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Evaluation of Cutaneous Adverse Drug Reactions Reported in a Teaching Hospital of Coastal Andhra

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Adverse drug reactions (ADR) can be manifested in different forms, among these cutaneous adverse drug reactions (CADRs) are the commonest. They have been steadily gaining importance and constitute a major proportion of all ADRs. As available data on CADRs is very less, more research is required to have reliable data, hence the current study was undertaken. This prospective study was carried out to evaluate the age and gender distribution, presenting complaints, spectrum of CADRs, causative drugs, causality, severity, and outcomes in patients with or suspected CADRs attending the department of Dermatology of Konaseema Institute of Medical Sciences & Research Foundation Hospital between January 2014 and June 2015. In cooperation with the Dermatologist, patient's reactions were analyzed based on morphology, and laboratory investigations. Causality was assessed as per the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment scale. Modified Hartwig and Siegel Scale was used for the severity assessment of reactions. CADRs occurred most commonly in the 31-40 years age group (32%) with no sign of the difference in both sexes. The most common complaint of CADRs by the patients was skin rash (42%) and diagnoses were Erythematous drug eruption (ERDE) and Fixed drug eruption (FDE) (28%). The commonest causative drug categories were antimicrobials (52%) and Non-Steroidal Anti-inflammatory Drugs (NSAIDs) (24%). Among antimicrobials, ciprofloxacin, and in NSAIDs, diclofenac were the commonest causative drugs. In causality, majority of the cases were under possible category (42%). Most of the reactions were mild (46%), and moderate (46%) in severity. The majority of the cases showed good recovery without any mortality or disability. The limitations of this study were the relatively small sample size, inability to confirm the particular causative drug in majority of the patients. Future research should focus on the genetic factors concerning to CADRs and molecular-level evaluation should be done for a better understanding of the pathophysiology of various ADRs.

Keywords: Antimicrobials; Antiepileptics; CADRs; Drug category; NSAIDs.

An Adverse drug reaction (ADR) is defined by World Health Organization (WHO) as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man"[1]. ADRs are implicated in significant morbidity and mortality. In India, 400,000 deaths were due to ADRs per annum, and out of all visits to the medical emergency department, 6 percent are drug-related[2]. ADRs constitute a major clinical problem in terms of human suffering and increased

healthcare expenses. Drugs are always connected with the risk of ADRs.

ADR can be manifested in different forms, among these cutaneous adverse drug reactions (CADRs) are the most common. They have been steadily gaining importance and constitute a major proportion of all ADRs. The CADRs range from rash to toxic epidermal necrolysis (TEN). CADRs are impacted by multiple elements like comorbidities, immune status, genomics, history of allergies, age, and sex.

The types of CADRs and the causative drugs are continuously changing over time, as new medications are being introduced into the market. The pattern of CADRs is also changing due to alterations in the drug of choice, drug interactions due to polypharmacy, and a rising trend in the public to self-medicate. CADR monitoring is an important aspect of ADR monitoring programs, not only for the collection of data but also for identifying and preventing risk factors. Epidemiological studies are deficient and underreporting of ADR is also a major problem in India. So available data on CADRs is very less, more research is required to have reliable data, hence the current study was undertaken.

In this study, age and gender distribution, common presenting complaints (symptoms), common diagnoses, causative drug category, severity of reactions, causality assessment, and outcome were evaluated.

METHODS

This prospective study was carried out to evaluate the demographic distribution of patients, spectrum of CADRs, different causative drug categories, outcomes of CADRs, common presenting complaints, severity of reactions, and their causality assessment.

Study subjects

Patients of all age groups and both sexes with or suspected CADRs attending the Dermatology department (including both outpatients and inpatients) of Konaseema Institute of Medical Sciences & Research Foundation Hospital were included in the study. Before beginning the research, the Institutional Ethics Committee approval was obtained. The study was carried out prospectively for 18 months between January 2014 and June 2015.

Sampling

50 consecutive patients who visited the Dermatology department (both outpatients and inpatients) of Konaseema Institute of Medical Sciences & Research Foundation Hospital with or suspected CADRs were included in the study.

Study procedure

Before involving the patients in the study written informed consent was obtained. Patients were evaluated for the pattern and severity of the reactions. A detailed history including the present, and past medical history, and history of previous drug reactions was noted. In cooperation with the Dermatologist, patient's reactions were analyzed based on morphology, clinical criteria, and laboratory investigations. Due to ethical concerns, a rechallenge test was not performed. Causality was assessed as per the WHO-UMC causality assessment scale. To determine the causality highest suspicious drugs were first discontinued. Modified Hartwig and Siegel Scale was used for the severity assessment of reactions.

