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DETECTION, ASSESSMENT, MANAGEMENT, PREVENTION AND DEVELOPMENT OF PHARMACOVIGILANCE SYSTEM AT THE TERTIARY HOSPITAL IN INDIA

Sudershan Goud Gokari*[1]and Dr. Vinesh kumar[2]

[1]Research scholar, Department of Pharmacy, SunRise University, Alwar, Rajasthan, India,

[2]Associate Professor, Department of Pharmacy, Lal Bahadur Shastri College of Pharmacy, Jaipur, Rajasthan, India.

Abstract:

An adverse drug reaction (ADR) is an injury caused by taking a medication. ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. The aim of the present study was to detect, document, assess and report the suspected ADRs and preparation of guidelines to minimize the incidence of ADRs. This prospective-observational study was conducted in the Department of General Medicine at a 500-bedded multi-specialty medical institution which is one of the largest hospitals in Hyderabad. Of the patients who experienced ADR during the study period 61% were male and 39% were female. Causality assessment through WHO scale indicated that 42% of them were possible. Causality assessment of suspected ADRs using Naranjo's scale showed that 63% of them were probable and the rest of them categorized as possible. The severity of 45% of reactions (using Hartwig scale) was reported as moderate and 14% considered as severe. This study strongly suggests that there is greater need for streamlining of hospital based ADR reporting and monitoring system to create awareness; and to promote the reporting of ADR among healthcare professionals of the country. Measures to improve detection and reporting of ADR by all health care professionals should be undertaken, to ensure patient's safety. The present study hints that pharmacists' involvement may not only greatly increase the reporting rate but also quality of reporting. It is suggested that the most appropriate approach of medication control to minimize the incidence of ADR is screening the total medication of the individual patient by a hospital/clinical pharmacist and by taking history of allergy as well as past medication and medical history.

Keywords: *Causality assessment, Naranjo's scale, Hartwig scale*

Corresponding Author:

Sudershan Goud Gokari,

13-3-087/62/1, Bharat nagar,
jiyaguda, Hyderabad,
Telangana 500006.
Email: sudershangoudg@gmail.com

QR code

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1. INTRODUCTION:

Adverse Drug Reaction:

An **adverse drug reaction** (**ADR**) is an injury caused by taking a medication.[1] ADRs may occur following a single dose or prolonged administration of a drug or result from the combination of two or more drugs. The meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial.[2] The study of ADRs is the concern of the field known as *pharmacovigilance*. An **adverse drug event** (**ADE**) refers to any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury.[3] An ADR is a special type of ADE in which a causative relationship can be shown.

Any noxious, undesired, or unintended response to ath erapeutic agent, which may be expected or unexpected, and may occur at dosages used for theprophylaxis, dia gnosis, or therapy of disease, or for modifying physiolo gic function. ADRs do not includetherapeutic failures, poisoning, accidental or intentional overdoses. ADRs o ccur in up to 15% of all drugadministrations, but are rar ely fatal[4]. They can be divided into type A—dose-dependent or predictable—ortype B—idiosyncratic or allergic—reactions.

Clinical findings Pruritus, nausea, vomiting, rash, conf usion, lethargy, etc.Culprits ADR are most commonly caused by analgesics and narcotics, antibiotics, cardiov ascular agents,anticoagulants, and psychotherapeutics.

Regulatory process In the preapproval clinical experien ce with a new medicinal product or its newusages, parti cularly as the therapeutic dose(s) may not be establishe d, all noxious and unintendedresponses to a medicinal product related to any dose should be considered adver se drug reactions; acausal relationship between a medic inal product and an adverse event is at least a reasonabl e possibility—i.e., the relationship cannot be ruled out.

CLASSIFICATION:

ADRs may be classified by e.g. cause and severity.

