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Original Research Article

A Prospective Study on Pattern of Adverse Drug Reactions Reported at Pharmacovigilance Centre of RIMS, Ranchi

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Conflict of interest: Nil

Abstract:

Background: Adverse drug reactions (ADR) are rated as fifth leading cause of death and accounts for approximately 5% of all hospital admissions. ADR monitoring plays a major role in pharmacotherapy, decision making in individual reports, regional, national and international programs. ADR monitoring can help to ensure that patients obtain safe and efficacious products. With the existing limited and inconsistent ADR data, more studies at institutional level can generate valid ADR information. Hence, this prospective study was designed to evaluate the pattern of ADRs in a tertiary care hospital.

Methods: In our study all spontaneously reported ADRs were evaluated based on data collected from various clinical departments. Suspected drugs were coded according to WHO-anatomical therapeutic chemical classification. The organ system involvement for ADR was labeled as per WHO-ADR terminology. ADRs were also categorized into two types - augmented (A) and bizarre (B) as per Rawlins and Thompson classification. Causality Assessment was performed using WHO Uppsala Monitoring Centre (UMC) Causality Assessment Criteria. Severity of the identified ADRs was assessed using modified Hartwig's criteria. The preventability of the reactions was assessed according to Schumock and Thornton's criteria.

Results: Out of all ADRs, 31.68% was type-A reactions while 68.32 % was type-B reactions. The commonly involved organ system was skin and appendages 56 (34.78%). The major causative drug class was antimicrobials (43.02%). The causality of most ADRs was "probable" (60.25%) followed by "possible" (34.78%). Most of the ADRs were moderate in nature (45.96%). Around 42.24% of the reported ADRs were definitely preventable.

Conclusion: Adverse drug reaction is one of the leading cause of hospital based admissions. Practicing rational use of medicines and avoiding medication errors, a major fraction of ADRs can be prevented. Proper awareness among health care personnel and involvement of drug controlling authorities can minimize this grave situation.

Keywords: Adverse drug reaction, Pharmacovigilance, Medication errors, Central Drugs Standard Control Organisation.

Introduction

The morbidity and mortality due to adverse drug reactions (ADRs) is one of the major health problems being recognized by health professionals and the public.[1,2] It has been estimated that approximately 2.9%-5.6% of all hospital admissions are caused by ADRs and as many as 35% of the hospitalized patients experience an ADR during their hospital stay. Incidence of fatal ADRs is 0.23%-0.41%.[3] India is a part of the WHO program for the global monitoring of ADRs that depend on spontaneous reporting. It is the most affordable system, which can identify serious reactions, rare ADRs as well as generate early safety signals for new drugs. The Central Drugs Standard Control Organisation (CDSCO) and Directorate General of Health Services under the Ministry of Health and Family Welfare, Government of India in collaboration with the Indian Pharmacopeia Commission (IPC), Ghaziabad is conducting a nation-wide Pharmacovigilance Program of India (PvPI) for protecting the health of the patient by assuring drug safety.[4] ADR monitoring centres (AMCs) are the corner stone of PvPI.[5] They are located in medical colleges and other institutes including peripheral hospitals. Despite the progress that has been made in pharmacovigilance, the burden on

public health of adverse reactions to medicines remains significant. Pharmacoeconomic studies on the costs of ADRs suggest that governments pay considerable amounts from their health budgets towards covering the costs associated with them.[6] Under reporting of ADR from health professionals is another big problem.[7] With the existing limited and inconsistent ADR data, more studies at institutional level can generate valid ADR information. The information about the various aspects of ADRs and their causality assessment can provide useful information to manage ADRs. Hence, this prospective study was designed to evaluate the causality assessment and pattern of ADRs in a tertiary care hospital.

Aim

To assess the pattern of adverse drug reactions from collected individual case safety report form.

Objectives

1. To assess the causality of reported ADRs.
2. To assess outcome of reported ADRs.
3. To assess the severity and seriousness of reported ADRs.
4. To assess the preventability of reported ADRs.

