

**ADVERSE DRUG REACTION MONITORING AND ASSESSMENT OF CAUSALITY IN INTENSIVE CARE UNIT, IN THE DEPARTMENT OF MEDICINE AT A TERTIARY CARE HOSPITAL OF CENTRAL INDIA****Pandey Vivek¹, Singh Amita*², Singh Prabhakar³, Raj Bhupendra⁴ and Dubey Vandana⁵**¹Tutor, Department of Pharmacology, SS Medical, College, Rewa, MP-486001.²Assistant Professor, Physiology, Department of, SS Medical, College, Rewa, MP-486001.³Professor, Department of Pharmacology, SS Medical, College, Rewa, MP-486001.⁴Professor and HOD, Department of Pharmacology, SS Medical, College, Rewa, MP-486001.⁵Sr. Biochemist, Department of, SS Medical, College, Rewa, MP-486001.***Corresponding Author: Singh Amita**

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Article Received on 06/10/2018

Article Revised on 27/10/2018

Article Accepted on 16/11/2018

ABSTRACTS

Adverse drug reactions (ADRs) are considered as one among the leading causes of morbidity and mortality. **Aims & Objectives:** The aims of study are to assess the causality of suspected ADRs and their frequency & pattern in intensive care unit of medicine department. **Material and Methods:** This study was conducted between August 2015 to July 2016. All cases that have suspected ADRs conform to WHO definition, having of age 18 years or more were enrolled in the study. Total 164 cases with suspected ADRs were presented during study. The data were analyzed by Microsoft word - excel version 2007. All the multiple responses were presented in terms of number and percentage. **Results:** Total 4860 patients were admitted in medicine ICU during study period, out of which 2714 were males and 2146 were females. Maximum 49 (29.13%) patients with suspected ADRs were belong to ≥ 60 years of age and minimum 13 (6.08%) were belong to 30-39 years of age group. Gastrointestinal system is the most commonly (35.21%) involved organ system and nausea is most commonly (19.13%) reported ADR, followed by vomiting, diarrhea and skin rashes. Among the drug groups antimicrobials were associated with maximum (17.73%) ADRs followed by NSAIDs (9.56%), hypoglycemics (6.08%), steroids and others. The causality assessments of suspected ADRs were evaluated as 55.65% being probable, 43.04% as possible and 1.3% was evaluated as being definite. **Conclusion:** In our study the gastrointestinal system is the most common affected organ system; nausea is the most common ADR and antimicrobials are the drugs having highest incidence of suspected ADRs. Causality assessments ADRs were evaluated as most common (55.65%) cause was as being probable, 43.04% as possible and minimum (1.3%) was evaluated as being definite.

KEYWORDS: Adverse drug reaction (ADR), Naranjo's Probability Assessment Scale, Polypharmacy, WHO.**INTRODUCTION**

An adverse drug reaction is as defined by WHO as "a response to a medicinal product which is noxious, unintended and occurs at doses normally used in men for the prophylaxis, diagnosis or treatment of disease or for the restoration, correction or modification of physiological function."^[1] Adverse drug reactions (ADRs) are considered as one among the leading causes of morbidity and mortality.^[2] The epidemiological importance of ADR is justified by its high prevalence rate – they causes 3% to 6% of hospital admissions at any age, and up to 24% in the elderly population; they have fifth rank among the all leading cause of death and moreover, they raised 5 to 10% of hospital costs.^[3]

According to center for health policy research, more than 50% of the approved drugs in the United States were

associated with some type of adverse effects which are not detected prior to the approval.^[4] At least one ADR has been reported to occur in 10 to 20% of hospitalized patient.^[5] It has been estimated that approximately 2.9-5% of all hospital admission are caused by ADRs and as many as 35% of hospitalized patients experience an ADR during their hospital stay.^[6] An incidence of fatal ADRs is 0.23%-0.4%.^[7]

Incidence of adverse drug events (ADEs) and adverse drug reactions (ADRs) are higher in the intensive care unit (ICU) than other areas of the hospital^[8] because patients of the intensive care unit (ICU) have multi organ dysfunction as well as altered pharmacokinetic parameters. Hence patients are more susceptible to adverse drug reactions (ADRs). Several parameters like age, sex, number of drugs, type of drugs have been act as