Statistical analysis

Variables were analyzed with descriptive statistics such as mean and standard deviation (SD) by using Microsoft Excel 2013. The results were represented in the form of percentages with tables and figures.

RESULTS

Incidence

In this prospective spontaneous ADR monitoring study, a total of 50 (0.11%) CADRs were recorded from a total of 43,842 patients visiting the dermatology department of Konaseema Institute of Medical Sciences & Research Foundation Hospital from January 2014 to June 2015.

Age and gender distribution

The mean age with standard deviation was 34.76 ± 15.66 years shown in Figure 1, the oldest being 65 years and the youngest being 2years. Majority of the subjects belonged to the 31-40 age group (32%). There is no significant difference in the incidence of CADRs between males (24) and females (26).

Common presenting complaints (symptoms)

The Data regarding various common presenting complaints were tabulated in Table 1.In this study majority of the patient's complaint was

skin rash/Eruption, followed by skin discoloration. Only a few patients presented with erythema and pruritus.

Clinical diagnoses of reactions

The proportions of various CADRs were shown in Table 2. Among all the reported CADRs ERDE and FDE were the most common variations. Only one case of each was reported in Hyperpigmentation, DRESS (Drug reaction with eosinophilia and systemic symptoms),TEN, stria, lichenoid eruption,and photosensitivity types of CADRs. Commonest CADRs ERDE and FDE occurred mainly due to antimicrobials (fluoroquinolones) and analgesics (diclofenac). Two cases of SJS, one case of TEN, and one case of DRESS were caused by Phenytoin, Lamotrigine, Nimesulide, and Phenytoin respectively.

Common causative drug categories

Drug categories causing CADRs were shown in Table 3. According to that, the commonest causative drug category was antimicrobials 52% followed by NSAIDs 24%, and antiepileptics 8%.

In fluoroquinolones, ciprofloxacin (14%), levofloxacin (2%) and ofloxacin (2%) were predominant. Among penicillins amoxicillin (10%) constitute the bulk of CADRs. Among

Table 1. Clinical presentation of CADRs with their frequency

Common presenting complaints	Frequency n (%)
Edema	2(4)
Erythema	1(2)
Skin discoloration	12(24)
Pruritus	1(2)
Pustules	3(6)
Rash/Eruption	21(42)
Vesicle	6(12)
Bulla	4(8)

Table 2. Showing distribution of various CADRs

Diagnosis	Frequency n (%)
EMF(Erythema multiforme) major	4(8)
Angioedema	2(4)
ERDE(Erythematous drug eruptions)	14(28)
SJS(Stevens-Johnson syndrome)	4(8)
FDE(Fixed drug eruptions)	14(28)
Hyperpigmentation	1(2)
Urticaria	3(6)
DRESS (Drug reaction with eosinophilia and systemic symptoms)	1(2)
TEN(Toxic Epidermal Necrolysis)	1(2)
Stria	1(2)
Acneiform drug eruption	3(6)
Lichenoid eruption	1(2)
Photosensitivity	1(2)