Cause

1. Type A: Augmented pharmacologic effects - dose dependent and predictable

   Type A reactions, which constitute approximately 80% of adverse drug reactions, are usually a consequence of the drug's primary pharmacological effect (e.g. bleeding when using the anticoagulant warfarin) or a low therapeutic index of the drug (e.g. nausea from digoxin), and they are therefore predictable. They are dose-related and usually mild, although they may be serious or even fatal (e.g. intracranial bleeding from warfarin). Such reactions are usually due to inappropriate dosage, especially when drug elimination is impaired. The term 'side effects' is often applied to minor type A reactions.[5]
2. Type B: Idiosyncratic

   Types A and B were proposed in the 1970s,[6] and the other types were proposed subsequently when the first two proved insufficient to classify ADRs.[7]

2. MATERIALS AND METHODS:

This prospective-observational study was conducted in the Department of General Medicine at a 500-bedded multi-specialty medical institution which is one of the largest hospitals in Hyderabad. The reason for selection of the Department of General Medicine was that many studies from literature showed that a great number of Adverse Drug Reactions were seen in this department.8

The study was carried out for a period of 12 months from December 2016 to June 2017 and involved a multidisciplinary spontaneous (voluntary) reporting program that relies on both the prospective and concurrent detection of suspected adverse drug reactions and drug interactions.

All patients of either sex and of any age who developed an ADR during the above mentioned time period were included in the study and the exclusion criteria were considered as the outpatient cases, patients who developed an ADR due to intentional or accidental poisoning, ADRs due to the fresh blood/blood products, drug overdose and patients with drug abuse and intoxication[9].

The protocol of the study was approved by the Research and Bioethical Committee of the hospital. The authors were permitted to utilize the hospital facilities to make a follow up of the prescriptions in the selected department.

ADR Reporting

Adverse drug reaction reports were accepted from all the healthcare professionals of different specialties irrespective of their status and types of services offered. The reporter was not required to prove cause and effect prior to the reporting of "suspected" adverse drug reaction. Various modes of reporting system was adopted including use of ADR notification form, telephone reporting, direct access, referral of patients

and personal meeting so as to ease the reporting of "suspected" ADRs[10]. Once the suspected ADR was reported, patients' medical records were reviewed and also patients and or healthcare professionals were interviewed as appropriate to collect all the necessary and relevant data pertaining to the "suspected" ADR.

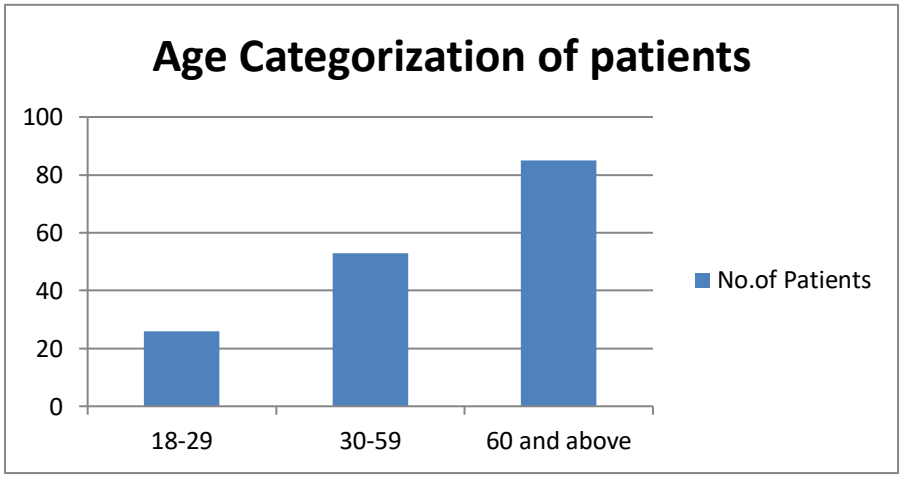
The details of data collected pertaining to the reported ADR include: description of event, suspected medication, other medications including over the counter medicines and medication on admissions, presenting complaints, past medical history, allergic status, possible involvement of risk factors of an ADR and previous exposure. Later all the collected data were further reviewed and documented in a suitably designed ADR documentation form.11 Then the reported event was subjected to evaluation, and analyzed to indicate how likely it was that the implicated drug caused the "suspected" adverse reaction.

