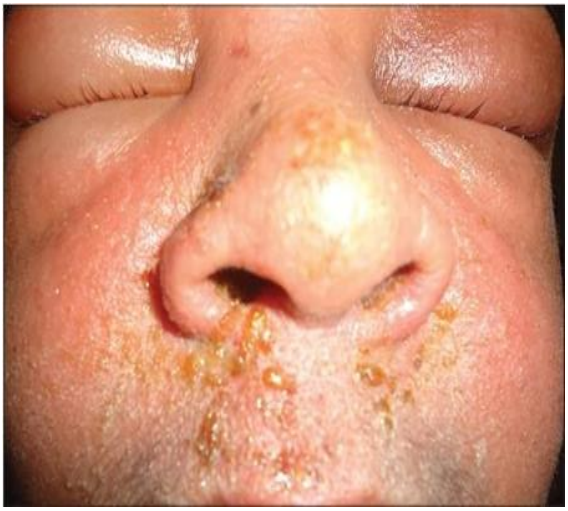

Photo 4: DHS due to Phenytoin

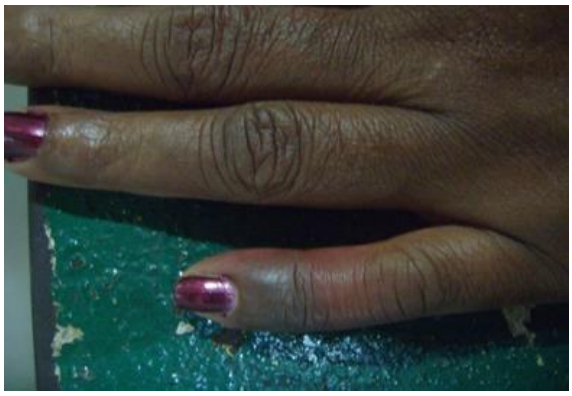

Photo 6: FDE due to Diclofenac

Table 1: incidence of cutaneous adverse drug reaction.

Total number of patients	Number of CADRs	Incidence
14,126	89	6.3

Table 2: age distribution

Age distribution	Number of patients
0-10	7
11-20	8
21-30	11
31-40	20
41-50	15
51-60	14
61-70	10
>70	4

Table 3: cutaneous adverse drug reaction

Rash type	Number (%)
SJS	20(22.5)
Maculopapular	20(22.5)
DHS	13(14.6)
FDE	8(9)
TEN	8(9)
Urticaria	7(7.9)
Erythroderma	4(4.5)
SDRIFE	2(2.2)
Bullous	1(1.1)
Eczema	1(1.1)
Angioedema	1(1.1)
EM	1(1.1)
Pustular	1(1.1)
AGEP	1(1.1)
Purpuric	1(1.1)
Total	89

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 4: cadrs among males and females

Rash Type	Sex		Total	Chi square	Significance (p value)
	Male	Female			
Maculopapular	14	6	20	1.169	0.280
FDE	5	3	8	0.032	0.859
Erythroderma	2	2	4	0.159	0.690
AGEP	0	1	1	1.489	0.222
Angioedema	0	1	1	1.489	0.222
Bullous	0	1	1	1.489	0.222
DHS	7	6	13	0.206	0.650
Eczema	1	0	1	0.687	0.407
Purpuric	1	0	1	0.687	0.407
Pustular	1	0	1	0.687	0.407
SDRIFE	1	1	2	0.077	0.781
SJS	10	10	20	0.977	0.323
TEN	4	4	8	0.333	0.564
Urticaria	6	1	7	2.159	0.142
EM	1	0	1	0.687	0.407
Total	53	36	89		

Table 5: Implicated Drugs

Drugs	NO (%)
Antimicrobials	
Penicillin	2
Amoxicillin	2
Cefadroxil	1
Cefixime	1
Cefotaxime	1
Ciproflaxacin	5
Dapsone	3
Cotrimoxazole	1
Doxycycline	1
Ofloxacin	2
Moxifloxacin	1
Piperacillin	1
Roxithromycin	1
Vancomycin	1
Amikacin	1
Gentamycin	1
Total	25(28)
Anticonvulsants	
Phenytoin	15
Carbamazepine	4
Phenobarbitone	1
Lamotrigine	5
Total	25(28)
Analgesics	2
Aspirin	7
Diclofenac	2
Mefanamic acid	1
Piroxicam	2
Paracetamol Total	14(15.7)
Antituberculous	5(5.6)
Ayurvedic	7(7.8)
Antifungals	
Fluconazole	3
Griseofulvin	1
Total	4(4.4)
Antivirals	1
Acyclovir Total	1(1.1)
Antihypertensives	1
Amlodipine Total	1(1.1)
Anticoagulants	1
Warfarin	1(1.1)
Total	
Others	
Allopurinol	2
Disulfiram	1
Methotrexate	1
Salazopyrine	1
Tamsulosin	1
Total	6(6.7)
Total	89

