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INTENSIVE MONITORING OF ADVERSE DRUG REACTION IN HOSPITALIZED PATIENTS IN A SOUTH INDIAN TERTIARY CARE HOSPITAL

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ABSTRACT

The aim of study was to describe the pattern of adverse drug reactions and evaluate the frequency, severity and preventable of adverse drug reactions from a medicine ward at tertiary care hospital. A prospective observational study was conducted for a period of 06 month. ADR profile was noted by intensive monitoring. The WHO definition of an ADR was adopted and causality assessment was determined using the Naranjo's algorithm scale. Severity and Preventability were assessed by using the criterion developed by Hartwig & Shamrock and Thornton. The overall occurrence of ADRs was observed as 19.01% (232/1220). Type A reactions accounted for 81.87% of the ADRs followed by Type B reactions (18.12%). More ADRs were observed in males when compared to females and were observed among the age group of 46 to 60 years (29.74%) frequently when compared to other groups. the most common drug class associated with ADRs were antibacterial. Gastrointestinal system was the most common organ system affected due to ADRs. The adverse drug reaction monitoring systems had their birth after the land mark event of thalidomide disaster. Use of intensive monitoring approach based on active surveillance of records might be helpful in better detection and documentation of ADRs and ensure better healthcare delivery to the patients.

Key Words:- Adverse Drug Reaction, Intensive Monitoring, Causality, Tertiary Care Hospital.

INTRODUCTION

Drugs are therapeutic tools with benefits to the patients and at sometimes they produce undesired effects along with the desired effect. Even though they are intended to cure, prevent or diagnose diseases, they can cause morbidity and mortality when improperly used. Thalidomide disaster of 1960s increased the interest in monitoring, detecting and preventing adverse drug reactions (ADRs) of drugs (Bemt & Egberts, 2007).

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Adverse drug reactions are defined as 'a response to a drug which is noxious and unintended and which occurs at doses normally used in man' (Edwards & Aronson, 2000). ADRs in hospital in-patients are generally divided into two types viz: Those who develop ADRs during hospitalization and those who are hospitalized due to ADRs. Incidence of ADR reports ranged from 1.9 to 37.3%. This wide variation was attributed to different method adopted to collect the information of ADRs (Venulet & Ten H, 1996). Two prospective studies from UK showed that 6.5% of patients were admitted to hospital due to ADRs. Although several methods are available for ADR monitoring, Spontaneous or voluntary reporting method was an important and most widely used

method of ADR reporting in the post-approval stages (Davies *et al.*, 2007; Fletcher, 1991). Chart review method was an important method for screening of medical records to identify adverse drug events due to drugs. Prospective screening of medical records is called intensive monitoring (Neale & Woloshynowych, 2003; Noren & Edwards, 2009). Screening of laboratory values is to identify any drug related adverse drug effects like a plastic anemia, hyperkalemia, hyperglycemia and hyponatremia etc. this method may be used to identify any drug induced ADRs. (Ramirez *et al*., 2010; Tavassoli *et al*., 2007). Patient interview could potentially help to identify undocumented adverse events connected to drug in the medical record (Palaian et al.2006). Irrespective of the different methods for collection and identification of patient risk factors for ADRs is essential for prevention (Blenkinsopp *et al*., 2007).present study were carried out to collect the data on ADR and use the data for further analysis of pattern, frequency, severity, and preventability of ADRs.

METHODOLOGY

A Prospective observational study was carried out in medicine department of private tertiary care hospital over the period of six months. Before initiation of the study independent ethical committee's approval was obtained (SL / IEC /10 Jan 2011). All patients who were admitted to the study wards during the study phase were included in the study. The oral informed consent was obtained from patients who were interviewed during the study phase. The researcher reviewed drug charts, medical and nursing notes of all the patients who were admitted in the study ward. The review was conducted to screen case records for the presence of any evidence of ADRs. Objective markers of ADRs, e.g. laboratory results, were identified from the case notes and the hospital computer system and the subjective markers of ADRs like headache, nausea and rash were identified through patient progress notes, discussion with the medical team and patient interview. After completion of data collection, case note analysis was performed to assess patient outcomes and to ensure that all the available details regarding the ADR had been collected. The collected data was documented separately in ADR documentation form for further assessment. An ADR alert card was provided to those patients who experienced such ADRs which by their nature cautions against re-exposure of the suspected drug. All ADRs were assessed by a panel of experts including the investigator. The panel assessed the causality, predictability and preventability using appropriate scales (Fig: 1)

Inclusion criteria

Patients of either sex hospitalized in medicine department were included.

