ORIGINAL ARTICLE e-ISSN: 2349-0659 p-ISSN; 2350-0964

Study of Clinicodemographic Profile of Adverse Cutaneous Drug Reactions in Indian Perspective

Buddhadev Panja[1], Satarupa Mukherjee[2], Debjani Goswami[3], Bibhuti Bhushan[4]*, Sipra Bhattacharjee[5], Sukanta Sen[1]

Abstract

Background: 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. **Materials and Methods:** A prospective and observational study was conducted in the Department of Pharmacology and Collaboration with Department of Dermatology in MGM Medical College and LSK Hospital. All cases of suspected CADRs in patients with systemically administered drugs were actively screen by a senior dermatologist. Causality assessment was done by a Pharmacologist using WHO UMC scale. Only those cases where the causality was certain probable/likely were recorded. **Results:** This sampling comprised of 77 CADRs over a period of 1 year from June 2012 to May 2013. The clinical pattern and spectrum of CADRs were studied in 77 subjects. A wide clinical spectrum of CADRs ranging fixed drug eruptions to serious Stevens Johnson syndrome (SJS) was observed. The predominant pattern of reactions observed was fixed drug eruptions FDE (35.1%) followed by acneiform eruptions (23.4%), erythema multiforme (9.1%), and phototoxic drug reactions (7.8%). The antimicrobials causing FDE were macrolides, cephalosporins, and fluoroquinolones. Among the NSAIDs causing FDE, most were due to diclofenac (70%). CADRs were seen most commonly in the 31–40 (26%) years age group followed by 11–20 (24.7%) years and 41–50 (19.5%) years with mean age 32.09 years. Only 5.2% patients were more than 60 years, oldest being 67 years. Antimicrobials were the most common drug group incriminated in 34% patients followed by NSAIDs in 29% cases and steroids in 25% cases. Among NSAIDs, maximum number of CADRs were caused by ibuprofen (40.9%) followed by diclofenac (36.4%), paracetamol (9%), aceclofenac (9%), and nimesulide (4.5%). Serious reactions were infrequent. **Conclusion:** Most of the reactions were mild (53%) to moderate (42%) requiring no major medical intervention. However, a larger and multi-centric study needs to be conducted across the state to obtain more information about CADRs among the state population.

Keywords: Bihar, Causality assessment, Cutaneous adverse drug reactions, Dermatology OPD, Severity

Asian Pac. J. Health Sci., (2022); DOI: 10.21276/apjhs.2022.9.4S1.16

Introduction

Cutaneous adverse drug reactions (CADRs) are by far the most common type of ADRs that may sometimes be life-endangering.[1] Even when they are not fatal, CADRs can cause major setback in clinical practice. CADRs have been steadily gaining importance. A large amount of data on CADRs is being constantly updated. Innumerable epidemiological and clinical studies have highlighted the various aspects of CADRs. CADRs, the most common manifestations of ADRs, occur in 2–3% of patients receiving drug therapy for various reasons.[2] The pattern of CADRs and the drugs responsible for them keep changing from time to time because of new drugs being made available for therapy, changing prescription pattern, increased use of drugs for treatment of diseases, drug interactions due to multiple drug therapy, and also due to a growing tendency for self-medication in the population. The clinical spectrum and pattern of CADRs may vary from mild to transient maculapapular rash to severe and potentially fatal Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). CADRs may be part of systemic manifestation with other system involvement or could be the only manifestation of ADR.[3-5] Drugs may also worsen pre-existing skin disorders. In spite of a large number of studies and case reports, the incidence of undesirable CADRs is, at best, an approximation. In a large percentage of ambulatory patients, the CADRs are mild and transient, and therefore go unnoticed by the patient and physicians. On the other hand, cutaneous symptoms of diseases that may appear to have a temporal relationship to the drug therapy are often erroneously classified as drug eruptions. Few prospective studies have been done on the Indian population with regards to causative drugs and appearance/type of rash.[6-9] The importance of factors affecting CADRs such as age, sex, underlying disease, immune status, genetic factors, environment factors and history of allergy, intercurrent infections, genetic predisposition,

[1]Department of Pharmacology, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal, India.

[2]Department of Pediatrics, ICARE Institute of Medical Sciences and Research, Banbishnupur, Purba Medinipur, Haldia, West Bengal, India.

[3]Department of General Medicine, IQ City Medical College, IQ City Road, Durgapur 713206, West Bengal, India.

[4]Department of General Medicine, Gouri Devi Institute of Medical Sciences and Hospital, G.T. Road, Rajbandh, Durgapur, West Bengal, India.

[5]Department of Pharmacology, Mata Gujri Memorial Medical College and Lions Seva Kendra Hospital, Kishanganj, Bihar, India.

Corresponding Author: Dr. Bibhuti Bhushan, Associate Professor, Department of General Medicine, Gouri Devi Institute of Medical Sciences and Hospital, G.T. Road, Rajbandh, Durgapur, West Bengal, India. E-mail: drbibhutibhushan1@gmail.com

How to cite this article: Panja B, Mukherjee S, Goswami D, Bhushan B, Bhattacharjee S, Sen S. Study of Clinicodemographic Profile of Adverse Cutaneous Drug Reactions in Indian Perspective. Asian Pac. J. Health Sci., 2022;9(4S1):98-106.

Source of support: Nil

Conflicts of interest: None

Received: 01/01/22 **Revised:** 03/02/22 **Accepted:** 12/02/22

and many others are coming into limelight.[10-13] The incidence and prevalence of CADRs may vary in different geographical regions due to difference in disease prevalence, pattern of drug use, and genetic and environmental factors. Effective monitoring of CADRs, both hospital-based and population-based, forms an integral part of ADR monitoring programs as well as part of national pharmacovigilance program, not only to generate valid data but also to identify assess predisposing/underlying risk factors and to evaluate treatment outcome. However, reporting and documentation of CADRs is not being effectively organized and implemented in Indian population and systemic epidemiological studies for the same seem to be inadequate. Population-based epidemiological studies are cumbersome and time consuming and hence difficult to organize compared to hospital–based studies. However, in the past few years, a few studies in the Indian population have been reported mainly from major hospitals. Since existing data regarding CADRs are rather limited, inconsistent, and even conflicting, more studies may be required to generate valid data and hence the present study was taken up. In the present study, the clinical pattern and spectrum of CADRs, the causative drugs, predisposing and underlying risk factors, and causal relationship of drugs were assessed.

