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Original Research Article

Study of Adverse Drug Reactions in Inpatients of Medicine Department in a Tertiary Care Hospital: A Cross - Sectional Study

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Abstract

Introduction: Adverse Drug Reactions (ADRs) cause considerable morbidity and mortality worldwide. Early detection, evaluation and monitoring of ADRs are essential to reduce harm to patients and thus improve public health. Spontaneous reporting system (SRS) by health care professionals is common method for reporting suspected ADRs. Chances of ADRs in medicine department are high due to various factors. ADR monitoring and evaluation are the key components of effective drug regulation systems, clinical practice and public health programmes.

Aim: To determine various types, pattern, severity and preventability of ADRs.

Methods: It was cross – sectional, observational study of 104 inpatients of medicine department of either gender. All patients who met study criteria and gave consent were enrolled in the study. ADRs were recorded in ADR reporting form. Documented ADRs were then assessed for causality, severity and preventability using WHO-UMC's causality assessment scale, Naranjo's causality assessment scale, Modified Hartwig and Siegel's severity assessment scale, Modified Schumock and Thornton's preventability assessment categories.

Results: Total 189 ADRs were observed in 104 patients. Predominant systems involved were gastrointestinal system (24.3%), general conditions and system disorders (22.8%). Common causative classes of drugs were antibiotics (56.9%) and steroids (23.9%). In Naranjo's and WHO UMC's causality assessment scale, 81.7% ADRs were possible. In Hartwig and Siegel's severity assessment scale, 51% of the ADRs were moderate. According to modified Schumock and Thornton's preventability assessment, 69.2% ADRs were definitely preventable.

Conclusions: Most of the ADRs were possible in causality, moderate in severity and definitely preventable in preventability.

Keywords: Adverse Drug Reactions (ADRs), inpatients of medicine department, causality, severity, preventability, Pharmacovigilance.

Introduction

Adverse Drug Reaction (ADR) is a response to a drug which is noxious and unintended which occur at a dose normally used in man for the prophylaxis, diagnosis, therapy of disease or for the modification of physiological function. Purposely excludes therapeutic failures, overdose, drug abuse, noncompliance and medication error. [1]

ADRs cause considerable morbidity and mortality worldwide. ADRs have a major impact on public health. It reduces patient's quality of life and impose a considerable financial burden on the health care systems. [2] It has been reported that ADRs account for 5% of all hospital admissions and occur in 10–20% of hospitalized patients. An overall incidence of serious and fatal ADRs among hospitalized patients is 6.7% and 0.32% respectively. [3] ADRs are implicated as 7th most common cause of death. [4]

The information collected during the pre-marketing phase is incomplete with regard to ADRs and this is mainly because patients used in clinical trials are limited in number and are not representative to the public at large. In addition, the conditions of use of medicines differ from those in clinical practice and the duration is limited. Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or drug interactions is often incomplete. Thus, post-marketing surveillance (pharmacovigilance) is important to permit detection of less common, but sometimes very serious ADRs. [5]

Spontaneous reporting system (SRS) by health care professionals is common and cost-effective method for reporting suspected adverse drug reaction. The main function of the SRS is early detection of signals of new, rare or serious ADRs. [6]

Chances of ADRs in medicine department are high due to various factors such as extremes of age, gender, polypharmacy, drug interactions, multiple and inter-current disease, increased length of hospital stay, past history of ADR or allergy, genetic factors, large doses, dietary and environmental factors. [7] Therefore, Study of adverse drug reactions in inpatients of medicine department in a tertiary care hospital was done.

So, this study was plan to determine various types, pattern, severity and preventability of adverse drug reactions and also reporting of various adverse drug reactions observed to AMC in a tertiary care hospital.

Materials and Methods

Study design and population: It was a cross – sectional, observational study of total 104 inpatients of medicine department in a tertiary care hospital. The research project was started after prior permission from the Institutional Human Research Ethical Committee (HREC) (No.GMCS/STU/ETHICS/Approval/2876/20, Date:11-02-2020).

Inclusion criteria:

1. Patients willing to give informed Consent.
2. Patients of 18 years and above of both genders having complaints of any ADR in inpatients of medicine department.
3. All suspected ADRs that confines within WHO's ADR definition.

Exclusion criteria:

1. Patients with associated ADRs due to medicines of alternate systems like

Ayurveda, Homeopathy, Siddha, Unani.
2. Reactions occurring due to transfusion of blood and blood Products.
3. Patients with uncomplicated malaria who are taking Artemisinin derivatives.

