

Cutaneous adverse drug reaction profile in a tertiary care out patient setting in Eastern India

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Abstract

Background:

Cutaneous adverse drug reactions (CADR) are the most frequent of all manifestations of drug sensitivity and manifest with varied and diverse morphology.

Aims:

To study the prevalence and clinical spectrum of CADR among patients attending outpatient department (OPD) in a tertiary care hospital.

Materials and Methods:

An observational study was undertaken over a 1-year period in dermatology OPD of a tertiary care teaching hospital in Eastern India. Patients presenting with suspected drug-related cutaneous lesions were included if drug identity could be ascertained. Clinical profiling was done. Drug history was recorded in a format specified in Indian National Pharmacovigilance Programme and causality assessment carried out as per World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria.

Results:

Commonest CADR in our study was morbilliform eruption (30.18%), followed by fixed drug eruption (24.52%), Stevens–Johnson syndrome (SJS)-Toxic epidermal necrolysis (TEN) and overlap of two (24.50%), exfoliative dermatitis (7.54%), urticaria (5.6%), phototoxic drug reaction (3.8%), pityriasis rosea-like eruptions (1.89%), and severe mucositis (1.80%). Drugs implicated were sulfonamides (17%), fixed-dose combinations of fluoroquinolones with nitroimidazoles (11.30%), analgesics (11.30%), antiepileptics (11.30%), beta-lactam antibiotics (9.40%), fluoroquinolones alone (7.50%), allopurinol (7.50%), and azithromycin (5.70%). Reaction latency varied from 1 to 43 days. Causality assessment was certain and probable for 18.9% and 41.5% of the reactions, respectively, and reactions were serious in 33.96% (95% confidence interval 21.21–46.71%).

Conclusions:

Cutaneous adverse drug reaction profile in this study is similar in many ways to studies conducted earlier in India. Incidence of life-threatening reactions like SJS-TEN was higher compared with studies conducted abroad. Reaction time and lesion patterns are helpful in identifying an offending drug in the

setting of multiple drug therapy.

KEY WORDS: Causality assessment, cutaneous adverse drug reaction, dermatologic pharmacology, pharmacovigilance

Introduction

An adverse cutaneous reaction caused by a drug is any undesirable change in the structure or function of the skin, its appendages or mucous membranes, and it encompass all adverse events related to drug eruption, regardless of the etiology.[1] Cutaneous adverse drug reactions (CADR) are the most frequent of all manifestations of drug sensitivity. They manifest with varied and diverse morphological pattern ranging from trivial urticaria to severe form of vasculitis or toxic epidermal necrolysis and cutaneous necrosis or gangrene. Fatal reactions to drugs are uncommon, but reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS-TEN) and exfoliative dermatitis may result in death even if the eruption is the only manifestation.

As innovation in medicine occurs and new drugs continue to be developed, there is potential for the occurrence of an increasing number of cutaneous drug reactions. However, the true incidence of drug eruptions is difficult to determine, largely because many mild and transitory reactions are not recorded. On the other hand, skin changes due to other etiology (e.g., viral exanthem misdiagnosed as morbilliform eruption and herpes labialis as bullous fixed drug reaction) are sometimes incorrectly attributed to drugs. Although the incidence of reactions to specific agents is obviously related to the quantity prescribed and every drug must be regarded as potentially capable of provoking abnormal reactions, certain drugs are more apt to do so than others. Commonly used drugs that are implicated in causing CADR are penicillins, sulfonamides, anticonvulsants, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors, fluoroquinolones, etc.[2] There are also chances of adverse unexpected outcomes to newly introduced drugs, causing inconvenience to both patients and physicians.

The pattern of cutaneous reactions differs among various drugs. Hence, understanding the precise nature of CADR may help narrow down the search for the offending agent. Knowledge of drugs that can cause CADR can help physicians in choosing safer drugs and therefore can be helpful to society at-large. Keeping these observations in the background, this study was undertaken to assess the clinicodemographic profile of suspected CADR in patients attending the dermatology outpatient department (OPD) in a tertiary care hospital in Eastern India.

