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PHARMACOVIGILANCE STUDY OF PATIENTS RECEIVING TREATMENT AT MEDICAL ICU OF C. U. SHAH MEDICAL COLLEGE & HOSPITAL, SURENDRANAGAR

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ABSTRACT: Background: Medical Intensive Care Unit (ICU) can be a potential place for Pharmacovigilance due to high frequency of Adverse Drug Reactions (ADRs). Regular evaluation can help in understanding the pattern of ADR and reduce the incidence of it. **Aims and Objectives:** To evaluate incidence of ADRs in patients receiving various modes of treatment at medical ICU of our tertiary care hospital and classify them. **Materials and Methods:** Study was carried out by actively observing 500 patients admitted at medical ICU over a period of 18 months. Suspected ADRs were reported and classified. Association between various factors was carried out by chi square test. **Results:** Total 59 (11.8%) ADRs were reported. Most common was hypotension 8 (13.56%) followed by headache 7 (11.86%). Highest group responsible for ADRs was fibrinolytic drugs 14 (23.73%). Coagulation and cardiovascular systems were commonest to involve with incidence rate of 16 (27.12%) and 14 (23.73%) respectively. Commonest type was A with incidence rate of 42 (71.19%). Significant association was noted between no. of drugs and increased incidence of ADRs (X^2=4.5) ($p<0.05$), while association was not statistically significant with age (X^2=2.01) ($p>0.05$) and hospital stay (X^2=2.98) ($p>0.05$). 34 (57.63%) were mild, 22 (37.29%) were moderate, while 03 (5.08%) were severe in nature. **Conclusion:** Hypotension and fibrinolytics were noted as most common ADR and group of drugs responsible respectively at our ICU. Incidence of ADRs was significantly increased with increased number of drugs prescribed. Active observation with Pharmacovigilance activity can evaluate incidence and pattern of ADRs in better way.

INTRODUCTION: Pharmacovigilance is the science of the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug related problem [1].

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To establish drug safety continues monitoring is must because clinical trials involve several thousand patients at most; less common side effects and Adverse Drug Reactions (ADRs) are often unknown at the time a drug enters the market [2].

Recently, Pharmacovigilance is gaining importance for doctors and scientists as the number of stories in the mass media of drug recalls increases [3]. Intensive Care Units (ICUs) came into existence for patients with special needs and include so many technologies to support medical care.

The chances of drug related complications are high here, requiring special attention towards patient safety [4]. In fact, ICU patients may be at higher risk for ADR because of multi-organ dysfunction and altered pharmacokinetic parameters [5]. In a comparative study of intensive care and general care units, it was reported that the preventable and potential Adverse Drug Events in ICUs to be nearly twice that of non-ICUs [6]. Medical ICUs can be considered as an optimal location for developing voluntary reporting incentives based on the frequency of events. Monitoring of ADRs helps in reducing the mortality and morbidity due to it [7].

So this study was carried out with overview aims of evaluating incidence of ADRs and assess role of age and polypharmacy in the development of ADRs at medical ICU of our tertiary care centre.

MATERIALS AND METHODS: The study was approved by Institutional Ethics Committee (H) (Approval no: CUSMC/IEC(H)/APPROVAL-25/ 3893/5/2010). It was an observational study which was carried out by active surveillance of medical ICU over a period of 18 months. Total 500 patients were included in the study.

Study was carried out by actively observing patients admitted at medical ICU over a period of 18 months to find the incidence of ADRs. Diagnosis of ADRs was done by the physicians. Total 500 patients irrespective of their age and sex were included in the study. All the patients were actively observed by regular visits of medical ICU. Active surveillance of all the patients was done by interviewing patients and/or physicians or by reviewing medical records and bedside charts. All the doctors, residents, interns and students were also encouraged to notify any suspected ADRs by either telephonic or direct reporting to the Dept. of Pharmacology. Reporting was done according to 'CDSCO ADR REPORTING FORM'.[8] Reporting form was consisting details like drug history and information like onset and nature of reaction, associated drugs and past history of similar or other allergic reactions.

On the basis of collected data, incidence of reported ADRs was calculated and classified according to age and gender. Reported ADRs were further classified by drug groups responsible and systems involved. ADRs were divided according to their types. Estimation of the magnitude of Association between risk factors like age, no. of drugs, hospital stay and incidence of ADRs was carried out by Chi square test. Severity assessment was done by modified Hartwig and Siegel's scale [9], which classifies severity of ADR as mild, moderate or severe based on factors like necessity of change in treatment, increased duration of hospital stay and disability produced by ADR. From the available data ADRs were analysed to determine rate of ADRs those treated without treatment, with treatment or turned fatal.