Study procedure: It was cross – sectional, observational study of 104 inpatients of medicine department of either gender. Any untoward event was labelled as adverse drug reaction after discussion with the treating physician. All patients with adverse drug reactions were explained about study and those who are willing to give consent were enrolled in the study. Patient selection was also depended on inclusion and exclusion criteria. A suitably designed data collection form used to collect patient's Socio-demographic details. Data of spontaneously reported ADRs were recorded in ADR reporting form (version 1.3). Documented ADRs were then assessed for causality, severity and preventability. ADR assessment was done by using WHO UMC's[8] and Naranjo's causality scale [9] for causality, modified Hartwig and Siegel's severity scale[10] for severity, modified Schumock and Thornton's categories[11] for preventability.

Data Analysis: Descriptive analysis was done by using Microsoft Excel. All data were expressed in numbers and percentages.

Results

Gender distribution of patients with adverse drug reactions is shown in Table 1. Total 104 inpatients of medicine department were enrolled and analysed. Out of total study population, 70.2% were male patients and 29.8% were female patients

Table 1: Gender distribution of patients with adverse drug reactions

Gender	Frequency	Percentage (%)
M	73	70.2%
F	31	29.8%
Total	104	100%

Age wise distribution of patients with adverse drug reactions is shown in Table 2.

Table 2: Age distribution of patients with adverse drug reactions

Age group (years)	Frequency	Percentage (%)
≤20	5	4.8%
21 - 40	33	31.7%
41-60	54	51.9%
>60	12	11.5%
Total	104	100%

Following Graph is showing various systems affected by ADRs. Highest ADRs are seen with Gastrointestinal system (24.3%) and lowest ADRs are seen with Hepatic system (0.5%). (Figure 1)

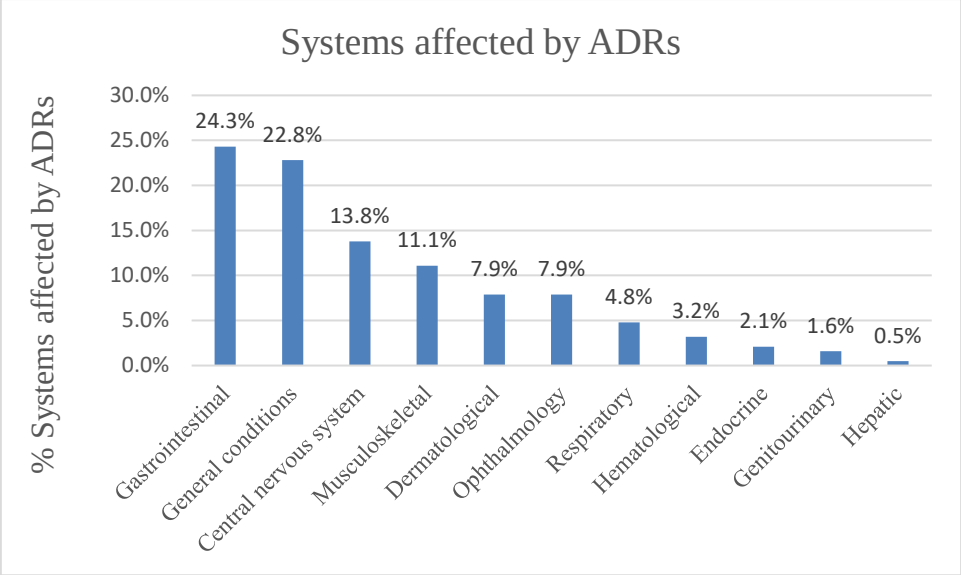

Figure 1: Systems affected by adverse drug reactions

Table 3 is showing frequency and percentage of observed adverse drug reactions. Total 189 ADRs were seen in study population. Most common being Headache (12.2%).