Materials and Methods

This cross-sectional study was conducted over 235 working days in a 1-year period from May 2008 to April 2009 in the Dermatology OPD of Medical College Hospital, Kolkata. The study was approved by the Institutional Ethics Committee. All patients attending this OPD (either self-presenting or referred by other departments of the institution) were screened and recruited if they presented with visible skin lesions suspected to be drug related and provided written informed consent for inclusion. Excluded were subjects who complained of only symptoms (e.g., itching) without visible skin lesions, those who could not recall the name of the suspect medicines consumed, and those whose lesions turned out to be disease related (e.g., viral exanthems, rash of rickettsial infections, and collagen vascular disease) on closer examination. A few subjects who reported to have consumed indigenous (ayurvedic and homeopathic) medicines were also excluded as the herbal ingredients could not be identified in their case.

The demography, nature of reaction, suspect medication use, and concomitant medication details were captured in the format recommended by the National Pharmacovigilance Programme in India. Description of the skin lesions and relevant additional clinical details were also recorded. The case causality assessment criteria recommended by the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) were followed for assessing causality of individual reactions.[3]

Results

In 235 working days, over 1-year period, 72 cases of suspected CADR were newly detected among 25,773

patients attending the dermatology OPD. Thus, the primary incidence was 0.28% (95% confidence interval [CI] 0.21-0.34%). Nineteen cases were excluded from further analysis: 2 refused to give consent, visible skin lesions were indistinct in 2, viral exanthems could not be excluded in 2, 1 case turned out to be lupus erythematosus, 8 patients failed to recall the correct name of the medication consumed, and 4 patients blamed indigenous medicines of unknown composition. The remaining 53 were included in the final evaluation—giving an incidence of 0.21% (CI 0.15-0.26%) or 2.05 per 1000.

The study population comprised 27 (50.90%) women and 26 (49.10%) men. The age range was 4-82 years, although the majority (52.80%) of the patients were in the 16-35 years band. Mean age at presentation was 33.8 ± 17.19 years, and there was no significant difference between men (33.2 ± 19.47 years) and women (34.4 ± 15.02 years) in this regard. The bulk of the cases (88.70%) was Hindus, while the rest were Muslims. The demographic profile in different reaction categories is summarized in [Table 1](#).

Among the various known patterns of CADR, morbilliform eruption (30.18%), fixed drug eruption (24.52%), and SJS-TEN and overlap of these two (24.50%) comprised the bulk of the cases. Other types seen were exfoliative dermatitis (7.54%), urticaria (5.6%), phototoxic drug reaction (3.8%), pityriasis rosea-like rash (1.89%), and severe mucositis (1.80%). Of these, cases of SJS-TEN/overlap of SJS-TEN and exfoliative dermatitis were life threatening and represented the severe variants of CADR (32.04%) in the study population.

Drugs suspected to cause CADR in the study population could be classified broadly into nine groups namely sulfonamides, fixed-dose combination (FDC) of fluoroquinolones with nitroimidazoles, analgesics, antiepileptics, beta-lactam antibiotics, fluoroquinolones alone, allopurinol, macrolides, and miscellaneous. Among them, the most commonly implicated group was sulfonamides and allied drugs (17.00%), comprising of co-trimoxazole, sulfasalazine, and di-amino di-phenyl sulfone (DDS). This was followed by FDC of fluoroquinolones with nitroimidazoles like ciprofloxacin, norfloxacin, ofloxacin with metronidazole, tinidazole, and ornidazole (11.30%), analgesics like paracetamol and diclofenac (11.30%), antiepileptics like phenytoin, carbamazepine and lamotrigine (11.30%), beta-lactam antibiotics like amoxicillin, ampicillin, cloxacillin and cephalosporins (9.40%), fluoroquinolones alone like ofloxacin and gemifloxacin (7.50%), allopurinol (7.50%), and azithromycin (5.70%). Miscellaneous group consisted of antitubercular drugs, thiazide, methotrexate, and multivitamin injection, which together accounted for 18.90% of the cases. [Table 2](#) denotes a cross-tabulation of drug categories and different clinical types of CADR in these 53 subjects.