Statistical Analysis: Chi square test was done by using MedCalc. Software version 7.6.0.0 ($p<0.05$ was considered as significant).

RESULTS: Total 500 patients were observed over a period of 18 months. Out of observed patients 59 (11.8%) ADRs were detected. Most of the patients had time reaction between 1 to 10 days.

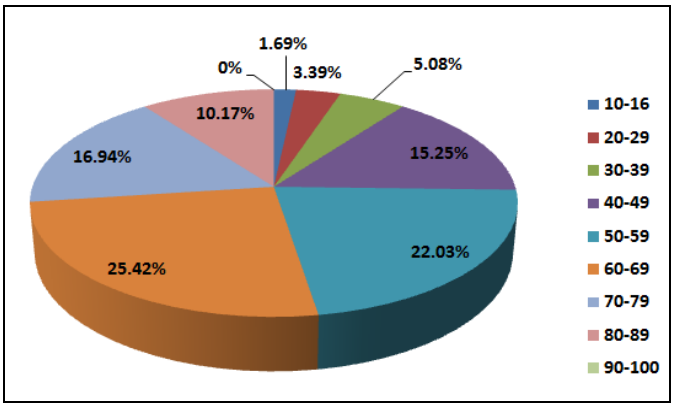

FIG. 1: AGE DISTRIBUTION OF THE ADR REPORTED POPULATION

Fig. 1 shows age wise distribution of patients with reported ADRs, which indicates that highest age group was 60-69 years with incidence of 15 (25.42%) followed by 50-59 years with 13 (22.03%) of the reported ADRs.

TABLE 1: GENDER WISE DISTRIBUTION OF PATIENTS WITH ADRS

Gender	No. of patients	Percentage (%)
Male	40	67.8
Female	19	32.2
Total	59	100

As shown in **Table 1** study male patients had higher incidence of ADRs 40 (67.8%) as compared to female patients 19 (32.2%).

TABLE 2: REPORTED ADVERSE DRUG REACTIONS

Type of reaction	No. of patients	Drugs responsible
Hypotension	6	Streptokinase
	1	Isosorbide mononitrate
	1	Metoprolol+Telmisartan
Headache	3	Glyceryl trinitrate
	4	Isosorbide mononitrate
Hypoglycaemia	5	Insulin
	1	Oral hypoglycaemic
Diarrhoea	2	Cefixime
	1	Cefotaxime
	1	Azythromycin
	1	Amoxicillin
Haemoptysis	3	Streptokinase
	1	Warfarin
Vomitting	3	Digoxin
	1	Chloroquine
Haematuria	1	Clopidogrel+Aspirin
	2	Enoxaparin
Bleeding from gum	2	Streptokinase
Bleeding in stool	1	Clopidogrel+Aspirin
	1	Streptokinase
Acute renal failure	1	Mannitol
	1	Losartan
Arrhythmia	2	Digoxin
Haematemesis	1	Enoxaparin
	1	Streptokinase
Cerebrovascular	1	Heparin
accident (CVA)	1	Streptokinase
Bradycardia	2	Metoprolol
Haematoma	1	Heparin
Oedema	1	Bromocriptine
Nephropathy	1	Diclofenac
Cough	1	Enalapril
Exacerbation of asthma	1	Atenolol
Abdominal cramps	1	Metronidazole
Fatigue	1	Digoxin
Nasal bleeding	1	Enoxaparin

All the reported ADRs are listed in **Table 2**, which reveals that total 59 patients were reported as having ADRs with incidence rate of 11.8%. It also indicates that out of all reported ADRs most common was hypotension 8 (13.56%) followed by headache 7 (11.86%).

TABLE 3: CLASSIFICATION OF CAUSATIVE AGENTS

Group of drugs	No. of ADRs	Percentage (%)
Fibrinolytic drugs	14	23.73
Organic nitrates	8	13.56
Anticoagulant drugs	7	11.86
Antidiabetic drugs	7	11.86
Antimicrobial drugs	6	10.17
Antihypertensive drugs	6	10.17
Antiarrhythmic drugs	6	10.17
Antiplatelet drugs	2	03.39
Antimalarial drugs	1	01.69
NSAIDs	1	01.69
Diuretics	1	01.69
Total	59	100

Table 3 shows classification of causative drugs according to their groups which indicates highest group responsible for ADRs was fibrinolytic drugs 14 (23.73%) followed by organic nitrates 8 (13.56%).