Aims and Objectives

The objectives of the study are as follows:

1. To study the nature, pattern, and clinical spectrum of suspected CADRs presenting in the OPD of a tertiary care hospital.
2. To investigate the demographic correlates for such CADRs.
3. To assess the causality for the adverse events and thus identify the offending drugs.
4. To classify the CADRs.

Materials and Methods

This prospective study was done to assess the clinical pattern and spectrum of CADRs of systemically administered drugs, and the causative drugs, predisposing, and underlying risk factors and causal relation.

Study Setting

Subject baseline and recruitment were done at the Dermatology Out-Patient Department of the Institute while the preparatory work; data analysis and archiving were done at the Department of Pharmacology.

Study Design

The present study was a prospective and observational study.

Ethical Considerations

The study protocol, Case Record Form (CRF), Patient Information Sheet, and the Informed Consent Forms (ICF) (Bengali, Hindi and English versions) were approved by the Institutional Ethics Committee (IEC) of the MGM Medical College, Kishanganj, Bihar. During the visit to the Dermatology OPD, all patients were screened for suspected CADRs and patients who fulfilled the study selection criteria were informed by the investigator, verbally, in vernacular, about the study in details (including the rationale, aims and objectives of the study, and potential risks and benefits of participation). All study-related activity started only after such consent was obtained.

Study Subjects

All patients attending the outpatient department (OPD) of Dermatology in M.G.M. Medical College and L.S.K. Hospital, Kishanganj during the period of June 2012–May 2013 were screened by a senior dermatologist. Those cases suspected of having a cutaneous adverse drug reaction (CADR) were further evaluated at the Department of Pharmacology, M.G.M Medical College and L.S.K. Hospital, Kishanganj for causality analysis.

Sampling

A total 13,495 consecutive patients attending the dermatology OPD of M.G.M. Medical College and L.S.K. Hospital, Kishanganj, Bihar were included in the study.

Inclusion Criteria

1. All patients attending the Dermatology OPD on systemically administered drugs with suspected CADRs for the time period of June 2012–May 2013.
2. A causality assessment of suspected CADR based on WHO-UMC algorithm[14,15] was used and only with certain, probable, and possible association were included in the study.

Exclusion Criteria

1. Other common dermatoses mimicking adverse cutaneous drug reactions like viral exanthems.
2. CADRs due to uses of topical drugs.
3. Those falling into the category of unlikely, conditional/ unclassifiable according to the causality-based algorithm (WHO-UMC) were not included in the study.

Study Design

A prospective and observational study was conducted in the Department of Pharmacology and Collaboration with Department of Dermatology in MGM Medical College and LSK Hospital. All cases of suspected CADRs in patients with systemically administered drugs were actively screen by a senior dermatologist. Causality assessment was done by a Pharmacologist using the WHO UMC scale.[14,15] Only those cases where the causality was certain probable/likely were recorded. Detailed clinical history, drug history, and relevant information like onset of reaction, its duration, and temporal association drug intake if any enlisted of all drugs taken preceding the onset of reaction and history of drug rashes. All the above information was captured in a predesigned ADR reporting form and CRF. An accurate drug history was obtained.

Names of all drugs and the duration of intake were noted. Attention was also paid to the sequence of events, to rule out other diseases mimicking drug rashes. The underlying disease for which drug were taken was also noted. History of previous drug allergies in self and family members were also noted. For each patient, a detailed history of previous drug reactions was documented and available case records were scrutinized to collect all valid data.

A through clinical evaluation was done to assess the site, nature and extent of rash, pattern of rash as to whether it was generalized, localized, flexural or sun exposed, severity and duration of the reactions, to detect any predisposing or underlying disease/pathological factors, and to assess any other organ/system involvement as a part of the drug reaction. Distribution of rash was noted. Any special or unusual finding was noted. The diagnosis of the CADR was done in consultation with expert dermatologists based on clinical and morphological criteria. Rechallenge test to confirm the causative drug was not done due to ethical considerations. When more than one drug was used, the drugs with the highest suspicion for causation were withdrawal in the order of suspicion and response to withdrawal was assessed and causality established.

The causal relationship with the offending/suspected drug(s) was established (as certain, probable, possible, unlikely, conditional, or unclassifiable) as per the WHO-UMC causality assessment scale. Assessment was performed for those drugs using WHO-UMC scale. To classify the adverse drug reaction as per Rawlins and Thompson classification: On general examination in addition to the general condition of the patient, attention was paid to the presence of features such as lymphadenopathy, icterus, and pyrexia.[14-16] Only certain probable and possible cases were considered for the study and the data were subjected to descriptive and statistical analysis.

Statistical Analysis

The data collected were analyzed statistically using descriptive statistics, namely, mean and standard deviation for quantitative variables and causal relationship was examined statistically. Wherever necessary, statistical tools such as MS Excel 2007 and MS word 2007 have been used to calculate the mean, SD, and percentages and generate graphs, tables, etc.

Results

Sociodemographic Profile of the Study Participants

A total of 77 patients were included in the study. Of them, 54.5% were males, 26% were children, and 74% were adults. As per socioeconomic status, maximum (37.7%) were in Class V, none were in class IV. Only 31.2% was belonged to the highest Class I. Of the study participants, majority (23.4%) were students. As per religion, 64.9% were Muslim and the rest all Hindu [Table 1].

