Original Article

Pharmacovigilance of Cutaneous Adverse Drug Reactions among Patients Attending Dermatology Department at a Tertiary Care Hospital

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Abstract

Context: Cutaneous adverse drug reactions (CADRs) are the most frequent of all manifestations of drug sensitivity that present with varied and diverse morphology and therefore, awareness about them is essential for diagnosis and prevention. **Aims:** To evaluate the clinical spectrum, morphology, causality, severity and preventability of cutaneous adverse drug reactions in a tertiary care hospital. **Setting and Design:** Descriptive study for six months in the Dermatology Department of a tertiary care hospital in Kerala. **Methods and Materials:** All patients of any gender and age who presented with visible skin lesions and were diagnosed or suspected cases of cutaneous adverse drug reactions were included in the study. All the relevant information was recorded using pre-structured proforma and ADR reporting form. **Statistical Analysis:** Data were analyzed using descriptive statistics. The quantitative variables were expressed as mean ± standard deviation and qualitative variables as frequencies and percentages. Odds ratio (OR) was calculated to assess the risk factors for severe cutaneous adverse drug reactions using SPSS 16. **Results:** Total 124 cutaneous adverse drug reactions were reported with mean age 39.22 ± 20.47 years, male:female ratio being 1:1.4. Most common cutaneous adverse drug reaction was maculopapular rash. Antibiotics accounted for maximum cases, of which beta-lactams were the most common. About 55.6% cutaneous adverse drug reactions occurred within 24 hours of drug administration. Mean hospital stay duration was 4.89 ± 6.23 days. Most reactions were either mild or moderate. Risk analysis revealed that concomitant use of more than one drug, delayed onset, oral route, more generalized area of involvement and medications prescribed for CNS indications were risk factors for severe cutaneous adverse drug reactions. All reactions were preventable. Majority got fully recovered. No fatality was observed. **Conclusion:** Identification and reporting of cutaneous adverse drug reactions reduces their future occurrences and encourages rational prescribing. The study emphasizes on having a deeper understanding of risk factors for serious cutaneous adverse drug reactions that may contribute significantly in improving their outcomes.

Keywords: *Causality assessment, cutaneous adverse drug reaction, pharmacovigilance*

Introduction

Adverse drug reactions (ADRs) constitute a major clinical problem in terms of human suffering and increased healthcare costs.[1] Clinical trials conducted in controlled conditions for a short duration do not give us a picture of complete spectrum of long-term and rare ADRs. The need for an active surveillance system to detect such ADRs was well realized by the World Health Organization (WHO) which formed the basis for starting the International Drug Monitoring Programme.[2] The Pharmacovigilance Programme of India was started with the objective of monitoring the safety of drugs and creation of an adverse drug reaction database for the Indian population.[3] India has contributed significantly to the global safety database ever since.[4]

Cutaneous Adverse Drug Reaction (CADR) is defined as any undesirable change in the structure or function of the skin, its appendages, or mucous membranes, and it encompasses all adverse events related to drug eruption, regardless of the etiology.[5] They manifest with diverse morphological pattern varying from mild to severe forms, sometimes resulting in serious morbidity and even mortality.[6] They comprise 10–20% of the reported ADRs, with an overall incidence rate of 2–3% in hospitalized patients and approximately 2–6% of all patients treated.[7-9] The incidence of CADRs in developed countries

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ranges from 1 to 3% among in-patients[7,10] In developing countries such as India, it is 2–5% among in-patients and 2.6% in the out-patient setting.[11,12] The objective of this study was to evaluate the clinical spectrum, morphology of cutaneous adverse drug reactions and their causality, severity, and preventability in a tertiary care hospital so as to obtain valuable information about the pattern of CADR in the local population.