3. RESULTS:

A total of 164 documented ADRs were identified in 2126 General Medicine ward admissions during the study period. The results of the age categorization revealed that the patients of 60 years and above age group experienced maximum ADRs which were about 52%, followed by 32% in age group between 30-59 years old and 16% in 18-29 years age group.

Table 1: Age Categorization of patients

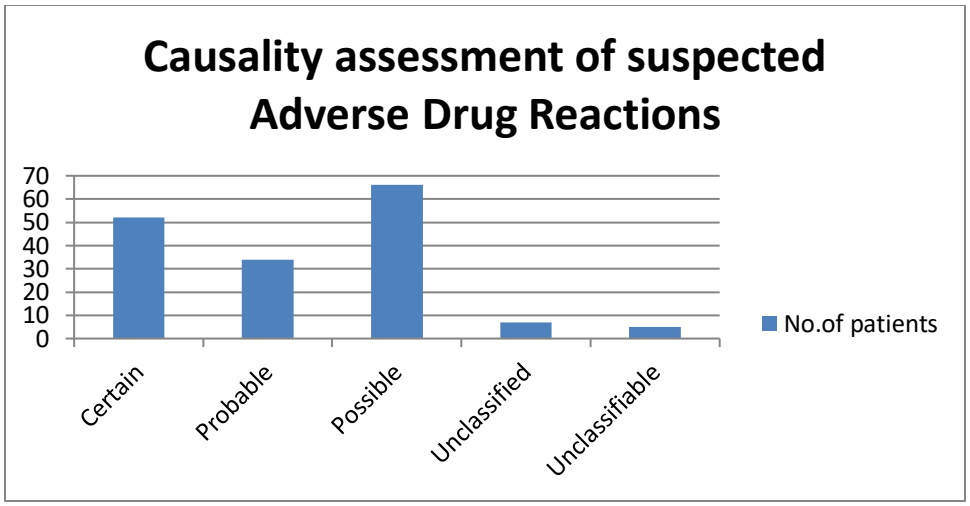
Age group	No.of Patients	Percentage
18-29	26	16
30-59	53	32
60 and above	85	52



Graph 1: Age Categorization of patients

Table 2: Causality assessment of suspected Adverse Drug Reactions (WHO scale)

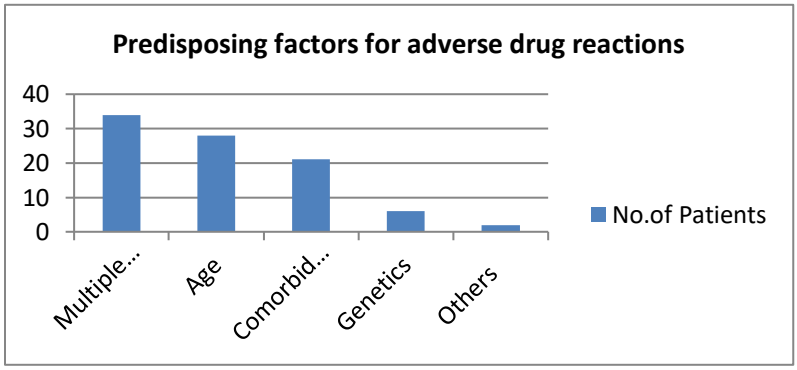
Causality Assessment scale	No.of patients	Percentage
Certain	52	32
Probable	34	21
Possible	66	40
Unclassified	7	4
Unclassifiable	5	3



