

## A STUDY OF ADVERSE DRUG REACTIONS IN PATIENTS ADMITTED TO INTENSIVE CARE UNIT OF A TERTIARY CARE TEACHING RURAL HOSPITAL

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### ABSTRACT

Adverse drug reactions (ADRs) are the common problems faced in the setups like ICU where the poly pharmacy is involved in treating the patients. Control of such events is possible if the culpable drug is known or if it is identified and reported. However, reporting of adverse drug reactions still remains in its infancy for problems in many. Awareness about adverse drug reactions can decrease irrational use of medicines, poly pharmacy and adverse drug-drug interactions.

A prospective, observational and non-interventional study was conducted over a period of 18 months in medical ICU of Dhiraj hospital, Piparia with the goal to highlight the responsibility of health care professionals in preventing, identifying, diagnosis, treating and reporting ADRs. The patients were monitored daily for ADRs. The data was analyzed for demographic parameters. The causality relationship between suspected drugs and the reactions were assessed by using various standard causality assessment scales.

1000 patients were enrolled for the study. Out of these 45 patients developed ADRs. Of these 27 males and 18 females developed ADRs showing male predominance (2.7%). The ADRs increased with increasing number of drugs administered. The drug class most commonly implicated with ADRs was antibiotics 24(53.33%). The system most commonly involved with an ADR was gastrointestinal tract 26.67%. Most commonly reported reaction were hypoglycemia (13.33%) and Rash (11.11%).

### INTRODUCTION

Although health care personnel are for patient's safety, mistakes and errors inevitably occur, particularly in a complex environment such as the Intensive Care Unit (ICU) [1]. Such errors have serious implication for patients well being, are costly for safety and are a major public motivation to strive for a safer health care system [2].

One factor that influences morbidity and mortality is a harmful, unpredicted reaction to a drug, an almost daily occurrence in hospitals. The ICU has been known to be the land of polypharmacy for many years. Polypharmacy is known to increase the risk of adverse drug reaction (ADRs), drug-drug and drug-disease interaction. It has been claimed that patients taking two drugs face a 13% risk of adverse drug interactions, rising to 38 % when taking four drugs and to 82 % if seven or more drugs are given simultaneously [3].

Adverse drug reactions (ADR) can occur at any stage of the treatment. Only 25% of ADR are either unpredictable or caused by an allergic reaction. In most instances (>70%) of ADR are related to dose of drug administered [4]. The critically ill patients in ICU are more vulnerable to ADR than others. Moreover, administration of multiple drugs, a common event in ICU leads to an increased incidence of ADR [5]. The incidence is variable and has been reported to be as high as 29.7 per 100 admissions in some medical centres [6].

ADRs are complex issues, which require special attention. They involve patients, medical professionals, pharmaceutical industries, drug regulatory agencies and academic scientists. Avoidable adverse effects will be reduced by more skillful prescription by doctors after understanding their patients and their diseases.

In this backdrop the study was undertaken to;

- Measure the incidence, types and nature of ADR, drugs causing the same in patients admitted in Medical ICU at Dhiraj Hospital, a tertiary care teaching rural hospital, Piparia, Vadodara.
- Highlight the responsibility of health care professionals in preventing, identifying, diagnosing, treating and reporting ADRs.

### MATERIALS AND METHODS

A prospective, observational and non-interventional study was carried out in the medical ICU, in department of medicine, at Dhiraj

Hospital in serially admitted patients over a period of 18 months. A total of 1000 patients were enrolled and the data was analyzed statistically. Patients with ADR, as a result of drugs initiated or continued in medical ICU were included in the study while, the patients with the community acquired ADR who were treated in medical ICU were excluded. The medical ICU was visited daily. Patients drug charts, medical & nursing notes and any evidence of ADR were noted. The patients who developed ADR were closely observed.

Patients of age 18 years and above, of either sex, who stayed more than 24 hours in medical intensive care units and patients developing ADRs in the medical intensive care units was included in the study.

Patients referred by or transferred from other department, discharged or transferred to other department within 24 hours of admission, community acquired ADR patients, patients who are uncooperative and patients who are not willing to participate in study were excluded from the study.

