RESEARCH

CLINICO-EPIDEMIOLOGICAL PROFILE OF CUTANEOUS ADVERSE DRUG REACTIONS AT RURAL TERTIARY CARE CENTRE

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Abstract

Background: Cutaneous adverse drug reactions (CADRs), also known as toxidermia, are skin manifestations resulting from systemic drug administration and it constituted 10%-30% among all reported adverse drug reactions (ADRs). These reactions range from mild morbilliform drug rash to much more severe reactions. **Materials and Methods:** A retrospective observational study was conducted at dermatology outpatient department of rural based tertiary care center for a duration of 03 years from August 2019 to July 2022, a total of 211 patients who had been clinically diagnosed or were suspected to have drug reactions were studied. **Result:** In this observation there was male preponderance (59.72%) and majority of patients were in their 3rd and 4th decade (40.28%) with maculopapular drug rash (33.17%) being most common clinical profile of CADRs, followed by urticaria (23.70%). Less frequently seen CADRs were acneiform eruptions (21), hair Loss (9), photodermatitis (9), generalised pruritus (7), erythroderma (2), pityriasis rosea (2), Stevens Johnson Syndrome-Toxic Epidermal Necrolysis (SJS-TEN) (4), lichenoid drug eruptions (3), Vasculitis (1) and pustular drug eruption (1). The most common group of drugs causing CADRs were antibiotics (40.28%), followed by NSAIDs (28.43%). **Conclusion:** Cutaneous Adverse Drug Reactions (CADRs) are price we pay for the benefits of modern drug therapy; knowledge of these reactions is important for treating physician as prompt recognition and treatment can prove lifesaving.

INTRODUCTION

The WHO defines an adverse drug reaction is as "any response to drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function".[1] Around10%- 30% of ADRs are reportedly cutaneous in nature.[2,3]

Six types of adverse drug reaction have been identified: dose related, non-dose related, dose related and time related, time- related, withdrawal and failure of therapy.[1]

Cutaneous drug reaction of have varied morphological presentation from mild reactions like morbilliform rash, urticaria to life threatening reaction like vasculitis, Steven Johnson syndrome, toxic epidermal necrolysis. As medical science is constantly evolving and new therapies, drugs and vaccines are constantly being developed, there is a significant risk of development of cutaneous adverse drug reaction. Cutaneous lesions due to other disorder may mimic the lesions of adverse drug reaction and many mild adverse drug reactions like morbilliform rash goes unreported, so the morbidity and mortality related to it cannot be estimated.[2]

Many drugs have specific presentation, so proper knowledge of it can help in narrowing down the spectrum of causative drug related to reaction, early recognition and stopping of offending agent and appropriate treatment can help to reduce mortality related to drug reaction.

The aim of this study is to identify the clinical presentations of cutaneous drug reactions in early stage in rural set up and thereby helping to prevent their extension into life threatening entity.

MATERIALS AND METHODS

This retrospective observational study was conducted at dermatology outpatient department of rural based tertiary care center to find out common

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clinical presentations of CADRs and drugs responsible for them. The duration of observation was 03 years from August 2019 to July 2022. A record of total of 211 patients who had been clinically diagnosed or were suspected to have drug reactions secondary to allopathic medicines were studied. The complete records in terms of detailed history, demographic profile of patient, presenting complaints, duration of lesions, drugs taken (monotherapy or polytherapy) before appearance of reaction, past history, family history and history of any associated systemic illnesses were considered for the study. Data were recorded in Microsoft excel, analysed and expressed in frequency and percentage.

RESULTS

Out of total 211 patients 126(59.72%) were male and 85 were female (40.28%), with male to female ratio being 1.48:1. [Figure 1] Majority of patients were in their 3rd decade (58) and 4th decade (44). [Figure 2] The mean age observed in our patients was 29.96 years and the range was 3months – 80 years.