Type of Reactions versus Class of Suspected Drugs

Among the FDE, antibiotics were the major (14.3%) suspected drug class followed by NSAIDS (13%) then antifungal (3.9%), nitroimidazoles (2.6%), and antihistaminic (1.3%). Steroids were not seen to cause any FDE. Among acneiform eruptions, all (23.4%) were associated with steroids. Erythema multiforme was all associated with NSAIDS (9.1%). Among phototoxic drug reactions, majority (5.2%) were associated with antibiotics followed by antihypertensive (1.3%) and anti-diabetics (1.3%). Only three patients had maculapapular rash caused by NSAIDS, antibiotic, and anti-epileptics. Morbiliform rash was seen in three patients of which 2 (2.6%) were due to antibiotics and 1 (1.3%) due to NSAIDS. A total four reactions were associated with anti-fungals, three FDE and one urticarial rash. Hyperpigmentation was seen in three patients, all were associated with antibiotics. Total three cases were diagnosed as having both FDE and urticaria and all were associated with antibiotics. Only one case of hypopigmentation was detected suspected to be due to steroid [Table 2 and Figure 1].

Type of Reaction and Sex Distribution

Of FDE majority were females (19.5%). Maculopapular rash, hypopigmentation, exfoliative dermatitis, and SJS were found to occur among the males whereas DRESS and FDE plus urticaria were found only females. Majority acneiform eruptions and majority erythema multiforme were seen to occur in males, 13% and 7.8%, respectively [Tables 3 and 4] [Figure 2].

Pattern of CADRs and Age Distribution

Of children, majority were suffering from acneiform eruptions (55%) followed by FDE (30%). Majority adults suffered from FDE (36.8%)

Table 1: Sociodemographic profile of the study population

Variables	*Groups*	*N*	*%*
Sex	Male	42	54.5
	Female	35	45.5
Age	Children (<18 years)	20	26
	Adult (≥18 years)	57	74
Age (years)	0–10	3	3.9
	11–20	19	24.7
	21–30	15	19.5
	31–40	20	26
	41–50	15	19.5
	51–60	1	1.3
	≥61	4	5.2
Socio-economic status	Class I	24	31.2
	Class II	14	18.2
	Class III	10	13
	Class IV	0	0
	Class V	29	37.7
Occupation	Student	18	23.4
	Teacher	3	3.9
	Service	5	6.5
	House-wife	20	26
	Farmer	17	22.1
	Businessman	14	18.2
Religion	Hindu	27	35.1
	Muslim	50	64.9

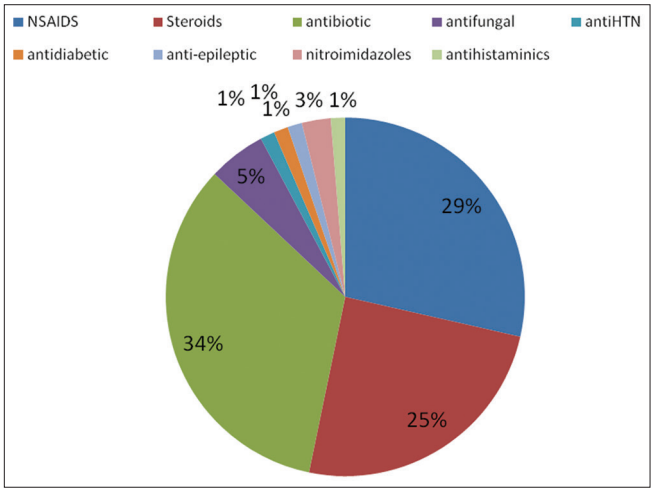

Figure 1: Suspected drug class with CADRs

Table 2: Type of reactions versus class of suspected drugs

Type of reaction	*Class of drugs*									
	NSAIDs n (%)	*Steroid n (%)*	*Antibiotic n (%)*	*Antifungal n (%)*	*Anti HTN n (%)*	*Anti DM n (%)*	*Anti epileptic n (%)*	*Nitroimid azole n (%)*	*Antihista mine n (%)*	*Total n (%)*
FDE	10 (13)	0	11 (14.3)	3 (3.9)	0	0	0	2 (2.6)	1 (1.3)	27 (35.1)
Maculopapular rash	1 (1.3)	0	1 (1.3)	0	0	0	1 (1.3)	0	0	3 (3.9)
Morbiliform rash	1 (1.3)	0	2 (2.6)	0	0	0	0	0	0	3 (3.9)
Acneiform eruptions	0	18 (23.4)	0	0	0	0	0	0	0	18 (23.4)
Hypopigmentation	0	1 (1.3)	0	0	0	0	0	0	0	1 (1.3)
Dress	0	0	1 (1.3)	0	0	0	0	0	0	1 (1.3)
Erythema multiforme	7 (9.1)	0	0	0	0	0	0	0	0	7 (9.1)
Phototoxic drug Reactions	0	0	4 (5.2)	0	1 (1.3)	1 (1.3)	0	0	0	6 (7.8)
Urticarial rash	1 (1.3)	0	1 (1.3)	1 (1.3)	0	0	0	0	0	3 (3.9)
Hyperpigmentatio	0	0	3 (3.9)	0	0	0	0	0	0	3 (3.9)
Exfoliative dermatitis	1 (1.3)	0	0	0	0	0	0	0	0	1 (1.3)
SJS	1 (1.3)	0	0	0	0	0	0	0	0	1 (1.3)
FDE+urticaria	0	0	3 (3.9)	0	0	0	0	0	0	3 (3.9)
Total	22 (28.8)	19 (24.7)	26 (33.8)	4 (5.2)	1 (1.3)	1 (1.3)	1 (1.3)	2 (2.6)	1 (1.3)	77 (100)

Table 3: Type of reaction and sex distribution

Type of reactions	*Male, n (%)*	*Female, n (%)*	*Total, n (%)*
FDE	12 (44.4)	15 (55.6)	27 (100)
Acneiform eruption	10 (55.6)	8 (44.4)	18 (100)
Erythema multiforme	6 (46.1)	7 (53.9)	13 (100)
Phototoxic drug reaction	2 (33.4)	4 (66.6)	6 (100)
Hypopigmentation	1 (100)	0 (0)	1 (100)
DRESS	0 (0)	1 (100)	1 (100)
Morbiliform rash	2 (66.6)	1 (33.4)	3 (100)
Maculopapular rash	3 (100)	0 (0)	3 (100)
Urticarial rash	2 (66.6)	1 (33.3)	3 (100)
Hyperpigmentation	2 (66.6)	1 (33.4)	3 (100)
Exfoliative dermatitis	1 (100)	0 (0)	1 (100)
SJS	1 (100)	0 (0)	1 (100)
FDE and urticaria	0 (0)	3 (100)	3 (100)
Total	42 (54.5)	35 (45.5)	77 (100)