Subjects and Methods

This was a descriptive study carried out for six months (May to October 2014) in the Department of Dermatology of a tertiary care teaching government hospital, Kerala, India. All patients of any gender and age who presented with visible skin lesions and were diagnosed or suspected of CADR in Department of Dermatology (self-presenting or referred) were included in the study. Patients who were unable to recall the name of suspected medicines consumed and those who diagnosed to have viral exanthems on examination were excluded. Approval was obtained from both Institutional Research Committee and Institutional Human Ethics Committee (IEC No 02/2014 dated 10.12.2013) before commencing the study. Confidentiality and anonymity of the patient's information was maintained during and after the study.

All the patients satisfying the inclusion criteria were enrolled in the study. A written informed consent was obtained from either the patient or guardian. All the relevant information regarding the patient including present complaints, past history especially drug allergy, laboratory data results mentioned in the medical records, clinical details, treatment received, and final outcome were recorded in a pre-structured proforma. Data on suspected CADRs like type and pattern, severity, dates on which reaction started and stopped were documented with the help of dermatologists in Central Drug Standard Control Organization Suspected ADR reporting forms.[13] Details of suspected medication like generic and brand names, dosages, route, frequency, indication, date of starting, and stopping drug, concomitant drugs with doses and frequency, were recorded. The patients from in-patient department (IPD) were followed up till their discharge from hospital and those from out-patient department (OPD) cases were followed up till their second visit. No invasive investigation was performed. Re-challenge was not attempted due to associated risks and ethical concerns.

The collected data were analyzed for demographic details, drug details, causality, preventability, and severity of adverse effects. Causality was assessed by using Naranjo's Algorithm, preventability by Schumock and Thornton scale and severity by modified Hartwig and Siegel scale.[14-16] Seriousness of reaction were categorized according to United States Food and Drug Administration criteria.[17] ADRs not coming under serious ADRs were categorized as "Not Serious" ADRs.

The data were sorted, coded, and entered into Statistical Package for the Social Science (SPSS) for Windows Version 16.0 (SPSS Inc., Chicago, USA) and subsequently analyzed. Quantitative Variables like age, hospital stay duration, concomitant drug use were expressed as Mean ± Standard deviation. Qualitative variables like gender, type of CADR, causative drugs, associated medical conditions, routes of administration, indications, area of involvement, causality, severity, preventability, and final outcome were expressed as frequency and percentage. Odds ratio (OR) was calculated to assess the risk factors for severe CADRs. Statistical significance was determined at 95% level of confidence interval ($P < 0.05$). The variables tested for identification of predictors for severe CADRs were age, gender, history of drug allergy, number of concomitant drugs, onset of reaction, area of involvement, route of drug intake, and indications for which medications were prescribed.

Results

Total 124 CADRs were reported in Department of Dermatology from both IPD and OPD over a period of 6 months. The mean age was 39.22 ± 20.47 years with a minimum age of 3 months and maximum of 85 years. Demography is summarized in Table 1. Male: female ratio was 1: 1.4.

As mentioned in summary of clinical profile [Table 2], more cases were reported from other Departments as compared to department of Dermatology itself (74.19%). IPD cases (78.23%) were found to be more than OPD. Of the total 97 IPD cases, 72 developed CADR during their hospital stay.

As shown in Figure 1, most common CADR was found to be maculopapular rash (33.06%) followed by urticaria (20.16%), pruritus (16.13%), and Stevens Johnsons Syndrome (6.45%). While oral erosions and erythema multiforme were seen in the older age, red man syndrome, and telangiectasia were the CADRs seen in younger age group.

Table 1: Demographic details of patients presenting with CADR

Variables	*n* (%)
Gender	
Male	52 (41.94%)
Female	72 (58.06%)
Age (years)	
Pediatric (0-18)	21 (16.94%)
Adult (19-65)	
Young (19-30)	29 (23.39%)
Middle (31-45)	46 (37.10%)
Older (46-65)	17 (13.71%)
Elderly (>65)	11 (8.87%)

