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RESEARCH ARTICLE

Adverse drug reactions: Two years' experience from a tertiary teaching hospital in Kerala

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ABSTRACT

Background: Adverse drug reactions (ADRs) have become a major clinical problem causing additional burden on the total cost of a patient's treatment. **Aims and Objectives:** To determine the characteristics of ADRs reported in a tertiary care center. **Materials and Methods:** Descriptive analysis of ADRs reported to the Department of Pharmacology over a period of 2 years from July 2012 to June 2014 was done. ADR reports were analyzed on the basis of patient characteristics, drug characteristics, predictability, preventability, severity, causality, and seriousness of the ADR. The continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as frequencies and percentages. Odds ratio (OR) was calculated to assess the risk factors for severe ADRs using SPSS 16. **Results:** From the 359 ADR reports, 377 ADRs were identified with mean age 43 ± 19 years. 95.3% affected single organ system, the most common being skin and appendages. The most common ADR reported was maculopapular rash. Antibiotics accounted for the maximum ADRs of which beta-lactams were the most common. 30.1% (108) ADRs occurred within 1 h of administration of the drug. In 12.73% (48) drug interactions (DIs) were cause of ADRs. Risk analysis showed that DIs (OR = 2.25, 95% confidence interval [CI] = 1.1-1.53), concomitant use of more than one drug (OR = 1.75, 95% CI = 1.97-3.18) and delayed onset ADRs (OR = 1.89, 95% CI = 1.22-3.51) were risk factors for development of severe ADRs. **Conclusions:** Skin and integumentary system was the most commonly affected system and beta-lactams were the most common drug class implicated to cause ADR.

KEY WORDS: Adverse Drug Reaction; Drug Interaction; Severity; Causality Assessment; Preventability

INTRODUCTION

Adverse drug reactions (ADRs) have become a concern of public health systems worldwide. India ranked 7th in the list of contributors to the global safety database for the year 2013.[1] In India, 0.7% ADRs are responsible for admission in hospital and 3.7% of the hospitalized patients experience ADRs, 1.8% ADRs being fatal.[2] Together with the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, Uppsala, the WHO promotes pharmacovigilance at the country level. As on May 2016, 124 countries have joined the WHO Programme for International Drug Monitoring, and 29 associate members are awaiting full membership.[3]

The WHO defines ADR as "A response to a drug which is noxious and unintended, and occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function."[4] When the Food and Drug Administration (FDA) approves a new drug

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for marketing, its complete adverse event profile may not be known because of the limitation of preapproval clinical trials. Typically, clinical trials for new drugs are of short duration and are conducted in limited populations that number up to 5000, therefore, the most common dose-related ADRs are usually detected in the premarketing phase while ADRs which are rare and those detected on long term use are not. To minimize the incidence of ADRs in patients, it is essential to recognize the rare and long-term ADRs. This will establish causal relationship with the drug and measures can be initiated to treat and prevent ADRs. India's vast population can provide data on the risk profile of medicines contributing significantly to the Uppsala Monitoring Centre database.[5] The data on ADR monitoring from the state of Kerala is sparse.[6-9] This study is an attempt to bridge gap in the literature pertaining to ADRs reported in Kerala as pointed out in previous studies.[8]

MATERIALS AND METHODS

This was a descriptive study carried out in the Department of Pharmacology of a 1700-bedded tertiary care teaching government hospital, Kerala, India. The data were received as a part of the pharmacovigilance program of the department, which was initiated on continuous basis from July 2012 from the inpatient Departments of Medicine, Surgery, Pediatrics, Obstetrics and Gynecology, Psychiatry, Dermatology, Cardiology, Orthopedics, Neurology and Pulmonology. The ADRs were reported in the Central Drug Standard Control Organization Suspected ADR reporting forms.[10] The institution received approval as an ADR monitoring center under the Pharmacovigilance Programme of India in February 2014 and access to Vigiflow was obtained in August 2014.

