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DETECTION, ASSESSMENT, MANAGEMENT, PREVENTION AND DEVELOPMENT OF PHARMACOVIGILANCE SYSTEM AT THE TERTIARY CARE HOSPITAL IN INDIA- AN INTERIM ANALYSIS

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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 55% were male and 45% were female. Causality assessment through WHO scale indicated that 38% of them were possible. Causality assessment of suspected ADRs using Naranjo's scale showed that 59% of them were probable and the rest of them categorized as possible. The severity of 38% of reactions (using Hartwig scale) was reported as moderate and 18% 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*

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INTRODUCTION:

Adverse medication reaction:

An **adverse medication reaction** (**ADR**) is a damage caused by taking a medication.[1] The ADRs is the concern of the field known as *pharmacoviqilance*. An **adverse medication event** (**ADE**) refers to any damage caused at the time a medication is used, whether or not it is identified as a cause of the damage.[1]

An ADR is a special type of ADE in which a causative relationship can be shown. ADR are most commonly caused by analgesics and n arcotics, antibiotics, cardiovascular agents, anticoagulants, and psychotherapeutics2.

Types of medication reactions:

Dose-related adverse medication reactions represent an exaggeration of the medication's therapeutic effects. For example, a person taking a medication to reduce high blood pressure may feel dizzy or light-headed if the medication reduces blood pressure too much. A person with diabetes may develop weakness, sweating, nausea, and palpitations if insulin or an oral antidiabeticmedication reduces the blood sugar level too much. This type of adverse medication reaction is usually predictable but sometimes unavoidable. It may cause if a medication dose is too high, if the person is unusually sensitive to the medication, or if another medication slows the metabolism of the first medication and thus increases its level in the blood Dose-related reactions are usually not serious but are relatively common.

Allergic medication reactions are not dose-related but require prior exposure to a medication. Allergic reactions develop when the body's immune system develops an inappropriate reaction to a medication (sometimes referred to as sensitization). After a person is sensitized, later exposures to the medication produce one of several different types of allergic reaction. Sometimes doctors do skin tests to help predict allergic medication reactions.

Idiosyncratic adverse medication reactions result from mechanisms that are not currently understood. This type of adverse medication reaction is largely unpredictable. Examples of such adverse medication reactions include rashes, jaundice, anemia, a decrease in the white blood cell count, kidney damage, and nerve damage that may impair vision or hearing. These reactions tend to be more serious but typically cause in a very small number of people. Affected people may have genetic differences in the way their body metabolizes or responds to medications.

Some adverse medication reactions are not related to the medication's therapeutic effect but are usually predictable, because the mechanisms involved are largely understood. For example, stomach irritation and bleeding often cause in people who regularly use aspirin or other nonsteroidal anti-inflammatory medications (NSAIDs). The reason is that these medications reduce the production of prostaglandins, which help protect the digestive tract from stomach acid

The aim of the present trial was to detect, document, assess and report the suspected ADRs and preparation of guidelines to minimize the incidence of ADRs.

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]

METHODOLOGY:

Present trial was to estimate the prevalence of adverse medication reactions at a private tertiary care hospital. This prospective-observational trail 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 Medication Reactions were seen in this department.4

The trail 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 medication reactions and medication interactions.

All patients of either sex and of any age who developed an ADR during the above mentioned time period were included in the trail 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, medication overdose and patients with medication abuse and intoxication.

The protocol of the trail 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 medication 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 medication 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. 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.1 Then the reported event was subjected to evaluation, and analyzed to indicate how likely it was that the implicated medication caused the "suspected" adverse reaction.

Designing of ADR Reporting System

ADR Notification Form

As a first step to the implementation of ADR reporting and monitoring system, a suitable "ADR notification form" (internationally known as "Yellow card") was designed [Figures 1(a) and 1(b)]. This was prepared based on a format similar to the "Yellow card" of the Committee on Safety of Medicines (CSM),7 and United Kingdom (UK) and Australia's Adverse Medication Reaction Advisory Committee's (AD-RAC) "Blue card",7 with necessary changes, to suit the present trail. This notification form contained only the basic and essential information such as patient demographic details, information about the suspected medication, description of event.

ADR Documentation Form

Similarly, a suitable ADR documentation form was designed to gather and document as much relevant data as possible pertaining to the reported reaction. The ADR documentation form was tailormade by the authors according to the need. The designed ADR documentation form contained the specific details regarding patient demography, description of event, medications suspected, medication used prior to the reaction with their complete dosing regimens, comorbidities, risk factors involved, patient allergic status, causality category, severity, predictability, preventability, management of reported adverse reaction, outcome of management and follow up details.

A "thank you note" was specially designed and basically meant to thank the reporters for participating in the program and also acknowledge the receipt of the report. Further, the information regarding percentage incidence, mechanism and management of reported ADRs were provided and personalized to each reporter with information pertaining to the ADR reported by the individual.

