A PROSPECTIVE STUDY OF CUTANEOUS ADVERSE DRUG REACTIONS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

INTRODUCTION: Adverse drug reactions are inevitable negative consequences seen with drug therapy and cutaneous adverse drug reactions are the commonest manifestations. These unwanted and unintended drug effects are responsible for responsible for significant morbidity and mortality.

OBJECTIVES: To study the clinical pattern of CADRs and to establish the causal relationship between drugs and reactions, to identify and assess the predisposing/underlying risk factors and to evaluate treatment outcome of CADRs.

SUBJECTS AND METHODS: This was a prospective study was carried out on 120 consecutive patients with suspected CADRs. The pattern, extent, severity and duration of the reactions were assessed and any other organ/system involvement as a part of the drug reaction was also assessed. Causality, severity and preventability of the reactions were also assessed.

RESULTS: The mean age of the study population was 40.98±20.61 years with little gender difference. The predominant patterns of reactions observed were erythematous eruptions (n=37, 30.8%) and urticaria (n=23, 19.2%). The common causative drugs were antimicrobials (n=52, 43.3%) followed by analgesics/NSAIDs (n=30, 25%) and antiepileptics (n=15, 12.5%). Among the antimicrobials, beta-lactams (n=19, 36.5%) and flouroquinolones (n=9, 17.3%) were the leading causative drugs. Among the analgesic/NSAIDs, diclofenac (n=9, 30%) was the leading causative drug. Among the antiepileptics, carbamazepine (n=6, 40%) and phenytoin (n=5, 6%) were the common offenders. The time interval between the drug exposure and the appearance of CADRs, was variable with different patterns of reactions. Majority of the reactions were mild to moderate , and serious reactions were infrequent. Most of the reactions were not preventable as the predisposing risk factors could not be ascertained.

CONCLUSION: Proper awareness cutaneous adverse drug reactions, early detection and timely withdrawal of the offending drugs and appropriate rescue measures may greatly contribute to reduce the incidence, frequency, severity and morbidity and possible mortality associated with drug therapy.

KEY WORDS: ADRs; Cutaneous adverse drug reactions; Drug eruptions; Pharmacovigilance

INTRODUCTION

Drugs are almost always coupled with inherent risk of adverse reactions no matter how safe and efficacious they are during clinical trials and subsequent widespread therapeutic use.[1] Adverse drug reactions (ADRs) are negative consequences of drug therapy and can be a major setback in clinical practice. WHO defines ADR as *"a response to a drug, which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."*[2] Therefore, ADRs are unwanted and unintended effects of drug therapy, which may be responsible for significant morbidity and mortality and can increase the cost of healthcare for the individual patient, healthcare delivery institutions and the community at large.[3] The incidence of ADRs varies from 6-7% of all hospitalizations and could be observed in 10-20% of patients receiving drug therapy.[4]

Cutaneous adverse drug reactions (CADRs) are the commonest manifestations of ADRs occurring in 2-3% of patients receiving drug therapy for various reasons.[5] The clinical spectrum and pattern of CADRs may vary from mild and transient maculopapular rash to severe and potentially fatal Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[3] Cutaneous manifestations of adverse drug reactions may be part of systemic manifestation with other organ system

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involvement or could be the only manifestation of the ADR.[6] Drugs may also worsen pre-existing skin disorders.[7] 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.

Effective monitoring of CADRs, both hospital-based and population-based, forms an integral part of ADR monitoring programmes as well as part of pharmacovigilance, not only to generate valid data but also to identify and assess predisposing/underlying risk factors and to evaluate treatment outcome. The present study was conducted to study the clinical pattern of CADRs and to establish the causal relationship between drugs and reactions, to identify and assess the predisposing/underlying risk factors and to evaluate treatment outcome of CADRs in Kempegowda Institute of Medical Sciences Hospital and Research Center (KIMSH & RC)—a tertiary care hospital in South India.

SUBJECTS AND METHODS

This prospective study was carried out on 120 consecutive patients attending the Dermatology OPD and inpatients admitted to KIMSH & RC with suspected CADRs after obtaining approval and clearance from the Institutional Ethical Committee between 2007 and 2008.