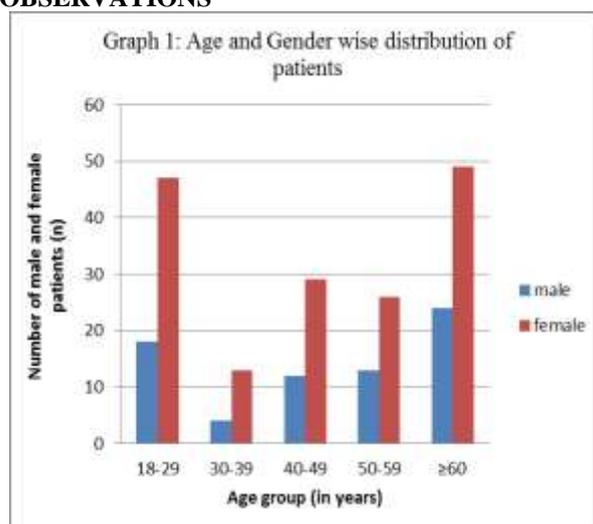
significant risk factors for the development of ADRs.^[9, 10] The ICU has been known to be the land of polypharmacy for many years. Polypharmacy is known to increase the risk of adverse drug reaction (ADRs), drug-drug and drug-disease interaction. It has been claimed that patients taking two drugs, face a 13% risk of adverse drug interactions, incidence rising up to 38% when taking four drugs and rose up to 82% if seven or more drugs are given simultaneously.^[11] The occurrence of ADRs is reported to be higher as it is influenced by various factors like age, gender, economic status, incidence and polypharmacy. Hence, this study was conducted to assess the pattern of ADRs & frequency along with causality of suspected ADRs in ICU admitted patients.

MATERIAL AND METHODS

This study was conducted after getting approval from institutional ethics committee, in the department of Pharmacology, SS Medical college and department of Medicine, Sanjay Gandhi Memorial Hospital, Rewa (M.P.) between Aug.2015 to July 2016, total 12 months of duration, to assess the incidence and pattern of ADRs and the group of drugs which are mostly associated with suspected ADRs among patients admitted in the department of Medicine. Total 164 cases with suspected ADRs were enrolled after taking their informed written consent with willingness to available for follow up. All cases that have suspected ADRs conforms to WHO's definition, having of age 18 years or more of either gender with suspected ADRs, patient with suspected ADRs developed after being admitted to the hospital or having suspected ADRs prior to being admitted in hospital. All the patients having unclear drug intake history, patient those not willing to complete the procedure, ADRs occurs due to alternative medicines like Ayurveda, Homeopathy & Unani system and patients having psychiatric illness were excluded from study. Before conducting the study; resident doctors, nursing staff and paramedical staffs were motivated to

report the suspected ADRs. Data of spontaneously reported suspected ADRs were collected by healthcare professionals. For each patient with suspected ADR, a detailed history including drug history, personal history, family history, present and past medical history and history of previous drug allergy were documented any untoward event was labeled as suspected adverse drug reaction after discussion with the treating physician. The causality of the suspected ADRs was assessed by using Naranjo's Probability Assessment Scale, in which causality is classified as definite (Score >9), probable (Score =5-8), possible (Score=1-4) and doubtful (Score=0). Data were analyses to detect any predisposing or underlying disease/pathological factors and to assess pattern, causality of suspected ADRs by using Microsoft word - excel version 2007. All the multiple responses were presented in terms of number and percentage.

OBSERVATIONS



Graph 1: Age wise distribution of patients and reported suspected ADR.

Table 1: Gender wise distribution of reported suspected ADR and its incidence.

S.no.	Gender wise distribution of patients	Numbers and percentage (%) of reported suspected ADRs	Number of patients with ADR/total number of patients admitted during the study period	Incidence of suspected ADR (%)
1	Male	106 (46.08%)	71/2714	2.61%
2	Female	124 (53.91%)	93/2146	4.33%
	Total	230 (100%)	164/4860	3.37%

Table 2: Frequency distribution of pattern of suspected ADRs reported during study period.