Table 3: Observed adverse drug reactions

Observed ADRs	Frequency	Percentage (%)
Diarrhoea	11	5.8%
Vomiting	19	10.1%
Abdominal pain	8	4.2%
Nausea	4	2.1%
Constipation	1	0.5%
Metallic taste	1	0.5%
Dry mouth	2	1.1%
Rash	10	5.3%
Itching	2	1.1%
Alopecia	1	0.5%
Purpura	1	0.5%
Red Patches	1	0.5%
Redness in both eye	1	0.5%
Eye pain	14	7.4%
Dry cough	1	0.5%
Nasal discharge	4	2.1%
Nasal blockage	4	2.1%
Vertigo	1	0.5%
Headache	23	12.2%
Drowsiness	1	0.5%
Giddiness	1	0.5%
Megaloblastic anemia	1	0.5%
Thrombocytopenia	3	1.6%
Raised APTT	1	0.5%
Nasal bleeding	1	0.5%

Facial pain	13	6.9%
Tooth pain	1	0.5%
Facial Swelling	6	3.2%
Gum Hypertrophy	1	0.5%
Chills	16	8.5%
Fever	15	7.9%
Rigors	12	6.3%
Raised S. create	3	1.6%
Raised S. transaminase	1	0.5%
Cushing syndrome	4	2.1%
Total	**189**	**100%**

Figure 2 is showing percentage of suspected class of drugs causing ADRs. Antibiotics causing highest ADRs (56.9%).

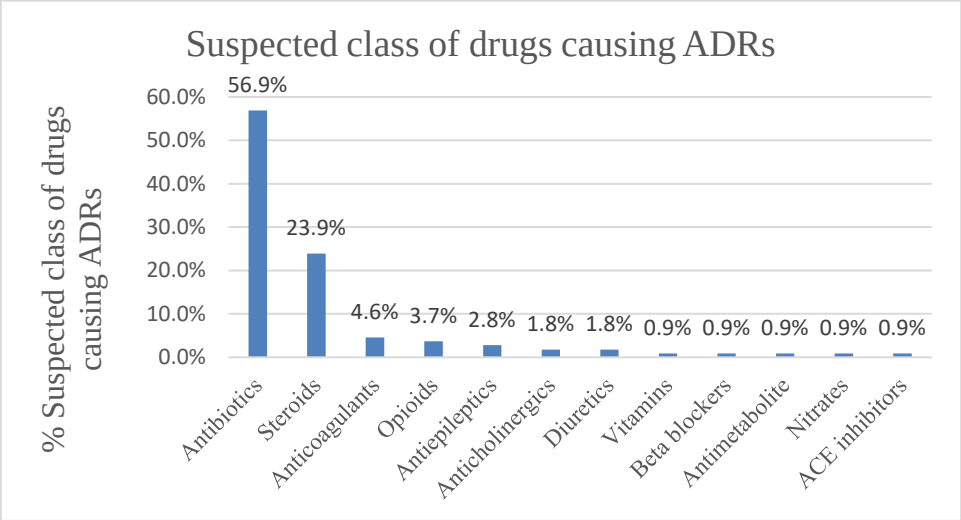

Figure 2: Suspected class of drugs causing ADRs

Table 4 is showing frequency and percentage of various suspected drugs causing ADRs. Injection amphotericin B is responsible for highest (14.7%) number of ADRs.

Table 4: Suspected drugs causing ADRs

Suspected Drug	Frequency	Percentage (%)
Tab. Hydroxychloroquine	8	7.3%
Inj. Amphotericin B	16	14.7%
Tab. Amoxycillin, Clavulanic acid	1	0.9%
Inj. Amoxycillin, Clavulanic acid	2	1.8%
Inj. Cefosulbactum	1	0.9%
Inj. Cefotaxime	1	0.9%
Inj. Ceftriaxone	3	2.8%
Inj. Clindamycin	1	0.9%
Inj. Vancomycin	2	1.8%
Inj. Meropenem	2	1.8%
Inj. Linezolid	1	0.9%
Inj. Levofloxacin	1	0.9%
Inj. Piperacillin, Tazobactam	10	9.2%

Tab. Chloroquine	6	5.5%
Tab. Azithromycin	1	0.9%
Tab. Favipiravir	1	0.9%
Inj. Metronidazole	5	4.6%
Inj. Prednisolone	3	2.8%
Inj. Dexamethasone	12	11.0%
Tab. Prednisolone	4	3.7%
Inj. Methylprednisolone	7	6.4%
Inj. Heparin	3	2.8%
Tab. Aspirin	1	0.9%
Tab. Rivaroxaban	1	0.9%
Tab. Phenytoin	2	1.8%
Tab. Valproate	1	0.9%
Inj. Atropine	2	1.8%
Inj. Furosemide	1	0.9%
Tab. Spironolactone	1	0.9%
Inj. Vit B12	1	0.9%
Tab. Labetalol	1	0.9%
Inj. Tramadol	4	3.7%
Tab. Hydroxyurea	1	0.9%
Inj. Nitro glycerine	1	0.9%
Tab. Enalapril	1	0.9%
Total	**109**	**100%**