The study was initiated after getting approval from Institutional Ethics Committee in June 2012. All patients of either sex and of any age whose ADRs were reported to the Department of Pharmacology from various inpatient departments of the medical college hospital using suspected ADR reporting form from July 2012 to June 2014 (2 years) were included in the study. ADR forms which described drug induced poisoning were excluded from data collection. The study tools used were the suspected ADR reporting form and structured Proforma. The data were entered in Excel sheet. The drugs and organ systems affected were classified based on therapeutic classification and the WHO-Adverse Reaction Terminology (WHO-ART), respectively. The investigators further analyzed the study parameters based on the ADR reports. Reports with incomplete details were completed by the investigators through single patient visits or from case records. The patients were not followed up until their discharge. Causality of ADR was assessed by the Naranjo's algorithm.[11] Severity of ADRs was assessed by modified Hartwig and Siegel scale.[12] Preventability was assessed using Schumock and Thornton scale.[13] Drug interactions (DIs) were identified using online versions of computerized interaction detection system Medscape® DI checker tool.[14] Seriousness of reaction (Death/Life-threatening/Initial or Prolonged Hospitalization/Permanent damage or Disability/Congenital Anomaly or Birth Defect/Required Intervention to prevent Permanent Damage/Other Serious) were categorized according to FDA criteria.[15] ADRs not coming under serious ADRs were categorized as "Not Serious" ADRs. Predictability was determined by classifying the ADRs as Type A (Augmented and Type B (Bizzare).[16] Type A (augmented) reactions are deemed to be predictable as it depends on the pharmacological action of the drug and can be directly proportional to the dose of the drug used. In contrast, Type B (Bizzare) reactions are unpredictable and non-dose dependent.

Data were analyzed using SPSS for Windows Version 16.0 (SPSS Inc., Chicago, USA). The continuous variables such as age, number of systems involved, and number of concomitant drugs were expressed as mean ± standard deviation. Categorical variables such as gender, suspected drug, drug class, systems involved, route of administration, temporal relation of ADR, type of ADR and its management, occurrence of DIs, predictability, preventability, severity, causality, and seriousness were expressed as frequencies and percentages. Odds ratio (OR) was calculated to assess the most common risk factors for severe ADRs. Statistical significance was determined at 95% level of confidence interval ($P < 0.05$, univariate analysis). The variables tested for identification of the predictors included age, gender, DIs, number of concomitant drugs and predictability.

RESULTS

Three hundred and seventy seven ADRs from 359 patients were obtained during the period of 2 years. The mean age was 43 ± 19 years with a minimum age of 2 months and maximum age of 85 years. Demography is summarized in Table 1. The maximum ADR reports were in the 46-60 years age group (27.9%) closely followed by 31-45 years age group (27.6%). The majority of the underlying disorders, which resulted in

Table 1: Demographic details

Variables	*n*=359 (%)
Gender	
Male	157 (43.7)
Female	202 (56.3)
Age (years)	
Pediatric (0-18)	36 (10)
Adult (19-60)	255 (71)
19-30	56 (15.6)
31-45	99 (27.6)
46-60	100 (27.9)
Geriatric (>61)	68 (19)

ADRs, were treated in medicine department followed by psychiatry as shown in Table 2.

The reported ADRs were summarized based on the WHO-ART System Organ Class as shown in Figure 1. The skin and appendages was most commonly affected followed by neurological disorders. The suspected medication affected both single (95.3%) and multiple organs resulting in a total of 377 ADRs.