Materials & Methods

This prospective observational study was done to assess the clinical pattern and spectrum of ADRs reported from various inpatients, outpatients and intensive care departments of RIMS, Ranchi. The study was conducted after obtaining approval and clearance from institutional ethics committee. Patients of either sex and of any age group having diagnosed with suspected adverse drug reaction in inpatient, outpatient and intensive care departments of RIMS, Ranchi with given informed consent were included in this study. ADR which occurred outside RIMS, Ranchi, ADR reported with incomplete data, suspected reactions due to blood and blood products and patients admitted for accidental or intentional poisoning due to drugs were excluded from the study. ADR reporting was done on the "Suspected Adverse Drug Reaction Reporting Form" provided by IPC.[8]

Data were collected in a case record form for the demographics, type of ADR, route of suspected offender drug, organ system involvement, indoor/outdoor/ICU settings, number of drug/drugs per treatment protocol/prescription, ADR classification and labeling with suspected offender, causality, outcome, severity and preventability. Suspected drugs were coded according to WHO-anatomical therapeutic chemical classification.[9] The organ system involvement for ADR was labeled as per WHO-ADR terminology.[10] ADRs were also categorized into two types - augmented (A) and bizarre (B) as per Rawlins and Thompson classification.[11] Causality Assessment was performed using WHO Uppsala Monitoring Centre (UMC) Causality Assessment Criteria.[12] Severity of the identified ADRs was assessed at different levels using modified Hartwig's criteria.[13]The preventability of the reactions was assessed according to Schumock and Thornton's criteria.[14] The reports were then uploaded in vigiflow software and sent to NCC, IPC Ghaziabad, which further sends the reports after analyzing to Uppsala Monitoring Centre, Sweden for maintaining ADR database, further analysis and signal detection. The data were extracted in Excel sheet using a structured format including age group, gender, diagnosis, drugs, organ system involved, types of ADR, onset of reactions, outcome, causality, seriousness, severity and preventability. Data were analyzed statistically by using SPSS (Statistical package for social science) version 20.

Results

In our present study around 68% reactions were of type B (Figure no.1).

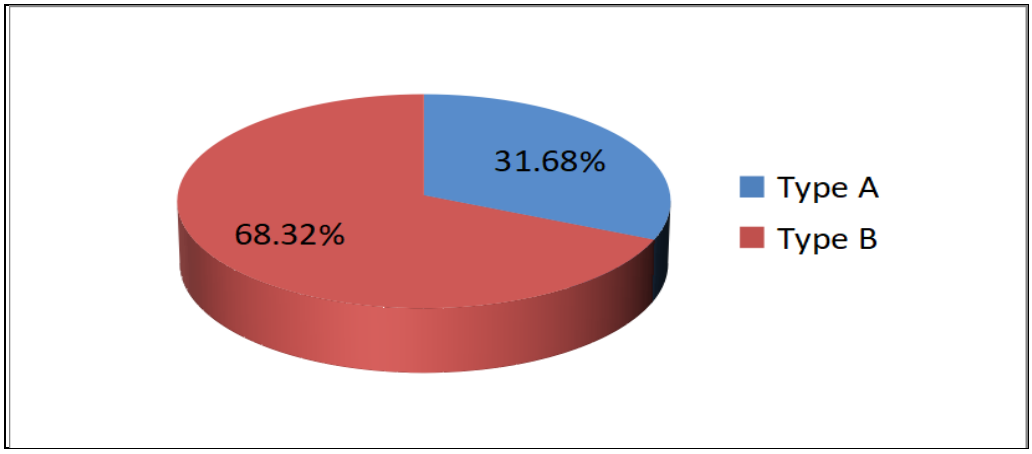

Figure 1: Type of adverse drug reaction

Among all suspected offenders a major proportion of drugs (76.54) were administered via oral route (Figure no.2)

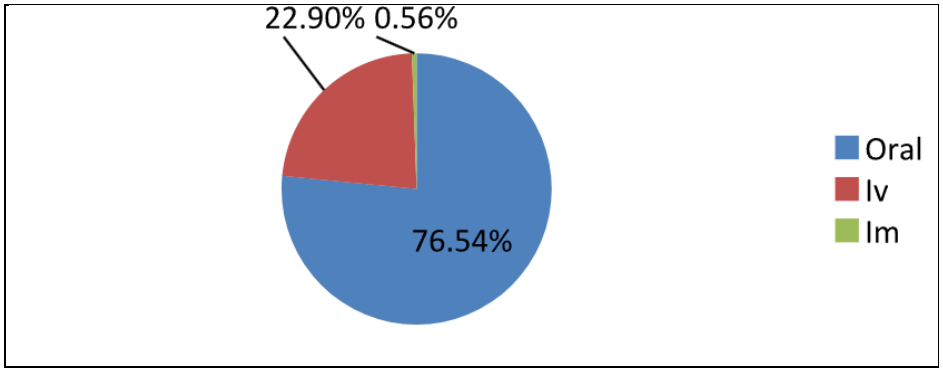

Figure 2: Route of suspected offender drugs causing ADR.