Objective markers of ADR (e.g. laboratory results are recorded from patient file) and subjective markers of ADR for example headache, nausea, rashes etc. were identified by history and patient's examination. Suspected ADRs were classified in terms of causality, severity and probability according to WHO, Hartwig and Naranjo scale respectively. They were assessed for suitability for White card reporting and classified as either Type A or Type B. Length of stay for each patient with ADR was recorded. Whether the ADR directly increased the length of stay was also observed. Patient information about age, sex & brief medical history, information about drugs like name (brand/ingredient and manufacture), dose, route, duration of therapy, indication, and start/stop dates were recorded in case record form.

Description of adverse drug reaction like its character, localization & severity was noted. The risk factors (e.g. impaired renal function, previous exposure to suspected drug, previous allergy, and social drug use) were identified and were recorded in ADR reporting form.

The patients willing to participate in the study were explained about the purpose and method of the study in the language they understood and only those patients were enrolled, who were willing to give a written consent in the informed consent form.

Confidentiality in respect to participating patients was maintained at all levels.

#### Collection of data

Information of all the patients admitted to the medical ICU, including relevant history, examination details, investigations and drug therapy was collected and recorded in the case record form. Any adverse drug reaction observed by the investigator or treating physician was noted in the adverse drug reaction reporting form. In this study only adverse drug reactions were monitored. No observations/remarks were made on the diagnosis or management of the patient. All the patients meeting the inclusion criteria were included in the study and were serially analyzed. The study was conducted on approval of the Institutional Ethics Committee

Data obtained included the ADRs that occurred in patients of either sex, of different age groups, the type of ADRs that occurred, the incident and the body system that was affected. ADRs were graded according to WHO-UMC criteria, their severity was analysed according to Hartwig scale and probability was assessed according to Naranjo scale.

#### RESULTS

A total of 1000 patients admitted to the medical ICU in a rural hospital during the study period of 18 months were enrolled for the study. Of the enrolled patients 665 were male and 335 were female patients.

A total of 45 patients (4.5%) suffered from ADRs of different types, of which 27(2.7%) were male patients and 18 (1.8%) were female patients. When assessed according to their ages we observed that the percentage of ADR was more common in patients aged between 41-50 years which showed 31.11% of ADR, while patients between 51-60 years showed 24.44% and the elderly patients above 60 years showed 22.22% of ADR, whereas patients between 31-40 years showed 15.55% and the occurrence of ADR was observed to be least in patients with age group of 18-30 years which was 6.66% (figure 1)

In our study we observed that of the enrolled patients, 45 patients belonging to either sex suffered with ADRs, 75.5% were of type A reactions(predictable type) and 24.5% were of type B reactions(unpredictable type) (figure 2).

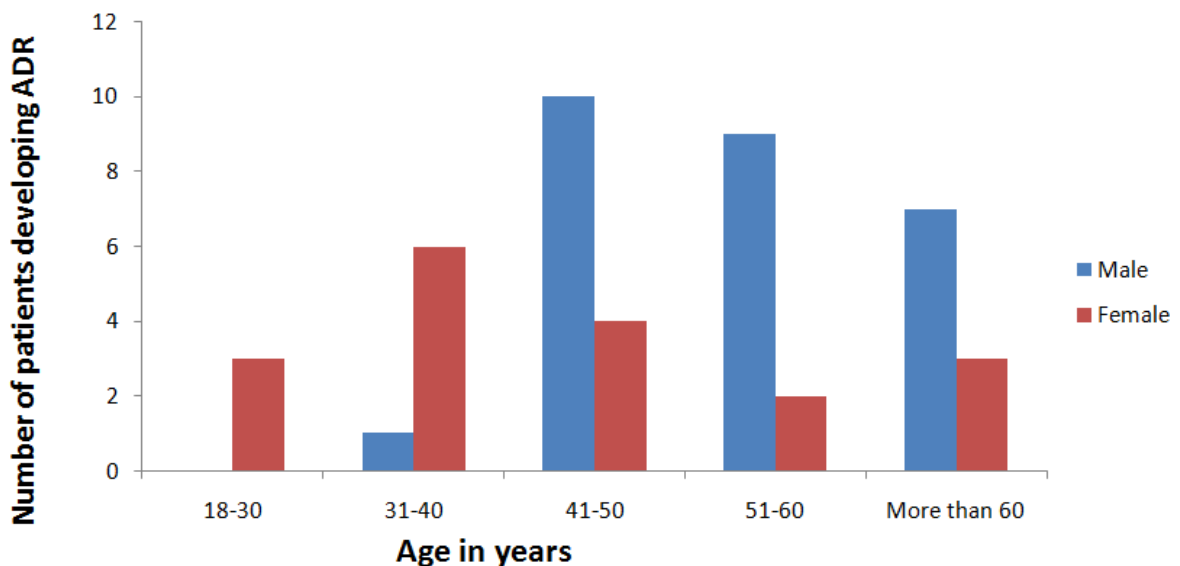


Fig. 1: Total percentage of ADRs in the patients enrolled (including both genders), grouped according to their ages.