Graph 2: Causality assessment of suspected Adverse Drug Reactions

Table 3: Predisposing factors for adverse drug reactions

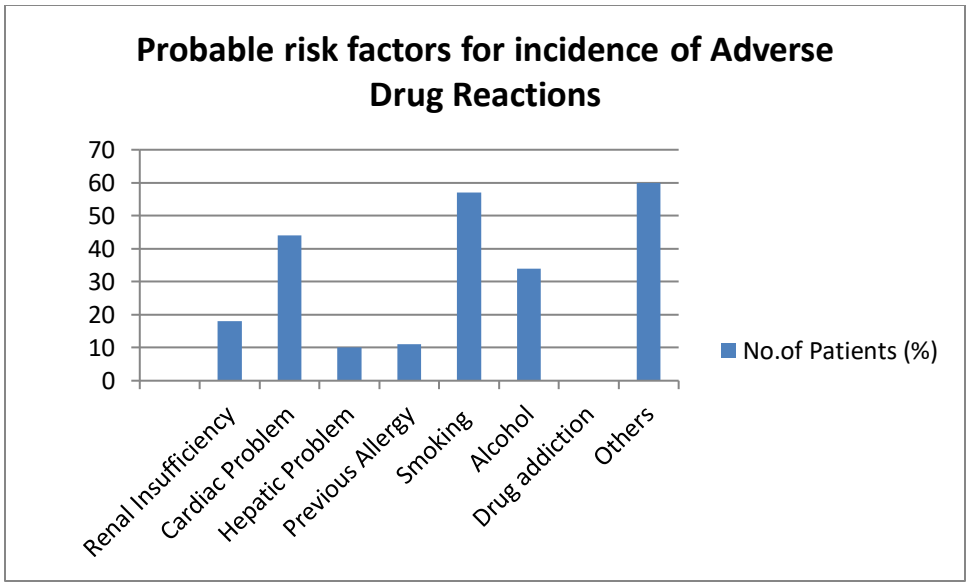
Factors	No.of Patients	Percentage
Multiple drugs	57	35
Age	46	28
Comorbid disease	32	20
Genetics	21	12
Others	8	5



Graph 3: Table 3: Predisposing factors for adverse drug reactions

Table 4: Probable risk factors for incidence of Adverse Drug Reactions

Risk Factors	No.of Patients (%)
Renal Insufficiency	18(11)
Cardiac Problem	44(27)
Hepatic Problem	10(6)
Previous Allergy	11(7)
Smoking	57(35)
Alcohol	34(21)
Drug addiction	00(00)
Others	60(37)

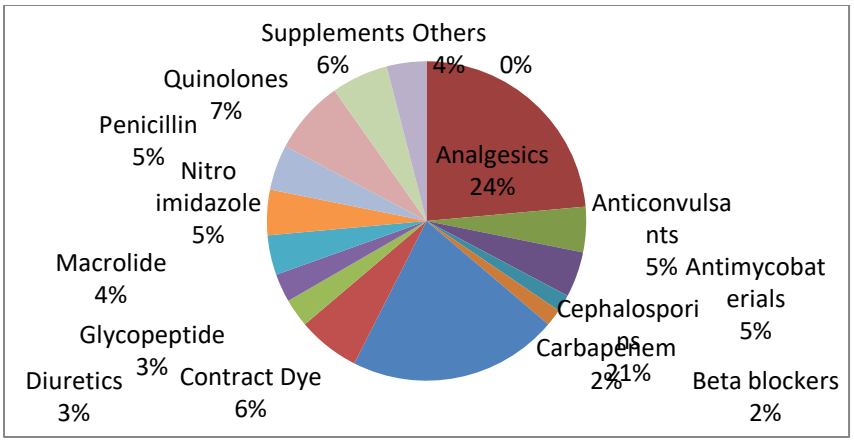


Graph 4: Probable risk factors for incidence of Adverse Drug Reactions

Of the patients who experienced ADR during the study period 61% were male and 39% were female. Causality assessment through WHO scale indicated that 42% of them were possible. Causality assessment of suspected ADRs using Naranjo's scale showed that 63% of them were probable and the rest of them categorized as possible

Table 5: Class of Drugs Associated with ADRs

Class of Drug	No.of Patients (%)
Analgesics	41(25)
Anticonvulsants	8(5)
Antimycobaterials	8(5)
Beta blockers	3(2)
Carbapenem	3(2)
Cephalosporins	37(23)
Contract Dye	11(7)
Diuretics	5(3)
Glycopeptide	5(3)
Macrolide	7(4)
Nitro imidazole	8(5)
Penicillin	8(5)
Quinolones	13(8)
Supplements	10(6)
Others	7(4)

