

Analysis of cutaneous adverse drug reactions in a tertiary care teaching hospital

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ABSTRACT

Background: Cutaneous Adverse Drug Reaction (CADR) is considered as one of the reasons for discontinuation of drug as well as medication non-adherence. This study analyses the common drugs causing CADR, clinical spectrum of different types of CADR, causality and drugs causing severe CADR.

Methods: This was a retrospective cross-sectional observational study conducted by the Department of Pharmacology, Coimbatore Medical College, Coimbatore, Tamil Nadu, India. The study was conducted using data collected in CDSCO's ADR reporting forms with CADR from June 2015 to July 2017. Patient's information, details related to adverse drug reaction, suspected medication details, concomitant medication history, causality and seriousness were recorded.

Results: A total of 102 CADR were evaluated in this study. The mean age of sample was 37.21 ± 20.33 years. Maximum number of cases was in the age group of 40-49 years. Male to female ratio was 0.96:1. The commonly incriminated drugs causing CADR were antimicrobial agents. Ciprofloxacin (21.57%), phenytoin (9.8%), diclofenac sodium (6.86%), anti-snake venom (6.86%) and vancomycin (3.92%) were the common drugs implicated in CADR. Maculopapular rash and itching were the most common CADR. Anticonvulsants especially phenytoin was commonly associated with severe CADR.

Conclusions: The present study has made an impact on all departments of this institution and awareness has been created about spontaneous reporting of all adverse drug reactions in CDSCO ADR reporting forms to the pharmacovigilance centres. Thus, sound knowledge about the adverse drug reactions may decrease the occurrence of drug induced morbidity and mortality.

Keywords: Cutaneous adverse drug reaction, Causality, Pharmacovigilance, Severe

INTRODUCTION

Adverse drug reactions are considered as an important cause of human suffering, hospitalization, increased health care costs and even death.¹ Cutaneous Adverse Drug Reactions (CADR) are considered as one of the most common adverse drug reactions. Studies have found that the incidence of CADR is 1-3% in developed countries and 2-5% in developing countries.²⁻⁴ Around 1% of the commonly used drugs produce CADR. It may range from transient maculopapular rash to fatal toxic epidermal

neurolysis.⁵ Due to emergence of new drugs, adverse drug reactions are also increasing in number. CADR need to be differentiated from other skin manifestations. The burden of ADRs is discontinuation of drug as well as medication non-adherence.

Therefore, knowledge about the specific pattern of CADR by specific drugs and common drugs causing CADR helps in better prescription writing, early diagnosis of CADR and prompt withdrawal of the causative drug. It will prevent morbidity and mortality and also improves the

patient's compliance. The objectives of this study were to analyse the clinical spectrum and pattern of CADR and to assess causality and severity of the CADR.

METHODS

This was a retrospective cross-sectional observational study conducted by the Department of Pharmacology, Coimbatore Medical College, Coimbatore, Tamil Nadu, India. The study was conducted using data collected in the CDSCO's ADR reporting forms with CADR from June 2015 to July 2017. All departments of the hospital were included in this study, which has enormous potential of the adverse drug reactions. Patients presented with incomplete history or difficulties in communication, cutaneous reactions due to accidental or intentional poisoning due to drugs, drug abuse, use of alternative medicines and error in drug administration were excluded from the study.

Patient's information, details related to adverse drug reaction, suspected medication details, concomitant medication history, relevant medical or medication history, causality and seriousness were recorded. Data entered in excel sheet for statistical analysis.

Causality of ADRs was evaluated by WHO-UMC assessment scale. Severity of ADRs was evaluated by Hartwig and Siegel's scale. Descriptive statistics was used for data analysis and results were expressed as percentages.

RESULTS

A total of 102 CADR were included in this study. The mean age of sample was 37.21 ± 20.33 years and the range were 1 month to 78 years. Of all CADR, maximum number of cases were in the age group of 40-49 years (19.61%) followed by 20-29 (17.65%), with least number in the age group ≥ 70 (5.88%) (Table 1).

Table 1: Age wise distribution of CADR.