S.no.	Pattern of Suspected ADRs reported during study period	Number and Percentage of suspected ADRs	
		Numbers	Percentage %
1	Nausea, vomiting & Diarrhea	44	19.13%
2	Skin rashes /Pruritus	29	12.6%
3	Gastritis/GI upset/burning sensation	26	11.3%
4	Rigor& chills	19	8.26%
5	Fever	12	5.21%
6	Breathlessness	9	3.91%
7	Oral ulcers	9	3.91%
8	Dryness of mouth	8	3.47%

9	Headache	8	3.47%
10	Deranged Liver function	8	3.47%
11	Weakness & sweating (hypoglycemia)	7	3.04%
12	Constipation	6	2.60%
13	Pedal edema	6	2.60%
14	Dizziness/drowsiness/disorientation	5	2.17%
15	Oral candidiasis	5	2.17%
17	Tinnitus	5	2.17%
18	Anxiety	4	1.73%
19	Swelling of lips	4	1.73%
20	Gum hypertrophy	3	1.30%
22	Hypotension	3	1.30%
23	Palpitation	3	1.30%
24	SJS	3	1.30%
25	Altered sensorium	2	0.86%
26	Bullous eruption	2	0.86%
	Total	230	100%

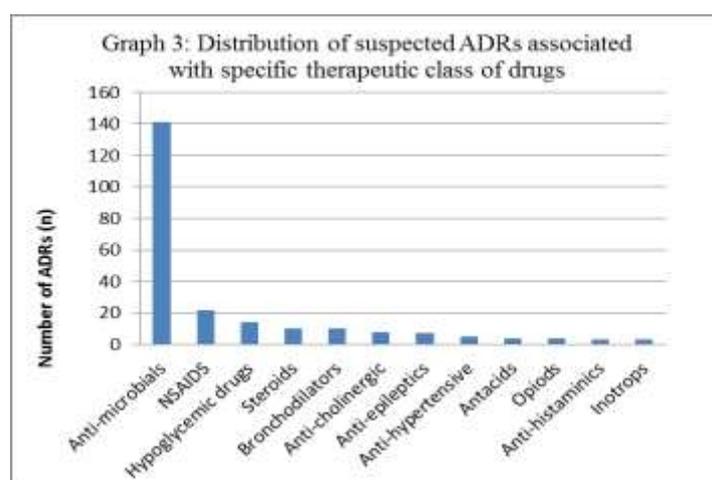


Table 3: Causality assessment of suspected ADRs according to Naranjo's Probability Assessment scale.

Sr. no.	Causality assessment of Suspected ADRs	Frequency distribution of suspected ADRs among patients					
		Number and Percentage of ADRs in male patients		Number and Percentage of ADRs in female patients		Number and Percentage of ADRs in total patients	
		Numbers	Percentage (%)	Numbers	Percentage (%)	Numbers	Percentage (%)
1	Definite	2	0.86%	1	0.43%	3	1.30%
2	Probable	61	26.52%	67	29.13%	128	55.65%
3	Possible	43	18.69%	56	24.34%	99	43.04%
	Total	106	46.08%	124	53.91%	230	100%

RESULTS

In this study total 4860 patients were admitted in medicine ICU during study period, out of which 2714 were males and 2146 were females. (Table1) Among which the maximum number (49 patients, 29.13%) of patients were belong to ≥ 60 years of age group followed by 18-29 years (47 patients, 26.52%); 50-59 years (26 patients, 20.0%); 40-49 years (29 patients, 18.26%) and minimum (13 patients, 6.08%) with 30-39 years of age group. (Graph1) Total 230 suspected ADRs were reported during study in total of 164 patients, of which 106 (46.08%) were reported in 71 males and 124 (53.91%) in 93 female patients. The overall incidence of suspected ADRs is 3.37%. (Table1) Among reported