Exclusion criteria

Patients who admitted to ward due to intentional or accidental poisoning, ADR due to fresh blood products, Drug overdose and Drug of abuse patients were excluded.

Statistical analysis

All results are expressed in absolute number and percentages (mean ± SD). Chi square test were used to find out the association between age and gender. P values of less than 0.05 were considered statistically significant.

RESULTS AND DISCUSSIONS

Patient characteristics

The total number of patients admitted in the Medicine department during the study phase was 1220. All the patients were intensively monitored by the investigator for ADRs. Over six months, a total of 320 ADRs from 232 patients (1.3 ADRs/patient) were identified and documented. Mean age (in years) of the patients was 45.95 ± 17.93. The occurrence of ADRs was more in males than in females (10.9 vs. 8.11%, χ2- 9.04, d.f.-1, $p < 0.0003$). Frequencies of ADRs among the age group of 46 to 60 years (29.74%) and 31 to 45 years (28.01%) were higher than other age groups (Table 1). Poly pharmacy was common in the study patients. Average number of drug taken by patients was 10 ± 4.50. The average length of stay of the patients was 6.06 ± 3.32 days.

Reaction characteristics

Of the 1220 patients hospitalized during the study period, 2.45 % of patients were admitted to the ward due to ADRs and the occurrence of ADRs throughout the hospital stay was 16.55% (202/1220). The overall occurrence of ADR was 19.01% (232/1220). Type A reactions were accounted for 81.87% of the ADRs followed by Type B reactions (18.12%) (Table 2). Drugs responsible for ADRs are presented in table 3. In this study most common drug class associated with ADRs was Antibacterial. Salbutamol produced the highest number of reactions (28; 8.75 %) followed by furosemide (25; 7.81%), ceftriaxone (14; 4.37%), Amlodipine (11; 3.43%) and Tramadol (10; 3.12%). The different organ systems affected due to ADRs are presented in table 4. The most common organ system affected due to ADR was gastrointestinal system (66; 20.62%). The majority of reactions were reported as vomiting (34; 10.62 %),

hypokalemia (33; 10.31%), followed by rash (30; 9.37 %), Tremor (26; 8.12%) and Dizziness (15; 4.68%).

Causality and preventability of ADRs

Using the Naranjo's algorithm, 195 (60.93%) ADRs were defined as 'probable' whereas 122 (38.12%) were defined as 'possible' and 3 (0.93%) were classified as' definite' in relation to the suspected drug. In 22.49% of cases, the reaction was considered to be preventable (definitely or probably preventable). The results are presented in Table.2. Based on the occurrence of the reaction with respect to the time of administration, 84 (26.25%) reactions were classified as acute, followed by 133 (41.56%) as sub-acute and 103 reactions (32.18%) as late onset (Table.2).

Predisposing factors

At least one predisposing factor was observed in all of these reports. Common predisposing factors like age, poly pharmacy and multiple disease state were noticed in 14.37, 66.87 and 40% of the cases respectively (Table 2). On average each patient had 3 coded diagnoses thus making multiple diseases as underlying risk factor for most of the patients.

Management and outcomes

In most (63.75%) of the patients, the suspected drugs were withdrawn from the treatment for the management of ADR and alternative treatment for the reaction was instituted in 25.31% of cases. An improvement in the ADR was observed in most (67.24%) of the cases if there was dose reduction (Table.5). The reactions were classified to mild (37.18 %), moderate (61.87%) and severe (0.93%). Outcome of the patients who had ADRs was generally good, with 263 (82.18) patients recovered from ADRs (Table.5).

Table 1. Demographic characteristic of patients

Characteristics	Number of Patients with ADR (n=232)	Number of ADR related hospitalization, (n=30)	ADR occurring during hospital stay, (n=202)
Male	133 (57.32)	26 (11.2)	107(46.12)
Female	99 (42.67)	14 (6.03)	85 (36.63)
Age group			
16-30	49 (21.12)	2(0.86)	47 (20.25)
31-45	65 (28.01)	4 (1.72)	61 (26.29)
46-60*	69 ((29.74)	12(5.17)	57 (24.56)
61-75	46 (19.82)	10 (4.31)	36 (15.51)
>76	3(1.29)	2 (0.86)	1(0.43)

*p<0.001 significantly different compared to other age groups.