The incriminated drugs were mostly (88.7%) physician prescribed. Drug reactions that were encountered in the study population because of OTC drugs included cases of fixed drug eruption (5.67%), SJS (3.8%), and morbilliform eruption (1.89%).

The indications of drug implicated in the development of CADR are highlighted in [Figure 1](#). Medications used for fever and upper respiratory tract infections (URTI) accounted for the majority (41.5%). The drugs for GI problem were responsible for FDR in all the cases, whereas medications for neurological problem gave rise to either morbilliform eruption or SJS/TEN.

Interval between drug intake and first appearance of cutaneous lesions (reaction time) varied from 1 to 43 days (mean 6.2 ± 8.61 , median=2) in different type of CADR. The duration of individual reactions was highly variable overall ranging between 2 and 180 days (mean 12.0 ± 25.07 , median=6). Reaction time of various types CADR and various drug groups are summarized in [Tables 3](#) and [4](#), respectively.

The causality profile of CADR of our study population was categorized as per WHO-UMC case causality assessment criteria. Among 53 subjects, in only 10 (18.9%) cases the causality association was certain and the majority were either probable/likely ($n=22$, 41.5%) or possible ($n=21$, 39.6%). Among the major categories of CADR, association could be made certain in 2 of 16 cases in morbilliform eruption, 3 of 13 cases in FDR, 2 of 13 cases in SJS-TEN. The inclusion criteria were so laid that unlikely, conditional, and unclassifiable cases did not get enrolled as analyzable subjects.

CADR resulting in disability was found in 50 (94.34%) cases, of which majority were accounted by morbilliform eruption ($n=16$, 30.1%) followed by SJS-TEN ($n=13$, 24.5%) and FDE ($n=10$, 18.8%).

Twenty-seven (50.94%) patients of serious CADR found in our study necessitated hospitalization and were mostly due to SJS-TEN (22.64%), extensive morbilliform eruption (13.20%), and exfoliative dermatitis (7.54%). Fatal outcome was noted in 5 (9.4%) cases of which 2 deaths occurred in TEN, 2 in exfoliative dermatitis, 1 in morbilliform eruption. The patient who had died in morbilliform eruption was suffering from HIV infection and died due to intercurrent illness. On the other hand, death resulted in 2 of 4 (50%) of exfoliative dermatitis, 2 of 12 (16.7%) of SJS/TEN, and 1 of 7 (14.3%) of morbilliform reaction. The only patient with morbilliform reaction who died was suffering from HIV infection; thus, co-morbidity contributed to the adverse outcome. Urticaria and FDE were the least serious of all the CADR and none resulted in any disability.

Ten patients (18.87%) in our series had positive history of cutaneous eruption following medications – eight of them had history of similar type of reaction following intake of similar medication, but two gave history of CADR caused by different medication. One of these two developed SJS to azithromycin for the first time and morbilliform eruption to co-trimoxazole few months later. Second patient was admitted for exfoliative dermatitis following multivitamin injection and again came to dermatology OPD for morbilliform eruption to diclofenac.

Discussion

Adverse cutaneous drug reactions are distressing to both the patient and physician. Mortality can occur in severe reactions, but even without this quality of life may be significantly diminished due to hospitalization, prolongation of hospital stay, and increased morbidity.[4] Furthermore, the development of a skin eruption is frequently cited as a reason for discontinuation of treatment without completing therapeutic course.[5] Drug reactions are a common reason for litigation too. Not warning a patient about potential adverse effects, prescribing a medicine to a previously sensitized patient, and prescribing a related medication with cross-reactivity are common medicolegal pitfalls and therefore should not be taken lightly.