Age group (years)	Frequency	%
<10	9	8.82
10 to 19	14	13.73
20 to 29	18	17.65
30 to 39	10	9.80
40 to 49	20	19.61
50 to 59	12	11.76
60 to 69	13	12.75
≥ 70	6	5.88
Total	102	

The study population comprised of 50 (49.02%) males and 52 (50.08%) females. The male to female ratio was 0.96:1. The most common suspected class of drugs causing CADR (Table 2) was antimicrobial agents (n=47, 46.08%) followed by antiepileptic drugs (n=13, 12.75%), NSAIDs (n=10, 9.8%), cancer chemotherapeutic agents and fixed

drug combinations (n=8, 7.84% in each). Commonly implicated drugs causing CADR were ciprofloxacin (n=22, 21.57%), phenytoin (n=10, 9.8%), diclofenac sodium (n=7, 6.86%), Anti snake venom (n=7, 6.86%) and vancomycin (n=4, 3.92%).

Table 2: Common suspected drugs causing CADR.

Suspected drugs	Frequency	%
Antiepileptic	13	12.75
• Phenytoin	10	9.8
• Carbamazepine	3	2.94
Antimicrobial	47	46.08
• Ciprofloxacin	22	21.57
• Vancomycin	4	3.92
NSAID	10	9.80
• Diclofenac	7	6.86
• Paracetamol	2	1.96
DMARD (Sulfasalazine)	1	0.98
Anti-snake venom	7	6.86
Anti-ulcer (Ranitidine)	2	1.96
Chemotherapeutic agents	8	7.84
• Gefitinib	3	2.94
• Imatinib	2	1.96
CVS drugs	2	1.96
• Warfarin	1	0.98
• Streptokinase	1	0.98
Antidiabetic (Metformin)	1	0.98
Anaesthetic (Propofol)	2	1.96
Antihistaminic (CPM)	1	0.98
Combinations	8	7.84

Table 3: Types of CADR.

CADR	Frequency	%
Maculopapular rash	29	28.43
Hyperpigmentation	2	1.96
Itching	23	22.55
Fixed drug Eruption	5	4.90
Facial edema	3	2.94
Urticaria	10	9.80
Steven Johnson Syndrome	4	3.92
Erythroderma	12	11.76
Exfoliative dermatitis	1	0.98
Toxic Epidermal Necrolysis	1	0.98
Angioedema	2	1.96
Oral lesions	4	3.92
Palmar Erythema	1	0.98
Icthyosis	1	0.98
Bullous Eruption	3	2.94
Dress Syndrome	1	0.98
Total	102	

On subgroup analysis, the most common implicated drug among antimicrobial agents was ciprofloxacin (n=22, 21.57%) followed by vancomycin (n=4, 3.92%).

Table 4: CADR and the associated drug.

CAADR	Suspected drug	Frequency
Maculopapular rash	Carbamazepine	1
	Docetaxel	1
	Sulfasalazine	1
	Ranitidine	1
	Carbamazepine	1
	Vancomycin	4
	Ciprofloxacin	5
	Amoxicillin	1
	Rituximab	1
	Warfarin	1
	Phenytoin	2
	Metronidazole	1
	Metformin	1
	Gefitinib	1
	Imatinib	2
	Gentamycin	1
Hyperpigmentation	Chlorpheniramine maleate	1
	Paracetamol+caffeine+phenylpropanolamine	1
Fixed drug Eruption	Cotrimoxazole	1
	Norfloxacin +metronidazole	1
	Gefitinib	1
	Ciprofloxacin	1
	Ciprofloxacin	1
Facial edema	Paracetamol	1
	Diclofenac Sodium	1
	Phenytoin	1
	Clotrimazole	1
Urticaria	Diclofenac sodium	2
	Propofol	1
	Anti-snake venom	4
	Ciprofloxacin	1
	Cefotaxime	1
	Penicillin	2
Exfoliative dermatitis	Ceftriaxone	1
	Carbamazepine	1
	Piperacillin	1
	Paracetamol	1
Oral lesions	Diclofenac sodium	1
	Phenytoin	1
	Fluconazole	1
Palmar Erythema	Amoxicillin	1
Itching	Ichthyosis	1
	Dapsone	1
	Ciprofloxacin	13
	Ranitidine	1
	Metronidazole	1
	Acyclovir	1
	Anti-Snake Venom	3
	Erythromycin	1
	Amoxicillin	1
	Ibuprofen	1
	Cisplatin	1

Among antiepileptic drugs, most common implicated drug was phenytoin (n=10, 9.8%) followed by carbamazepine (n=3, 2.94%). Among NSAIDs, most common implicated drug was diclofenac sodium (n=7, 6.86%) followed by paracetamol (n=2, 1.96%).