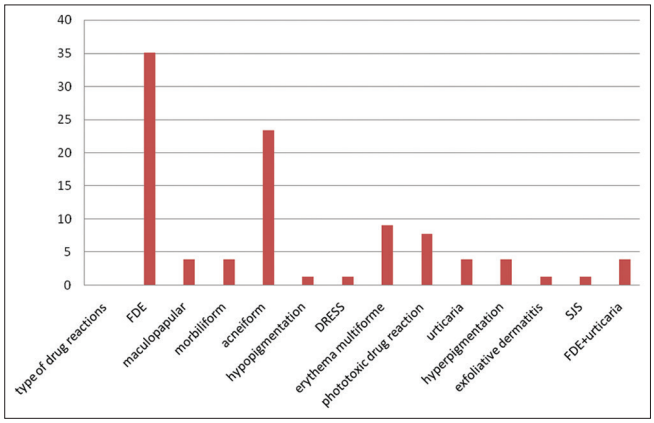

Figure 2: Frequency of pattern of CAD

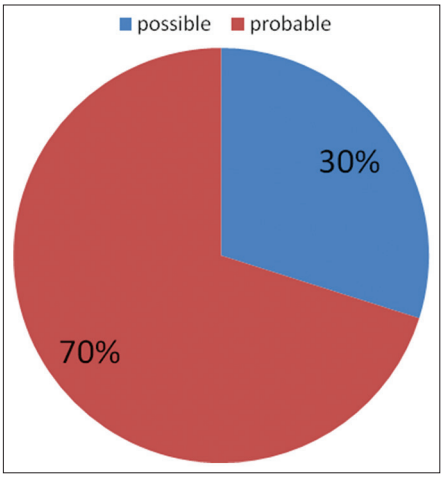

Figure 3: Probability of CADRs

followed by acneiform eruptions (12.2%), erythema multiforme (12.2%), phototoxic drug reactions (10.5%), hyperpigmentation (5.2%), FDE plus urticaria (5.2%), urticarial rash (3.5%) morbiliform rash (3.5%), maculapapular rash (3.5%), exfoliative dermatitis (1.7%), SJS (1.7%), DRESS (1.7%), and hypopigmentation (1.7%) [Table 5 and Figure 3].

Determinants of Severity of CADRs

For the ease of statistical analysis, mild and moderate type of reaction was grouped as non-severe reactions. Among the severe reactions, majority (75%) were males. Males were 2.615 times more prone to have severe reactions but the result is not statistically significant (p = 0.399). All severe reactions were seen in adult, Hindu patients. None of the children and none of the muslins were seen to have severe reactions. Majority of severe cases were seen in antibiotic group (50%) of drugs followed by NSAID (25%) and steroid (25%). All other drug classes (antifungal, anti-HTN, anti-diabetics, and anti-histaminic) were not associated with any severe reaction. As per the route of drug administration, all the severe reactions were associated with oral drugs (100%). The majority of severe reactions were associated with twice daily drug intake (50%). Among the severe reactions, 50% were seen in continuous drug use and rest 50% were seen in intermittent use of drugs ($P = 0.404$). About 50% of severe reactions were associated with physicians prescribed drug consumption whereas rest 50% with self-prescribed drug (odds ratio – 0.281, p = 0.196). The majority of severe drug reactions were associated with combination drugs (75%). Addictions were not associated with severe drug reactions (p = 0.370). H/O recurrences were not associated with severe drug reactions (p = 0.917) [Table 6 and Figure 4].

Frequency of Different Groups of Antibiotics associated with CADRs

Among the different groups of antibiotics, maximum number of CADRs were associated with sulfone group anti-leprotics (dapsone

Table 4: Types of NSAIDS versus type of reactions

Offending drug generation name	*FDE n (%)*	*Maculapapular rash n (%)*	*Morbilifom rash n (%)*	*Erythema multifore n (%)*	*Urticarial rash n (%)*	*Exfoliative dermatitis n (%)*	*SJS n (%)*	*Total n (%)*
Paracetamol	1 (4.5)	1 (4.5)	0	0	0	0	0	2 (9)
Diclofenac	7 (31.8)	0	0	0	1 (4.5)	0	0	8 (36.4)
Ibuprofen	1 (4.5)	0	1 (4.5)	7 (31.8)	0	0	0	9 (40.9)
Nimesulide	0	0	0	0	0	0	1 (4.5)	1 (4.5)
Aceclofenac	1 (4.5)	0	0	0	0	1 (4.5)	0	2 (9)
Total	10 (45.3)	1 (4.4)	1 (4.5)	7 (31.8)	1 (4.5)	1 (4.5)	1 (4.5)	22 (100)

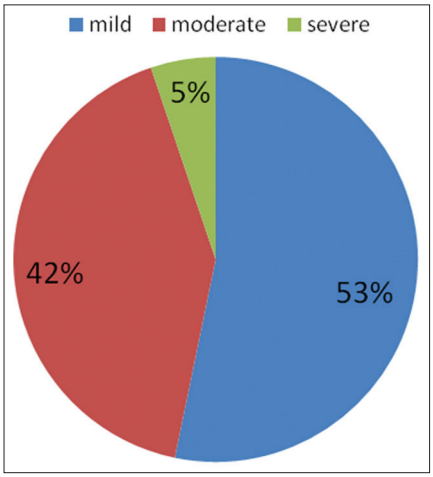

Figure 4: Frequency of severity of CADRs

19.2%) and cephalosporins (ceftriaxone 19.2%) followed by fluoroquinolones (15.4% – ciprofloxacin 75% and ofloxacin 25%), tetracyclines (doxycyclines 15.4%), macrolides (azithromycin 15.4%), phenazine dye antileprotics (7.7%), and penicillins (amoxicillin7.7%) [Tables 6 and 7] [Figure 5].