It is an utmost necessity for a dermatologist to have a comprehensive understanding of the clinical spectra of CADR, as well as knowledge of the drugs which are frequently incriminated in such adverse reactions. This would help reduce or minimize the extent of iatrogenic morbidity and mortality.

Relative incidence rate of CADR among new patients attending dermatology OPD were found to be 2.05 per 1000 in our study. This is lower than the figures reported in earlier Indian studies, such as those by Chatterjee, *et al.*[6] (26 per 1000) and Ghosh, *et al.*[7] (285 per 1000) but similar to a Scandinavian study where the rate was 0.14 per 1000.[8] One possible explanation for this low incidence rate was that the study was conducted in a tertiary center, so that minor rashes may not have come to the dermatology OPD or patients could have been treated by physicians in other disciplines. Furthermore, 19 of the original 72 subjects screened (26.39%) had to be excluded from the final evaluation in spite of having recognizable features of CADR, largely because they failed to state the names of the offending drugs or took indigenous medicines with non-declared or non-identifiable active ingredients. Another considerable factor was that there was no patient of CADR caused by antiretroviral drugs although our study was conducted in a tertiary care center, as the department that provides antiretroviral therapy was usually managing skin reactions on their own without referral to the dermatology department.

Age range of our study was 4-82 years, which is similar to other studies[9,10] and shows that no age is exempted from CADR.[11] The mean age of our study population was 33.8±17.19 years, and the majority (52.8%) of the patients belonged to the age group of 16-35 years, which is similar to the previous studies.[11] Our study showed that men and women are equally vulnerable (male:female ratio 0.96:1), which is similar (0.87:1) to the study done by Padukadan and Thappa in South India[11] but lower than those reported by studies done outside India[12,13] where the ratio of male:female was 1:1.18. Our study result also differs from the studies done at Chandigarh by Sharma, *et al.*[9,14] where a male predominance was seen. As all these studies were institution based, this difference in demographic profile can be accounted by the difference in the demography of the patients attending the clinic.

Cutaneous adverse drug reaction was found to be caused more commonly (88.7%) by prescribed drugs than over-the-counter (OTC) drugs. This can reflect a changing trend that more patients were buying

medication after visiting doctors. Understandably the patients reported early to the treating physician and a vigilant doctor can thus detect a CADR before it turns serious. This fact can be utilized for early detection if the prescribing physician is having high index of suspicion for CADR. Similar finding was noted in a study from Goa,[15] which reported that 75.45% of dispensed drugs were prescribed drugs and the remainder 24.55% was OTC preparations. In this study, morbilliform or maculopapular eruption was the commonest reaction encountered as cited in the literature.[9,12,16] This was followed by fixed drug eruptions and severe bullous CADR (i.e., SJS/TEN/SJS-TEN overlap syndromes). A high incidence of TEN and SJS has been reported from Indian studies,[11,16,17] while Western studies[18] have found occurrence of SJS/TEN as rarity. This might reflect the close surveillance, and the tendency to withdraw suspected drugs even in cases of minor (e.g., in the stage of erythema multiforme) skin reactions in Western countries and frequent usage of drugs in combination or FDC in Indian setup.

Fixed drug eruption was most commonly caused by FDC of quinolone with a nitroimidazole in our study; however, morbilliform eruptions were the commonest pattern when quinolones were used alone. From this observation, it can be hypothesized that the nitroimidazole may be responsible for causing FDE when quinolone-nitroimidazole combination is used. The fact that CADR was most frequent in patients with fever and URTI may be because this condition needs polypharmacy (e.g., antibiotics of different categories, analgesics).