The causality assessment of ADRs using the Naranjo's causality assessment scale showed Possible (81.7%) followed by Probable (18.3%) and no ADRs in Doubtful and Definite categories. (Figure 3)

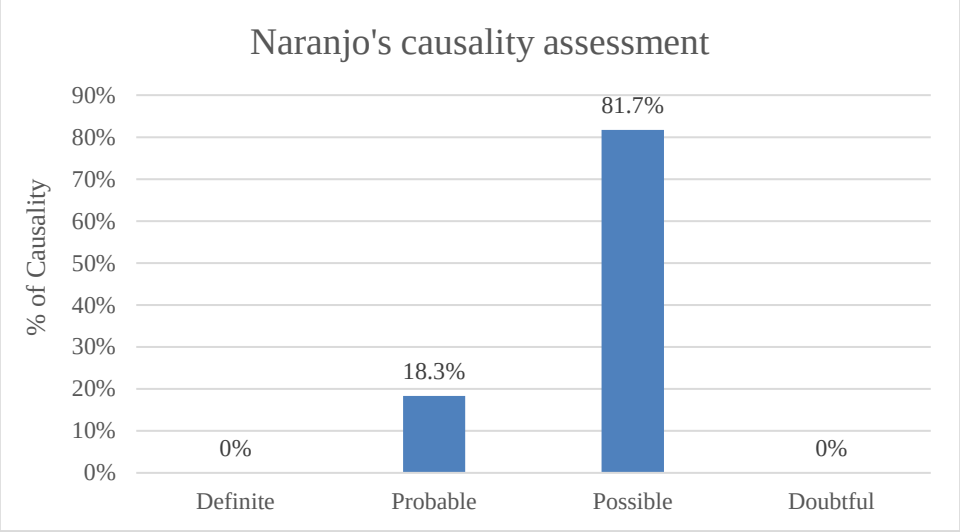

Figure 3: Naranjo's causality assessment scale

The causality assessment of ADRs using the WHO UMC's causality assessment showed Possible (81.7%) followed by Probable (18.3%) and no ADRs in Certain, Unlikely, Conditional and Unassessable categories. (Figure 4)

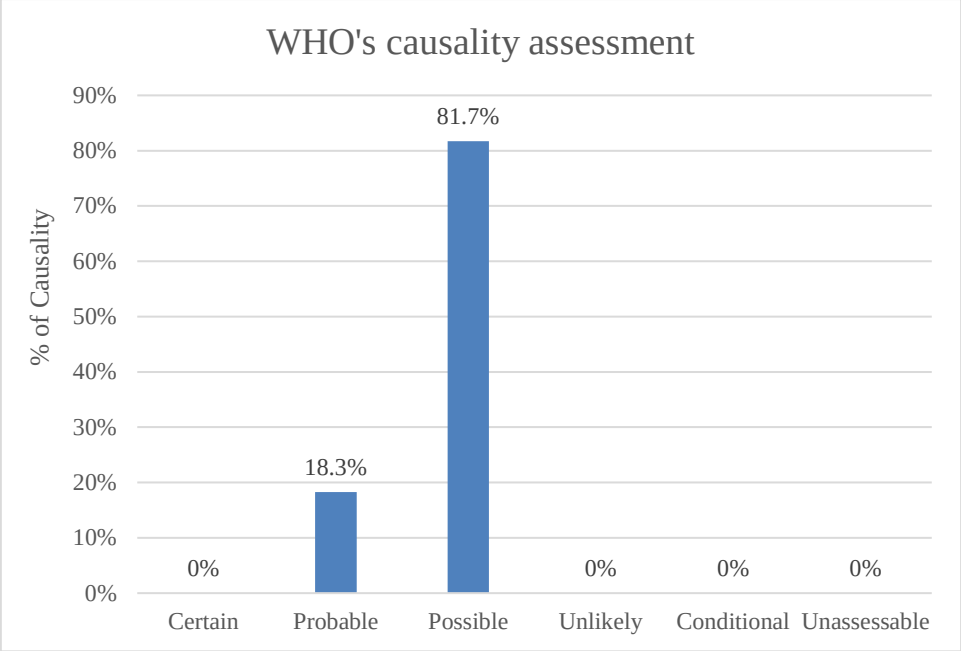

Figure 4: WHO UMC's causality assessment

The severity assessment by Modified Hartwig and Siegel's severity assessment showed Moderate (51%) followed by Mild (49%) and no ADRs in Severe category. (Figure 5)