Age Distribution of the Study Population

Of the study population, majority (26%) were between 31 and 40 years and children below 10 comprised of 3.9%. The majority of the cutaneous adverse drug reactions were suspected to have been caused by antibiotics (34%), then NSAIDS (29%) followed by steroids (25%). Anti-diabetic (pioglitazone), antihypertensive (amlodipine), anti-epileptic (lamotrigine), and antihistaminic (cetrizine) accounted for 1.3% of reactions each [Table 5].

Frequency of Pattern of CADRs

As per the pattern of reaction, maximum were FDE (35.1%) followed by acneiform reactions (23.4%), erythema multiforme (9.1%), and phototoxic drug reactions (7.8%). Maculopapular rash, morbiliform rash, urticarial rash, and hyperpigmentation all comprised of 3.9%. Only one patient suffered from Stevens Johnson's syndrome after consuming NSAIDs. Furthermore, one person suffered from DRESS/DHS after consuming dapsone [Figure 3].

Probability of CADRs

As per the WHO-UMC scale, majority were possible (70%) rest of all probable (30%). None of the reactions were classified as certain [Figure 3].

Table 5: Pattern of CADRs and age distribution

Type of reactions	*Age<18 years n (%)*	*Age more than 18 years n (%)*	*Total n (%)*
FDE	6 (22.3)	21 (77.7)	27 (100)
Acneiform eruption	11 (61.1)	7 (38.9)	18 (100)
Erythema multiforme	0 (0)	7 (100)	7 (100)
Phototoxic drug reaction	0 (0)	6 (100)	6 (100)
Maculopapular rash	1 (33.4)	2 (66.6)	3 (100)
Morbiliform rash	1 (33.4)	2 (66.6)	3 (100)
DRESS	0 (0)	1 (100)	1 (100)
Hypopigmentation	0 (0)	1 (100)	1 (100)
Urticaria	1 (33.4)	2 (66.6)	3 (100)
Hyperpigmentation	0 (0)	3 (100)	3 (100)
Exfoliative dermatitis	0 (0)	1 (100)	1 (100)
SJS	0 (0)	1 (100)	1 (100)
FDE+urticaria	0 (0)	3 (100)	3 (100)

Drug Used Monotherapy or Combination Therapy

Among drug reactions, majority were associated with single drug use (50.6%) followed by combination of two separate drugs (35%), FDC (9%), and polypharmacy (5%).

Route of Administration of Suspected Drugs

Among the route of drug intake, majority were oral route administrations (93.5%) and only 6.5% were given parenterally (all intravenously).

Frequency of Drug Administration

Among the total patients, majority took the drug once daily (46.8%) followed by twice daily (40.3%), once a week (6.5%), and thrice daily (3.9%).

Frequency of Severity of CADRs

As per the severity, majority were mild (53%), while moderate were 42%. Only 5% were graded as severe [Figure 4].

Discussion

During the study period, 13495 patients attended dermatology OPD in MGM Medical College and LSK Hospital, Kishanganj, from Bihar and of which 77 patients were confirmed or suspected to have cutaneous adverse drug reactions (CADRs). Hence, the incidence of CADRs in this study was found to be 5.7 per 1000 outpatient. However, the studies done by Mehta *et al*.[7] and Mani *et al*.[6] have reported incidence of 12/1000. The studies done in hospitalized patients have generally shown a higher incidence 20–22/1000 patient. The reason for this is perhaps due to that inpatients in general, more often tend to have associated with underlying comorbid conditions such as infections, autoimmune disorders, and malignancies which are

Table 6: Determinants of severity of CADRs

Determinants	*Non severe n (%)*	*Severe n (%)*	*Total*	*Odds ratio*	*95% CI*	*p value*
Sex						
Male	39 (53.4)	3 (75)	42	2.615	0.260–26.33	0.399
Female	34 (46.5)	1 (25)	35			
Age						
<18 years	20 (27.3)	0 (0)	20			
>18 years	53 (72.6)	4 (100)	57			
Religion						
Hindu	23 (31.5)	4 (100)	27			
Muslim	50 (68.4)	0 (0)	50			
Class of drugs						
NSAIDs	21 (28.7)	1 (25)	22			
Steroids	18 (24.6)	1 (25)	19			
Antibiotics	24 (32.8)	2 (50)	26			
Others	10 (13.6)	0 (0)	10			
Route of administrations						
Oral	68 (93.1)	4 (100)	72			
Parental	5 (6.8)	0 (0)	5			
Frequency of drug intake						
OD	37 (50.6)	1 (25)	38			
BD	29 (39.7)	2 (50)	31			
TDS	3 (4.1)	0 (0)	3			
Weekly	4 (5.4)	1 (25)	5			
Continuous or intermittent						
Continuous	51 (69.8)	2 (50)	53	0.431	0.057–3.261	0.404
Intermittent	22 (30.1)	2 (50)	24			
Pattern of consumption						
Physician prescribed	57 (78)	2 (50)	59	0.281	0.037–2.152	0.196
Self prescription	16 (21.9)	2 (50)	18			
Monotherapy or combination therapy						
Single drug	38 (52)	1 (25)	39			
FDC	7 (9.6)	0 (0)	7			
Combination	24 (32.8)	3 (75)	27			
Polypharmacy	4 (5.8)	0 (0)	4			
Addiction						
No	38 (52)	3 (75)	41	2.763	0.274–27.817	0.370
Yes	35 (47.9)	1 (25)	36			
H/O recurrence						
No	53 (72.6)	3 (75)	56	1.132	0.111–11.530	0.917
Yes	20 (27.3)	1 (25)	21			
Total	73	4				