Our study showed that the reaction time for morbilliform eruption and urticaria varied from 1 to 30 days, for fixed drug eruptions 1 to 7 days, for SJS-TEN 1 h to 2 weeks, and for exfoliative dermatitis 1 to 43 days. This profile is similar to the study by Sharma, *et al.*, [9] but slightly different from the study by Sushma, *et al.* [16] The CADR profile of our study is compared with similar studies in Table 5. 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. Not only this implies that physicians need to enquire about recent medications but also it is desirable that physicians should be vigilant about CADR even to not-so-recent drug history (especially for allopurinol and dapsone). Also, in a cases of polypharmacy, reaction time may be helpful in suggesting the offending drug, which in turn will prevent unnecessary withdrawal of an innocent medication.

It needs to be highlighted that mortality from CADR results mostly from exfoliative dermatitis and SJS/TEN; thus, 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.

Our study screened a large number of subjects and a corresponding wide spectrum of commonly used drugs. However, there were also some limitations. Causality assessment had its share of uncertainty in polypharmacy cases, especially as rechallenge was not attempted deliberately owing to ethical reasons. The hospital caters primarily to a lower socioeconomic stratum so that exposure to most newer drugs was limited in our study population. Long-term follow-up and monitoring of the patients could not be done. Finally, as already stated, there is the problem of inherent underreporting of mild and self-limiting cases.

Conclusion

Notwithstanding these limitations, we can state that the drugs causing CADR showed difference in terms of clinical manifestations and reaction time, which can serve as useful clues for physicians. Major bulk of CADR result from physician prescribed drugs. Hence, awareness on part of the physician can help in timely detection of cutaneous reactions, thereby restricting damage from them.

Footnotes

Source(s) of support: Nil.

Conflicting Interest: No.

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Figures and Tables

Table 1

Characteristic	Morbilliform	Fixed drug eruption	SJS-TEN overlap	Phototoxic	Urticaria	Exfoliative dermatitis	Others	Overall
N (%)	16 (30.18)	13 (24.5)	13 (24.5)	2 (3.8)	3 (5.67)	4 (7.54)	2 (3.8)	53 (100)
Age range	18-65	4-82	9-56	13-60	55-60	21-48	18-30	4-82
Mean±SD	33.4±13.61	32.6±21.91	29.4±14.95	36.5±33.23	59.0±6.08	38.3±11.95	21.0±8.48	33.8±17.19
Sex ratio (M:F)	6:10	11:2	5:8	0:2	2:1	1:3	1:1	26:27