Among different known patterns of CADR (Table 3), the most common reported was maculopapular rash in 28.43% of cases followed by itching in 22.55%, erythroderma in 11.76%, urticaria in 9.8% and Steven Johnson syndrome and oral lesions in 3.92% each.

Maculopapular rash was caused mainly by ciprofloxacin (17.24%) (Table 4) followed by vancomycin (13.8%), Itching by ciprofloxacin (56.52%) followed by Anti snake venom (13%), urticaria by Anti snake venom (40%) followed by penicillin (20%), fixed drug eruption by ciprofloxacin, paracetamol, diclofenac, phenytoin, clotrimazole (20% each).

Table 5: Severe CADR associated with the drug.

CAADR	Suspected drug	Frequency
Steven Johnson Syndrome	Phenytoin	1
	Dapsone	2
	ATT Drug (INH, rifampicin, streptomycin)	1
Erythroderma	Phenytoin	3
	Gefitinib	1
	Metronidazole	1
	Ciprofloxacin	1
	Ampicillin	1
	Diclofenac sodium	1
	Cefotaxime	1
	Ofloxacin+ornidazole	1
Cefixime+ofloxacin	1	
Bullous eruption	Ibuprofen+paracetamol	1
	Diclofenac sodium	2
Dress Syndrome	Cotrimoxazole	1
Toxic epidermal necrolysis	Phenytoin	1
Angioedema	Phenytoin	1
	Propofol	1
	Streptokinase	1

Severe CADR (Table 5) were observed in 27 (26.47%) of the cases. Among severe CADR, Steven Johnson syndrome was induced by dapsone (50%) followed by phenytoin and antitubercular drugs (25% each), one case of toxic epidermal necrolysis and one case of dress syndrome by phenytoin, Erythroderma by phenytoin (25%), bullous eruptions by diclofenac sodium (33%) and cotrimoxazole (33%) and angioedema by propofol and streptokinase (50% each).

According to WHO-UMC causality assessment criteria (Figure 1), out of 102 CADR, 61 (59.8%) were found

probable, 40 (39.22%) possible and 1 (0.98%) certain. Re-challenge was not done due to ethical issues.

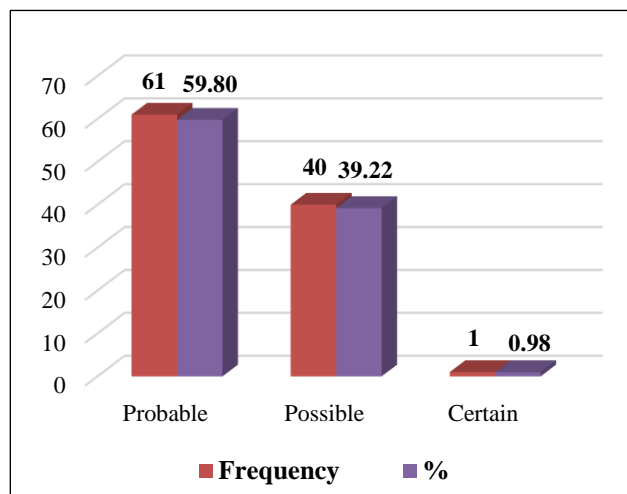


Figure 1: WHO-UMC causality assessment.

DISCUSSION

CADR are distressing to both the clinicians and the patients. Every clinician should have the knowledge about the clinical spectra of CADR as well as common drug causing CADR. One of the important aspects of therapeutics is adverse drug reaction monitoring. However, it is not considered important in most of the cases. Many adverse drug reactions are not reported voluntarily and are undocumented. To overcome this, establishment of pharmacovigilance centre in the hospitals has become an utmost necessity.