suspected ADRs; the nausea is most commonly (19.13%) reported followed by vomiting and diarrhea, Skin rashes and pruritus (12.60%), Gastritis/GI upset and burning sensation (11.30 %), Rigor and chills (8.26%), Fever (5.21%), Breathlessness and oral ulcer (3.91%), Headache, deranged liver function and dryness of mouth (3.47%), Weakness & sweating (hypoglycemia) 3.04%, pedal edema and constipation (2.60%). Oral candidiasis, dizziness, drowsiness and disorientation (2.17 %), anxiety and swelling of lips (1.73%) whereas SJS, Gum hypertrophy and palpitation (1.30%) and altered sensorium and Bullous eruption were seen with minimum (0.86%) incidence. (Table2) Amongst different groups of drug; antimicrobials were reported with

maximum (61.30%) ADRs followed by NSAIDs (9.56%), hypoglycemics (6.08%), steroids and bronchodilators (4.34%) and anti-cholinergic drug (3.47%). Anti-epileptics were associated with 3.04%, antacids and opioids 1.73% and anti-histaminic and Inotropes were associated with minimum 1.30% ADRs. (*Graph2*) In this study Causality assessment of suspected ADRs were evaluated as 55.65% being probable, 43.04% as possible and 1.3% was evaluated as being definite. (*Table3*).

DISCUSSION

In the present study maximum number of patients (29.13%) with suspected ADRs were belong to ≥ 60 years of age group. This was similar to the spontaneous study conducted by *Jose J et al^[12]* (2006), in which significantly higher percentage of suspected ADRs were occurs among geriatric patients compare to adults. This may occur because geriatric patients have higher incidence of admission in the intensive care unit (ICU) with multi-organ dysfunction as well as altered pharmacokinetic parameters. Hence they are more susceptible to appear adverse drug reactions.^[13,14] In the present study the overall incidence of ADRs were very low (3.37%) compare to two other meta-analysis conducted by *Lazarou et al^[7]* (1998) and *Murphy BM et al^[6]* (1993) in which the incidence of ADRs were 15.1% and 35% respectively. This discrepancy could be due to relatively small sample size, inclusion of only the medicine ICU patients and also due to the under reporting of cases. The reasons for under reporting are more likely due to lack of initiative, fear of personal liability etc. The higher incidence of ADRs was seen in female population (4.33%) compare to male population (2.61%) in our study, this is similar to the study conducted by *Camargo AL et al^[13]* (2006). There are various reasons have been proposed to explain the higher incidence of ADRs in females like difference in pharmacodynamic response, drug metabolism through CYP 3A4 whose activity is higher in females than males. *Camargo AL et al^[13]* (2006). Female gender may have enhanced tissue sensitivity, lower body weight and sex related differences in pharmacokinetic parameters. Pharmacological, immunological and hormonal differences are also responsible for the higher incidences of ADRs.^[15,16,17] In our study the most commonly reported ADR is nausea, vomiting and diarrhea (19.13%) followed by skin rashes and pruritus (12.60%). This result was dissimilar to the earlier study conducted by *Jose J et al^[7]* (2006), in which the highest incidence of reported ADR was diarrhea (12.24%) and another study conducted by *Saravanan S S et al^[18]* (2014), in which diarrhea was the commonest (28.57%) reported ADR followed by skin rashes (14.28%). In our study the highest percentage (61.30%) of ADRs were reported with antimicrobials followed by NSAIDs (9.56%), and lowest (1.30%) with anti-histaminic and Inotropes, which was similar with the previous studies conducted by *Murphy BM et al^[6]* (1993); *Arulmani R et al^[19]* (2008); *Wester et al^[15]* (2007); *Gour et al^[16]* (2008);

Vora et al^[17] (2011) where most of the ADRs were associated with antimicrobials & NSAIDs. Various other studies^[20,21] also supports the results of our study in which the maximally suspected ADRs were associated with the antimicrobials. These findings probably indicate the pattern of drug usage in clinical practice. In our study the majority (55.65%) of suspected ADRs was evaluated as being probable followed by possible (43.04%) and minimum (1.30%) were evaluated as being definite according to Naranjo's Probability Assessment scale. The findings of our study is similar to *Giovanni et al^[22]*, (2006) and *Jha et al^[23]*, (2007) study.

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