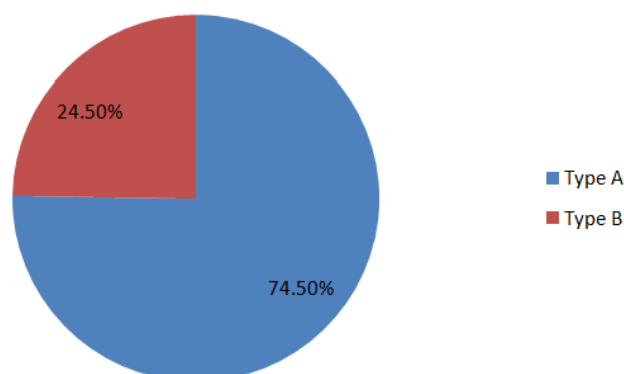


Fig. 2: Percentage of different types of Adverse Drug Reactions

We have observed that gastrointestinal system was most commonly affected (26.67%) followed by blood and skin (20% each). Other systems involved included, central nervous system (15.56%),

musculoskeletal (8.89%) and cardiovascular system (6.67%). The least system affected with adverse drug reactions was respiratory system (2.22%) (Table 1)

Table 1: System associated with adverse drug reactions

Systems involved	No. of ADRs(n=45)	Percentage (%)
Gastrointestinal	12	26.67
Blood	9	20.00
Skin	9	20.00
Central nervous system	7	15.56
Musculoskeletal system	4	8.89
Cardiovascular	3	6.67
Respiratory	1	2.22

Of the different groups of drugs that were administered to the patients at the time of treatment in the medical ICU, antimicrobials (53.33%) were the drugs which were most involved in causing adverse drug reactions, followed by antidiabetics (13.33%). Other groups involved

included, whole blood and related drugs (8.89%) each, diuretics (6.67%), analgesic (6.67%) and drugs of autonomic nervous system (6.67%). The least implicated groups were antimalarials (4.44%), laxatives (4.44%) and anti-tubercular drugs (4.44%). (Table 2)

Table 2: Drug classes and drugs involved in adverse drug reactions

Drug classes	Number of ADRs(%)	Drug classes	Number of ADRs (%)
<b>Anti microbial drugs</b>	<b>24(53.33)</b>	<b>Antidiabetic drugs</b>	<b>6(3.33)</b>
Ceftriaxone	4	Insulin	6
Levofloxacin	3	<b>Blood &amp; related drugs</b>	<b>4(8.89)</b>
Cefoperazone	2	Whole blood	2
Sulbactam	2	Streptokinase	1
Metronidazole	4	Enoxaparin	1
Amoxicillin	1	<b>Diuretic s</b>	<b>3(6.67)</b>
Doxycyclin	2	Mannitol	1
Ciprofloxacin	3	Furosemide	1
Cefotaxim	2	Torseamide	1
Ampicillin	1	<b>Analgesics</b>	<b>3(6.67)</b>
<b>Autonomic nervous system</b>	<b>3(6.67)</b>	Aspirin	2
Atropine	2	Tramadol	1
Dobutamine	1	<b>Laxatives</b>	<b>2(4.44)</b>
<b>Antimalarials</b>	<b>2(4.44)</b>	Liquid paraffin & milk of magnesia	2
Chloroquine	1	<b>Corticosteroids</b>	<b>1(2.22)</b>
Artesunate	1	Budesonide	1
<b>Vitamins</b>	<b>1(2.22)</b>	<b>Antitubercular drugs</b>	<b>2(4.44)</b>
Vitamin K	1	Pyrazinamide	1
<b>Vaccines</b>	<b>1(2.22)</b>	Cycloserin	1
Hepatitis B vaccine	1	Intravenous fluids	1(2.22)

## DISCUSSION

Adverse drug reactions (ADRs) are global problems and are of major concern, affecting patients of either sex and patients belonging to all age groups. They impose considerable economic burden on the society and the already stretched health-care systems [7]. The administered drugs can produce predictable but tolerable toxic side effects at therapeutic doses which are related to their pharmacology. In addition, unpredictable toxicity can occur which is unrelated to the pharmacological actions of these compounds. Although there are many problems which can be associated with the introduction of drugs to human bodies, ADRs represent a major drug related problems [9].