Table 2. ADRs Assessment Details

Parameters	Number of ADRs (n=320)
Type of Reaction	
Type A	262 (81.87)
Type B	58 (18.12)
Causality	
Definite	3 (0.93)
Probable	195 (60.93)
Possible	122 (38.12)
Onset of ADRs	
Acute (< 1 h)	84 (26.25)
Sub-acute (1 to 24 h)	133 (41.56)
Latent (> 48 hrs)	103 (32.18)
Severity	
Mild	119 (37.18)
Moderate	198 (61.87)
Severe	3 (0.93)
Preventable	
Definitely preventable	49 (15.31)

Probably preventable	23 (7.18)
Not preventable	248 (77.5)
Predisposing Factors**	
Age	46 (14.37)
Gender (Female)	28 (8.75)
Multiple and inter-current disease	128 (40.0)
Polypharmacy	214 (66.87)

****the total number of predisposing factor was different from the total number of ADR reports.

Table 3. Drugs Involved in ADRs

Drug	WHO-ATC Code	No of ADRs (%)	ADRs (No)
Salbutamol	R03AC02	28 (8.75)	Tremor (22), Hypokalaemia(4), Constipation (2)
Furosemide	C03CA01	25 (7.81)	Hypokalaemia (25)
Ceftriaxone	J01DD04	14 (4.37)	Rash (9), Diarrhoea (3), Bronchospasm (2)
Amlodipine	C08CA01	11 (3.43)	Oedema peripheral (4)Constipation (6) Anaemia megaloblastic (1)
Clonidine	C02AC01	10 (3.12)	Hypotension(3), Dizziness(3), Headache (4)
Tramadol	N02AX02	10 (3.12)	Vomiting (6), Nausea (3), Pruritus (1)
Phenytoin	N03AB02	10 (3.12)	Allergic reaction (2), Nystagmus (2),Gastric pain (1)
Chloroquine	P01BA01	9 (2.81)	Vomiting (8), Tremor (1)
Prednisolone	A07EA01	6 (1.87)	Diabetes mellitus (1),Peptic ulcer (2), Hypertension (3)
Insulin (Human)	A10AB01	6 (1.87)	Hypoglycemia (3),Hypokalaemia (2),Vomiting (1)
Warfarin	B01AA03	6 (1.87)	Prothrombin decreased (4),Oedema (1), Allergic reaction (1)

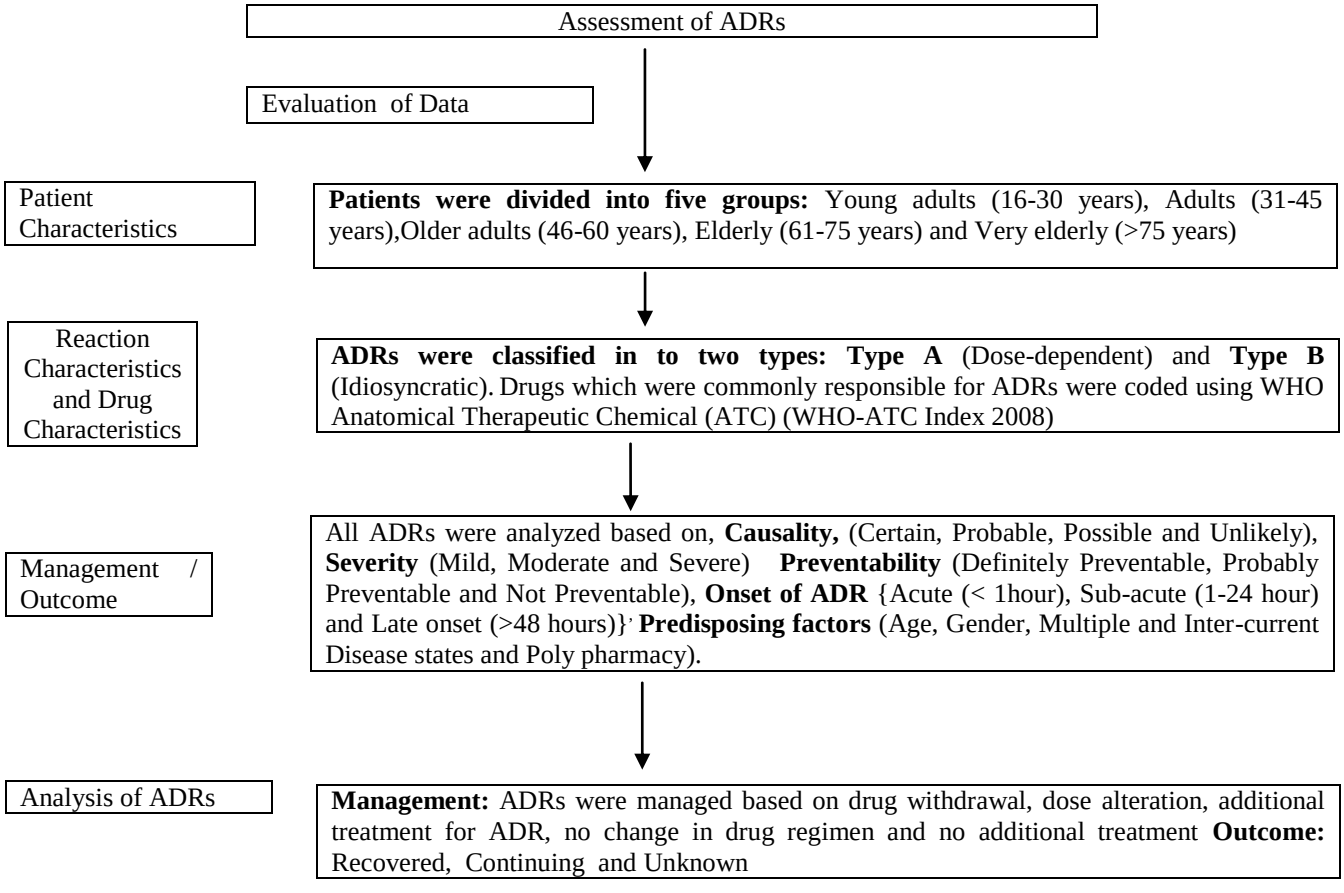
Table 4. Different Organ systems affected due to ADRs