Table 2: Summary of clinical profile

Variables	*n* (%)
Department from where CADRs were reported	
Dermatology	32 (25.81)
Referral (other departments)	92 (74.19)
Patients	
IPD	
Reaction appeared during hospital stay	72 (58.07)
Admitted due to reaction	25 (20.16)
OPD	27 (21.77)
Hospital stay duration	
<7 days	71 (57.26)
7-14 days	21 (16.94)
>14 days	5 (4.03)
Associated medical condition	
Hypertension	11 (8.87)
Diabetes Mellitus/Pregnancy	7/7 (5.64)
Smoking/Alcoholism	6/6 (4.84)
Others	26 (20.97)
History of drug allergy	
Yes	21 (17)
No	103 (83)
Routes of administration	
Oral	58 (46.77)
Intravenous	46 (37.1)
Intramuscular	3 (2.42)
Intradermal	13 (10.48)
Topical	4 (3.23)
Area of involvement	
Generalized	55 (44.35)
Localized	69 (55.65)
Seriousness of reactions	
Serious	35 (28.2)
Non serious	89 (71.8)
Management	
Continued drug at the same dose	2 (1.61)
Continued drug at reduced dose	1 (0.8)
Drug discontinued but no treatment required	47 (37.9)
Drug discontinued and treatment given	74 (59.68)
Causality	
Probable	104 (83.87)
Possible	5 (4.03)
Definite	15 (12.9)
Preventability	
Definitely preventable	113 (91.1)
Probably preventable	11 (8.87)
Not preventable	Nil
Outcome	
Lost to follow up	1 (0.81)
Continuing	9 (7.26)
Recovering	16 (12.9)
Recovered	98 (79)

According to Figure 2, the most common drug group responsible for causing CADRs was antibiotics (59, 47.58%) followed by non-steroidal anti-inflammatory drugs (20, 16.13%) and anticonvulsants (17, 13.71%). Drugs implicated for maximum number of cases were cephalosporins (15.32%), penicillins (14.52%), and phenytoin (9.68%). Table 3 shows the top drug classes and suspected CADRs along with top drugs responsible in each category.

As shown in Table 4, maximum reactions appeared between one to 24 hours as well as one to seven days of taking drugs. Most frequent CADR appearing within a week of drug intake was Maculopapular Rash (29.8%) and beyond 1 week was Stevens Johnsons syndrome (4.03%). Maximum reactions appearing within an hour of drug intake were due to penicillins (4.84%) and those appearing during 1–7 days or more were due to phenytoin (9.68%). Hospital stay duration among IPD cases ranged from 1 to 40 days with mean duration of 4.89 ± 6.23 days. While 71 (57.26%) patients stayed in hospital for less than 7 days, 5 had prolonged hospital stay of more than 2 weeks.

Mean number of drugs in cases having history of concomitant drug use was 2.01 ± 1.33. While 13 patients received the offending drug only, 111 patients received one or more concomitant drugs [Figure 3]. Medications used for CNS-related disorders (meningitis, seizures, stroke, headache, neuralgia) and fever associated with upper respiratory tract infections (URTI) accounted for majority (23.4% each) of the cases as depicted in Figure 4.

As summarized in Table 2, most common associated medical condition was hypertension (8.87%). About 17% cases gave history of drug allergy. Majority of patients received the drug orally (46.77%). Reactions were found to be localized in 55.65% cases and rest were generalized. About 28.2% cases were serious that required either hospitalization or intervention. No fatality was observed.