As shown in Figure 2, antibiotics accounted for 119 (33.1%) ADRs. Among the antibiotics, 76 (63.8%) were due to beta-lactams followed by 9 (4.7%) each due to macrolides and quinolones. Table 3 shows the top drug classes and suspected ADRs in this study. The top ADRs were maculopapular rash (MPR) (70), pruritus (34) and gastritis (28) as shown in Table 3. Oral route was the most common route of administration of drugs 236 (55.7%) followed by parenteral 123 (34.3%). As depicted in Figure 3, the suspected ADR occurred immediately (less than an hour) after administration of drug in 108 (30.1%) patients and was delayed (more than 1 month) in 82 (22.8%). Following the suspected ADR the offending drug was discontinued in 329 (91.6%) of the 359 patients, used with dose reduction in 26 (7%) and continued in same dose in four patients. Of the 377 ADRs, 152 (40.3%) received symptomatic and 98 (25.99%) specific treatment as shown in Table 4.

Of the 377, ADRs 207 (53.6%) were predictable Type A reactions, 232 (61.5%) were definitely preventable and 280 (74.2%) had "probable" causality as summarized in Table 4. Seriousness as depicted in Figure 4 shows that the majority of 227 (63.2%) were serious ADRs. There were no reports of death and the majority of ADRs had recovered at the time of reporting (Figure 5).

Out of the 359 reports, data about concomitant drugs was available in 289 patients who received at least one concomitant drug. The mean concomitant drug use was 2.51 ± 1.5. Two backache patients who developed rashes (suspected drugs-paracetamol, ranitidine) had Ayurvedic drugs (liquid preparation, ingredients not known) as concomitant medication. DIs accounted for 48 (12.73%) ADRs of which 46 (96.3%) were significant and two

Table 2: Type of underlying disorders and departments from where the ADRs were reported

Department	*n*	Department	*n*
Medicine	107	Cardiology	28
Acquired immunodeficiency syndrome	15	Coronary artery disease	23
Anemia	10	Congestive heart failure	4
Cancer	4	Atrial fibrillation	1
Chronic kidney disease	2	Pulmonology	19
Diabetes	7	Chronic obstructive pulmonary disease	7
Hepatitis	6	Bronchial asthma	5
Hypertension	7	Tuberculosis	7
Leptospirosis	4	Psychiatry	46
Meningitis	2	BPAD	22
Pleural effusion	2	Schizophrenia	16
Pneumonia	15	Psychosis	5
Poisoning	2	Mania	2
Systemic lupus erythematosis	2	Others	1
Upper respiratory tract infection	20	Neurology	40
Urinary tract infection	4	Epilepsy	32
Others	5	Cerebrovascular accident	5
Surgery	32	Others	3
Acid peptic disease	3	Orthopedics	30
Appendicitis	3	Osteoarthritis	13
Hyperthyroidism	8	Backache	12
Incisional hernia	2	Others	5
Road traffic accident	6	Pediatric	36
Chronic pancreatitis	2	Gastroenteritis	3
Others	8	Upper respiratory tract infection	25
Dermatology	11	Urinary tract infection	5
Obstetrics and gynecology	10	Others	3