Organ System Involved (SOC, Code) (n, %)	Observed ADRs & MedDRA Code (n, %)
Gastro-intestinal system disorders (10017947), (66, 20.62)	Vomiting (10047700), (34, 10.62), Diarrhea (10012735), (12, 3.75), Constipation (10010774) (10, 3.12), Nausea (10028813), (4, 1.25), Gastritis (10017853), (3, 0.93), Peptic ulcer (10034341), (2, 0.62), Gastric pain (10017814), (1, 0.3).
Central & peripheral nervous system disorders (10029205), (59, 18.43)	Tremor (10044565), (26, 8.12), Dizziness (10013573), (15, 4.68), Headache (10019211), (13, 4.06), Drowsiness (10013649), (3, 0.93), Hypertonia (10020852), (2, 0.62)
Skin and appendages disorders(10040785) ,(52, 16.25)	Stevens Johnson Syndrome (10042033), (2, 0.62), Urticaria (10046735), (4, 1.25), Pruritus (10037087), (2, 0.62), Rash Erythematous (10037855), (2, 0.62), Rash (10037844), (30, 9.37), Rash Maculopapular (10037868), (10,3.12), Angioedema (10000672), (2, 0.62),
Metabolic and nutritional disorders (10027433) ,(48, 15.0)	Hypokalaemia (10021018), (33, 10.31), Diabetes mellitus (10012601), (1, 0.31), Hypoglycemia (10021005), (7, 2.18) Hyperglycemia (10020639), (7, 2.18)
Body as whole - general disorders (10018065), (14, 4.37)	Oedema (10030095), (1, 0.31), Allergic reaction (10001717), (4, 1.25), Fatigue (10016256), (3, 0.93), Fever (10016558), (6, 1.87)
Heart rate and rhythm (cardiac) disorders (10007541) ,(1, 0. 31)	Bradycardia (10006093), (1, 0.31)

Table 5. Management and Outcome Details of ADRs

Management	Number (%) (n=320)
Drug withdrawn	204 (63.75)
Dose altered	20 (6.25)
Additional treatment given	81 (25.31)
No change in drug regimen and no additional treatment	15 (4.68)
Outcome	
Improved	156 (67.24)
Not improved	66 (28.44)
Unknown	10 (4.31)
Final outcome	
Recovered	263 (82.18)
Continuing	25 (7.81)
Unknown	32 (10.0)