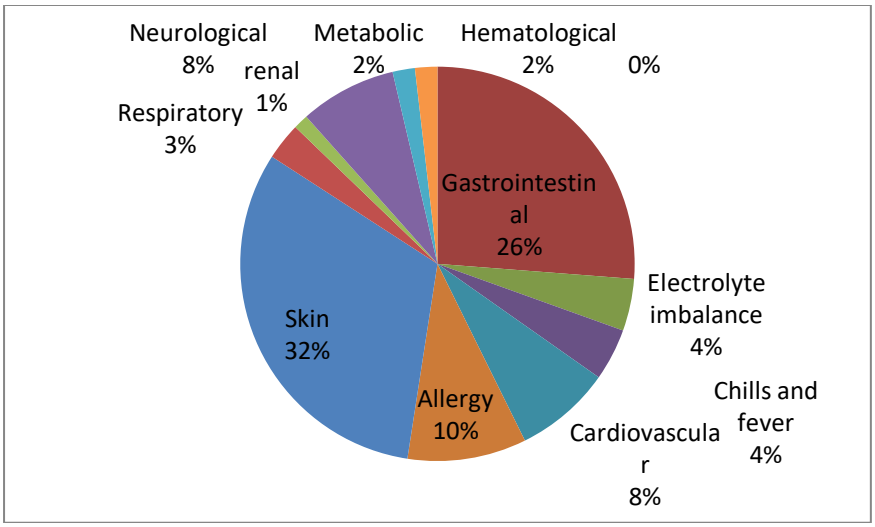


Graph 5: Class of Drugs Associated with ADRs

In our retrospective study ADRs were commonly associated with Analgesic (25%) followed by Cephalosporins (23%), Quinolones (7%) and Contrast Dye (6%). Our prospective study shows that ADRs were most common in Chemotherapy (33.3%) followed by Fluroquinolones and Sympatholytics (11.1%).

Table 6: Organ Systems Affected by ADRs & commonly Occurring Reactions

Organ System Affection	No.of Patients (%)
Gastrointestinal	43(26)
Electrolyte imbalance	7(4)
Chills and fever	7(4)
Cardiovascular	13(8)
Allergy	16(10)
Skin	52(32)
Respiratory	5(3)
renal	2(1)
Neurological	13(8)
Metabolic	3(2)
Hematological	3(2)



Graph 6: Organ Systems Affected by ADRs & commonly Occurring Reactions.

Our retrospective data shows the organ systems most commonly affected by ADRs were Skin (32%) followed by Gastrointestinal System (26%), Allergies (10%) and Neurological (8%). Our prospective analysis shows that Skin (11%) and Gastrointestinal system (7%) predominance.

4. DISCUSSION:

The incidence of suspected ADRs was found to be 1.82% and is comparable with the study done by Rao et al,[3] which evaluated the reports of ADRs in the inpatients at a south Indian hospital for their incidence and pattern and found that the incidence of ADRs was 2.8% in hospitalized patients. Pirmohamed et al[12] concluded from a prospective analysis of about 18,820 patients in UK in which about 1225 admissions were related to ADRs giving a prevalence of 6.5%. This is consistent with the findings of Arulmaniet al [10].

Pirmohamed et al have shown a greater percentage of geriatric population suffering from adverse reactions which is consistent with the present results that mentioned before [11].

According to the present findings the ADRs in the hospital patients were more documented in males which is consistent with the earlier report by Gupta et al. Sex ratio in admitted patients might be an intervening factor but does not seem to be a major determinant.