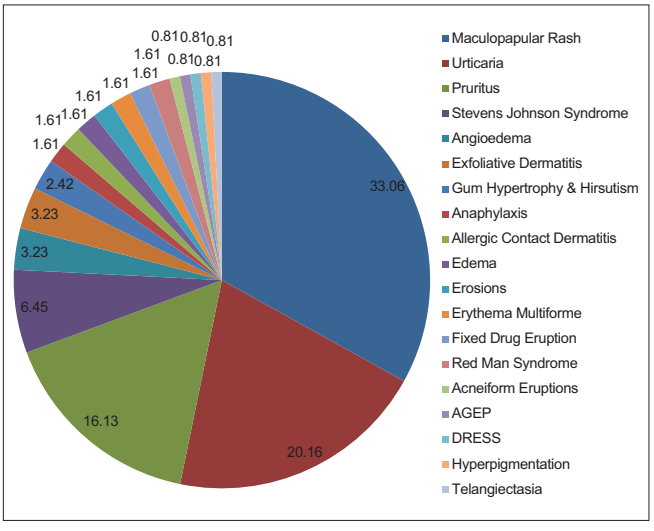

Figure 1: Cutaneous adverse drug reactions

Table 3: Top drug classes and CADR with drugs

Drug class	Top drugs	*n* (%)
Antibiotics	Cephalosporins (19), Penicillins (18) Vancomycin (8) Ciprofloxacin (8)	59 (47.58)
Non steroidal anti-inflammatory drugs	Diclofenac (11), Paracetamol (8)	20 (16.13)
Anticonvulsants	Phenytoin (12), Carbamazepine (3)	17 (13.71)
Antiretroviral	Nevirapine (5)	5 (4)
H_2 Blockers	Ranitidine (4)	4 (3.23)
Steroids	Mometasone (2), Betamethasone (2)	4 (3.23)
CADR	**Top drugs**	***n* (%)**
Maculopapular Rash	Penicillins (7), Ciprofloxacin (5), Nevirapine (5), Diclofenac (4)	41 (33.06)
Urticaria	Cephalosporins (8), Penicillins (7), Vancomycin (3), Diclofenac (2)	25 (20.16)
Pruritus	Penicillins (4), Ciprofloxacin (4), Cephalosporins (3)	20 (16.13)
Stevens Johnson Syndrome	Phenytoin (4), Allopurinol (2)	8 (6.45)
Angioedema	Paracetamol (2)	4 (3.23)
Exfoliative Dermatitis	Cephalosporin, Phenytoin, Vancomycin, Levetiracetam	4 (3.23)
Gum Hypertrophy &Hirsutism	Phenytoin (3)	3 (2.42)

Table 4: Top CADR with Reaction latency

CADR	Reaction latency				*n* (%)
	<1 h	1-24 h	1-7 days	>7 days	
Maculopapular Rash	9	14	14	4	41 (33.06)
Urticaria	10	10	5	0	25 (20.16)
Pruritus	8	10	2	0	20 (16.13)
Stevens Johnson Syndrome	0	0	3	5	8 (6.45)
Angioedema	1	0	3	0	4 (3.23)
Exfoliative Dermatitis	0	0	2	2	4 (3.23)
Gum Hypertrophy and Hirsutism	0	0	0	3	3 (2.42)
Anaphylaxis	2	0	0	0	2 (1.6)
Total	30	34	29	14	107

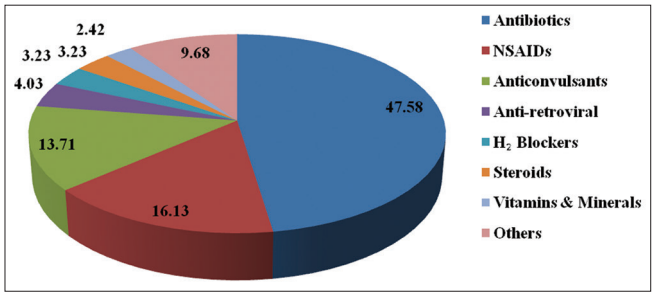

Figure 2: Drug class causing reactions

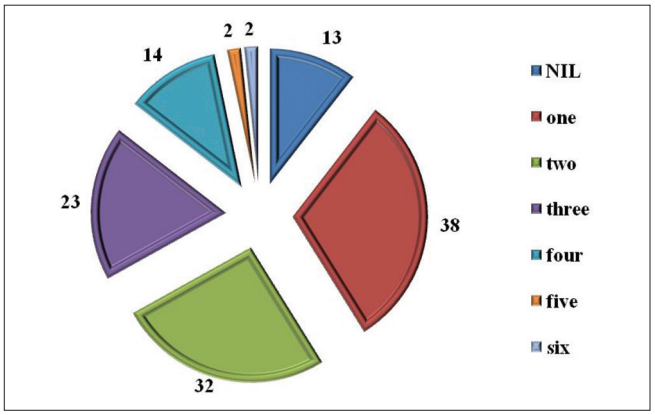

Figure 3: Cases with respective number of concomitant drugs

Majority (79%) got fully recovered while 12.9% were still recovering. One case lost to follow-up. About 91.1% were definitely preventable and 83.87% had probable causality.