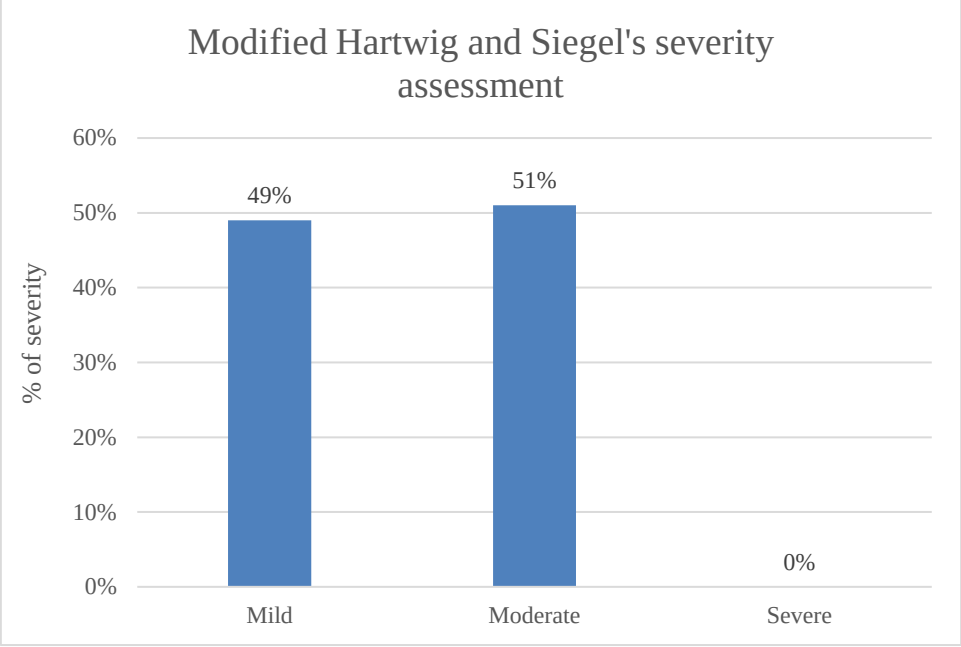

Figure 5: Modified Hartwig and Siegel's severity assessment

The severity assessment by Modified Schumock and Thornton's preventability assessment showed Definitely preventable (69.2%) followed by Probably preventable (30.8%) and no ADRs in Not preventable category. (Figure 6)

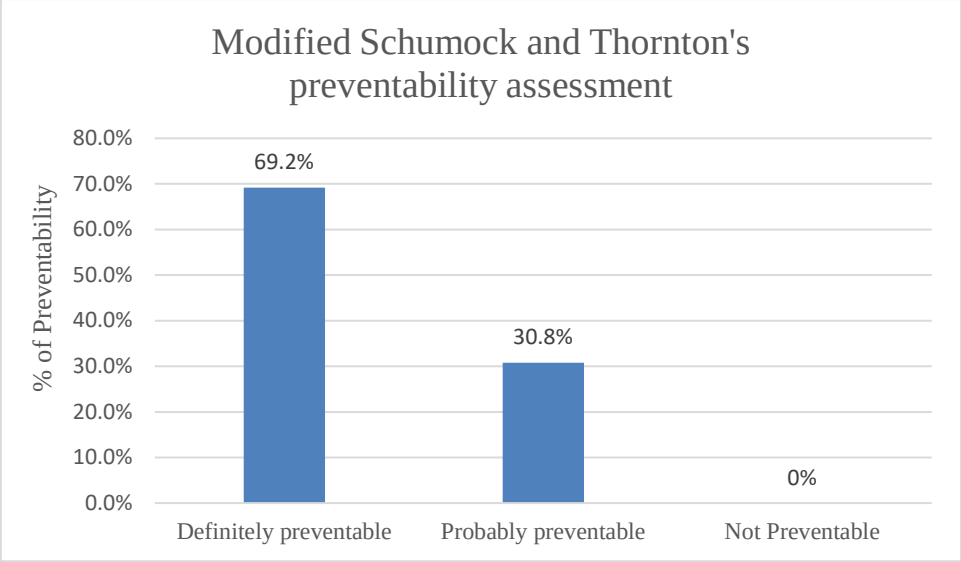

Figure 6: Modified Schumock and Thornton's preventability assessment

Outcome of patients showed Not recovered (65.4%) followed by Recovered (33.7%) and Recovering (1%) phase. (Figure 7)