In table no.1, we can see that maximum ADRs were cutaneous (34.78%) followed by gastrointestinal (22.98%) and nervous system (20.50%).

Table 1: Organ system involvement as per WHO-ART classification

Organ system involvement	Number	Percentage (%)
Skin and appendages disorders	56	34.78
Gastro-intestinal system disorders	37	22.98
Central and peripheral nervous system disorders	33	20.50
Cardiovascular disorders	12	7.45
Respiratory system disorders	7	4.35
Musculoskeletal disorders	5	3.10
Urinary system disorders	3	1.86
Endocrine system disorder	3	1.86
Hepatobiliary system disorder	3	1.86
Miscellaneous	2	1.24

In treatment orders/prescriptions in which ADR took place it was observed that in around 47% cases 5 or more than 5 drugs were prescribed (Table no. 2).

Table 2: Drugs administered per prescriptions /Orders.

Drugs administered per Orders	Number	Percentage (%)
1 drug	3	1.86
2 drugs	16	9.94
3 drugs	37	22.98
4 drugs	29	18.01
5 drugs	34	21.12
6 drugs	28	17.39
7 drugs	14	8.69

Maximum suspected offender drugs were antimicrobials and drugs that act on central nervous system (Table no.3).

Table 3: Distribution of offender drugs according to various modules mentioned in textbook of Pharmacology.

System	Drugs	Percentage (%)
Antimicrobials	77	43.02
Central nervous system	41	22.90
Autocoids	28	15.64
Chemotherapy	19	10.61
Cardiovascular system	2	1.12
Hypolipidemic drugs	2	1.12
Miscellaneous	10	5.59

In cutaneous ADRs Maculopapular rash, Fixed drug eruption & Steven-Johnson syndrome were the major reactions while in GIT related ADRs nausea, vomiting and diarrhea were maximum. Extrapyramidal symptoms were dominant in CNS related ADRs and hypotension was found as most common ADR in CVS (Table no. 4).

Table 4: Distribution of ADRs with types, numbers and suspected offenders

ADR According to Organ system (Total 161)	ADR subclass	Number	Suspected offender drug	Type of reaction
Skin and appendages disorder (56)	Maculopapular rash	14	Ceftriaxone (3), Cefpodoxime (3) Azithromycin (3), Ibuprofen (3), Diclofenac (2), Moxifloxacin (1) Lamotrigine (1), Rifaximine (1), Ursedeoxycholic acid (1),	B
	Fixed drug eruption	12	Onidazole(3), Tinidazole(2) Fluconazole(2), Norfloxacin(2), Paracetamol(2), Diclofenac(2), Ketorolac(1).	B
	Steven-Johnson Syndrome	11	Amoxycillin-Clavulanic acid (3), Ceftriaxone (2), Paracetamol (2), Cefopodoxime(1) Co-trimoxazole (1), Sulphasalazine(1), Norfloxacin(1), Valproate(2), Ibuprofen(1), Naproxen(1), Mefenamic acid(1),	B
	Urticaria and Angioedema	8	Norfloxacin (3), Trypsin+diclofenac+serratiopeptidase(3), Piperacillin+tazobactum(2) Ibuprofen (2)	B
	Skin Hyperpigmentation	5	HRZE (2), Amlodipine (1), Ofloxacin (1), Dapsone (1)	B
	Exfoliative dermatitis	3	Carbamazepine (1), HRZE (1), Amikacin (1)	B
	Toxic epidermal necrolysis	3	Lithium (1), Nevirapine (1), Lamotrigine (1), Valproic acid (1)	B
Gastrointestinal system disorders (37)	Nausea	9	Cisplatin+paclitaxel+fluorouracil (3), Cyclophosphomide+epirubicin(3), Cefoperazone+salbactum(2), HRZE (1),	A
	Vomiting	8	Cisplatin+paclitaxel+fluorouracil (3), Cyclophosphomide+epirubicin(2), Lithium (1) Carboprost(1) Imipenem (1)	A-7, B-1
	Diarrhea	6	Clindamycin (2), Ceftriaxone (2), Fluoxetine (1), Amoxycillin+clavulanic acid (1), Terbinafine (1).	A-5, B-1
	Gastritis	5	Cefuroxime (3), Linezolid (1), Ketorolac (1), Cisplatin (1)	A-2, B-3
	Dysphagia	5	Cisplatin (3), Multivitamin (2), Ivermectin (2)	B
	Decreased appetite	2	Cisplatin+paclitaxel+ fluorouracil (1), Paclitaxel+carboplatin (1)	A
	Constipation	1	Aripiprazole	B
	Metallic taste	1	Satranidazole	B
Central and peripheral nervous system disorders (33)	Extrapyramidal Syndrome	8	Haloperidol (3), Amisulpride(2), Aripiprazole(1),Olanzapine(1), Risperidone(1)	A
	Dizziness	6	HRZE (2), Ceftriaxone (2), Ciprofloxacin(2)	B-6
	Akathisia	6	Olanzepine(2), Amisulpride(2), Iloperidone, Quetiapine	A-4, B-2
	Numbness	3	Pregabalin (3),	A
	Dystonia	3	Risperidone (2), Haloperidol (1)	A
	Psychosis	2	Imipenam+cilastatin(2)	B
	Ringing in ears	2	Etodolac (1), HRZE (1)	B
	Nightmares	2	Mirtazepine(2)	B
	Tremor	1	Haloperidol	A
Cardiovascular disorders	Hypotension	4	Hydrxyethyl starch (2), Netilmicin, Iron sucrose,	B
	Oedema	4	Piroxicum, Rifaximine, Diclofenac, Amlodipine	A-1, B-3