Patients of both sexes and of all age groups with suspected CADRs willing to give written informed consent and comply with the study were included and patients with reactions where drugs taken were not known or unclear were excluded from the study.

A detailed history including drug history, personal history, family history, present and past medical history and history of previous drug reactions were recorded. Available case records were scrutinized to collect any valid data. A thorough clinical evaluation was done to assess the pattern, extent, severity and duration of the reactions and assess any other organ/system involvement as a part of the drug reaction. The diagnosis of the CADR was done in consultation with expert dermatologists based on clinical and morphological criteria. When more than one drug was used, the drugs with the highest suspicion for causation were withdrawn 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.[8] Severity of the reactions was assessed using adapted Hartwig rating scale.[9] The preventability of reactions was assessed based on Schumock and Thornton criteria.[10] Only certain, probable and possible cases were considered for the study and the data was subjected to descriptive and statistical analysis.

The criteria for the diagnosis of CADRs included:

1. Time interval between the drug intake and the onset of the reaction within a specific time as described in the literature for each reaction (erythematous drug eruption/maculopapular rash <7 days; urticaria 7-21 days; SJS/TEN: 1-3 weeks; drug hypersensitivity syndrome 2-6 weeks; photodermatitis up to 1 year; and fixed drug eruption 30 minutes-16 hours). The reaction was not considered as drug-induced if the drug was administered after the onset of the CADR.
2. Improvement in the condition of the patient after dechallenge/withdrawal of the suspected drug.
3. Rechallenge test was not included for ethical reasons and possible associated risks. The offending/suspected drug(s) were discontinued and appropriate treatment instituted and the treatment outcome was evaluated.

Laboratory investigations were done only in selected cases for aiding the diagnosis and treatment of the conditions including hematological tests (WBC, TC, DC, and absolute eosinophil count) and biochemical tests (serum electrolytes, blood sugar, liver function tests, renal function tests, and HIV).

Followup was done for severe, chronic or persistent reactions to assess the clinical progress and to evaluate treatment outcome. Severe cases of CADRs such as SJS and TEN were followed up on a weekly basis after initial

hospitalization till the resolution of cutaneous reactions. Minor and non-serious cases like erythematous drug eruptions and urticarial rashes were followed up only if there was no resolution of the reactions after the initial treatment or if the rashes reappeared.

The data was analyzed statistically using descriptive statistics namely mean and standard deviation for quantitative variables and the causal relationship was examined using z test.

RESULTS

The mean age of the study population was 40.98±20.61 years—the oldest being 83 and the youngest being 4 years. Male to female ratio was 1.07 and the majority of patients belonged to the 21-30 age group (n=25, 20.9%). The presenting complaints/symptoms are summarized in **Table 1**.

Table 1 : Presenting complaints / symptoms

Presenting complaints / symptoms	Gender n (%) n=120		
	Male	Female	Total $
Edema	1 (0.8)	4 (3.3)	5 (4.2)
Erythema	3 (2.5)	5 (4.2)	8 (6.7)
Skin discoloration	5 (4.2)	4 (3.3)	9 (7.5)
Pain	1 (0.8)	–	1 (0.8)
Pruritus	37 (30.8)	22 (18.3)	60 (50)
Pustules	1 (0.8)	1 (0.8)	2 (1.6)
Skin rash / eruption	39 (32.5)	40 (33.3)	92 (65.8)
Vesicle / bulla	4 (3.3)	6 (5)	10 (8.3)
Worsening of existing dermatosis	1 (0.8)	–	1 (0.8)

$ Symptoms overlap and total percentage may not add up to 100%

The clinical spectrum of CADRs was wide. **(Table 2)** The most common patterns included erythematous drug eruptions, urticaria and fixed drug eruptions (FDE). Acneiform drug eruptions were seen exclusively in females who were on oral contraceptives. Solitary lesions were observed in some cases of FDE (n=7, 5.8%), urticaria (n=4, 3.3%), angioedema and drug-induced cutaneous lupus (n=1, 0.8% each) whereas all the other cases had multiple skin lesions (⩾2).