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 6: Stevens Johnson Syndrome

Antimicrobials	
Ciprofloxacin	3
Ofloxacin	1
Piperacillin	1
Dapsone	1
Amikacin	1
Total	7
Anticonvulsants	
Phenytoin	2
Carbamazepine	1
Total	3
Antivirals	1
ATT	1
Ayurvedic	1
NSAIDS/Analgesics/Antipyretics	
Diclofenac	2
Mefanamic acid	1
Total	3
Antifungals	
Fluconazole	1
Griseofulvin	1
Total	2
Others	2
Total	20

Table 7: Maculopapular Rash

Antimicrobials	
Amoxicillin	1
Cefadroxil	1
Ciprofloxacin	1
Cefotaxime	1
Doxycycline	1
Vancomycin	1
Total	6
Anticonvulsants	
Phenytoin	6
Carbamazepine	1
Total	7
NSAIDS/Analgesics/Antipyretics	
Diclofenac	2
Ayurvedic	2
Antifungals	1
Anticoagulants	1
Others	1
Total	20

Table:8 Drug Hypersensitivity Syndrome

Anticonvulsants	
Phenytoin	4
Lamotrigine	4
Total	8
Ayurvedic	1
Antimicrobials	
Dapsone	1
Penicillin	1
Total	2
NSAIDS/Analgesics/Antipyretics	1
Others	1
Total	13

Table 9: Urticaria

Antimicrobials Cefixime	1
Gentamycin	1
Ofloxacin	1
Moxifloxacin	1
Total	4
Antihypertensives	1
Anticonvulsants	1
NSAIDS/Analgesics/Antipyretics	1
Total	7

ISSN (O): 2687-5365; ISSN (P): 2753-6556

DISCUSSION

Adverse drug reactions form an important and common problem in both inpatient and outpatient setting. It is important to keep oneself updated with the knowledge on latest trends in drug reaction with newer drugs, newer manifestations of older drugs, diagnosis, and management of these drug reactions.

This study was done in Govt. Medical College, Kozhikode, a tertiary care referral hospital with large outpatient and inpatient numbers. A total of 89 cutaneous adverse reactions were documented, over a period of one year.

The incidence of cutaneous ADRs in this study was found to be 6.3 per 1000 patients. Most of the studies on CADRs from India reported an incidence of >10 per 1000 patients. Mehta et al reported an incidence of 10 per thousand and Mani et al reported an incidence of 12 per thousand patients. [2,3] The lower incidence of CADRs in our study as compared to above may be because of minor CADRs being dealt by other departments in the tertiary care centre. Conversely the incidence of severe drug reaction are noted more as it is a referral centre.

We observed a male preponderance(M:F=1.47:1) as already been reported.[3,4] Although not entirely clear, these differences have been attributed to gender related differences in pharmacokinetic, immunological and hormonal factors as well as difference in the hospital seeking behaviour among males and females.

In this study the maximum number of cases were seen in the age group of 31-40(20 cases), followed by 15 cases in 41-50 age group. As has been seen previously,[4] in this study also the number of cases became lesser with extremes of age, with 7 cases in 0-10 yrs and 4 cases in age group >70yrs age. This may because of the number of the drugs exposed is less.

Of the various types of cutaneous adverse drug reactions in all age groups, commonest patterns were maculopapular rash (22.5%) and Stevens Johnson syndrome (22.5%) followed by DHS (14.6%) and FDE (9%). Malhotra et al, reported morbilliform rash in 29.63%, SJS/TEN in 22.22% and urticaria in 9.26% cases as common patterns of reaction.5Jhaj et al reported 50% cases of morbilliform rash,21% cases of urticaria,13.9% cases of SJS and 4.9% cases of TEN.[6]

The high incidence of SJS (22.5%) in this study may be attributed to the fact that, being a tertiary care institute, severe cases of drug reactions were referred here from other hospitals. Also due to the increased number of referred cases from Neuromedicine and Neuro surgery department, mainly induced by anticonvulsants. Mortality of SJS and TEN was found to be 5% and 12.5% respectively in this study. The average reported mortality rate for SJS is 1-5% and up to 25-35% for TEN.[7] Barvalia et al reported a mortality of 9% for SJS and 26.7% for TEN.[8] Low mortality in our study might be attributed to the use of Intravenous immunoglobulin in the patients.