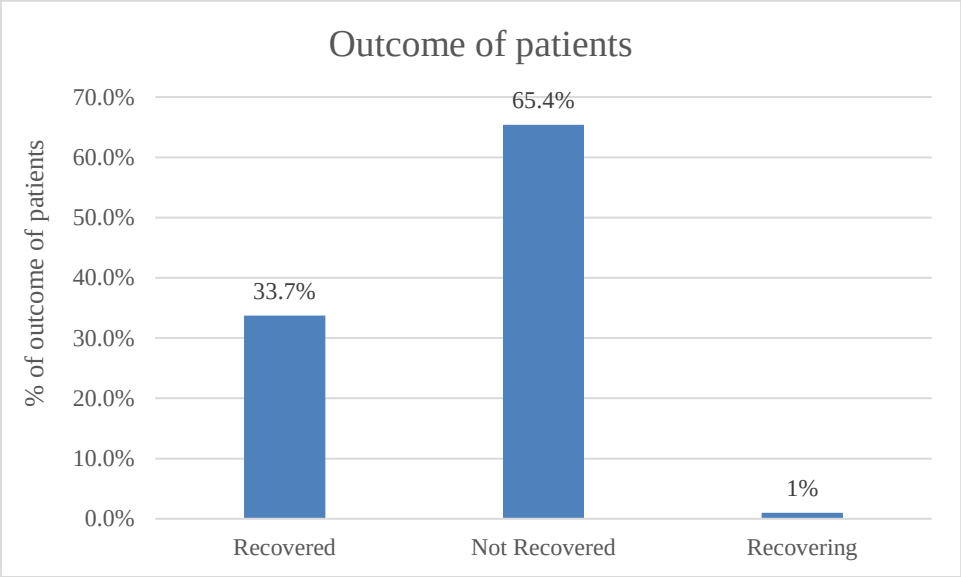

Figure 7: outcome of patients

Discussion

Adverse drug reactions (ADRs) have major impact on public health and it is the seventh leading cause of death. It has been reported that ADRs account for 5% of all hospital admissions and occur in 10–20% of hospitalized patients. So, ADRs impair the quality of life of patients and increase economic burden on health care system. [4]

In India there is paucity of ADR reporting and its monitoring, thus monitoring the drug safety is one of the major problems in our country. It is very necessary to enhance the awareness regarding early detection, reporting, management, further prevention of ADR to ensure the drug safety and quality of life. [12]

Spontaneous reporting system is most common system of ADRs reporting. The main function of the spontaneous reporting

system is early detection of signals of new, rare or serious ADRs. Spontaneous reporting system has advantage of covering of large number of patients and wide range of drugs. It is therefore a cost effective method of monitoring drug safety. [6]

The occurrence of ADRs in medicine department is reported to be higher as it is influenced by various factors like age, polypharmacy, multiple diseases, increased length of hospital stay, dietary and environmental factors. [13]

So, this study was conducted in medicine department with the aims to determine various types, pattern, severity and preventability of adverse drug reactions and reporting of various adverse drug reactions observed to Adverse drug reactions Monitoring Centre (AMC) in a tertiary care hospital.

It was cross – sectional, observational study of 104 inpatients of medicine department of either gender. Any untoward event was labelled as adverse drug reaction after discussion with the treating physician. Data of spontaneously reported ADRs were recorded in ADR reporting form. Documented ADRs were then assessed for causality by Naranjo's and WHO UMC's causality assessment scale, severity by modified Hartwig and Siegel's severity assessment scale and preventability by modified Schumock and Thornton's preventability assessment scale.

In present study, majority of ADRs were in male patients (70.2%) compared to female patients (29.8%). Similarly, study done by Shanmugam Sriram et al. reported higher incidence of ADRs in male patients. [14] But, Singh H et al. found more ADRs in female patients compared to male patients. [15] Thereby, concluding that influence of gender is just an incidental finding and it does not affects number of ADRs reported.

Demographic analysis showed that out of total patients, 51.9% patients were within the age range of 41 to 60 years followed by 31.7% of 20 to 40 years,11.5% of more than 60 years and 4.8% in ≤ 20 years group. These results revealed higher incidence of ADRs in adults over other age groups. Abhik Saha et al. reported majority of ADRs among the age group of 41-50 years. [16] In a study by Ramya Ravichandar et al. the percentage of ADRs found was higher in adults and the geriatric population. [17] This might be due to the fact that most adult and geriatric patients presented with comorbidities such as diabetes mellitus, hypertension, renal failure, myocardial infarction, heart failure and dyslipidaemia which forces them to receive multiple drug therapy. It is known that multiple drug therapy and co-morbidities predispose patients to ADRs.