As summarized in Table 5, severity assessment showed that there were equal numbers of mild and moderate reactions (37.9% each). Most common implicated drug was phenytoin (8.87%). There were a total of 30 severe CADRs of which the most frequent was Stevens Johnson Syndrome (8, 26.7%). Other severe CADRs observed were maculopapular rash (5, 16.67%), exfoliative dermatitis (4, 13.33%) followed by two cases each of urticaria, erythema multiforme, gum hypertrophy and hirsutism, oral mucosal lesions and one case each of angioedema, fixed drug eruption, allergic contact dermatitis, DRESS (drug reaction with eosinophilia and systemic symptoms) and AGEP (acute generalized exanthematous pustulosis). Risk analysis revealed that concomitant use of more than one drug, delayed onset ADRs, oral route of drug intake, more generalized area of involvement, and medications prescribed for CNS indications were the risk factors for severe CADRs.

About 59.68% were managed by discontinuing the offender drug and treating them by giving Injection Pheniramine and

Table 5: Severity of CADR and predictors of severe CADR

Variable			*n* (%)
Mild			47 (37.9)
Moderate			47 (37.9)
Severe			30 (24.2)
Variable	**Severe (*n*, %)**	**Chi-square**	**Odds ratio (95% CI, *P*)**
Age			
Pediatric	3 (2.42)	1.353	0.469 (0.128-1.719, 0.245)
Adult	20 (66.7)	0.021	0.938 (0.391-2.247, 0.885)
Geriatric	7 (23.3)	1.957	2.080 (0.735-5.887, 0.162)
Gender			
Female	18 (60)	0.061	1.11 (0.481-2.566, 0.805)
Patients			
In-patient	29 (96.7)	7.9	11.088 (1.436-85.622, 0.005)
Drug Class			
Anticonvulsants	15 (50)	44.056	46 (9.54-221.795, 0.00)
CADR			
Stevens Johnson Syndrome	8 (26.7)	26.795	5.273 (3.620-7.681, 0.00)
Exfoliative Dermatitis/DRESS	4 (13.3)	12.951	4.615 (3.284-6.486, 0.00)
Reaction Latency			
More than 7 days	12 (40)	18.574	8.286 (2.867-23.948, 0.00)
Hospital stay duration			
More than 7 days	22 (73.3)	19.996	7.192 (2.847-18.171, 0.00)
History of allergy	4 (13.3)	0.365	0.697 (0.215-2.260, 0.546)
Route			
Oral	24 (80)	17.548	7.059 (2.627-18.970, 0.00)
IV	6 (20)	4.957	0.338 (0.126-0.903, 0.020)
Concomitant			
More than 1 drug	24 (80)	7.297	3.673 (1.376-9.806, 0.007)
Indications			
CNS	17 (56.7)	24.462	8.936 (3.482-22.935, 0.00)
Area of involvement			
Generalized	21 (70)	10.545	4.118 (1.696-9.997, 0.001)
Outcome			
Recovering	13 (43.3)	32.608	23.196 (5.965-90.196, 0.000)

Dexamethasone. In 37.9% cases, drug was discontinued but no further treatment was required. Drug was continued at same dose in two cases.