The most common cause of maculopapular rash in this study were anticonvulsants (35%) mainly phenytoin, followed by antimicrobial drugs (30%). This was similar to various other studies. [3,9,10,11] Anticonvulsants as a cause of maculopapular rashes could partially be explained by the fact that prophylactic anticonvulsants given for increased number of head injury cases came in neurosurgery department of our hospital.

Drug hypersensitivity syndrome was seen in (14.6%). Anticonvulsants were the most common cause. This was similar to various other studies.[12,13] Akpinar et al reported 8.5% of DHS.[14] Noel et al reported 4% cases.[15]

Fixed drug eruptions were encountered in 8.9% of the patients. NSAIDS constituted the major causative drugs (62.5%). Commonest causative agent was paracetamol (25%). FDE due to paracetamol was reported previously by Drummond et al and Thomas et al,[16,17] FDE due to Diclofenac, Naproxen and Celecoxib were reported previously.[18,19] Most of the earlier studies showed increased proportion of sulphonamides in the causation of FDE.[4,20] This difference may due to the reduced usage of sulphonamides nowadays.

Stevens Johnson syndrome constituted 22.5% of all cases while TEN constituted 9% of all cases. SJS was most commonly due to antimicrobials. Ciprofloxacin was the most drug causing SJS. Anticonvulsants were the most frequent drugs implicated for TEN in our study, as is reported from Malaysia.[21] whereas antimicrobials were the commonest drugs in other studies. [22-24] This was probably due to increased use of antibiotics in developed countries. Drugs implicated reflect the wide variation in the drugs prescribed from place to place.

Seven cases of urticaria (7.8%) have been noted similar to study conducted by Noel et al.[15] The most common cause of urticaria was antimicrobial drugs, followed by analgesics and antipyretics. This was also similar to the other studies .[11,25,26]

Four cases of erythroderma (4.4%) have been noted similar to a previous study.[15] About 75% of erythroderma was due to ATT. This is similar to the previous studies.[27] Pyrazinamide induced erythroderma has been reported by Jaisuresh.[28] Zhang et al reported Efavirenz induced exfoliative dermatitis.[29]

Systemic ayurvedic drug intake resulted in 2 maculopapular rash, 1 SJS, 1FDE,1DHS,1 case each of purpura and eczema in this study contrary to the popular belief. Chowdhury et al also reported herbal medicine induced Stevens Johnson syndrome.[30]

Symmetrical drug related intertriginous and flexural exanthema (SDRIFE) has been reported in two patients due to Diclofenac and ATT. Binitha et al reported SDRIFE due to Ranitidine.[31] Sikar Akturk et al reported SDRIFE due to oral Metronidazole.[32] Hydroxyzine induced Baboon syndrome reported by Akkari et al.[33]

ISSN (O): 2687-5365; ISSN (P): 2753-6556

CONCLUSION

- The incidence of CADRs among dermatology patients was 6.3 per thousand patients in 2013.
- Cutaneous ADRs occur most commonly in the 31-40 years age group and the mean age was 40.77yrs.
- Male to Female ratio was 1.47 in this study.
- Maculopapular rash and SJS were the common type of cutaneous adverse drug reactions.
- The second most common CADR was Drug Hypersensitivity Syndrome.
- There was no significant sex predilection noted in any of the types of drug reaction.
- Antimicrobials and Anticonvulsants were the most common cause of CADRs and the most common drugs were phenytoin (16.85%) diclofenac (7.86%), and ayurvedic (7.86%).
- Antimicrobials were the most common cause of maculopapular reactions, Stevens Johnson syndrome and urticaria.
- Anticonvulsants especially phenytoin and Lamotrigine were the most common causes of Drug Hypersensitivity syndrome.
- NSAIDS were the most common cause of FDE especially Paracetamol.
- The most common type of CADR to NSAIDs was FDE, maculopapular rash, SJS.
- Maculopapular rash, SJS and DHS were the most common type of CADR caused by Phenytoin.
- Most common cause of SJS was antimicrobials and the most common cause of TEN was anticonvulsants.
- Ciprofloxacin was the most common antimicrobial agent causing SJS.
- Among the anticonvulsant phenytoin and carbamazepine were most commonly incriminated for SJS and TEN respectively.
- Mortality due to SJS and TEN are decreasing.
- Antimicrobials were the most common cause of urticaria especially quinolones.
- Majority of erythrodermas were due to anti tuberculous treatment.
- Ayurvedic treatment induced SJS, DHS, FDE, maculopapular rash, eczema, purpura are found in the study.
- Two cases of Symmetrical Drug related Intertriginous and flexural exanthema following ATT and Diclofenac were also recorded.
- Mean incubation period for the various drug eruptions was 11 days for maculopapular reactions,8 days for Stevens Johnson syndrome,23 days for Toxic Epidermal Necrolysis,18 days for drug hypersensitivity syndrome,3 days for urticaria and 2 days for fixed drug eruptions.
- Though there were many similarities in the findings between our study and other reported studies following were some unique findings in our study.
- Quinolones induced SJS are rising.
- Newer anti epileptics like lamotrigine causing significant number of adverse cutaneous drug reaction.
- Ayurvedic drug can also induce severe cutaneous adverse reaction contrary to the popular belief.
- Anticonvulsants induced CADRs are increasing.