(12)	Tachycardia	2	Misoprostol (2)	B
	Bradycardia	1	Dextrose	A
	Syncope	1	Iron sucrose	B
Respiratory system disorders (7)	Dyspnea	4	Haloperidol (2), Misoprostol, Olanzapine	B
	Throat pain	1	Ofloxacin + Ornidazole	B
	Chest tightness	1	Ferrous fumerate	B
	Chest pain	1	Mitrazepine	B
Muskulo-skeletal system disorder (5)	Generalised weakness	2	HRZE (1), cyclophosphomide+epirubicin+flurouracil (1)	B
	Myopathy	2	Pitavastatin(1), Atrovastatin(1)	B
	Joint pain	1	HRZE	B
Urinary system disorder (3)	Urinary retention	2	Haloperidol (1), Nortryptline(1)	A
	Hematuria	1	Cyclophosphomide	B
Endocrine system disorder (3)	Diabetes mellitus	1	Aripiprazole	B
	Galactorrhoea	1	Levosulpiride	A
	Cushing's syndrome	1	Prednisolone	A
Hepatobiliary system disorder (3)	Hepatitis	3	HRZE	B
Miscellaneous (2)	Shievering	1	Cefuroxime	B
	Increased salivation	1	Haloperidol	A

In Causality assessment as per WHO UMC scale (Figure no.3) the most common category was probable (60.25%). In 67% cases patients completely recovered (Figure no. 4) and in 93% encounters the offender drug was stopped (Figure no 5).