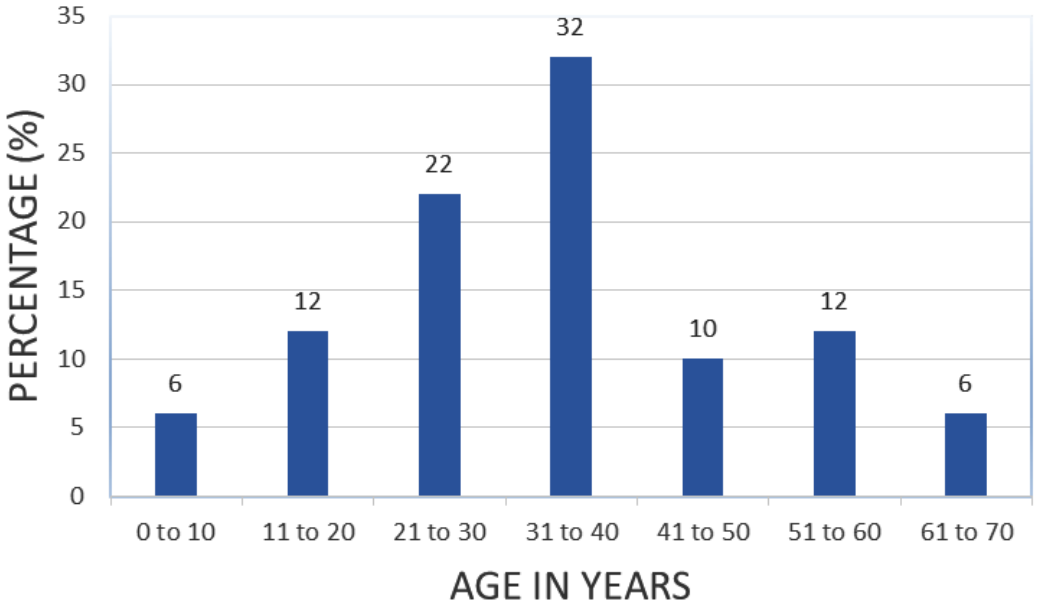

Fig. 1. Demographic details of patients presenting with CADRs

Anti-Tuberculosis Therapy (ATT), rifampicin (4%) and isoniazid (4%) were involved in CADRs. In cephalosporins, only cefixime was involved. Other antimicrobials involved in CADRs were antiamoebic (metronidazole 4%), Anti-Retroviral Therapy (ART) (nevirapine 4%), tetracyclines (doxycycline 2%), antimalarial (artesunate 2%).

In others group category CADRs were due to KCl, Doxylamine, and Theophylline.

Severity of reactions

The severity of reactions was graded as mild, moderate, and severe using Modified Hartwig and Siegel Scale as shown in Table 4. Severe cases of CADRs were very less in this study, while mild & moderate CADRs were more & equal in number. There were no reactions with the severity of 6 and 7 on the Modified Hartwig and Siegel Scale.

Causality assessment

Causality of the CADRs with regard to suspected drugs was assessed by using WHO-UMC causality assessment criteria and shown in Table 5. Majority of the cases causality was assessed under the possible category. Only a few cases fall under certain & conditional categories.

Outcome assessment of CADRs with severity

Different outcomes of CADRs were shown in Table 6. Majority of the cases (26%) fall under the category of "reaction persisted during observation but showed improvement". Also, reaction resolved without sequelae and resolved with sequelae categories were equal in percentage (22%). The cases that come under the reactions persisted during observation without improvement category were12%. However, 18% of cases were not available for follow-up, hence categorized under unknown outcome conservatively. Fortunately, there were no deaths or progression of lesions during this study.

Table 3. Showing distribution of various drug categories causing CADRs

Drug category	Frequency n (%)
Antimicrobials	26(52)
Analgesics/NSAIDs	12(24)
Anticancer	2(4)
Antiepileptics	4(8)
Corticosteroids	3(6)
Others	3(6)

Table 4. Showing the association of drug categories with the severity of CADRs

Drugcategory	Severity of reactionsn (%)		
	Mild	Moderate	Severe
Antimicrobials	13(26)	13(26)	-
Analgesics/NSAIDs	6(12)	5(10)	1(2)
Anticancer	-	1(2)	1(2)
Antiepileptics	-	2(4)	2(4)
Corticosteroids	1(2)	2(4)	-
Others	3(6)	-	-
Total	23(46)	23(46)	4(8)

Table 5. Showing the association of drug categories with Causality assessment

Drug category	Causality n (%)				
	Certain	Probable	Possible	Unlikely	Conditional
Antimicrobials	1(2)	7(14)	14(28)	4(8)	-
Analgesics/NSAIDs	-	3(6)	3(6)	4(8)	2(4)
Anticancer	1(2)	1(2)	-	-	-
Antiepileptics	-	1(2)	2(4)	1(2)	-
Corticosteroids	-	1(2)	1(2)	1(2)	-
Others	-	1(2)	1(2)	1(2)	-
Total	2(4)	14(28)	21(42)	11(22)	2(4)

Table 6. Showing outcome of CADRs with various severity levels

Outcome	Severity of reactions n (%)			
	Mild	Moderate	Severe	Total
Resolved without sequelae	5(10)	6(12)	-	11(22)
Resolved with sequelae	5(10)	6(12)	-	11(22)
Reaction persisted during observation but showed improvement	6(12)	5(10)	2(4)	13(26)
Reaction persisted during observation without improvement	1(2)	5(10)	-	6(12)
Unknown	6(12)	1(2)	2(4)	9(18)

DISCUSSION

The present study was carried out to evaluate the age and gender distribution, common presenting complaints, common diagnoses, causative drug categories, severity of reactions, causality assessment and outcome after the intervention of CADRs in 50 subjects. The mean age with standard deviation was 34.76 ± 15.66 years and majority of the subjects belonged to the 31-40 age group (32%).Which is in accordance with the study conducted at Vijaypura, where the mean age was 35.71±19.87 years, and the maximum number of CADRs were observed between the ages of 21-40 years[3]. Similar results were seen in studies conducted by Sharma V. K et al[4] and Pudukadan D et al[5]. In contrast to the present results, a study conducted at Coimbatore showed, patients in the age group 41-60 years experienced a maximum of CADRs and the mean age was 49.26 years[6]. There were mild differences in the results of different studies, which may be due to different geographical variations. Normally pediatric and geriatric age groups were more prone to CADRs, due to low immunity and consuming more medications. However, in this study extremes of age group patients were less, compared to adults.