Discussion

CADRs are one of the most common reasons demanding discontinuation of treatment without completing therapeutic course. In previously sensitized patients drugs should be used with caution keeping in mind the possibility of cross sensitivity. In the present study, total 124 patients were studied and various morphological patterns of CADRs were observed. Maximum patients belonged to the age group of 31–45 years with mean age of 39.22 ± 20.47 years. This age group had majority of cases most probably due to relatively higher exposure to antibiotics. These findings were in accordance with few other studies.[11,18-20] Variable and unpredictable pharmacokinetics may dictate the occurrence of ADRs in extremes of age as evident in our study in which CADRs affected a three month old as well as 85 year old.[21] CADRs in the elderly might be also due to increased use of medications.

Females (58.06%) were affected more than males (41.94%). Similar result has been reported in other studies.[11,22,23] This differs from others where a male predominance was seen.[18,20] Alomar *et al.*, opined that the female population is inherently at a risk of developing ADRs due to their anatomical and physiological variability.[21] Apart from this the gender difference may be attributed to consumption of multiple drugs and high elderly population in females.[23]

Of the 124 patients, a quarter (25.8%) were from the dermatology department and the rest were referred from other Departments, similar to another study where 23.98%

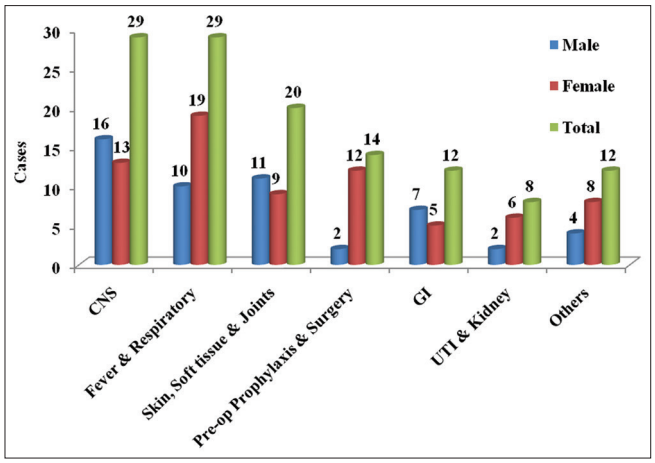

Figure 4: Gender wise distribution of indications for which drugs were administered

of CADRs were reported directly to dermatology.[24] This signifies the importance of having awareness regarding ADR reporting among health care professionals of every department in a hospital. IPD cases were more (78.23%) as compared to OPD cases (21.77%) which coincide with previous studies.[23,25] One possible explanation for this low incidence of OPD cases may be attributed to the study setting, a tertiary care center as non-serious rashes might have been tackled at primary level. Of the total 97 IPD cases, 72 experienced CADR during their hospital stay which directly correlates to the fact that in-patients usually suffer from severe ailments and are prescribed more number of drugs.

The most common drug group responsible for causing CADR was Antibiotics (46.77%) followed by Non-Steroidal Anti-inflammatory Drugs (16.13%) and Anticonvulsants (13.71%). Studies performed elsewhere have found similar results as in ours.[12,20,24,26] Amongst antimicrobials the Beta lactams contributed to maximum CADRs which is comparable to the other reported rates.[10,20]

Most common CADR was maculopapular rash (33.06%) followed by urticaria, pruritus, and Stevens Johnsons Syndrome as cited in the literature.[18,24,26] All the SJS reactions were severe and required hospitalization and similar reports are seen in other studies.[26,27] The drug utilization habit, co-morbidities, immunological, and pharmacogenetic traits of the population studied influence the frequency of CADR in a population.

In this study, 26.6% CADRs occurred within 1 hour and 84.6% developed within first 10 days of drug administration emphasizes on the need of observing the patients closely in the initial period of treatment. In a study 94.28% patients developed CADRs within first 10 days of administration of implicated drug.[28] All the reactions appeared while patients were on drug. Considering the different drugs and their respective reaction times, it appears that antimicrobials and analgesics tend to have short reaction latency, whereas antiepileptics and allopurinol have longer latency. In case of polypharmacy, reaction time may be helpful in suggesting the offending drug, which in turn will prevent unnecessary withdrawal of a necessary medication.