Table 2: Clinical spectrum / pattern of reactions

Reactions	Gender n (%) n=120			
	Male	Female	Total	Z test
Acneiform drug eruption	–	8 (6.7)	8 (6.7)	0
AGEP	1 (0.7)	1 (0.7)	2 (0.8)	0
Angioedema	1 (0.8)	4 (3.3)	5 (4.2)	-8.2
Cutaneous vasculitis	1 (0.7)	2 (0.8)	3 (2.5)	-3.9
Drug-induced bullous pemphigoid	1 (0.7)	–	1 (0.7)	0
Drug-induced cutaneous lupus	1 (0.7)	3 (2.5)	4 (3.3)	-6.3
Drug induced pemphigus	–	1 (0.7)	1 (0.7)	0
Drug induced psoriasis	1 (0.7)	–	1 (0.7)	0
Erythematous drug eruption $	23 (19.2)	14 (11.7)	37 (30.8)	2.7
FDE	10 (8.3)	6 (5)	16 (13.3)	2.8
Hyperpigmentation	3 (2.5)	2 (1.7)	5 (4.2)	2.2
Photosensitivity	3 (2.5)	3 (2.5)	6 (5)	0
SJS / TEN	3 (2.5)	4 (3.3)	8 (6.7)	-2.8
Urticaria	14 (11.7)	9 (7.5)	23 (19.2)	2.4

$ Include maculopapular, morbilliform and purpuric rashes

Analysis of the total body surface (TBS) involvement showed that <10% TBS was involved in 82 (68.2%) cases of CADRs whereas involvement of 10-20% of TBS was seen in 17 cases (14.1%); 20-30% in 12 cases (9.9%); and >30% involvement of TBS in only 9 cases (7.4%). CADRs which showed >30% TBS involvement included urticaria (n=4, 3.3%), SJS/TEN (n=3, 2.5%), drug-induced bullous pemphigoid and drug-induced psoriasis (n=1, 0.8% each). All the cases of acneiform drug eruptions, FDE, acute generalized exanthematous pustulosis (AGEP), cutaneous vasculitis, drug-induced cutaneous lupus and photosensitivity involved <10% of TBS. The commonly involved areas included the extremities (n=78, 65%), chest (n=56, 46.5%), abdomen (n=44, 36.5%), face (n=26, 21.5%) and trunk (n=20, 16.5%). Oral and conjunctival mucous membranes were involved in cases of SJS/TEN, angioedema and drug-induced bullous pemphigoid.

A total of 42 single-drug and 6 drug-combination formulations were implicated as causative drugs **(Table 3)**. Most commonly implicated drugs include diclofenac sodium (n=9, 7.5%), combination of ethinyl estradiol and levonorgestrel (n=7, 5.8%), amoxicillin, carbamazepine, ciprofloxacin, ibuprofen, and minocycline (n=6, 5% each),

cotrimoxazole and phenytoin sodium (n=5, 4.2% each) and paracetamol and phenobarbitone (n=4, 3.3% each). All the other drugs/combinations were involved in ⩽ 2.5% of cases each. There were no formulations containing natural/herbal remedies.

Table 3: Causative drugs

Name of the drug (generic)	Gender n (%)		n=120
	Male	Female	Total
Aceclofenac sodium	2 (1.7)	1 (0.8)	3 (2.5)
Amoxicillin	4 (3.3)	2 (1.7)	6 (5)
Ampicillin	1 (0.8)	2 (1.7)	3 (2.5)
Carbamazepine	3 (2.5)	3 (2.5)	6 (5)
Cephalexin	2 (1.7)	1 (0.8)	3 (2.5)
Chloroquine	1 (0.8)	2 (1.7)	3 (2.5)
Ciprofloxacin	5 (4.2)	1 (0.8)	6 (5)
Cotrimoxazole	2 (1.7)	3 (2.5)	5 (4.2)
Diclofenac sodium	4 (3.3)	5 (4.2)	9 (7.5)
Ethinyl estradiol + levonorgestrel	–	7 (5.8)	7 (5.8)
Furosemide	1 (0.8)	2 (1.7)	3 (2.5)
Ibuprofen	4 (3.3)	2 (1.7)	6 (5)
Minocycline	3 (2.5)	3 (2.5)	6 (5)
Paracetamol	1 (0.8)	3 (2.5)	4 (3.3)
Phenobarbitone	2 (1.7)	2 (1.7)	4 (3.3)
Phenytoin sodium	3 (2.5)	2 (1.7)	5 (4.2)
Others [$]	22 (13.3)	19 (10.8)	41 (24.2)