The most common clinical patterns of CADRs in this observation was maculopapular rash seen in 33.17% patients, i.e 46 male and 24 females, followed by in descending order urticaria affecting 23.70% patients (27 male and 23 female) FDE in 9.95% (12 male and 9 female), EM seen in 4.27% (5 male and 4 female), SJS-TEN among 1.90% (3males and 1 female), angioedema seen in 1.42% (2 male and 1female). Others CADRs includes seen in 25.59% (31 males & 23 females), which includes generalised pruritus, acneiform eruptions, lichenoid drug reaction, Telogen effluvium, acute generalised eruptive pustulosis (AGEP), erythroderma, vasculitis and photodermatitis. [Table 1]

In our study, antibiotics were found to cause CADRs among 85(40.28%) of patients, followed by NSAIDs affecting 60 (28.44%) patients, antiepileptic 21(9.95%), covid vaccine 7 (3.32%) and other group of drugs like anti-fungal, antimalarial, oral corticosteroids, antipsychotic, antihypertensive, levamisole, antidiabetics, warfarin, diuretics, heparin affecting 38(18.01%). [Table 2]

Among patients presented with maculopapular rash most common drug implicated was penicillin group of antibiotics (11), and diclofenac, ibuprofen and nimesulide were responsible for 9, 4 and 3 cases respectively.

Urticaria the most commonly caused by cephalosporins (9) especially in paediatric age group, followed by NSAIDs among which diclofenac 8 and ibuprofen 6 cases each, penicillin and fluroquinolones 7 of each case. Post covid vaccination 6 cases of urticaria were noted.

Carbamazepine among antiepileptic group and nimesulide among NSAIDS were found to cause 2 cases of SJS – TEN each. FDE was seen among 21 cases most common drug implicated were NSAIDs 12(20%) and antibiotics 8 (9.52%). Total 9 cases of erythema multiforme were noted, in which cephalosporins, penicillins and fluroquinolone group of antibiotics were responsible for 02 cases each and NSAIDs seen in 3 (5%) cases. Post covid vaccination vasculitis seen in 1 patient. [Table 3]

The mean duration of drug intake and emergence of symptoms was evaluated, the lowest time was recorded for angioedema (6 hrs) and longest for lichenoid drug eruption (10 days). The mean duration for other CADRs were FDE (20 hrs), urticaria (30.27 hrs), SJS (3.45 days), TEN (3.78 days), vasculitis, AGEP, pruritus and pityriasis rosea (4 days), exfoliative dermatitis (7 days) and acneiform eruption in (8 days).

Between monotherapy and polytherapy, there was no discernible difference in clinical presentation.

Less frequently seen CADRs were acneiform eruptions (21), hair Loss (9), photodermatitis (9), generalised pruritus (7), erythroderma (2), pityriasis rosea (2), lichenoid drug eruptions (3) and pustular drug eruption (1).