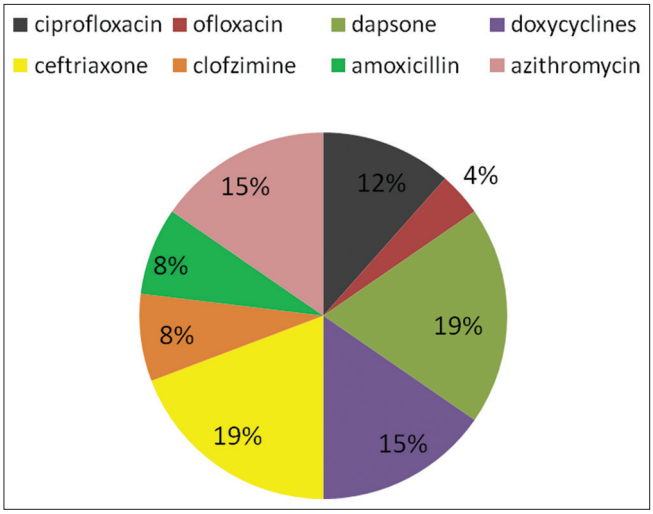

Figure 5: Common antimicrobials implicated and associated with CADRs

known to predispose to drug reactions.[11,17] Of the 77 patients in our study, 20 (26%) were children. Mean age of the study population was 32.09 years (±14.12 3) and the female: male ratio

Table 7: Frequency of different groups of antimicrobials associated with CADRs

Class of drugs	*Frequency*	*Percentage*
Cephalosporins	5	19.2
Sulfone group antileprotics	5	19.2
Tetracyclines	4	15.4
Fluoroquinolones	4	15.4
Macrolides	4	15.4
Penicillins	2	7.7
Phenazine dye anti-leprotics	2	7.7
Antibiotics	Total=26	100%

was 0.83:1. A study conducted in tertiary care hospital in South India reported that the mean age of CADRs was 37.06 years[18] and the female: male ratio was 0.87:1. One possibility to explain the gender difference may be due to their genetic makeup or adherence to the drug, more due to variability in the number of male and female patients attending in different center and so frequently attending patients have higher chances of CADRs. Furthermore, probably males being bread earner of the family, get more attention or there is a male dominance in the Indian rural society. However, Chatterjee *et al*. have found a very high number of females in comparison to males (male: female 0.63:1) in their study on CADRs.[19]

Most of our patients (26%) belong to the age group of 31–40 years. Only 5.2% patients were more than 60 years, the oldest being 67 years. Only 3.9% patients were <11 years, the youngest being 8 years. This may be explained by the fact that children (<11 years) are exposed to a lesser number of drugs and the immune system is not as well developed in children. In the study by Raksha MP at al from Gujarat, India, the majority of patients belong to the age groups 41–50 years (22%) followed by 21–30 years (21%). About 10% were more than 60 years, and 8% were <11 years.[20]

There youngest patient was 1 year old and the oldest patient was 80 years old. This difference in various studies may be related to the regional variation in the health-care seeking behavior of the population. Adverse reaction to drug increases with age. This may be due to the increased use of medications by the elderly, increased potential for drug-drug interactions, and altered drug handling by the body.[21] In our study, the most of the patient had consumed the suspected drug due to infective etiology (61%) as fever, respiratory tract infections, and leprosy. This finding is similar to Gopikrishnan *et al*.[22] and Raksha *et al*.[20]

In the presents study, antibiotics were the most common drug group incriminated in 34% patients followed by NSAIDs in 29% cases and steroids in 25% cases. Remaining cases were caused by pioglitazone, amlodipine, lamotrigine, and cetirizine, etc. Antimalarials and antitubercular drugs which prominently figure in notable studies are absent here. Hotchandani *et al*.[23] showed that antimicrobials 61.4%, NSAIDs 22.9%, and anti-epileptic drug 10% were the most prominent group of drugs responsible for CADRs. Even Sharma *et al*.,[9] Pudukadan *et al*.,[18] and Chatterjee *et al*.[19] found antimicrobials, NSAIDs, and anticonvulsants as the offending drug groups. Similar to their finding, antimicrobials followed by NSAIDs were the most common drug group in the present study but anticonvulsants (lamotrigine) was incriminated in only 1.3% patients with CADRs in our studies. This may be due to the absence of any neurology OPD in our center. Furthermore, in contrast to other studies, 25% cases were incriminated to steroids. This may be due to the endemicity of leprosy in the area. These leprosy patients are often prescribed steroids for Type 1 and 2 reaction. Similar to the present study, Sachin *et al*. from Nagpur also reported steroids as the third most common group (12.61%) causing CADRs preceded by antimicrobials (55%) and NSAIDs (18.56%).[24] Antimicrobials and NSAIDs are commonly prescribed by the physicians and general practitioners even illegally practicing quacks for trivial illness so there are more chances of developing reactions to these groups.

In the present study, among antibiotics, cephalosporins (ceftriaxone) and sulfone group anti-leprotics (dapsone) were the most common causing CADRs (19.2% both) followed by fluoroquinolones (15.4%), tetracycline (15.4%), macrolides (15.4%), clofazimine (7.7%), and penicillins (amoxicillin 7.7%). In the study from Korea by YM son *et al*., among antimicrobials penicillins and cephalosporins were responsible for majority of CADRs [Table 7 and Figure 5].[25]

In the study by Balpande *et al*. from Nagpur India,[26] among antimicrobials causing CADRs maximum were due to sulfonamides (36.1%) followed by penicillins (21.2%), metronidazole (14.8%), fluoroquinolones (12.7%), cephalosporins (6.3%), tetracyclines (6.3%), and dapsone (2.1%). In contrast to the study of Nagpur, the high percentage of CADRs due to dapsone could be explained by the higher prevalence of leprosy in the study area and also because dapsone is being used for many other dermatoses such as dermatitis herpetiformis, lichen planus, and bullous pemphigoid. However, similar to our study, dapsone-induced CADRs was found (17.2%) in patients in a study from south India by Pudukadan *et al*.[18] Sulfonamides in our study were not responsible for any of our cases. This is in contrast to others studies.[27,28] This may be partially because these drugs are avoided most of the times unless really required, as G6PD deficiency is common in India. Similar to our study, Faiza Al-Raaie *et al*. from Oman have reported much lower incidence of CADRs due to sulfonamides.[27] Among NSAIDs, maximum number of CADRs were caused by Ibuprofens (40.9%) followed by diclofenac (36.4%), paracetamol (9%), aceclofenac (9%), and nimesulide (4.5%). Similar results were obtained by Balpande *et al*.[26]

In our study, fixed drug eruptions (FDE) were most common reaction pattern (35.1%) followed by acneiform eruptions (23.4%), erythema multiforme (9.1%), and phototoxic drug reactions (7.8%). Some other studies found.[9,20] That FDEs were as most common drug reaction followed by maculapapular rash and urticaria. Others studies found[26] urticaria/angioedema (32.75%) as the most common CADRs followed by maculopapular rash (26.72%), FDE (20.68%), photosensitivity (12.06%), and acneiform eruptions (4.31%). A study from Kolkata[19] also found urticaria (27.19%) as the most common morphological variety of CADRs followed by FDE (25.16%).This variation could be due to different pattern of drug usage and different ethnic group characteristic in different parts of a country. In our study, all FDEs (14.3%) were caused by antibiotics followed by NSAIDs (13%). The antimicrobials causing FDE were macrolides, cephalosporins, and fluoroquinolones. Among the NSAIDs causing FDE, most were due to diclofenac (70%).