Regrettably, the adverse reactions to the medication are generally not well studied and the mechanism of some in causing the ADRs remains poorly described. The problem is further exacerbated by the inadequate training that clinicians receive in the basic principle of applied pharmacology and therapeutics. The adverse drug events may be attributable to the drugs, diagnostic agents, the biologicals, nutrients, fluids, electrolytes, a pharmaceutical excipient or even the common components of the drug delivery systems. Occasionally more than one agent is involved in causing the ADRs regardless of the route and mode of drug administration.

Often the adverse drug reactions are not recognized and go unreported. The principle limitation of ADR detection is the lack of awareness, of, what constitutes an ADR. Most of the ADRs are brought to medical attention by subjective reports and patients complaints.

Therefore it is important to determine the presence of ADRs for the following three reasons:

- 1) To take immediate action on particular patients,
- 2) To take action to prevent future accident in patients in general, and
- 3) To avoid medico-legal problems or negligence litigation.

The post marketing surveillance of drugs is very important in analyzing and managing the risks associated with drugs once they are available for the use of the general population. Spontaneous reporting of ADRs has contributed significantly to successful pharmacovigilance. The health professional's contribution in this regard, has encouraged ongoing ascertainment of the benefit risk ratio of some drugs as well as detection of unsuspected and unusual ADRs those were previously undetected during the initial evaluation of a drug. In spite of these, under-reporting of the adverse drug reactions remains a major draw-back. It is estimated that only 6-10% of all ADRs are reported. In some of the developing countries it might be very difficult to attribute the adverse reactions to a particular drug. This may be due to the cultural attitude of many people who use obscure indigenous drugs, practice self-medication, and go from one doctor to another doctor.

With multiple drugs used for the patients admitted in medical ICU, the ADRs were more common with the antimicrobial agents followed by antidiabetic medications, blood and related drugs that occurred in the form of hypoglycemia, rashes, itching, dizziness, diarrhoea, vomiting, abdominal pain, epigastric distress, joint pain etc. The elderly populations are at high risk because of the number of medications consumed, complicated drug regimens, and clinical states often presented. About 80% of elderly patients routinely take

prescription and non-prescription medications concurrently. Some patients may see multiple physicians for acute and chronic conditions, as well as obtain medication from more than one community pharmacy or mail-order pharmacy [9].

The elderly populations are at high risk because of By the causality assessment of ADRs according to the WHO criteria, that, of the 45 occurred adverse drug reactions, most of ADRs were possible (51.11%) and probable (40%) in nature and some of them were certain (4.44%).

According to severity assessment scale of Hartwig, of the 45 adverse drug reactions 35.56% of adverse drug reactions were in level-2 and level-3 each and 28.89% of adverse drug reactions were in level-1. So that 29 (64.45%) of ADRs were mild in nature while 16 (35.56%) of ADRs were moderate in nature.

According to Naranjo probability assessment criteria, out of 45 adverse drug reactions 20 (44.44%) reactions were probable, 23 (51.11%) reactions were possible and 2 (4.44%) were doubtful.

Of the reported adverse drug reactions the treatment with some of the suspected drug causing adverse drug reaction was continued (53.33%), some of the suspected drug causing adverse drug reactions were discontinued (26.67%) while for few of the drugs the dose was reduced (15.56%), none of them were replaced, while some were added with other drugs (4.44%). The culpable drugs did not leave the patients with any sequel. However, 68.89% recovered from the recorded ADRs and 17.78% were continued with treatment while consequences of 13.33% not known as patients were transferred to ward and were failed to follow up. None of the drugs causing ADR led to mortality among the recorded cases.

#### CONCLUSIONS

In this prospective, observational and non interventional study carried out in a rural hospital, suspected cases of any kind of ADR to the drugs administered during the treatment in medical ICU were independently interviewed and cases were recorded.

4.5% of patients of the enrolled patients were victims of ADR. 2.7% were male patients and 1.8% was female patients of the total

recorded case of ADR. 75.5% were predictable and 24.5% of them were unpredictable type of ADRs.

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