In current study, most of the adverse drug reactions were observed affecting gastrointestinal system (24.3%). This is in accordance with studies done by Anup Kumar et al. in which gastrointestinal system was most commonly affected system. [18] Mostly drugs were disintegrated, distributed, metabolized and absorbed through gastrointestinal system. so, the system is frequently exposed to all chemicals and drugs leads to development of gastrointestinal symptoms. Next most common systems involved were general conditions and system disorders (22.8%) followed by central nervous system (13.8%) and dermatology system (7.9%). Contrary to the present study, Arulmani R et al. found dermatology system (34.4%) followed by central nervous system (18.9%) and gastrointestinal system (17.7%) were most commonly involved in adverse drug reactions. [19] Arpita Singh et al. observed that ADRs affecting the dermatology system was common followed by general conditions and system disorders followed by ADRs affecting gastrointestinal system. [20]

Hepatobiliary system (0.5%), genitourinary system (1.6%) and endocrinal system (2.1%) were less commonly affected in the study. A.P. Gor et al. came up with similar results in which hepatobiliary system (3%), genitourinary system (1%) and endocrinal system (1%) were less commonly involved. [21] These findings suggest that lower incidence of adverse drug reactions affecting hepatobiliary system, genitourinary system and endocrinal system.

It was observed that, musculoskeletal system (11.1%), ophthalmology system (7.9%), respiratory system (4.8%) and hematology system (3.2%) were also affected by ADRs. Study done by Kavita Dhar et al. also found musculoskeletal system (7.93%) and hematology system (1.58%) involvement in adverse drug reactions. [22]

Out of all adverse drug reactions received in the study, headache (12.2%) was the most commonly reported ADR followed by vomiting (10.1%), chills (8.5%), fever (7.9%) and eye pain (7.4%) etc. Study carried out by Donepudi Pavan Kumar et al. showed skin rash (40.5%) followed by headache (26.2%) and diarrhoea (21.4%) were the most common ADRs.[17] Study conducted by Seema Rani et al. noticed vomiting, diarrhoea and fever as a commonest adverse drug reaction. [23] Gunjan P. et al. demonstrated vomiting and chills as a most common ADRs. [24]

Giddiness (0.5%), drowsiness (0.5%), Constipation (0.5%) etc were less commonly reported ADRs in present study. Similar observations were made by Kumari PM et al. [25]

Among the all ADRs, major proportions of ADRs were seen with antibiotics (56.9%). Which is in agreement to studies done by Priyadarshini et al. and Priya et al. [26][27] This is due to the antibiotics are commonly prescribed to the patients. But, contrary to the present study M. Ramesh et al. observed cardiovascular agents followed by antibiotics were common causative agents. [28] Steroids (23.9%) were next common classes of drugs suspected to be in causation with ADRs.

Beta blocker (0.9%), nitrate (0.9%), vitamins (0.9%) and ACE inhibitors (0.9%) were least commonly implicated in adverse drug reactions. Alexandra Alexopoulou et al. detected beta blockers, angiotensin convertase enzyme inhibitors and diuretics were less commonly involved drugs in adverse drug reactions. [29]

In this study, other class of drugs like anticoagulants (4.6%), Opioids (3.7%) and antiepileptics (2.8%) were also suspected in causation with adverse drug reactions. Similarly, study done by Mahesh N. Belhekar found anticoagulants (8.5%) and angiotensin convertase enzyme inhibitors (2.6%) were involved in adverse drug reactions. [30]

In current study, highest number of ADRs were observed with amphotericin B (14.7%) followed by dexamethasone (11%), piperacillin and tazobactam (9.2%), hydroxychloroquine (7.3%). Compared to these, in a study by Mukeshkumar B. Vora et al. chloroquine, aspirin and enalapril were the most common suspected drugs in adverse drug reactions. [31] Penicillin, sulphonamides and amoxicillin were most common causative agents in a study done by Chau Tran et al. [32]

Results of this study showed that linezolid (0.9%), furosemide (0.9%), Clindamycin (0.9%) were least commonly involved drugs in ADRs. Mukhtiar Singh et al. found minimum ADRs due to furosemide, and dexamethasone. [33] Linezolid and clindamycin were less frequently responsible for ADRs in a study by Amit Dang et al. [34]