Skin rash/Eruption was a common symptom in our patients. Similar results were found in a study in Kerala, with a rash as a common complaint (33.06%)[7]. However, in another study in Korea, itching was the common presenting complaint (61.0%)[8]. These variations in presenting complaints may be attributed to genetic and environmental factors.

In this study, it was observed that the presentation of CADRs was varying from mild erythematous drug eruptions to life-threatening Toxic epidermal necrolysis. Among these, ERDE and FDE were commonest, which were similar to studies conducted at Punjab[9], and Nagpur[10]. In contrast to the present results, a study done at Vijayapura[3] and Bengaluru[11] showed that FDE was the second least common. ERDE and FDE were most commonly caused by fluoroquinolones, and diclofenac in our study. Two cases of SJS, one case of TEN, and one case of DRESS were caused by Phenytoin, Lamotrigine, Nimesulide, and Phenytoin respectively. However, in a study conducted in Punjab[12] cephalosporins were the most common causative drugs for ERDE. Also, in the same study, SJS was caused by ciprofloxacin. These variations could be due to different patterns of drug usage and different ethnic group characteristics.

The commonest causative drug categories in our patients were concurrent with the results of a study in Kerala, where antimicrobials were highest (47.58%) followed by NSAIDs (16.13%) and antiepileptics (13.71%)[7]. However, in a study conducted at Sree Balaji Medical College, though NSAIDs constitute the bulk of CADRs, the second commonest was antimicrobials, unlike NSAIDs seen in the present study[13]. Among antimicrobials, ciprofloxacin, and amoxicillin were the predominant drugs in our study, which is in accordance with a study conducted at Maharashtra[14]. Which were prescribed for indications like fever, pharyngitis, and Gastroenteritis. These differences may be due to variations in a geographical area, different disease patterns, and different types of treatment options.

The severity of reactions was graded by using the Modified Hartwig and Siegel Scale as mild, moderate, and severe. In mild and moderate cases antimicrobials were the commonest and in

severe cases, antiepileptics were the commonest group to cause CADRs. Also, mild and moderate cases were equal in number and occupies a major proportion of CADRs. A Kerala study showed a similar trend, where mild, and moderate CADRs were 37.9% in each and 24.2% were in severe[7]. Similar results were found in a study conducted by Berihun Haile D et al[15].

According to WHO- UMC causality assessment criteria, only 4% of cases were considered certain. Even though a rechallenge was not attempted due to ethical reasons, based on pre-challenge information from medical history, causality assessment was made as certain in these cases. Among all cases, 28% were assessed under probable, and a majority (42%)of the cases were assessed under possible, which is in a similar trend to Vijayapura study[3], and opposite to studies done in Gujarat, where more cases of probable was followed by certain and possible categories[16,17].

In the outcome assessment, "reaction resolved without sequelae and resolved with sequelae", categories were equal in percentage. In all the cases of moderate and severe reactions, the patients were duly warned against future exposure. An alert card was given to those with serious reactions. Studies conducted at Rajahmundry[18,] Kerala[7], Vijayapura[3], and Manipal[19] showed similar results in the perspective of the outcome. In the present study, the SJS, TEN, and DRESS showed good recovery, whereas in other studies[4,5,20,21,22] deaths were reported because of serious organ involvement and septicemia.

Limitations

The major limitation of our study is it compiles only 50 ADRs, a rechallenge test was not performed due to ethical reasons, and some minor drug reactions encountered by clinicians have not been informed. However, a search in the active form of ADRs was done in this work which has the advantage of not depending on the quality of the records. Despite the limitations and variations in the study, this data may help clinicians to report the ADRs and to avoid irrational drug use.

CONCLUSION

The results of this study were slightly different from other studies. This is maybe due to geographical variations, varied drug consumption habits, and different disease patterns. In clinical practice, proper awareness of the occurrence of the reactions and special precautions while prescribing drugs, early detection, timely withdrawal of the offending drugs, and appropriate rescue measures may greatly contribute to reducing the incidence, frequency, severity, morbidity, and possible mortality. Furthermore, studies are required in this area for obtaining more data on CADRs.

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Conflict of Interest

None declared.

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