Summary

Cutaneous adverse drug reactions are an important group of disorders which pose considerable amount of diagnostic and therapeutic challenges. The incidence of CADRs is estimated to be 1-2% in the general population.

Newer insights have been developing in the field of factors affecting CADRs and the need for studies in the Indian population regarding the newer trends in cutaneous adverse effects is immense.

This study was thus aimed at assessing the age, sex incidence and clinical pattern of cutaneous drug eruptions in the IP and OP patients.

The sampling comprised of 89 patients of CADRs over a period of one year from January 2013 to December 2013.

These patients were assessed using the WHO based algorithm of causality assessment of adverse drug reactions. A total of 89 cases of cutaneous adverse drug reactions to 37 drugs have been included. The incidence of CADRs in the patients seen at the Dermatology department was 6.3 per thousand patients. CADRs were seen most commonly in the 31-40 years age group with mean age of 40.77yrs. There was progressive decline in the number of CADRs towards the extremes of age.

The most common cutaneous adverse drug reaction seen in our patients were maculopapular rash and Stevens Johnson syndrome in 22.5% each, Drug Hypersensitivity Syndrome in 14.6%, fixed drug eruption and toxic epidermal necrolysis in 9% each, urticaria in 4.5%.

Male to Female ratio was 1.47 in this study. Maculopapular rash and SJS were the common type of cutaneous adverse drug reactions. The second most common CADR was Drug Hypersensitivity Syndrome. There was no significant sex predeliction noted in any of the types of drug reaction.

Antimicrobials and Anticonvulsants were the most common cause of CADRs. Antimicrobials were the most common cause of maculopapular reactions, Stevens Johnson syndrome and urticaria. Anticonvulsants especially phenytoin and Lamotrigine were the most common causes of Drug Hypersensitivity syndrome. NSAIDS were the most common cause of FDE especially Paracetamol. The most common type of CADR to NSAIDs was FDE, maculopapular rash, and SJS. Maculopapular rash, SJS and DHS were the most common type of CADR caused by Phenytoin

Most common cause of SJS was antimicrobials and the most common cause of TEN was anticonvulsants. Ciprofloxacin was the most common antimicrobial

ISSN (O): 2687-5365; ISSN (P): 2753-6556

causing SJS. Among the anticonvulsant phenytoin and carbamazepine were most commonly incriminated for SJS and TEN respectively.

Antimicrobials were the most common cause of urticaria especially quinolones. Majority of erythrodermas were due to anti tuberculous treatment. Ayurvedic treatment induced SJS, DHS, FDE, maculopapular rash, eczema, purpura are found in the study. Two cases of Symmetrical Drug related Intertriginous and flexural exanthema following ATT and diclofenac were noted.

Mean incubation period for the various drug eruptions were in concordance with other studies. It was 11 days for maculopapular reactions,8 days for Stevens Johnson syndrome,23 days for Toxic Epidermal Necrolysis,18 days for drug hypersensitivity syndrome,3 days for urticaria and 2 days for fixed drug eruptions. The advantages of this study are it provides newer trends in cutaneous adverse drug reactions, and is potential source of information on drug and host related factors for drug allergies.

Future research should focus on the genetic factors in relation to CADRs and molecular level evaluation should be done for better understanding of the pathophysiology of various adverse drug reactions. Therefore it would be useful for every institution to maintain a drug reaction registry.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556