TABLE 4: CLASSIFICATION OF ADRs ACCORDING TO SYSTEM INVOLVED

System	No. of ADRs	Percentage (%)
Coagulation system	16	27.12
Cardiovascular	14	23.73
Gastrointestinal	10	16.95
Generalised	08	13.56
Metabolic	06	10.17
Renal	03	5.08
Respiratory	02	3.39
Total	59	100

As shown in **Table 4** Coagulation and cardiovascular systems were most common to involve with incidence rate of 16 (27.12%) and 14 (23.73%) respectively.

TABLE 5: CLASSIFICATION OF ADRs ACCORDING TO TYPES

Type	No. of ADRs	Percentage (%)
A (Augmented)	42	71.19
B (Bizarre)	01	1.69
C (Continuous use)	08	13.56
D (Delayed)	00	00
E (End of dose)	08	13.56
F (Failure of therapy)	00	00
Total	59	100

Table 5 reveals that most common type was A with incidence rate of 42 (71.19%) followed by Type C and E with incidence rate of 08 (13.56%).

TABLE 6: ASSOCIATION BETWEEN VARIOUS FACTORS AND INCIDENCE OF ADRs

Characteristic	Category	Total patients	Reported ADRs
No. of drugs	< or = 6	228	20
	>6	272	39
Age	< or = 50	175	12
(Years)	>50	325	47
Hospital stay	< or = 5	252	23
(Days)	>5	248	36

Table 6 indicates co-relation of no. of drugs, age and duration of hospital stay with incidence of ADRs. On application of chi-square test it reveals that there is significant association between no. of drugs and increased incidence of ADRs (X^2=4.5) ($p<0.05$), while association was not statistically significant with age (X^2=2.01) ($p>0.05$) and hospital stay (X^2=2.98) ($p>0.05$).

TABLE 7: MODIFIED HARTWIG AND SIEGEL'S SEVERITY ASSESSMENT

Severity	No. of ADRs	Percentage (%)
Mild	34	57.63
Moderate	22	37.29
Severe	03	05.08
Total	59	100

Classification of ADRs according to modified Hartwig and Siegel's scale is shown in **Table 7**, which reveals that 34 (57.63%) were mild, 22 (37.29%) were moderate, while 03 (5.08%) were severe in nature.

TABLE 8: TREATMENT AND OUTCOME OF REPORTED ADRs

Treatment and outcome	No. of ADRs	Percentage (%)
No treatment	35	59.32
Resolved with treatment	20	33.90
Not resolved with treatment	02	03.39
Fatal	02	03.39
Total	59	100

Table 8 displays treatment and outcome after occurrence of ADRs. Amongst all ADRs 35 (59.32%) resolved without any treatment, while 20 (33.90%) resolved with treatment. On the other side 2 (3.39%) ADRs were not resolved even after treatment and 2 (3.39%) resulted in fatal outcome.

DISCUSSION: This study was carried out with an aim of evaluating incidence of ADRs in medical ICU of our tertiary care centre. Total 500 patients were observed actively through period of 18 months. Incidence rate of ADRs in this study was 11.8%. A study conducted by Park [10] reported incidence of 32%. Other studies [11-13] have been reported with higher incidence rate. Much of this large variability may be due to differences in the definitions used of the same type of event and also in methods used to detect events.

Age wise distribution of the patients diagnosed as having ADRs indicates that highest age group was 60-69 years with incidence of 15 (25.42%) followed by 50-59 years with 13 (22.03%) of the reported ADRs with increase in incidence rate with age. Earlier studies [14-18] have also observed same pattern of relation of age with ADRs in various clinical settings. Higher numbers of ADRs were observed in male (67.8%) patients as compared to females (32.2%). This is in consonance with other studies [7, 19] conducted in India which has reported male preponderance. This may be due to higher rate of male admission in the study or geographical similarity of study population.

A wide variety of ADRs were reported in this study. Out of all reported ADRs most common was hypotension 8 (13.56%) followed by headache 7 (11.86%). Other reported ADRs were hypoglycaemia (10.17%), diarrhoea (8.47%), haemoptysis (6.78%), Vomitting (6.78%), haematuria (5.08%), bleeding from gum, bleeding in stool, acute renal failure, arrhythmia hematemesis, CVA, bradycardia (3.39% each), haematoma, oedema, nephropathy, cough, exacerbation of asthma, abdominal cramps, fatigue and nasal bleeding (1.69% each) in descending order. The most common events were hypoglycaemia, prolonged activated partial thromboplastin time, and hypokalaemia [20]. Clinical spectrum included acute renal failure (ARF, 11.4%), hepatic injuries (5.4%), haematological dysfunction (4.2%), seizures (3.3%), upper gastrointestinal bleed (3.3%) and cutaneous ADRs (3.3%). [5] It indicates that most of the ADRs reported in this study are in consonance with above studies. A study conducted by Rivkin [21] on adverse event leading to admission to medical ICU revealed that bleeding was the most common ADRs resulted in ICU admission. In this study also large numbers of bleeding ADRs were reported either due to drugs administered in ICU or as a reason of admission in ICU. Minor variations in observed ADRs may be due to variation in pattern of drugs prescribed to medical ICU patients.