Causality assessment was done by using WHO and Naranjo scale. The assessment done by using WHO scale reveals that 42% of ADRs were possibly drugrelated, 23% of ADRs were probably drug-related, whereas 30% were classified as certainly related to drug. Assessment by Naranjo scale showed that 63% of ADRs were possibly drug-related, whereas 37% were classified as probably or definitely related to the drug. These results matches with Davies et al[15] study which had assessed the feasibility and established the methodology for conducting a large prospective study to fully assess the impact of ADRs on inpatients. Causality assessment showed that 62% of ADR were possibly drug-related whereas 32% were classified as probably or definitely related to the drug and almost two-thirds of reactions were potentially avoidable.

Severity of the suspected ADRs assessed using Modified Hartwig and Siegel Scale, revealed that 12% of suspected ADRs were severe, 49% of ADRs were moderate and 39% of ADRs were mild in severity. These were comparable with the review conducted by Shuster [13] in reporting ADR from the Institute of Safe Medication Practices (ISMP) in cooperation with the FDA's MEDWATCH program during the month of June 2005 in a 200-bedded community hospital which reported 36 distinct admissions due to ADRs, with 9% of the cases categorized as severe, and 76% of the events were regarded as moderate.

Systems most commonly affected were gastrointestinal in 37% of patients, dermatological in 25% of patients, central nervous system in 14% of patients, followed by cardiovascular in 12% of patients. The results were comparable with an international study conducted by Suh et al, which revealed that the system most badly affected was the dermatological and gastrointestinal system. [14]. The drug class mostly associated with ADR was antibiotics in 23% of cases, followed by

NSAIDs in 19% in the present study. Murphy and Frigo developed and implemented an ADR reporting program in Loyola University Medical Center, a 563-bed tertiary care teaching hospital located in the western suburbs of Chicago. This study revealed that the most common adverse reactions were rash; and antibiotics were the most commonly implicated drug class. The results were also comparable with other studies like one done by Classenet al which indicated that NSAIDs have caused extensive damage to human health.

Preventability of suspected ADRs were assessed by using Modified Schumock and Thornton scale, revealed that 28% of ADRs were definitely preventable while 7% of ADRs were probably preventable. This study revealed that an increased risk of ADRs is suspected in elderly patients, and that almost one-thirds of reactions were preventable. Knowledge of pharmacological principles and how aging affects drug kinetics and response were essential if we are to promote safe prescribing practices.

The provision of "alert card" was aimed at preventing the occurrence of the similar ADR to the same drug and/or other drug(s) belonging to similar class or other classes of drugs which shows cross sensitivity reaction with suspected drug(s) in the same patient in the future.

Under-reporting is a major problem even in western countries where the pharmacovigilance system is well established. In India the major problem is a lack of proper system of pharmacovigilance. Our ability to anticipate and prevent such ADRs can be facilitated by the establishment of standardized approaches and active reporting of suspected ADRs by all healthcare professionals including physicians, dentists, nurses and pharmacists. This could be further improved by pharmacist involvement for encouraging them through conducting educational programs on pharmacovigilance, lectures, newsletters, personalized letters, etc to aid and increase reporting of ADR.

5. CONCLUSION:

This study strongly suggests that there is greater need for streamlining of hospital based ADR reporting and monitoring system to create awareness; and to promote the reporting of ADR among healthcare professionals of the country. Measures to improve detection and reporting of ADR by all health care professionals should be undertaken, to ensure patient's safety. The present study hints that pharmacists' involvement may not only greatly increase the reporting rate but also quality of reporting. It is suggested that the most appropriate approach of medication control to minimize the incidence of ADR is screening the total medication of the individual patient by a hospital/clinical pharmacist and by taking history of allergy as well as past medication and medical history. Hospital/clinical pharmacists have also a greater role to play in the area of pharmacovigilance to strengthen the national pharmacovigilance program. Developing and maintaining electronic documentation of patients' medical records may serve as a valuable tool to detect early signals of potential ADRs. In addition, creating intranet facilities within a hospital may help in easy access for healthcare professionals to updated patients' medical records resulting in possible detection and prevention of ADRs. Also, the implementation of a computerized reporting system in hospital setup may hasten reporting of ADRs and is suggested.

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