$ Others (n ⩽ 2) included:

a. diclofenac + paracetamol (0m, 2f), indomethacin (1m, 1f), metronidazole (1m, 1f), nimesulide (1m, 1f), norfloxacin + tinidazole (1m, 1f), prednisone (0m, 2f) and rifampicin (2m, 0f) (n=2, 1.7% each)

b. albendazole (1m), amikacin (1m), amoxicillin + clavulanic acid (1m), atenolol (1m), amoxicillin + cloxacillin (1m), azithromycin (1f), cefadroxil (1f), ceftriaxone (1m), cefuroxime (1f), cefuroxime axetil (1f), dapsone (1f), enalapril (1f), iron dextran (1f), hydrochlorothiazide (1m), isoniazid (1m), ketoconazole (1m), levofloxacin (1m), loperamide (1m), losartan potassium (1m), mefenamic acid (1f), olanzapine (1m), piperacillin + tazobactam (1m), rabies vaccine (Rabipur) (1m), simvastatin (1f), tetanus toxoid (1m), tizanidine (1m) and tramadol (1f) (n=1, 0.8% each)

Among the analgesics/NSAIDs, diclofenac (n=9, 30%), diclofenac + paracetamol (n=2, 1.7%) and aceclofenac (n=3, 2.5%) were commonly implicated followed by ibuprofen (n=6, 20%). Other drugs included paracetamol (n=4, 3.3%), indomethacin (n=2, 1.7%), nimesulide (n=2, 1.7%), mefanamic acid (n=1, 0.8%), and tramadol (n=1, 0.8%).

Carbamazepine (n=6, 40%), phenytoin (n=5, 4.2%) and phenobarbitone (n=4, 3.3%) were the antiepileptic drugs that were implicated in causing CADRs.

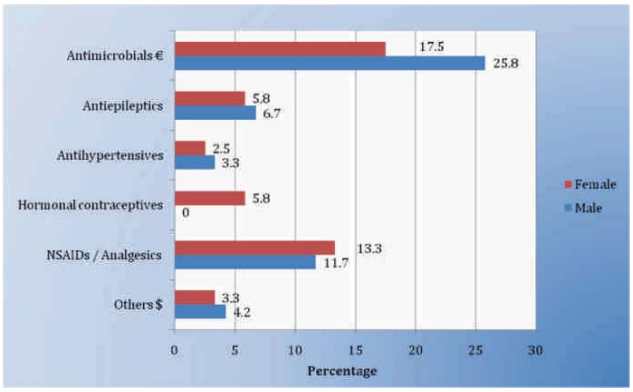
Among the antihypertensives/diuretics, atenolol was incriminated in worsening of pre-existing psoriasis (n=1, 0.8%) and enalapril and furosemide produced photosensitivity (n =1, 0.8% each); furosemide was implicated in drug-induced bullous pemphigoid and drug-induced cutaneous lupus (n=1, 0.8% each); hydrochlorothiazide caused hyperpigmentation (n=1, 0.8%); and losartan potassium caused erythematous drug reaction (n=1, 0.8%).

Ethinyl estradiol+levonorgestrel 0.03 mg+0.15 mg combination (n=7, 5.8%) and prednisolone (n=1, 0.8%) led to acneiform drug eruptions—all in female patients. Others agents which caused CADRs included loperamide, olanzapine, tizanidine, Rabipur vaccine, tetanus toxoid, iron dextran, and simvastatin (n=1, 0.8% each).

Figure 3 shows the temporal correlation between drug exposure and onset of reactions (reaction time). The reactions quickest to appear (<24 hours) included angioedema, urticaria and FDE, and slowest to appear (>2 weeks) were hyperpigmentation and photosensitivity reactions. Most cases of urticaria (14 out of 23) and 2 cases angioedema manifested within 2 hours of drug intake. FDE appeared at variable intervals—6 cases in <24 hours, 8 after 24 hours, and 2 after 1 week of drug intake. SJS and TEN appeared between 1 to 4 weeks after drug intake. Reactions like urticaria and angioedema appeared with single exposure and were not related to duration of exposure whereas SJS/TEN, hyperpigmentation, and photosensitivity resulted from continued or intermittent administration.