ADRs: Adverse drug reactions, BPAD: Bipolar affective disorder

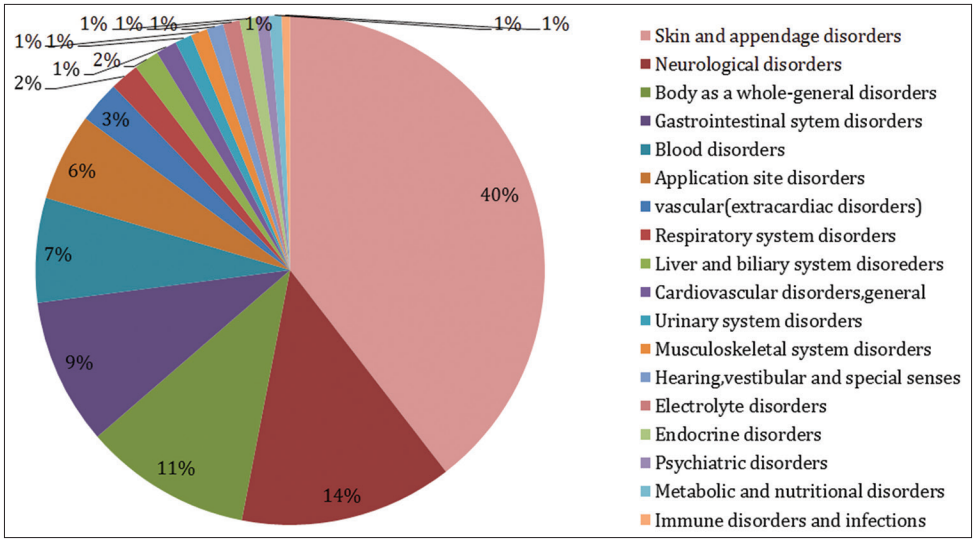

Figure 1: Distribution of adverse drug reaction reports based on system organ class

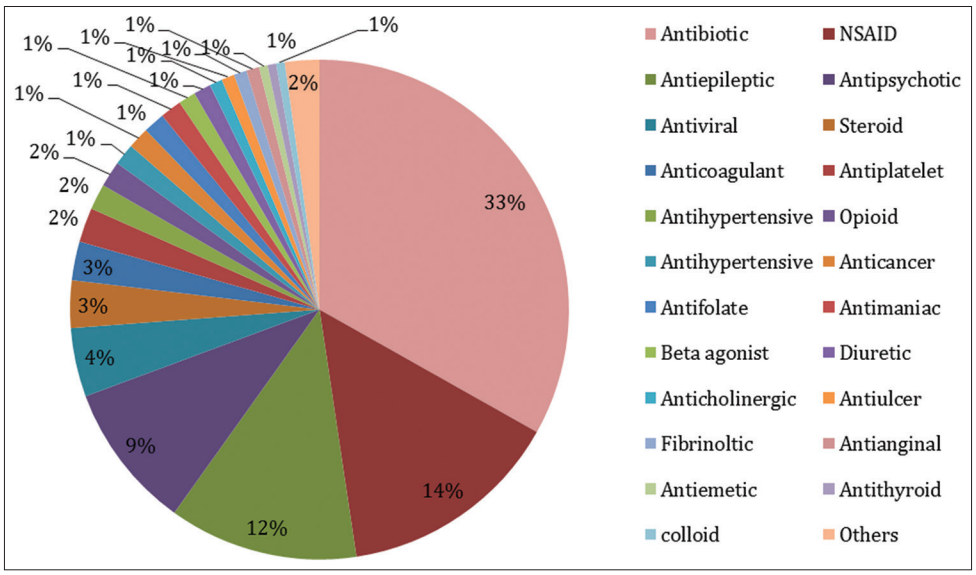

Figure 2: Distribution of adverse drug reactions based on drug class

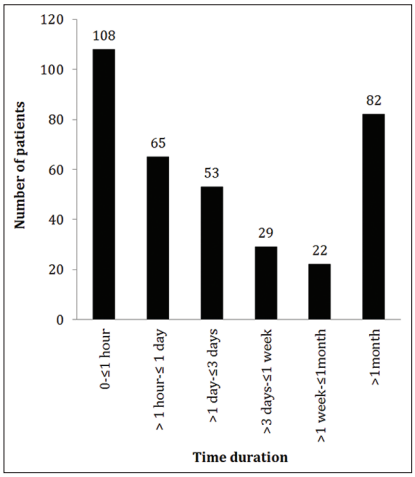

Figure 3: Temporal relationship of drug administration and onset of suspected adverse drug reaction

were minor. As summarized in Table 5, the majority of 39 (81.3%) were pharmacodynamic interactions and the rest pharmacokinetic interactions. 18 patients received various fixed dose combinations such as Amoxicillin + Clavulanic acid, Ampicillin + Cloxacillin, Ceftriaxone + Sulbactam, Piperacillin + Tazobactam, and antituberculosis therapy. 19 patients gave history of previous drug allergy to different medications.