Mean hospital stay duration was 4.89 ± 6.23 days. Of the 97 IPD patients, about 50.8% had hospital stay only for 1–3 days while 13.7% stayed for approximately 2 weeks. Similar results were observed in other study.[27] Prolonged hospital stay in SJS was expected as all these patients had varying degrees of epidermal detachment. Prompt intensive management is required for these patients in the hospital setup to reduce further damage, disability, or in rare cases mortality.

Most common associated medical disorder was Hypertension (8.87%) followed by Diabetes Mellitus (5.64%). Seven females were pregnant. Similar co-morbidities have been reported by other studies.[11,19,25]

About 21 cases gave history of drug allergy. Reports suggest that patients with past history of ADRs are more likely to experience further ADRs.[29] Health care professionals should elicit proper history regarding drug allergy or previous ADRs before prescribing medications.

Maximum CADRs developed with oral route (46.77%) followed by Intravenous (37.09%). It is a well-established fact that as the number of drugs increases the chance of developing adverse drug reactions also increases.[21] This might be largely due to drug interactions. However, in our study, 30.65% patients received only one concomitant drug and the mean usage was 2.01 ± 1.33, which is comparable to the findings of another study.[28] Medications used for CNS related disorders and fever associated with upper respiratory tract infections (URTI) accounted for the majority (23.4% each) of the cases. In another study done in Kerala, 27.9% of reactions developed following drug intake for an infectious illness.[27]

In the present study, 55.65% CADRs were localized and the rest were generalized. Majority of the generalized cases were due to maculopapular rash. 70% of the severe cases were generalized. Findings are comparable to another study wherein upper extremities were observed as frequent area of involvement.[29]

Majority of the reactions were either mild or moderate in severity (37.9% each) followed by severe ones. Risk analysis revealed that concomitant use of more than one drug, delayed onset ADRs, oral route of drug intake, more generalized area of involvement, and medications prescribed for CNS indications were the risk factors for development of severe CADRs. Concomitant use of more than one drug and delayed onset ADRs have been mentioned as predictors of severe ADRs in another study.[4]

About 71.8% cases were non-serious and rests were serious. No fatality was observed. Morbidity due to

serious reactions suggests that they should be regarded as dermatological emergencies (as these disorders lead to skin failure) and should always be treated in indoor setup with close monitoring of fluid-electrolyte balance, temperature regulation, and asepsis. The management protocol for CADRs in this institution was comparable to other studies.[27,28]

Majority of the reactions belonged to Probable category (83.87%) on causality assessment which is similar to the findings of other studies.[20,25,30] The main reason may be because re-challenge was not done so definite association could not be made. Moreover, laboratory investigation such as drug plasma level was not carried out in most of the cases. History taking in detail about drug intake and allergy also aid in assessing causality association between drug and reaction.

All reactions were preventable, same as observed in other study.[29] Careful history taking and exercising caution during prescription of the drugs can prevent most of the adverse drug reactions. Evaluation of final outcome revealed that 79% of the reactions got fully recovered while 12.9% were still recovering. About 7.26% of the total reactions continued without any sign of improvement and further investigations and assessments were carried out in such cases.

Limitations of the study

The study is single institution based. Patients who developed ADRs in the hospital may not be truly reflective of the whole population which may be exposed to a large variety of drug formulations in contrast the drug availability in hospital pharmacy. Exposure to most new drugs was limited.

Causality assessment had its own share of uncertainty in polypharmacy cases, especially as rechallenge was not attempted owing to ethical reasons. Long-term follow-up and monitoring of the patients could not be done. There is also the problem of inherent underreporting of mild and self-limiting cases.

Conclusion

CADR differ in terms of manifestations and reaction latency. A careful history taking and a cautious approach during prescription of drugs can prevent most of the reactions. This study highlights the importance of having a deeper understanding of CADRs as well as identification of risk factors for severe reactions that may contribute significantly in improving their outcomes.

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Conflicts of interest

There are no conflicts of interest.

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