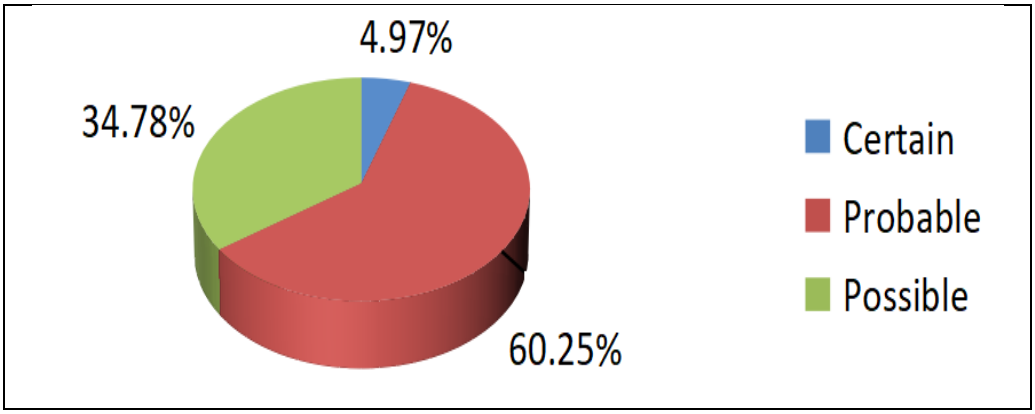

Figure 3: Causality assessment as per WHO UMC scale

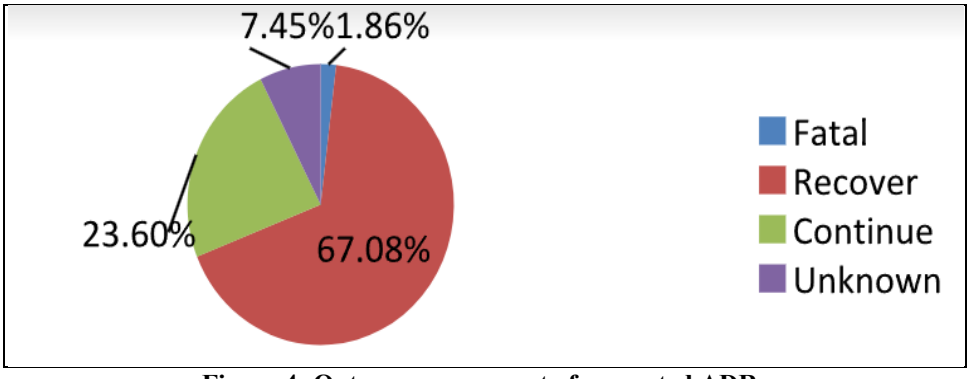

Figure 4: Outcome assessment of suspected ADRs

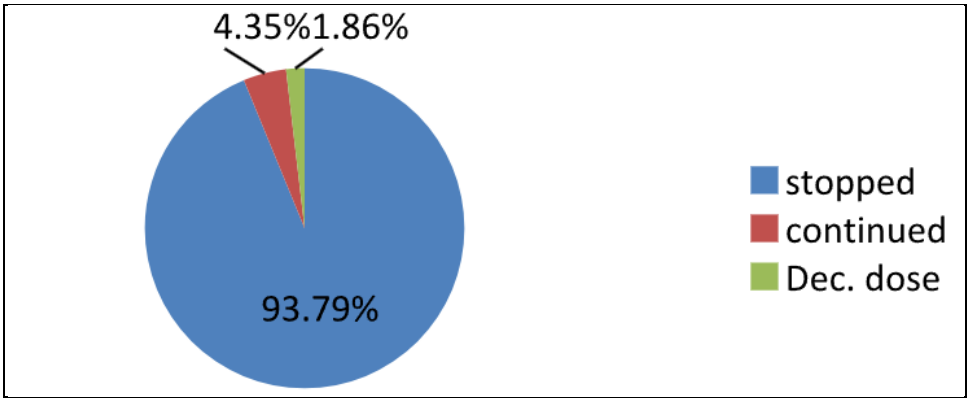

Figure 5: Action taken for suspected offender drug after diagnosing ADR

69.56% ADRs were not serious (Figure no. 6), 45.96% were moderate (Figure no. 7) and 42.24% ADRs were definitely preventable (Figure no. 8)