Figure 1 shows category-wise causative drugs that were implicated. Antimicrobials (n=52, 43.3%) were the commonest causative drug category followed by analgesics/NSAIDs (n=30, 25%) and antiepileptics (n=15, 12.5%).

Figure 1: Causative drug category



€ Antimicrobials included antibiotics and synthetic antimicrobials (n = 41, 34.2%, 24m, 17f), antifungal (n = 1, 0.8%, 1m, 0f), antihelminthic (n = 1, 0.8%, 1m, 0f), antileprotic (n = 1, 0.8%, 0m, 1f), antimalarials (n = 3, 2.5%, 2m, 1f), antiprotozoals (n = 2, 1.7%, 1m, 1f) and antitubercular agents (n = 3, 2.5%, 3m, 0f).

$ Others included antidiarrheal (n = 1, 0.8%, 1m, 0f), antihyperlipidemic (n = 1, 0.8%, 0m, 1f), antipsychotic (n = 1, 0.8%, 0m, 1f), corticosteroids (n = 2, 1.7%, 0m, 2f), hematinics (n = 1, 0.8%, 0m, 1f), skeletal muscle relaxant (n = 1, 0.8%, 1m, 0f) and vaccines (n = 2, 1.7%, 2m, 0f).

Figure 2: Causative drug category - Antimicrobials

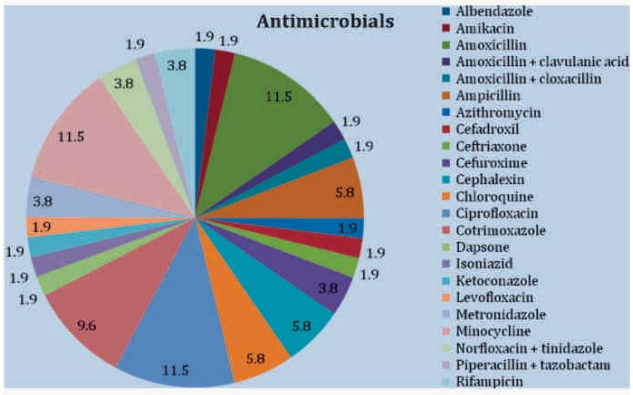
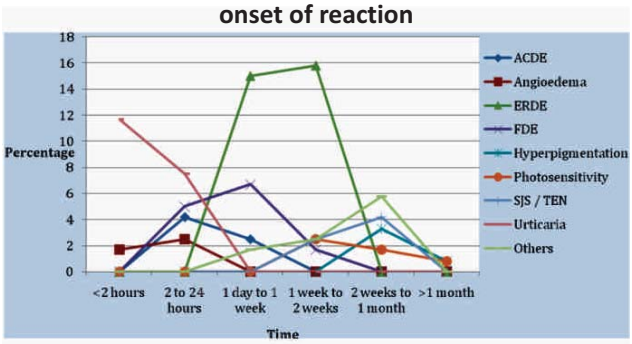


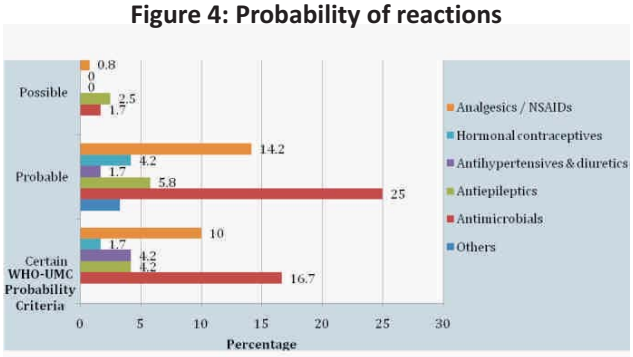
Figure 2 shows the antimicrobials which were implicated in causing CADRs. Beta-lactam antibiotics (penicillins and cephalosporins) and their combinations were the leading causative drugs (n=19, 36.5%) followed by flouroquinolones (n=9, 17.3%) and all the other antimicrobials together were responsible for 24 cases (46.2%). The pattern of reactions with antimicrobials included erythematous drug eruptions, urticaria, FDE, AGEP, cutaneous vasculitis, SJS/TEN, acneiform drug eruptions and photosensitivity. Serious CADRs like SJS/TEN were produced by amoxicillin (n=1, 0.8%) and cotrimoxazole (n=2, 1.7%). Less common reactions like drug-induced cutaneous lupus were produced by isoniazid (n=1, 0.8%) and minocycline (n=2, 1.7%). Chloroquine (n=2, 1.7%) was the only antimicrobial which produced hyperpigmentation.