Fig 1. Assessment of ADRs



DISCUSSION

In this study, overall incidence of ADRs was 19.01% in the study population. The incidence of ADRs of this study was higher than other studies reported from Indian institutions but these studies employed spontaneous reporting method to collect data on ADRs (Arulmani *et al*., 2008; Jose & Rao, 2006; Ramesh *et al*., 2003). Hospitalizations caused by ADRs were 2.45% in this study whereas Pirmohamed et al and Pattanaik et al reported the incidence of around 5% for ADR related admissions (Pirmohamed *et al*., 2004; Pattanaik *et al*., 2009). However, in those studies, patients from specialty care also included. Low rates of reporting frequently occur in spontaneous reporting method. However, in case of intensive monitoring the detection rate is better than spontaneous reporting system. In a recent study report indicated that they need for active surveillance system for monitoring of ADRs compared to the traditional spontaneous reporting systems which result in under reporting and often insufficient details in the report (McClure, 2009). In the present study more ADRs could be identified because of the availability of full time staff for this purpose. This showed the need for allocation of resources by the concerned hospitals to implement active surveillance/intensive monitoring programs so as to enhance the detection and possibly take steps to prevent ADRs.

The present study showed that males experienced higher incidence of ADRs when compared to females which is similar to the results of Camargo *et al.,* (2006).Several reasons have been put forth for this observed difference. Men and woman show different pharmacodynamic response to various drugs probably so with drugs having low therapeutic range (Gleiter & Gundert-Remy 1996). In others study shows that male patients were found to have more ADRs than female population. Jose & Rao reported their results based on the spontaneous reports from the entire hospital whereas in the present study the population is restricted to one unit of medicine department. This might have had some bearing on the present observation of higher number of ADRs in males. The ADRs were significantly higher with increasing number of drugs administered. In previously reported studies shown that increasing number of drugs had correlation with ADRs (Nguyen *et al*., 2006; Somers *et al*., 2003). These studies were reported from geriatric practice set up. But in our study patients all age groups had poly pharmacy suggesting the role of this factor on the development of ADRs.

Adverse drug reactions due to anti-bacterial were observed with more frequency in this study. Many previous studies have implicated anti-bacterial as the commonest class for ADRs. Cardiovascular drugs were the second most common drug class with furosemide (7.81%) being the most commonly implicated drug. The findings which were observed in the study are similar to other reported studies (Bordet *et al*., 2001). When individual drugs were considered salbutamol (8.75%) was commonly associated with ADRs in the current study. Salbutamol was mostly administered through nebulization and the ADRs noted were type 'A' suggesting the dosing problems while administering this drug. Therefore there is a need for careful titration of the dose based on the patients' tolerance.

When organ systems affected were studied, Gastro-intestinal system was the organ system most commonly affected by the ADRs with vomiting as the most common individual reaction caused mostly by anti-malarial drugs and narcotic analgesic (Tramadol). This study showed the level of gastric intolerance of patients to this class of drugs. These findings substantiate previously reported studies on gastric ADRs (Thong *et al*., 2003).

Drug withdrawal was usually the first step employed in the management of ADRs. In this study also the offending drugs were withdrawn in most of patients. This appears to be the standard practices as reported by other authors. Most of the reactions in this study were assessed as probable which is similar to the other reports. Many reactions that were classified into 'probable' could have been classified into 'definite' if the 'rechallenging' could have been conducted. It was practically impossible due to technical and ethical reasons for such studies. The most of the reactions were mild to moderate severity and these results are similar to those reported by Jose et al and Arulmani et al .Only a small percentage of reactions were severe in nature and mostly skin reactions accounted for that. ADRs were less preventable when compared to available reports (Hopf *et al*., 2008; Howard *et al*., 2003; Suh *et al*., 2000). The present study results showed that it is possible to increase the rate of detection of ADRs using intensive monitoring approach. Coupled with such enhanced detection a good reporting system will help to generate sufficient data on drug related morbidity in the Indian settings. Such data generated from Indian clinical settings will be a useful tool for clinicians for practicing safe therapeutics.

CONCLUSION

Drugs help patients by aiding in diagnosis, prevention or curing ailments but the down side is that drug itself results in morbidities either with improper use or sometimes even with proper use. In the Indian context adverse drug reaction monitoring were growing, but there

is no permanent national level comprehensive program to cover all aspects of detection, evaluation, documentation of ADRs. Documentation and analysis of ADRs provide number of valuable information on incidence, pattern, risk factors, predictors, and economic impact on health care. Use of intensive monitoring approach based on active surveillance of records might be helpful in better detection and documentation of ADRs.

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