In the study by Monalisa Jena *et al*. from Bhubaneswar, the most common culprit of FDE were NSAIDs (52%, nimesulide) followed by antimicrobials (fluoroquinolones, azithromycin, and cephalosporins).[29] Chatterjee *et al*. also found antimicrobials were only causing FDRs.[19] In our study among the FDE, 55% were females and 45% were males. The most common (75%) morphological variety of antifungal induced reactions were FDE and also all the nitroimidazole (100%) induced reactions were FDE. The second most common reaction was acneiform eruptions (23.4%), 56% were males and 44% females. In the study by Pudukadan *et al*., all acneiform eruptions were reported in all female patients.[18] In our study, all acneiform eruptions were caused by steroids. In the study from Bhubaneswar, three patients had acneiform eruptions, two due to ATD and one due to ampicillin.[29]

In our study, 9.1% had erythema multiforme, all due to NSAIDs, ibuprofen. In the study by YM son *et al*., 6.4% cases were erythema multiforme.[25] As per the Hartwig severity scale, 53% CADRs were mild, 42% were moderate, and 5% were severe.[30] The results are similar to the study done by Amit Dang *et al*.[31] were 55.84% of reactions were mild in severity. It is also similar to the study done by Arulmani *et al*. from south India.[32] However, it is different from the results of certain other studies[33] where more moderate reactions were observed. In our study, the majority of severe CADRs were caused by antibiotics. In the study by Chatterjee *et al*.,[19] 1.62% CADRs (carbamazepine, allopurinol, nimesulide, and phenytoin) were severe, all were admitted for treatment and 0.67% death were reported. In our study, the drugs implicated for severe CADRs were nitroimidazoles, dapsone, nimesulide, and methyl prednisolone. All of them were admitted and treated symptomatically and no deaths were reported.

A causal relationship between the drug and the reaction was assessed using the WHO-UMC classification for causality assessment depending on the lag period between the start of drug and appearance of the reaction and the available data about the drug. In our study, 70% cases were possible and 30% were probable. None of the reactions could be scaled as certain because rechallenge was not done (due to ethical issue). According to the study from Gopikrishnan *et al*. in Gujarat, 70% were probable, 21% were possible, and 9% was certain.[6] Our study results are also the contradictory to the findings of Shrivastava *et al*.[34] from Nagpur where the most of the ADR belong to probable followed by possible categories. However, our result is similar to the findings of Murphy and Frigo where more possible reactions were documented.[35]

According to Rawlins and Thompsons classification, ADRs are categorized as Type B 85.7% and Type A as 14.3%. In the study by Amit Dang *et al*.,[31] similar results were obtained, Type B 77% against Type A 23%. The most of the published data showed that the Type A reactions were commonly reported than the Type B reactions.[36] However, the ease in diagnosing hypersensitivity and anaphylactic reactions and the high severity might have been able to inspire us in reporting such reactions more commonly. Furthermore, the large number of reactions which were reported for antibiotics, which usually are Type B in nature, must have contributed to this higher share of Type B reactions in our study. In our study, all patients with CADRs were evaluated for presence of any comorbidity. Only 3.9% patients had hypertension, rest 96.1% were normal without any comorbidity. All patients with comorbidities had either mild or moderate reactions and none had severe reactions. Multiple medical problems increase the chance of developing adverse drug eruptions.[37]

Limitations

The present study is a hospital-based study. Hence, it may not reflect the actual condition prevalent at the community. The sample size was small to project the findings at the population level. Small duration of study period was the major limitation of our study. Rechallenge could not be performed due to several reasons. Since the most of the patients attending the OPD of this hospital belong to relatively poor socioeconomic status, the pattern of drug usage among them is mostly restricted to drugs that are supplied free of cost from the hospital. As a consequence, the suspected drugs were mostly from the hospital OPD supply list. This was an important limitation of this study as the suspect drug data generated from this study may not be truly reflective of the pattern in other tertiary care center catering to patients of higher socioeconomic status. Despite the limitations of spontaneous reporting of adverse drug reactions, it can still be considered as an effective tool in Pharmacovigilance. Results of this study cannot be generalized. Cost associated with CADRs at community set up has not been estimated. Single center study, hence, prevalence rate in the state of Bihar cannot be estimated.

Conclusion

The clinical pattern and spectrum of CADRs were studied in 77 subjects. A wide clinical spectrum of CADRs ranging from fixed drug eruptions to serious Stevens Johnson syndrome (SJS) was observed. The predominant patterns of reactions observed were fixed drug eruptions. Antimicrobials were the most common drug group incriminated in 34% patients followed by NSAIDs in 29% cases, steroids in 25% cases. Among antimicrobials cephalosporin (ceftriaxone) and sulfone group anti leprotics (dapsone) were the most common causing CADRs. Among NSAIDs, maximum number of CADRs were caused by ibuprofen. Serious reactions were infrequent. Only one SJS was detected probably caused by nimesulide. Most of the reactions were mild (53%) to moderate (42%) requiring no major medical intervention. However, a larger and multi-centric study needs to be conducted across the state to obtain more information about CADRs among the state population.