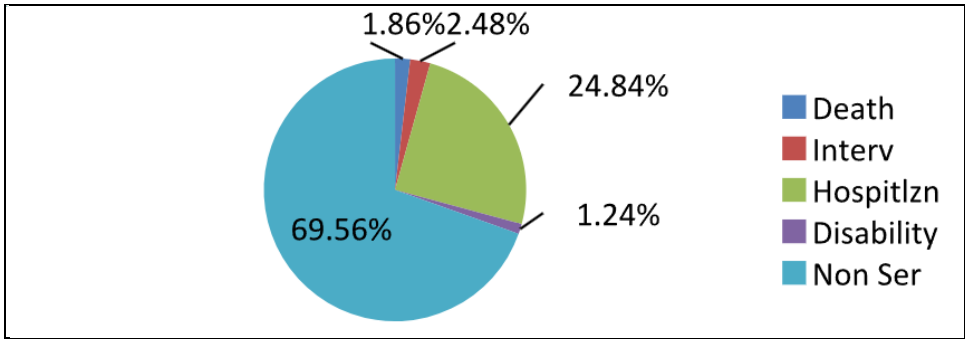

Figure 6: Seriousness assessment of suspected ADRs

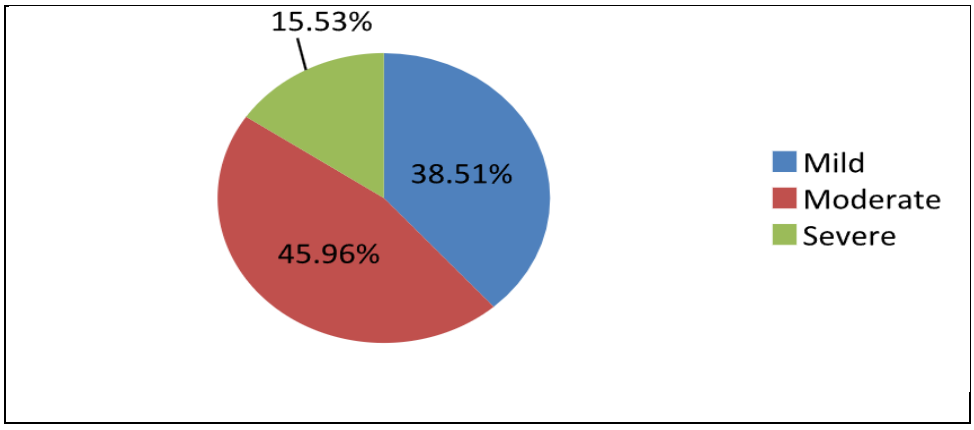

Figure 7: Severity assessment of suspected ADRs

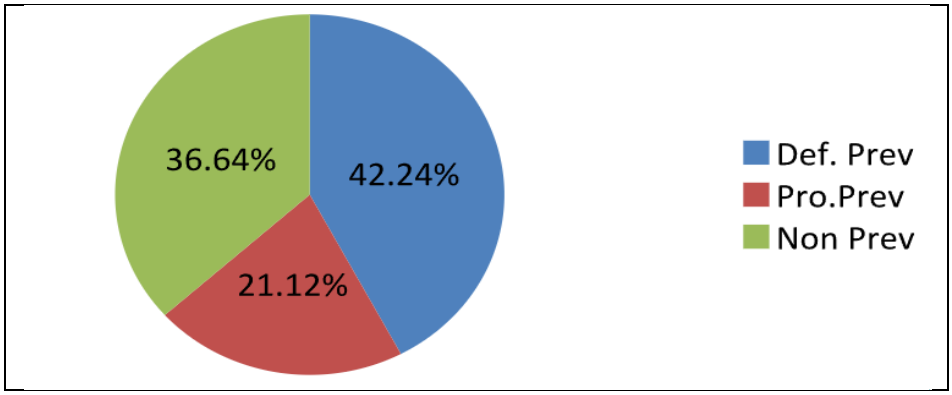

Figure 8: Preventability of suspected ADRs

Discussion

At our AMC data was collected from various clinical departments and ADR reporting was done on the "Suspected Adverse Drug Reaction Reporting Form" provided by IPC. The 161 suspected ADR reports received from various clinical departments from September 2020 to August 2021 were analysed for demographic profile of patients, organ system involved, the type and pattern of ADR reported, causative drugs, outcome, causality, severity, and preventability assessment. The age group in the range of 41-50 years (22.98%), was most commonly involved in ADRs followed by 31-40 years (19.87%) and 21-30 years (18.01%). It is likely that this population is attending hospital more frequently and is a major population receiving drug therapy. This finding also indicates more involvement of younger age group from ADRs. These findings are comparable with the previous studies. [15,16]

The gender distribution showed male preponderance (55.28%) as compared to females (44.72%).[15,16]

According to Rawlins and Thompson classification, which classifies ADR as type A (Augmented/ Predictable) and type B (Bizarre/Unpredictable), Out of all ADRs, 31.68% was type-A reactions while 68.32 % was type-B reactions. It means that 31.68% reactions are augmented, and medication errors are mostly responsible for such reactions. Various previous studies have established this. Maximum offender drugs were administered via oral route followed by iv, sc and im route.[17]