Application of Hartwig and Siegel scale revealed that 191 (53.2%) ADRs were moderate in severity (Table 6). Risk analysis showed that DIs, concomitant use of more than one drug and delayed onset ADRs were risk factors for development of severe ADRs as summarized in Table 6.

Some notable ADRs encountered during the index period were valproate induced hyperammonemic delirium,[17] Stevens Johnsons Syndrome (SJS) and toxic epidermal necrolysis (TEN), drug-induced nystagmus, antituberculosis treatment-induced hepatotoxicity. There were six ADRs due to supra-pharmacological doses of drugs. Two were

Table 3: Top drug classes and suspected adverse drug reactions with drugs

Drug class	**Top drugs**	***n*=359 (%)**
Antibiotics	Amoxicillin (15), Ampicillin (15), Benzylpenicillin (14), Cefotaxime (13), Azithromycin (9)	119 (33.1)
Nonsteroidal anti-inflammatory drugs	Paracetamol (17), Diclofenac (15), Aspirin (12)	52 (14.5)
Antiepileptics	Phenytoin (25), Carbamazepine (9), Sodium valproate (8)	44 (12.3)
Antipsychotics	Haloperidol (16), Clozapine (7), Risperidone (3)	34 (9.5)
Antivirals	Nevirapine (7), Zidovudine (6), Stavudine (2)	16 (4.5)
Steroids	Prednisolone (4), Methylprednisolone (3), Dexamethasone (3)	11 (3)
Anticoagulants	Heparin (6), Warfarin (3)	9 (2.5)
Adverse drug reactions	**Top drugs**	***n*=377 (%)**
Maculopapular rash	Paracetamol (10), Amoxicillin (8), Diclofenac (7) Cefotaxime (5), Nevirapine (3)	70 (18.57)
Pruritus	Ampicillin (5), Cefotaxime (5), Paracetamol (3) Phenytoin (2), Metronidazole (2)	34 (9.01)
Gastritis	Azithromycin (4), Diclofenac (3), Amoxicillin (3), Aspirin (3), Metronidazole (2)	28 (7.42)
Extrapyramidal symptoms	Haloperidol (17), Risperidone (5), Olanzapine (2)	27 (7.16)
Erythema and induration	Piperacillin+Tazobactam (4), Ampicillin (3), Diclofenac (2), Ceftriaxone (2)	25 (6.63)
Steven Johnsons Syndrome/Toxic Epidermal Necrolysis	Phenytoin (6), Carbamazepine (4)	18 (4.77)
Hypersensitivity reaction	Phenytoin (2), Ibuprofen (2)	13 (3.44)

Table 4: Causality assessment, preventability, predictability, and treatment of ADR

Variable		***n* (%)**	***n*=377**
Causality	Score		
Possible	3	30 (8.0)	97 (25.8)
	4	67 (17.8)	
Probable	5	134 (35.5)	280 (74.2)
	6	121 (32.1)	
	7	25 (6.6)	
Preventability	Definitely preventable	232 (61.5)	
	Probably preventable	74 (19.6)	
	Not preventable	71 (18.8)	
Predictability	Predictable	207 (53.6)	
	Not predictable	170 (46.3)	
Management of ADR	Self limiting	127 (33.7)	
	Specific treatment	98 (26)	
	Symptomatic treatment	134 (40.3)	

ADRs: Adverse drug reaction

carbamazepine induced nystagmus and vertigo; two were due to accidental daily ingestion of methotrexate with one patient developing oral ulceration and the other SJS; one was tremor due to lithium (2.1 mEq/L) and one was warfarin-induced bleeding (International Normalized Ratio 7.9).

DISCUSSION

This study shows descriptive analysis of ADRs reported to the Department of Pharmacology of a Government Medical College in Kerala from July 2012 to June 2014. 377 ADRs were reported.