In this study, the age of the sample ranges from 1 month to 78 years and mean age of the sample was 37.21 ± 20.33 years which is similar to other studies.^{6,7} This shows that no age is exempted from the development of CADR. Maximum number of CADR were in the age group of 40-49 years (19.61%), which is in accordance with the literature reports that CADR increase with age.^{8,9} This may be due to polypharmacy and altered drug metabolism as the age progresses. These findings are similar to other studies by Kongkaew C et al, and Solensky R et al.^{10,11}

Present study has found male:female ratio was 0.96:1 which showed almost equal vulnerability of men and women towards CADR. These findings are in accordance with two other studies by Saha A et al (0.96:1) and Padukadan D et al, (0.87:1).^{4,12} Some studies have reported a slight female predominance.¹³⁻¹⁸ However, male predominance was reported by some studies.^{6,19-21} These differences may be due to difference in demography of the patients included in those studies.

In present study, the most common suspected class of drugs was antimicrobial agents (46.08%) mainly ciprofloxacin followed by vancomycin. The next class of drugs were antiepileptic drugs (12.75%) mainly phenytoin followed by

carbamazepine and NSAIDs (9.8%) mainly diclofenac followed by paracetamol. These are in accordance with the reported literature.^{4,6,9,15,20,22,23}

In this study, maculopapular rash (28.43%) was the most commonly encountered CADR which is in accordance with previous studies, followed by itching/pruritis (22.55%), erythroderma (11.76%) and urticaria (9.8%).^{6,14,17,18,20,24-30}

Among maculopapular rash patients, ciprofloxacin (17.24%) was the causative agent in majority of them, which is similar to a study by Nandha R et al, It was followed by vancomycin (13.8%) and phenytoin (6.89%).¹⁷ But earlier studies by Ghosh S et al, found amoxicillin to be common in maculopapular patients.²⁵ Maximum number of itching due to ciprofloxacin (56.52%) followed by anti-snake venom (13%). Maximum number of urticaria due to Anti snake venom (40%) followed by penicillins (20%) which is in accordance with those reported by Jhaj R et al, Sharma VK et al, and Chatterjee S et al, found paracetamol to be common among urticaria patients.^{6,15,31} Maximum number of fixed drug eruptions due to diclofenac, paracetamol, ciprofloxacin, phenytoin and clotrimazole (20% each). This is similar to those reported in other studies.^{6,9,12}

Severe CADR were observed in almost one-third (26.47%) of the cases, which match with earlier studies.^{32,33} In this study, 3 cases of Steven Johnson Syndrome (SJS), 1 case of Toxic Epidermal Necrolysis (TEN) and 1 case of DRESS syndrome were reported, whereas Lihite RJ et al, has shown two cases of TEN and one case of SJS.³⁴ Anticonvulsants were the major group of drugs implicated in severe CADR, which is similar to those reported in other studies.^{20,35} According to this study, SJS/TEN were common with anticonvulsants, which match with those reported from Asian studies and European studies.^{23,36} Whereas Padukadan D et al, has reported dapsone and anticonvulsants as the commonly incriminated group of drugs in severe CADR.⁴

In this study, 59.8% of the CADR were found probable and 39.22% possible according to WHO-UMC causality assessment criteria which is similar to those reported by Chatterjee S et al, and Suthar J et al.^{15,16} Whereas Shah SP et al, reported higher percentage under possible category.¹⁹ Very low percentage (0.98%) fall under definite (certain) category which is also reported in other studies.^{16,20} Re-challenge was not done due to ethical issues.

CONCLUSION

From the present study, an impact has been made on all departments of this institution and awareness has been created about spontaneous reporting of all adverse drug reactions in CDSCO ADR reporting forms to the Pharmacovigilance centres. Antimicrobial agents were the commonly incriminated drugs causing CADR. The most common CADR were maculopapular rash and itching.

Anticonvulsants were commonly associated with severe CADR. Though, the frequency of severe CADR were low, at times it may become life threatening. Thus, sound knowledge about the adverse drug reactions may decrease the occurrence of drug induced morbidity and mortality.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Human Ethics Committee (Ref no.0133/2018)

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