The commonly involved organ systems were skin and appendages 56 (34.78%) followed by gastrointestinal system 37 (22.98%), and central and peripheral nervous system 33 (20.50%). A study conducted by Patidar D et al (2013) also reported dermatological ADRs to be the most frequent (68.75%), followed by central nervous system (9.37%), and gastrointestinal ADRs (6.25%).[16]Another study conducted by Agrawal M et al (2015) reported that the dermatological system (65.38%) was the most affected organ system followed by gastro-intestinal related ADRs (26.92%).[18] In a study conducted by Bhattacharjee P et al. gastrointestinal ADRs (30.82%) was the leading reaction followed by dermatological ADRs(29.70%).[15]

In comparisons of various clinical settings maximum ADRs were discovered from outdoors (87.58%) which is very much similar to other studies. In 76(around 47%) out of 161 prescriptions /treatment orders, 5 or >5 drugs was administered which denotes polypharmacy. It may be rationale or irrational. Irrational polypharmacy often increases pharmacodynamic and pharmacokinetic drug interactions which ultimately increase the chances of adverse drug reactions. [19,20]

In our study only one offender drug was suspected in 88.82% (143) cases and 2 offenders in 11.18% (18) cases. Some previous studies have found more than 1 suspected offender in significant numbers. [21,22]

The major causative drug class was antimicrobials (43.02%). This finding is similar with many epidemiological studies. [23-25] In our study, commonly observed antimicrobial group was β-lactam antibiotics. They are reported as most frequent cause of serious cutaneous reactions like SJS in India. After antimicrobial drugs the drugs acting on CNS were most common offender (22.90%) followed by drugs belonging to Autocoid system which includes NSAIDs and Prostaglandins (15.64%). In some studies, similar findings were observed whereas in some studies autocoids were second most common offender after antimicrobials. [26,27] The causality of most ADRs was "probable" (60.25%) followed by "possible" in (34.78%). Only 4.97% ADR was categorized as "certain". Earlier studies also reported "probable" to be a common causal relationship. This trend was also observed in some similar studies. [22-24] The "certain" relatedness is rare these days as it is not ethical to rechallenge the patient with the same causative drug, hence the assessment infrequently goes to probable category. Due to causality assessment, ADRs have today assumed a differential diagnostic role in clinical medicine. Since these scales are subjective in nature as well as the rechallenege part has become redundant, we should be exploring and designing better causality assessment scales.

In outcome assessment, 3 fatalities have been reported. 67.08% reactions recovered. In 23.60% cases ADRs were persisting and in 7.45% cases the outcome was unknown. This is because of early discharge on patients request and communication related issues. Similar trend was seen in a study conducted by Badyal DK.[28] In 93.97% patients the suspected drug was stopped, in 4.35% patients the suspected drug was continued with same dose while in 1.86% patients the dose of suspected drug was reduced.

As far as seriousness of the ADRs is concerned, it was non-serious in majority of the cases (69.56%). Whileit was serious in the rest of the cases (30.44%). The seriousness was indicated in of terms patients who underwent hospitalization (28.84%), required intervention (2.48%), suffered disability (1.24%), and the fatal cases (1.86%). The skin was the most commonly involved system in serious ADRs. Toxic epidermal necrolysis resulted in all 3 fatalities. This is in contrast to the previous study showing acute renal failure as the prime cause of fatality.[29]

According to modified Hartwig and Siegel scale, most of the ADRs were moderate in nature

(45.96%) followed by mild (38.51%) and severe (15.53%). Majority of the patients recovered completely from the ADR. This result was in accordance with Shamna et al and Kala et al where majority was moderate reactions followed by mild and severe ones. [30,31] The same outcome was seen in studies conducted by Shareef SM and Vijayakumar TM.[32,33]

In this study, Preventability assessment by modified Schumock and Thorton scale revealed that 42.24% of the reported ADRs was definitely preventable, 36.64% were probably preventable, 21.12% were non preventable. The main reason for the preventability was type A reactions which results due to polypharmacy and inappropriate use of antimicrobial agents. This highlights an important area for improvising the drug utilization. This can be minimized by increasing awareness among physicians. In contrast studies conducted by Jose et al and Adithan S, et al found that maximum ADRs were non preventable. [34,35]

Conclusion

This study shows ADRs are very common in this tertiary health care teaching hospital. No ADR with a new drug was observed in this study. For more precise outcome further studies must be conducted in different centers with larger sample size. Proper awareness program among health care staffs and application of standard treatment guidelines among physicians may decrease the incidence of ADRs.

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