This study also revealed that Amphotericin B was suspected in causation of headache, fever with chills and rigors. ADRs like

diarrhoea, rash and itching were suspected to be associated with piperacillin and tazobactam, meropenem, ceftriaxone and linezolid. Redness of eye in association with ceftriaxone and rash due to vancomycin were also reported. Abdominal pain and diarrhea in association with azithromycin were found. Chloroquine were most commonly involved in vomiting. Vomiting and diarrhoea due to hydroxychloroquine were also reported. Facial swelling, eye pain, nasal discharge and blockage were associated with steroids like dexamethasone, methyl prednisolone and prednisolone. In some of the adverse drug reactions like thrombocytopenia due to heparin, nasal bleeding due to rivaroxaban, purpura and red patches due to aspirin were suspected. Among ACE inhibitors enalapril was found in causation of dry cough. Among anticholinergics atropine was found to be in causation with dry mouth. Some cases of headache due to nitrates were also noticed.

The Causality of all ADRs was assessed using Naranjo's and WHO UMC's causality assessment scale. In Naranjo's causality assessment 81.7% ADRs were possible, 18.3% ADRs were probable. Where no ADRs belonged to doubtful (0%) and definite (0%) categories. These are in accordance with study done by Sivanandy Palanisamy et al. [35] In contrast to this study, most of the adverse drug reactions were probable in a study by Syed Afzaluddin Biyabani et al. [36], Mirjam Kauppila et al. showed 20.6% definite, 33.8% probable, and 45.6% possible adverse drug reactions. [37] This increase in definite category has been attributed to more complete information that is available at the time of assessment.

According to WHO UMC's causality assessment scale 81.7% ADRs were possible, 18.3% ADRs were probable and no ADRs belong to certain (0%), unlikely (0%), conditional (0%) and unassessable (0%). Most of the reactions were possible in the study because multiple drugs were prescribed at the same time. Similarly, Meda Venkatasubbaiah et al. identified majority of the adverse drug reactions were possible. [38] In contrast, most of the adverse drug reactions were probable in a study by Dr. Gira Sulabh et al. [39]

The Grading of Severity of ADRs was done according to modified Hartwig and Siegel's severity assessment scale. It was found that 51% of the ADRs were moderate, 49% of ADRs were mild and no ADRs were belong to Severe reactions (0%) category. Since majority of ADRs did not require any change in therapy or additional treatment. Moderate ADRs included fever, chills, rigors, rash, itching like hypersensitivity reactions and cushing syndrome required symptomatic management and drug withdrawal. These results are concurrent with study by M. Shamna et al. moderate reactions were more than mild. [40] Jahirul Islam Laskar et al. found 41% ADRs were moderate and 37% were severe reactions. [41]

The analysis of the preventability of ADRs was done according to modified Schumock and Thornton's preventability assessment scale. Out of the total ADRs received, 69.2% ADRs were definitely preventable, 30.8% ADRs were probably preventable and no ADRs in not preventable(0%) category. Which is similar to study done by Ramya Ravichandar et al. [1] But, in a study done by Pankaj Daulat et al. [17], probably preventable reactions were more compared to definitely preventable.

In this study, 65.4% patients were not recovered, 33.7% recovered and 1% patients were at recovering phase from adverse drug reactions at the time of reporting. But, in a study done by Ganesan S et al. majority of patients recovered from adverse drug reactions. [42] In a study of Prakash H. Bhabhor 31.5% patients recovered, 46% patients recovering and

10% patients have unknown outcome from adverse drug reactions. [43]

Thus, this study provides basic information regarding the safety profile of various drugs. Assessment of three different parameters of the ADR were noted, namely the causality, severity and preventability. [44]

Limitations of study:

As study was spontaneous in nature so patients were not followed.

Reporting from clinician was lacking because of work related stress, busy outpatient setting, and many clinicians do not consider reporting a priority.

Conclusions

In present study, adverse drug reactions monitoring was done in inpatients of medicine department in a tertiary care hospital. Based on observation made in present study following conclusions emerge:

- Reported ADRs ranged from mild reactions like headache, vomiting and diarrhoea to moderate reactions like fever, chills and rigors.
- No fatalities due to ADR were reported.
- Predominant systems involved were gastrointestinal system (24.3%), general conditions and system disorders (22.8%) and central nervous system (13.8%). Common causative classes of drugs were antibiotics (56.9%), steroids (23.9%).
- Most of the ADRs were possible in causality, moderate in severity and definitely preventable in preventability.

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