The mean age of the study participants was 43 ± 19 years which was comparable to that of other studies.[8,18] The majority of ADRs occurred in the adult population compared to the pediatric and geriatric age groups. This was comparable to other studies.[7,8] Extremes of ages have critical impact on the occurrence of ADRs because of their variable and unpredictable pharmacokinetics.[19] However, in this study, we could not see an increased incidence of ADRs in pediatric and geriatric age group. The low incidence might be due to the fact that the prescribers might have been more cautious in prescribing medications to the extreme age groups. This study analyses only ADRs reported to the Department of Pharmacology, and hence, might not reveal the complete picture of ADRs in tertiary care hospital.

There was a female preponderance in the study population which was consistent with several other studies.[8,20-22] However, other studies have shown male predominance in contrast to our findings.[7,9] Literature states that anatomical and physiological differences in the females alter the pharmacokinetic and pharmacodynamics of the drugs and predispose them to more ADRs.[19]

As seen in supporting literature, the skin and appendages was the most commonly affected organ in this study too, with MPR being the most common observed ADR.[6-9,23] Adverse cutaneous reactions are one of the most common type of ADRs and it encompasses any undesirable change in the structure or function of skin, its appendages or

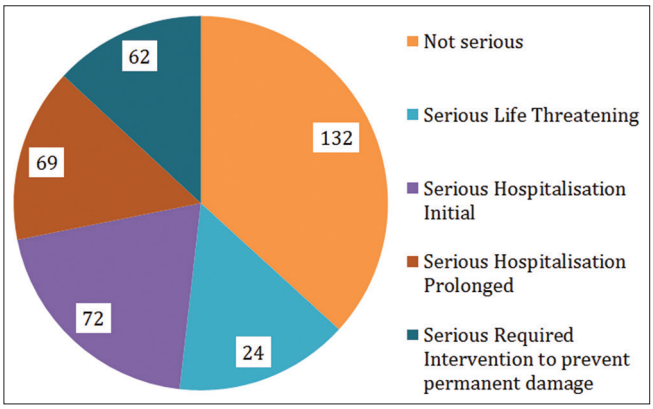

Figure 4: Seriousness of adverse drug reaction in each patient based on Food and Drug Administration definition

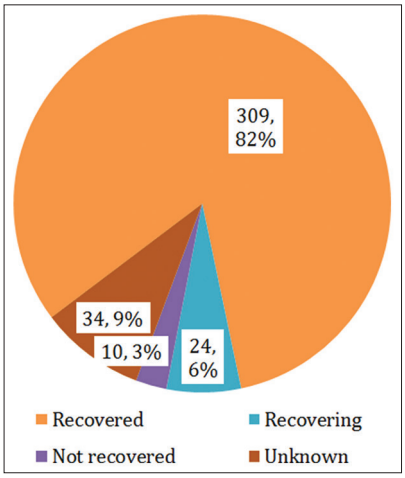

Figure 5: Outcome of adverse drug reactions at the time of visit of patient (unknown outcome refers to lack of data)

mucous membranes.[24] The development of cutaneous ADRs was a common reason for discontinuation of treatment.[25] The life-threatening drug-related skin eruptions were angioedema (9), SJS (14), TEN (3), and one SJS-TEN overlap.

In our study antibiotics accounted for 33.1% of the reactions, of which the majority were due to beta-lactams which was in accordance with several other published literature.[8,9,23] Antibiotics, the second most prescribed drugs worldwide though deemed to be safe with rational use, is not without ADRs.[26]

Polypharmacy plays an important role in the occurrence in the development of adverse DIs. Only 31 patients received ≥5 medications at the time of occurrence of ADR in this study. The concomitant drug usage was 2.51 ± 1.5. ADRs were significantly increased with polypharmacy therapy.[20,27-29] Alomar et al. state that too many medications amounts to increased risk of ADR.[19] Polypharmacy can be due to the presence of more than one ailment or consultation of more than one physician or inability to keep track of medication use by the elderly.