References

1. Grover S. Severe cutaneous adverse reactions. Indian J Dermatol Leprol 2011;77:3-6.
2. Laurence DR, Bennett PN, Brown MJ. Unwanted effects and adverse drug reactions. Clinical Pharmacology. 8th ed. London: Churchil Livingstone; 1997. p. 121-37.
3. Sacerdoti G, Vozza A, Ruocco V. Identifying skin reactions to drugs. Int J Dermatol 1993;32:469-78.
4. Venning GR.Validity of anecdotal reports of suspected adverse drug reactions: The problem of false alarms. Br Med J (Clin Res Ed) 1982;284:249-52.
5. Venulet J, Blattner R, Von Bulow J, Berneker GC. How good are articles on adverse drug reactions? Br Med J (Clin Red Ed)1982;284:252-4.
6. Mani MZ, Mathew M. A study of 218 drug eruptions. Indian J Dermatol Venerol Leprol 1983;49:109-117.
7. Mehta TK, Marquis L, Shetty JN. A study of 70 cases of drug eruptions. Int J Dermatol 1971;37:1-5.
8. Sehgal S, Balachandran C, Shenoi SD. Clinical study of cutaneous drug reactions in 80 patients. Indian J Derrnatol Venerol Leprol 2003;69:6-7.
9. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: Clinical pattern and causative agents-a 6year series from Chandigarh, India. J Postgrad Med 2001;47:95-9.
10. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: A report from the Boston collaborative drug surveillance program on 15438 consecutive inpatients, 1975-1982. JAMA 1986;256:3358-63.
11. Cohen AD, Friger M. Sarov B, Halevy S. Which intercurrent infections are associated with maculopapular drug reactions? A case-control study. Int J Dermatol 2001;40:41-4.
12. Ozkaya-Bayazit E, Akar U. Fixed drug eruption induced by trimethoprim sulfamethoxazole: Evidence for a link to HLA-A30 B13 Cw6 haplotype. J Am Acad Dermatol 2001;45:712-7.
13. Sharma VK, Sethuraman GG. Adverse cutaneous reactions to drugs: an overview. J Postgrad Med 1996;42:15-22.
14. The Use of the WHO-UMC System for Standardised Case Causality Assessment. Available from: https://www.who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf [Last accessed on 2021 Dec 12].
15. Edwards IR, Aronson JK. Adverse drug reactions: Definitions, diagnosis, and management. Lancet 2000;356:1255-9.
16. Rawlins MD, Thompson JW. Pathogenesis of adverse drug reactions. In: Davies DM, editor. Textbook of Adverse Drug Reactions. Oxford: Oxford University Press; 1977. p. 10.
17. Descamps V, Valance A, Edlinger C. Association of human herpes 6 infection with drug reaction with eosinophilia and systemic symptoms. Arch Dermatol 2001;137:301-4.
18. Pudukadan D, Thappa DM. Adverse cutaneous drug reactions: Clinical pattern and causative agents in a tertiary care center in South India. Indian J Dermatol Venerol Leprol 2004;70:20-4.
19. Chatterjee S, Ghosh AP, Barhhuiya J, Dey SK. Adverse cutaneous drug reactions: A one year survey at a dermatology outpatient clinic of a tertiary care hospital. Indian J Pharmacol 2006;38:429-31.
20. Raksha MP, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol 2008;74:80.

21. Sullivan JR, Shear NH. Drug eruptions and adverse drug effects in aged skin. Clin Geriatr Med 2002;18:21-42.
22. Anjaneyan G, Gupta R, Vora R. Clinical study of adverse cutaneous drug reactions at a rural based tertiary care centre in Gujarat. Natl J Physiol Pharm Pharmacol 2013;3:129-36.
23. Hotchandani SC, Bhatt JD, Shah MK. A prospective analysis of drug induced acute cutaneous reactions reported in patients at a tertiary care hospital. Indian J Pharmacol 2010;42:118-9.
24. Hiware S, Shrivastava M, Mishra D, Mukhi J, Puppalwar G. Evaluation of cutaneous drug reactions in patients visiting out patient departments of Indira Gandhi government medical college and hospital (IGGMC and H), Nagpur. Indian J Dermatol 2013;58:18-21.
25. Son YM, Lee JR, Roh JY. Causality assessment of cutaneous adverse drug reactions. Ann Dermatol 2011;23:432-8.
26. Balpande KG, Borkar AS, Bardwaik RT. Study of clinical pattern in patients with cutaneous drug reactions. Int J Med Pharm Sci 2013;3:34-9.
27. Al-Raaie F, Banodkar DD. Epidemiological study of cutaneous adverse drug reactions in Oman. Oman Med J 2008;23:21-7.
28. Puavilai S, Choonhakarn C. Drug eruptions in Bangkok: A 1-year study at Ramathibodi Hospital. Int J Dermatol 1998;37:747-51.
29. Jena M, Mishra S, Panda M, Mishra SS. Cutaneous adverse rug reaction monitoring of different drugs in dermatology OPD of a tertiary care teaching hospital. Int J Cur Res Rev 2013;5:77-82.
30. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49:2229-32.
31. Dang A, Bhandare P.N. The profile of voluntary reported adverse drug reactions at a tertiary care hospital: A fifteen month prospective study. J Clin Diagn Res 2012;6:1504-9.
32. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. Br J Clin Pharmacol 2007;65:210-6.
33. Gholami K, Shalviri G. The factors which are associated with the preventability, predictability and the severity of adverse drug reactions. Ann Pharmacother 1999;33:236-40.
34. Shrivastava M, Uchit G, Chakravarti A, Joshi G, Mahatme M, Chaudhari H. Adverse drug reactions reported in Indira Gandhi government medical college and hospital, Nagpur. JAPI 2011;59:1-4.
35. Murphy BM, Frigo LC. The development, implementation and the results of a successful multidisciplinary adverse drug reaction reporting progress in a university teaching hospital. Hosp Pharm 1993;28;1199-204.
36. Laurence DR, Bennett PN, Brown MJ. Unwanted effects and adverse drug reactions. In: Clinical Pharmacology. 9th ed. New Delhi, India: Elsevier; 2006:135-150.
37. Hafner JW Jr., Belknap SM, Squillante MD, Bucheit KA. Adverse drug events in emergency department patients. Ann Emerg Med 2002;39:258-67.