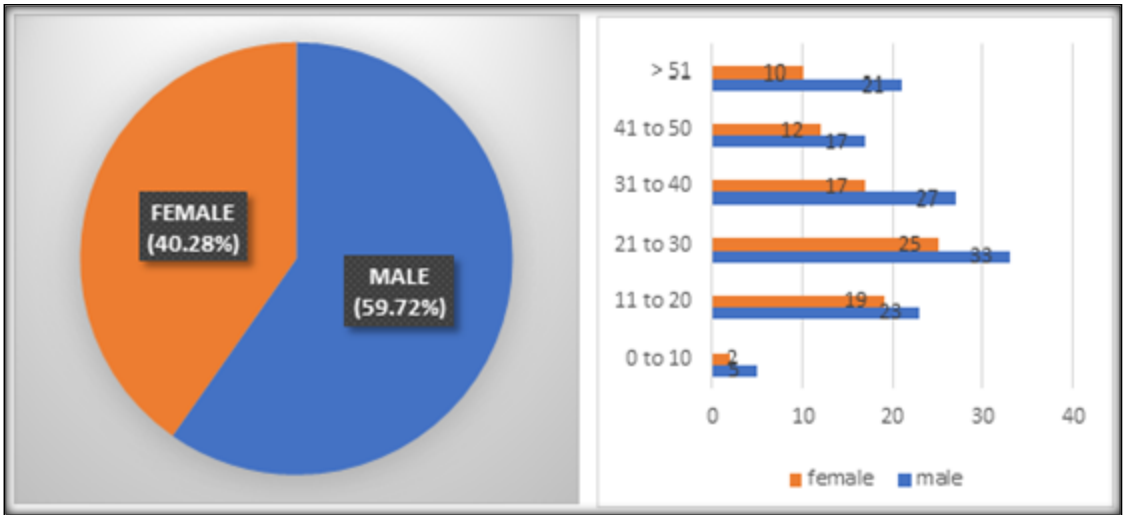

Figure 1: Sex distribution

Figure 2: Age distribution

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Table 1: Sex wise distribution of various CADRs

CADRs Profile	Sex		Total
	Male	Female	
Maculopapular	46	24	70
Urticaria	27	23	50
FDE	12	9	21
EM	5	4	9
SJS-TEN	3	1	4
Angioedema	2	1	3
Others	31	23	54
Total	126	85	211

Table 2: CADRs and Drug Groups responsible for them

Drug Groups	CADR Profile							Total
	Maculopapular Rash	Urticaria	FDE	EM	SJS-TEN	Angioedema	Other CADRs	
Antibiotics	33 (38.82%)	27 (31.76%)	9 (10.59%)	6 (7.06%)	0	1 (1.18%)	9 (10.59%)	85 (40.28%)
NSAIDs	18 (30%)	16 (26.67%)	12 (20%)	3 (5%)	2 (3.33%)	2 (3.33%)	7 (11.67%)	60 (28.44%)
Antiepileptics	19 (90.48%)	0	0	0	2 (9.52%)	0	0	21 (9.52%)
Covid Vaccine	0	6 (85.71%)	0	0	0	0	1 (14.29%)	7 (3.32%)
Others	0	1 (2.63%)	0	0	0	0	37 (97.37%)	38 (18.01%)
Total	70	50	21	9	4	3	54	211

Table 3: Drugs Implicated in various CADRs

Drugs		CADR Profile							Total
		Maculopapular Rash	Urticaria	FDE	EM	SJS-TEN	Angio-edema	Other CADRs	
Antibiotics	Cephalosporins	9	9	1	2	0	1	3	25
	Penicillins	11	7	1	2	0	0	0	21
	Fluroquinolones	6	7	1	2	0	0	2	18
	Co-trimoxazole	2	1	0	0	0	0	0	3
	Anti-tuberculous treatment (ATT)	3	0	0	0	0	0	4	7
	Others	2	3	6	0	0	0	0	11
NSAIDs	Diclofenac	9	8	4	1	0	2	5	29
	Ibuprofen	4	6	5	1	0	0	0	16
	Others	5	2	3	1	2	0	2	15
Antiepileptics	Phenytoin	6	0	0	0	0	0	0	6
	Carbamazepine	13	0	0	0	2	0	0	15
Covid vaccination		0	6	0	0	0	0	1	7
Others		0	1	0	0	0	0	37	38
Total		70	50	21	9	4	3	54	211

DISCUSSION

Prevalence of ADRs was 7% of hospital admissions, and cutaneous ADRs were accountable for 2-3% of the overall hospital admissions.[2,4]

Adverse cutaneous drug reactions are due to immunologic and non-immunologic mechanism. Immunological reactions also known as drug allergy require activation of host immunological pathway and overdosages, side effects, exacerbation of preexisting conditions, cumulative toxicity, drug induced chromosomal damage, teratogenicity etc. are non-immunologic mediated.[5]

In our study and also in other various studies there was male predominance noted.[6,7] As previous studies state that maximum patients were in 3rd and 4th decade which is consistent with our study. Patients among age group of 20-49 years were most commonly affected due to antibiotics group of drugs, most probably due to increase exposure to antibiotics among this age group.[8] In other study conducted by Kauppinen,[9] the maximum number of cases were seen in the 6th decade, this can be due to the increased use of medications by the elderly, increased potential for drug-drug interactions and altered drug handling by the body. The differences across the research might be attributed to geographical differences in the population's health care seeking behaviour.[10]

The most frequent morphological patterns of cutaneous adverse medication reactions identified in prior studies included exanthematous, urticarial and/or angioedema, Fixed Drug Eruption, and Erythema Multiforme.[11] The majority of earlier investigations have shown results that consistent with those of our study. The most typical kind of eruption is maculopapular, which is followed by urticaria, and/or angioedema and FDE.