The pivotal role of DIs in the incidence of ADRs had been identified. Published literature reveals that the prevalence of potential drug - DIs resulting in ADRs ranged from 1.3% to 60% and 26% ADRs requiring hospitalization are due to DIs.[28] Alomar et al. states that the cause and significance of DIs are multifaceted as it not only involves several factors related to drug such as dose, route of administration, duration of treatment, serum level and its metabolism but also patient-related factors including the age, gender, weight, nutritional and hydration status, habits like smoking and alcoholism, disease condition and finally genetic predisposition.[19] In this study, 12.73% ADRs were due to DI, of which the majority were significant pharmacodynamic interactions and were delayed in onset. This was in accordance with other studies done elsewhere.[28,30] In a study by Lucca et al., there was no association of DI with age of the patient or gender.[28]

As cited in some studies[7,9,28] causality by Naranjo's algorithm was mainly probable in this study while in others[6,8,20,23] majority of ADRs had a possible causality. Post marketing safety signals have made causality assessment profoundly important.[8] Seriousness based on the Unites States FDA criteria revealed that the majority were serious ADRs which required initial or prolonged hospitalization. This was in line with other similar studies.[8,29]

The preventability of ADRs was assessed by the Schumock and Thornton scale. The review of literature showed that 60-70% of ADRs was preventable.[29] In accordance with the other studies majority of the ADRs reported were definitely or probably preventable and majority had recovered from the ADR at the time of reporting. However, Remesh et al. opined that the majority of the ADRs encountered in their study were not preventable.[6]

Predictability assessment was carried out by categorizing the ADRs into Type A and B. Studies have reported predictability assessment varying from 69% to 96%.[29] In this study, 53.6% ADRs were predictable.

Severity of the ADRs was assessed using the modified Hartwig and Siegel scale. In this study, 53.2% ADRs were moderate in severity followed by mild in severity (30.9%). Remesh et al. states that the majority of ADRS were moderate in severity.[6] Pradeep et al. states that 12.1%, 82.85%, and 5.05% were mild, moderate, and severe ADRs, respectively.[8] Sai et al. states that 65% of the ADRs were of Grade 3 severity which equals to moderate in severity.[9] Chawla et al. found that 24.1% were mild, 38.6% and 37.1% were classified as moderate and severe category, respectively.[23]

The predictors of severe ADRs were assessed using univariate analysis with significance at $P < 0.05$. Use of more than one concomitant drug (OR = 1.75, 95% CI = 1.97-3.18); occurrence of DIs (OR = 2.25, 95% CI = 1.1-1.53) and delay in onset of ADRs (OR = 1.89, 95% CI = 1.22-3.51) were

Table 5: Drug interactions as a cause of ADR

Type	Interaction	Drugs	ADRs	*n*=48
Pharmacodynamic (39)	Increased anticoagulation/platelet aggregation-synergism	Aspirin+Clopidogrel	Hematemesis, Gastritis Hypersensitivity	8
		Aspirin+Heparin	Hemoptysis, epistaxis Petechiae	5
		Aspirin+Streptokinase	Hypersensitivity	1
		Aspirin+Warfarin	Hematuria	1
		Aspirin+Tenecteplase	Gum bleed	1
		Clopidogrel+Diclofenac	Gastritis, hematemesis	1
		Clopidogrel+Atorvastatin	Hemoptysis	1
	Either increases toxicity of the other Increases renal dysfunction	Enalapril+Aspirin	Elevated serum creatinine	1
		Enalapril+Carvedilol	Elevated serum creatinine	1
	Increased neurotoxicity Multiple mechanisms	Haloperidol+Lithium	Oculogyric crisis, Tremor, Convulsion	3
	Increased antidopaminergic effect	Haloperidol+Olanzapine	Tardive dyskinesia	2
		Haloperidol+Risperidone	Acute dystonia	4
		Haloperidol+Clozapine	Acute dystonia	1
		Clozapine+Olanzapine	Drug-induced parkinsonism	1
	Synergism	Zidovudine+Lamivudine	Anemia (hemoglobin=4.5)	1
		Lamivudine+Nevirapine	SJS	1
	Increase gastritis	Etoricoxib+Thiocholchicoside	Gastritis, malena	1
	Leflunomide increases toxicity of methotrexate by pharmacodynamic synergism	Methotrexate+Leflunomide	Malena, Gastritis, Maculopapular rash SJS, Pancytopenia Mucositis	4
	Altered potassium levels	Metoprolol+Spironolactone	Fatigue, Shivering	1
Pharmacokinetic (9)	Alteration in metabolism, Unspecified mechanisms	Carbamazepine+Phenytoin	Nystagmus	3
	Decreased metabolism	Ciprofloxacin*+Carbamazepine	SJS	1
		Ciprofloxacin*+Deriphylline	Convulsion	1
		Escitalopram*+Warfarin	Oral mucosal bleeding	1
		Valproate*+Risperidone	Tremor	2
		Valproate*+Lamotrigine	SJS	1