This study also focused on causative groups responsible for detected ADRs. Highest group responsible for ADRs was fibrinolytic drugs 14 (23.73%) followed by organic nitrates 8 (13.56%). Other groups were anticoagulant drugs, antidiabetic drugs (11.86% each), antimicrobial drugs, antihypertensive drugs, antiarrhythmic drugs (10.17% each), antiplatelet drugs (3.39%) antimalarial drugs, NSAIDs and diuretics (1.69% each). Another study [22] conducted on ICU showed that ADRs were most frequently caused by the nitrates, opiates and ultra-short acting benzodiazepines. In this study most frequent causative group was fibrinoltytic agents because of the higher admission rate of cardiovascular patients such as myocardial infarction and heart failure.

Detected ADRs were also classified according to their system involvement. Coagulation and cardiovascular systems were the most common to involve with incidence rate of 16 (27.12%) and 14 (23.73%) respectively. Other affected systems were gastrointestinal (16.95%), generalised (13.56%), metabolic (10.17%), renal (5.08%) and respiratory (3.39%). Another study revealed that gastro-intestinal system was most commonly affected (26.67%) followed by blood and skin (20% each) [19]. Organ systems most commonly affected were the metabolic/hematologic (32.9%), gastrointestinal (17.8%), genitourinary (11.8%), and cardiovascular (10.5%) [23]. Systems involved in other studies are identical to this study, however some difference is there which is attributed to variation in prescribing patterns of drugs. It is obvious from above discussion that comparison of reported rates between studies is extremely difficult and, thus, any differences in rates should not be interpreted simply as reflecting differing levels of the quality of care between institutions, but more as reflecting differences between study methodologies.

Further, evaluation of ADRs was done by defining types of reactions. It indicates most common type was A with incidence rate of 42 (71.19%) followed by Type C and E with incidence rate of 08 (13.56%). Similar results were obtained by Park [10] in a study conducted on medical ICU with 74% detection of type A ADRs. This suggests that even though drugs prescribed in medical ICU are of rare category, ADRs caused by them are mainly augmented.

This study has also implemented on correlation between various risk factors and ADRs. It revealed that numbers of ADRs were increased with increase in number of drugs, age and duration of hospital stay, however statistical significant association was established only with number of drugs. Increase in number of prescribed drugs significantly increase number of potential adverse drug reaction due to drug-drug interaction [24]. A study conducted by Bemt *et al.,* [25] on risk factors for ADRs in hospitalised patients has also demonstrated significant association with number of drugs. It is clear from above studies that number of drugs is a significant risk factor. Carbonin [26] showed that age was not an independent risk factor for adverse drug events in hospitalized patients, which justifies observation of this study. Furthermore, hospital stay was strongly associated with ADRs in this study; however it was not statistically significant. This observation is in contrast to a study conducted by Graf [27] on ICU, which showed significant association. Severity assessment by modified Hartwig and Siegel's scale revealed that 34 (57.63%) were mild, 22 (37.29%) were moderate, while 03 (5.08%) were severe in nature. Similar study [19] conducted on ICU observed that 64.45% and 35.56% were the rates for mild and moderate ADRs respectively. Results of both the studies are comparable.

This study has also emphasised on treatment and outcome of reported ADRs. Amongst all ADRs 35 (59.32%) resolved without any treatment, while 20 (33.90%) resolved with treatment. On the other side 2 (3.39%) ADRs were not resolved even after treatment and 2 (3.39%) resulted in fatal outcome. Similarly, in a study done on medical ICU, Park[10] reported that 80% of the ADRs required intervention. In another study on medical ICU by Rivkin [21] 4% fatal ADRs were reported, which is higher as compared to this study. It indicates that requirement of treatment and outcome ultimately depends on type of event. This study was carried out on small number of patients and within a limited period of time, which is the limitation of this study. Further studies are warranted for better evaluation of ADRs in medical ICU.

CONCLUSION: From the results and discussion we conclude that most common ADRs at our tertiary care medical ICU were hypotension and headache. Fibrinolytic was the most common drug group responsible for ADRs. Coagulation system was the most common system involved. Incidence of ADRs was significantly increased with increased number of drugs prescribed. Most of the detected ADRs were of mild in nature. Active observation with Pharmacovigilance activity can evaluate incidence and pattern of ADRs in better way.

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CONFLICT OF INTEREST: Nil

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