Figure 3: Temporal correlation – drug exposure and onset of reaction



The severity of reactions was graded as mild, moderate, and severe using Hartwig scale (Table 4).[9] Moderate reactions were the most common (n=77, 64.2%) followed by mild reactions (n=35, 29.2%) whereas severe reactions were the least frequent (n=8, 6.7%). The latter were seen with antimicrobials like cotrimoxazole (n=2, 1.7%) and amoxicillin (n=1, 0.8%); antiepileptics like phenytoin (n=2, 1.7%), carbamazepine (n=1, 0.8%); and analgesics/NSAIDs like diclofenac (n=1, 0.8%) and ibuprofen (n=1, 0.8%). There were no reactions with the severity of 6 and 7 on the Hartwig scale.

Figure 4: Probability of reactions



The probability of reactions was assessed according to the WHO-UMC causality assessment criteria as certain, probable and possible as shown in Figure 4.[8] Only 6 cases

(5%) were considered as certain as there was definite time relationship to drug intake and the event; which was pharmacologically definitive; could not be explained by other diseases or other drugs; and with definite response to withdrawal. Out of these, 4 cases (3.3%) were SJS—causative drugs being amoxicillin, carbamazepine, cotrimoxazole, and diclofenac (n=1, 0.8% in each), and 2 cases (1.7%) of TEN—offending drug being phenytoin (n=2, 1.7%). Cases assessed as probable (n =65, 54.2%) had reasonable time relationship with drug intake and appearance of the event; could not be explained by disease or other drugs; and had reasonable response to withdrawal. Possible reactions (n=49, 40.8%) had reasonable time relationship to drug intake which could also be explained by disease or other drugs and information on drug withdrawal being unclear.

Table 4: Severity of reactions on modified Hartwig scale €

Drug category	Severity of reactions₣ n (%) n=120				
	Mild		Moderate		Severe
	1	2	3	4	5
Antimicrobials	5 (4.2)	12 (10)	25 (20.8)	7 (5.8)	3 (2.5)
Antiepileptics	–	3 (2.5)	8 (6.7)	1 (0.8)	3 (2.5)
Antihypertensives / diuretics	–	4 (3.3)	3 (2.5)	–	–
Hormonal contraceptives	–	–	7 (5.8)	–	–
Analgesics / NSAIDs	–	9 (7.5)	19 (15.8)	–	2 (1.7)
Others	1 (0.8)	1 (0.8)	7 (5.8)	–	–
Total	6 (5.0)	29 (24.2)	69 (57.5)	8 (6.7)	8 (6.7)

€ Assessed using Hartwig scale (1, 2=mild; 3, 4=moderate; 5, 6, 7=severe)
₣ Reactions with severity 6 and 7 on Hartwig scale were not reported

Table 5 shows serious CADRs, which required hospitalization and ICU monitoring. Only 8 cases (6.7%) were serious reactions—required hospitalization and ICU monitoring and included SJS (n=5, 4.2%) and TEN (n=3, 2.5%). The causative drugs for SJS were amoxicillin, cotrimoxazole, diclofenac, carbamazepine, and ibuprofen (n=1, 0.8% in each), and phenytoin (n=2, 1.7%) and cotrimoxazole (n=1, 0.8%) caused TEN. All these cases were of grade 5 on the Hartwig severity scale—not resulting in death/disability. There was no other systemic involvement in any of these cases.