*Denotes drug that affects the hepatic enzyme and inhibits the metabolism of the other drug. SJS: Stevens Johnsons Syndrome, ADRs: Adverse drug reaction

found to be independent predictors of severe ADRs in this study. However, we did not find any significant age or gender difference in the prediction of severe ADRs. Predictability of ADRs was also found unrelated to the severity of the ADR in this study. Shet et al. found that age, gender, baseline clinical features, coinfections and concomitant medications were not significantly associated with development of a severe ADR.[22]

Strengths and Limitations

This study attempts to bridge the gap in literature on ADR data in Kerala. A sincere attempt has been made to study the severity, preventability, predictability, associated DIs and predictors of severity which are lacking in the majority of the published literature. The main limitation of this study is that it represents only the ADRs reported to the Department of Pharmacology and not the complete picture of ADRs occurring in the tertiary care center. The duration of hospital stay of the study patients due to ADRs and the related costs of ADRs were not calculated as there was no follow-up of the patients. The food-DI history was not elicited and analyzed.

CONCLUSION

The maximum number of ADRs reported in our study was with antibiotics and the most common ADRs reported were MPRs. Most of the ADRs reported had probable causality, were moderate in severity, were definitely preventable and predictable. The majority of patients had recovered from the ADRs at the time of reporting. DIs, concomitant use of

Table 6: Severity of ADRs and predictors of severe ADRs

Variable	Level	*n* (%)	*n* = 359
Severity			
Mild	1	4 (1.1)	111 (30.9)
	2	107 (29.8)	
Moderate	3	57 (15.9)	191 (53.2)
	4a	82 (22.8)	
	4b	52 (14.5)	
Severe	5	57 (15.9)	57 (15.9)
	6, 7	0	

Variable	Severe (*n*=57)	Chi-square	Odds ratio (95% CI*, *P* value)
Age			
Pediatric	3	1.71	0.45 (0.13-1.53, 0.19)
Adult	43	0.64	1.31 (0.68-2.50, 0.42)
Geriatric	11	0.01	1.03 (0.50-2.10, 0.94)
Gender			
Female	36	1.31	1.40 (0.78-2.51, 0.25)
Drug interaction	13	5.21	2.25 (1.10-1.53, 0.02)
>One concomitant drug	38	3.46	1.75 (1.97-3.18, 0.04)
Delayed onset	19	4.23	1.89 (1.22-3.51, 0.04)
Predictable ADRs	29	0.12	1.11 (0.63-1.95,0.72)

CI: Confidence interval, ADRs: Adverse drug reaction

more than one drug and delayed onset ADRs were found to be risk factors for the development of severe ADRs. Drug safety is a major challenge for the health-care workers. Early identification of ADRs, conscious effort to prevent them by restricting polypharmacy and prudent selection of concomitant drugs to reduce DIs can help in decreasing the morbidity and mortality associated with ADRs.

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