Demographic profile in different reaction categories

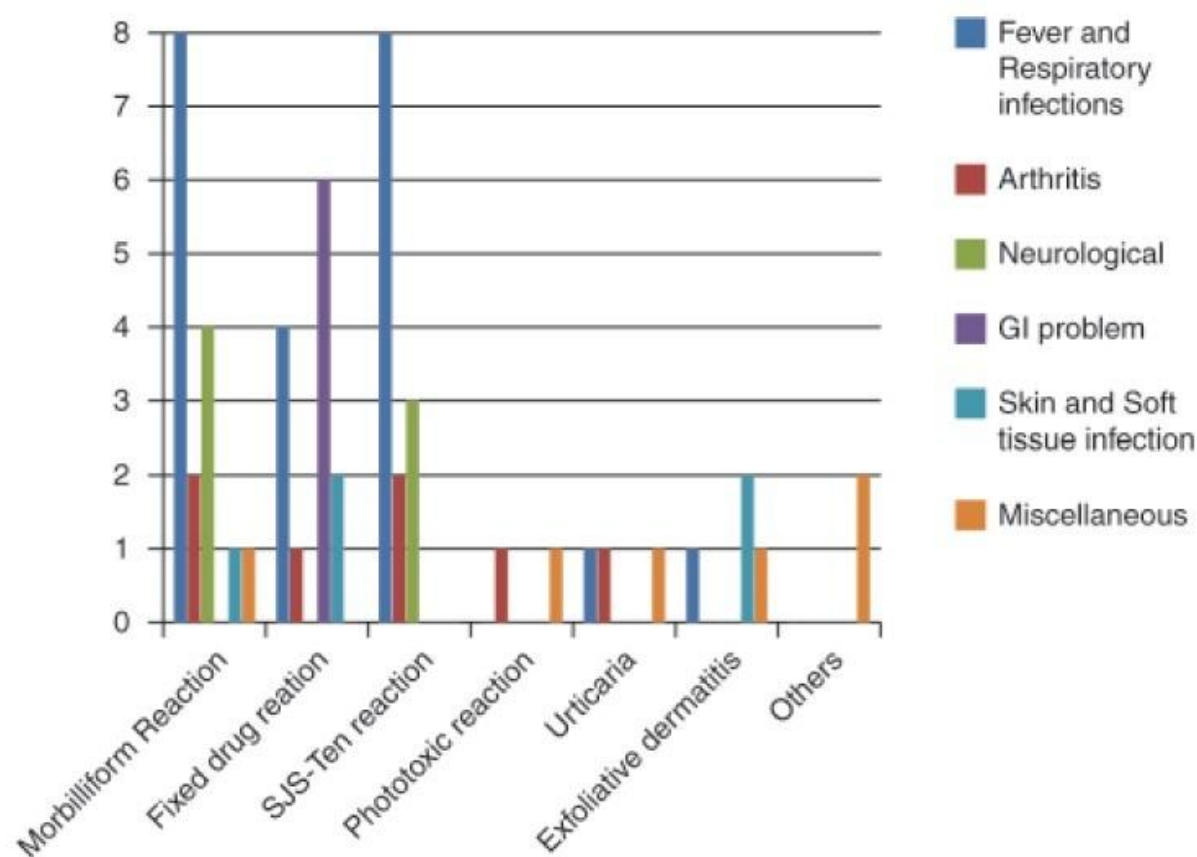
Table 2

Drug group	Morbilliform (%)	Fixed drug eruption (%)	SJS-TEN overlap (%)	Phototoxic (%)	Urticaria	Exfoliative dermatitis	Others (%)	Overall (%)
Sulfonamides	2 (3.8)	3 (5.67)	3 (5.67)	0	0	1 (1.89)	0	9 (17)
Quinolone + Nitroimidazole	0	5 (9.43)	1 (1.89)	0	0	0	0	6 (11.3)
Fluoroquinolones	3 (5.67)	0	1 (1.89)	0	0	0	0	4 (7.5)
Macrolides	1 (1.89)	0	2 (3.8)	0	0	0	0	3 (5.7)
Beta-lactams	3 (5.67)	2 (3.8)	0	0	0	0	0	5 (9.4)
Analgesics	2 (3.8)	2 (3.8)	1 (1.89)	1 (1.89)	0	0	0	6 (11.3)
Antiepileptics	3 (5.67)	0	3 (5.67)	0	0	0	0	6 (11.3)
Allopurinol	0	0	1 (1.89)	0	2 (3.8)	1 (1.89)		4 (7.5)
Others (e.g., thiazides, atorvastatin, ATD, methotrexate)	2 (3.8)	1 (1.89)	1 (1.89)	1 (1.89)	1 (1.89)	2 (3.8)	2 (3.8)	10 (18.9)

All = Antitubercular drugs

Drug categories associated with different clinical types of cutaneous drug reactions

Figure 1



Indication for drug intake in the major cutaneous drug reaction categories

Table 3

	Morbilliform	Fixed drug eruption	SJS-TEN overlap	Phototoxic	Urticaria	Exfoliative dermatitis	Others	Total
Reaction time	<i>n</i> =16	<i>n</i> =13	<i>n</i> =13	<i>n</i> =2	<i>n</i> =3	<i>n</i> =4	<i>n</i> =2	<i>n</i> =53
Median (in days)	2.5	1	3	5.5	11	17.5	3.5	2
Range (in days)	1-30	1-7	1-15	4-7	1-20	1-43	2-5	1-43
Mean±SD (in days)	6.12±8.37	2±1.77	5.23±5.13	5.50±2.12	13.33±13.65	19.75±17.57	3.5±2.12	6.20±8.61
Duration of present episode*	<i>n</i> =14	<i>n</i> =13**	<i>n</i> =10	<i>n</i> =2	<i>n</i> =3	<i>n</i> =2	<i>n</i> =1	<i>n</i> =45
Median	5	5	7	10.5	5	27.5	12	6
Range (days)	2-18	2-15	3-21	7-14	2-7	13-42	12	2-42
Mean±SD (days)	6.36±4.12	6±3.37	8.4±5.76	10.5±4.85	4.7±2.52	27.5±20.51	12	7.84±6.7