Table 5: Serious CADRs

Causative drug	Drug category	Gender n (%) n=8		
		Male	Female	Total
Amoxicillin	Antimicrobial	1 (12.5)	–	1 (12.5)
Carbamazepine	Antiepileptic	–	1 (12.5)	1 (12.5)
Cotrimoxazole	Antimicrobial	1 (12.5)	1 (12.5)	2 (25)
Diclofenac sodium	NSAID	1 (12.5)	–	1 (12.5)
Ibuprofen	NSAID	–	1 (12.5)	1 (12.5)
Phenytoin sodium	Antiepileptic	–	2 (25)	2 (25)
Total		3 (37.5)	5 (62.5)	8 (100)

$ Serious CADRs recorded were SJS (n=5) and TEN (n=3)
€ Required hospitalization / prolongation of existing hospitalization and ICU monitoring, assessed as per Hartwig scale (5, 6, 7)

With most of the drugs (n=99, 82.5%), the route of administration was oral; whereas it was IM in 8 cases (6.7%) and IV in 13 cases (10.8%). All the drugs given IV were antimicrobials. Most of the drugs given IM were analgesics/NSAIDs. Oral route being the most commonly employed route for drug administration, the reactions were obviously more with this route.

In 60 patients (50%), single causative drugs (monotherapy) were suspected/incriminated. Only 12 patients (10%) received fixed dose combination. In all other cases, the causative drugs (single or FDC) were used along with other concomitant drugs for comorbid conditions.

In majority of cases, (n=103, 85.8%), the drug consumption was on the basis of a valid prescription including 21 cases (17.5%) where the drugs were administered under supervision in the clinic/hospital setting (IM or IV). In 17 cases (14.2%), drug consumption was by self-medication including refilling of previous prescriptions. Most of the self-medications (15 out of 17) involved analgesics/NSAIDs reflecting the prevalent pattern of using these drugs as non-prescription/over-the-counter drugs. In this study, it was observed that all the antimicrobials, antiepileptics and antihypertensives were consumed only on the basis of a valid prescription.

The causative drugs needed to be stopped in 107 patients (89.1%)—either already withdrawn or withdrawn at the time of initial examination. Only in 13 cases (10.9%),

which involved antitubercular, antileprotic and hormonal contraceptives, drugs were continued as the reactions were mild and because of the limited options for effective alternatives.

The preventability of reactions was assessed based on Schumock and Thornton criteria (Table 6).[10] Preventability of reactions showed good correlation with history of allergy to the causative agent. However, there was no clear correlation between the allergic history/past reactions with the severity of the observed reactions. There was a positive history of allergy to causative drugs or related drugs of the same class in 8 cases (6.7%), history of allergy to unrelated drugs in 17 cases (14.2%), seasonal and environmental allergies in 28 cases (23.3%) and history of food allergy in 11 cases (9.2%). There was some family history of allergy in 27 patients (22.5%).

Table 6: Preventability of reactions

Drug category	Preventability€ n (%) n=120			
	Definitely preventable	Probably preventable	Not preventable	Total
Antimicrobials	3 (2.5)	7 (5.8)	42 (35)	52 (43.3)
Antiepileptics	2 (1.7)	–	13 (10.8)	15 (12.5)
Antihypertensives/diuretics	–	1 (0.8)	6 (5)	7 (5.8)
Hormonal contraceptives	–	7 (5.8)	–	7 (5.8)
Analgesics / NSAIDs	3 (2.5)	6 (5)	21 (17.5)	30 (25)
Others	–	–	9 (7.5)	9 (7.5)
Total	8 (6.7)	21 (17.5)	91 (75.8)	120 (100)

€ Based on Schumock and Thornton criteria

Majority of the study subjects were non-smokers and non-alcoholics with little relevance between personal habits and the pattern and prevalence of CADRs. Comorbid conditions in the subjects included diabetes mellitus, hypertension, epilepsy, asthma, chronic renal dysfunction and psychiatric disorder, which were treated with appropriate therapeutic measures. The severity of reactions had little relevance with the comorbid conditions. However, the possibility of concomitant drugs interacting with the causative drugs could not be ruled out.