According to a study from South India, maculopapular rash and FDE were the two most

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frequent cutaneous adverse drug eruptions.[12] This difference may result from various drug use habits and different characteristics of various ethnic groups.

In oppose to the previous studies,[13] in our study most common cause of maculopapular rash was antibiotics 33 cases out of 70 mainly by the penicillin group of drugs.

Contrary to Mehta TK et al,[7] Kuppinen K et al,[9] and Kaur S et al,[14] findings NSAIDS accounted for the most prevalent medication categories to cause FDE mostly caused by ibuprofen and diclofenac followed by antibiotics,[9] which were responsible for 08 instances, Tetracycline was listed by Pasricha,[15] as the most typical FDE cause.[16] Dapsone was the most frequent cause of FDE in a report from South Africa,[17] but just one incidence of dapsone-induced FDE was identified in our investigation. Despite being relatively common, this presumably reflects some regional and/or ethnic diversity. In contrast to earlier studies, antibiotics were found most common group of drugs causing urticaria in our study.[13]

In the majority of the studies,[17,18] antibiotics were the most often implicated medicines in SJS-TEN, in contrast to our study that anticonvulsants and NSAIDS were implicated in 2 of each case, mostly because of carbamazepine. In our study, one patient's condition deteriorated and succumbed as a result of SJS-TEN.

Antibiotics were the primary cause of EM in our study, whereas lichenoid drug eruptions were caused by antihypertensives (amlodepine, atenolol), antidiabetics (glibenclamide), and antifungals (griseofulvin). Lichenoid eruptions were seen in fifth decade, while the 21–40 age range was most affected by EM. ATT seen in causation of maculopapular rash and generalised pruritus in our study.

In accordance with the preceding studies,[19] Antibiotics accounted for 85 (40.28%) of the medications in our study. The other frequent offenders are NSAIDs, anticonvulsants (phenytoin and carbamazepine).[10] Antibiotics and NSAIDs are the pharmaceuticals most regularly prescribed in public and private hospitals as well as widely used by the general population to self-medicate for minor alignment, which may explain why these drugs cause the majority of responses.

In our study patients on polytherapy were 31(14.69%). According to a study by Anderson et al, patients undergoing monotherapy had a considerably reduced risk of CADRs than those getting polytherapy. In their study, 21% of patients receiving monotherapy had CADRs, compared to 60% of those receiving polypharmacy. Other studies done by Castro-Pastrana et al and Kumar et al states the same. Due to the higher prevalence of polypharmacy among senior patients, polypharmacy is a well-known predictor of cutaneous adverse drug reactions among them.

Apart from monotherapy and polypharmacy, factors like ethnicity, age, pregnancy, breast feeding, pre-existing renal and liver issues, cardiovascular disorders are few other considerations while assessing the severity of CADRs and early onset of reactions. Hence, medical professional can select the most effective medication regimen by taking these aspects into account during a medical examination.[20]

CADRs related to ART could not be observed in our analysis since patients on ART continued their care at a neighbouring government ART centre and one more possibility might be current ART drugs having good safety and tolerability profile.

CONCLUSION

Cutaneous Adverse Drug Reactions are price we pay for the benefits of modern drug therapy. They are expensive in terms morbidity caused and monetary loss and, it can also sabotage the doctor-patient relationship. Every drug we prescribe have its own profile of adverse drug reaction which can range from common minor reactions to rare but life-threatening reactions, knowledge of these reactions is important for treating physician as prompt recognition and treatment can prove lifesaving.

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