*Five patients died during the course of the disease and 3 of them (one patient each of morbilliform, SJS-TEN overlap, and others category) could not be followed up, hence were excluded from the analysis of duration (from onset to recovery). Among the five patients who died, the duration of suffering (from onset to death) was 20 days for morbilliform (*n*=1), 8±7.07 days for SJS-TEN overlap (*n*=2), 6.5±0.71 days for exfoliative dermatitis (*n*=2). **Two patients of FDR were having repeated episodes (the maximum duration was 180 days before being diagnosed)

Reaction time (time of reaction onset following commencement of exposure) and duration (duration from onset to recovery) in days of the different types of cutaneous drug reactions

Table 4

Drug group	Reaction time (days)	Reaction time (days)	Reaction time (days)	Total no. of reactions (%)
	Range	Mean±SD	Median	
Sulfonamides	1-13	11.2±13.45	7	9 (17)
Quinolone + nitroimidazole	1-2	1.3±0.52	1	6 (11.3)
Fluoroquinolones	1-9	3.5±3.69	2	4 (7.5)
Macrolides	3-8	5.7±2.52	6	3 (5.7)
Beta-lactams	1-4	2.0±1.22	2	5 (9.4)
Analgesics	1-7	2.3±2.42	1	6 (11.3)
Antiepileptics	2-30	9.3±10.61	5	6 (11.3)
Allopurinol	1-28	16.3±11.47	18	4 (7.5)
Others (e.g., thiazides, atorvastatin, AIT), methotrexate	1-14	4.4±4.52	2.5	10 (18.9)

AITD = Antitubercular drugs

Variation in reaction time in different drug categories

Table 5

CADR types and pattern	Sushma <i>et al.</i> , ^[16] 2005	Jhaj <i>et al.</i> , ^[17] 1999	Sharma <i>et al.</i> , ^[8] 2001	Patel and Marfatia, ^[10] 2008	Present study, 2011
Number of subjects	<i>n</i> =56	<i>n</i> =144	<i>n</i> =500	<i>n</i> =200	<i>n</i> =53
Sex ratio (male:female)	1:1	1:1	1:0.60	1:0.79	1:1.04
Commonest offending drug	Antiepileptics	Antibiotic	Co-trimoxazole	Co-trimoxazole	Sulfonamides (co trimoxazole, sulfasalazine, DDS)
Morbilloform (reported reaction time)	35% (2-7 days)	50% (NA)	34.6% (30 min to 3 week)	18 (NA)	30.1% (1-30 days)
Fixed drug eruption (reported reaction time)	4% (1 day)	0%	30% (2 days to months)	30.5% (NA)	24.5% (1-7 days)
SJS-TEN overlap (reported reaction time)	35% (1-3 weeks)	10/75 (NA)	NA (few hours to 1 week)	5% (NA)	24.5% (1 h to 2 weeks)
Phototoxic (reported reaction time)	4% (3-4 weeks)	0%	0%	2% (NA)	3.8% (4-7 days)
Urticaria (reported reaction time)	7% (1-3 days)	21.5% (NA)	NA (30 min to 3 weeks)	18.5% (NA)	5.0% (1-28 days)
Exfoliative dermatitis (reported reaction time)	4% (6 weeks)	0%	NA (6 weeks)	2.5% (NA)	7.54% (1 day to 6 weeks)

NA = Data not available

Comparison of CADR pattern of this study with other studies

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