Abnormal laboratory values were evident mainly in moderate and severe reactions. Though the majority of CADRs have an allergic basis, AEC was elevated in only 56 cases (46.7%) which showed good correlation with history of allergy/past reactions. Some studies have suggested AEC to be of little diagnostic value, but American Academy of Dermatology has suggested that AEC >1000/mm^3 may indicate a serious CADR.[11, 12] None of the patients were positive for HIV and other laboratory findings correlated with the comorbid conditions.

CONCLUSION

CADRs are the most common adverse drug reactions in clinical practice, showing wide variation, ranging from mild self-limiting to serious life-threatening reactions. The pattern of reactions differs in different geographical regions because of genetic and ethnic differences, disease prevalence, differing pattern of drug prescription and consumption.

In the present study, a wide clinical spectrum of CADRs ranging from mild erythematous eruptions to serious SJS/TEN was observed. The mean age of the study subjects was 40.98 years with little gender difference, which was in conformity with other reported studies.[5, 13, 14] However, in some studies, female preponderance and male preponderance have been reported.[15, 16]

The predominant patterns of reactions observed were erythematous eruptions and urticaria, which was in accordance with other studies, but some studies have reported maculopapular exanthema and FDE being common.[13, 14, 17, 18] The common causative drugs were antimicrobials followed by analgesics/NSAIDs and antiepileptics consistent with the other observations, reflecting the fact that the antimicrobials are the most commonly prescribed and utilized drugs in the population.[14, 16, 17] Among the antimicrobials, beta-lactams and flouroquinolones were the leading causative drugs, amoxicillin among beta-lactams and ciprofloxacin among the flouroquinolones, probably because these two antimicrobials are widely prescribed—similar to an earlier observation.[5] Some studies have shown cotrimoxazole and dapsone as the leading causative antimicrobials.[13, 14] However, in the present study, cotrimoxazole and dapsone were involved only in 6 cases, probably reflecting declining use of these drugs. Among the analgesic/NSAIDs, diclofenac was the leading causative drug—involved in erythematous drug reactions, FDE, urticaria and SJS, probably reflecting widespread use of this drug. In other studies,

paracetamol and aspirin were widely implicated reflecting their extensive use by self-medication as over-the-counter analgesics.[13, 14] Among the antiepileptics, carbamazepine and phenytoin were the common offenders. These two, being frontline antiepileptics and widely prescribed, were the common causative drugs for serious reactions like SJS/TEN as also observed in other studies.[5, 13, 14, 16, 17]

The reaction time, i.e., the time interval between the drug exposure and the appearance of CADRs, was variable with different patterns of reactions. Angioedema and urticaria appeared within 24 hours, hyperpigmentation, photosensitivity and SJS/TEN after 1 week, whereas the reaction time for FDE varied from a few hours up to 2 weeks—almost in conformity with an earlier reported study.[13] Drug-induced bullous pemphigoid, cutaneous lupus, pemphigus, and psoriasis and hyperpigmentation, photosensitivity, and SJS/TEN always manifested following repeated exposure to the causative drugs, whereas angioedema and urticarial reactions occurred with single exposure.

Majority of the reactions were mild to moderate, and serious reactions were infrequent and included SJS and TEN. In the present study, the SJS and TEN did not have visceral involvement (except elevated hepatic transaminases in all cases and abnormal renal parameters in 2 cases) and showed good recovery, whereas in other studies, deaths were reported because of serious organ involvement and septicaemia.[5, 13, 14, 16, 17] In these serious CADRs, early detection and timely withdrawal of the offending drug may prevent the further progress of complications.

The present study also revealed that most of the reactions were not preventable as the predisposing risk factors could not be ascertained. However, in 55% of the cases, a clear history of allergic disease/past reactions including seasonal and environmental allergy was elicited. Since majority of the CADRs may have an allergic basis, a thorough evaluation eliciting proper drug history and allergic disease before prescribing and prior testing in doubtful history would have prevented many of the reactions.

In clinical practice, a proper awareness of the occurrence of the reactions and special precautions while prescribing drugs with well known potential for CADRs like beta-lactam antibiotics, NSAIDs, and antiepileptics, early detection and timely withdrawal of the offending drugs and appropriate rescue measures may greatly contribute to reduce the incidence, frequency, severity and morbidity and possible mortality.

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