An ADR "alert card" was designed and provided to patients who developed an ADR. The "alert car"′ was designed on a similar format as that used in other countries like Australia. The "alert card" provided the details of suspected ADR, suspected medication, and date of onset of reaction on one side while other side of the "alert card" contained the demography and address of the patient. The size of the "alert card" was handy and had the appearance of a visiting card

Criteria for Reportable ADR

In the present trail, the World Health Organization (WHO) definition of an ADR was adopted as a criterion for reporting any suspected reaction. The WHO defines an adverse medication reaction as "one which is noxious and unintended, and which causes at doses used in man for prophylaxis, diagnosis or therapy of disorder, or for the modification of physiological function.1"

Assessment of ADR Reports

All the reported events were evaluated, after collecting adequate data from appropriate sources, as to explore the likely involvement of suspected medication in causing the reported event. In assessing the causality, concerned clinician and/or unit chief

opinion was obtained. After having assessed the causal relationship between the suspected medication and the adverse reaction, irrespective of their causality category, the reports were subjected to further analysis including their severity, predictability and preventability of reported reactions.

Causality Assessment

The causality relationship between suspected medication and reaction was established by using WHO and Naranjo's causality assessment scales. The causality of reported reactions was categorized to any one of the following categories based on the scale used:

WHO Assessment Scale:8 Certain, probable, possible, unassessable/unclassifiable, unlikely, conditional/unclassified.

Naranjo's Assessment Scale:9 Definite, probable and possible;

Assessment of Severity

The severity of reported reactions was assessed by using Hartwig scale10 and was categorized into mild, moderate and severe.

Assessment of Predictability

The predictability of the reported ADRs was assessed by using developed criterion for determining predictability of an ADR and was categorized as predictable or not predictable based on the incidence rate of reported adverse medication reaction.

Assessment of Preventability

The preventability of reported ADRs was assessed by using Modified Schumock and Thornton scale11 and was categorized as definitely preventable, probably preventable and not preventable. When an event was reported, all patients who experienced an ADR were followed from the day of reporting of an ADR until the discharge of patients to gather updated information regarding the changes and the progress in the patients' condition and management. Also, at the time of discharge "alert card" was provided to those patients who met the criteria for the issue of alert card.

Feedback to Reporters

Feedback on reported adverse medication reaction was provided to all reporters after analyzing the reported reaction. The feedback was personalized to each reporter with all necessary information pertaining to the reported ADR such as its percentage incidence, mechanism of ADR and management of reported adverse medication reaction. The feedback on reported ADR was provided by means of issue of "thank you note".

Reporting Suspected ADRs

The suspected ADRs were reported to the pharmacovigilance center through online and by direct mailing also.

RESULTS:

A total of 50 documented ADRs were identified in 117 General Medicine ward admissions during the trial period. The results of the age categorization revealed that the patients of 60 years and above age group experienced maximum ADRs which were about 56%, followed by 33% in age group between 30-59 years old and 11% in 18-29 years age group.

Table 1: Age Categorization of patients

Age group	No.of Patients	Percentage
18-29	4	08
30-59	15	30
60 and above	31	62

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

Causality Assessment scale	No.of patients	Percentage
Certain	16	32
Probable	12	24
Possible	19	38
Unclassified	2	4
Unclassifiable	1	2

Table 3: Predisposing factors for adverse medication reactions

Factors	No.of Patients	Percentage
Multiple medications	32	74
Age	30	50
Comorbid disorder	19	38
Genetics	4	13
Others	4	6

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

Risk Factors	No.of Patients (%)
Renal Insufficiency	4(10)
Cardiac Problem	25(50)
Hepatic Problem	2(4)
Previous Allergy	3(6)
Smoking	18(36)
Alcohol	13(25)
Medication addiction	00(00)
Others	19(38)

Of the patients who experienced ADR during the trail period 55% were male and 45% 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 59% of them were probable and the rest of them categorized as possible. The severity of 49% of reactions (using Hartwig scale) was reported as moderate and 12% considered as severe. On the basis of Modified Schumock and Thornton scale, 16 (28%) and 4 (7%) reactions of the suspected ADRs were definitely and probably preventable, respectively. In 18 (37%) of cases the ADR was managed by withdrawal of medication and in 10 (21%) patients the dose of medication was altered. While in 12 (25%) of cases the severity of ADR was safely decreased, 37 (75%) patients recovered from the reaction. No fatal cases were reported. Dechallange was done in 18 (37%) and the affected patients were not subjected to rechallenge. Multiple medication therapy, age and comorbid disorders were identified as the major predisposing factors for causerence of ADRs. The major risk factors for causing ADRs were identified as cardiac problems, smoking, alcohol intake, etc.

DISCUSSION:

The incidence of suspected ADRs was found to be 1.82% and is comparable with the trail 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 Arulmani et al. [13].

Pirmohamed et al have shown a greater percentage of geriatric people suffering from adverse reactions which is consistent with the present results that mentioned before [12].

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 [14]. 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 medication related, 23% of ADRs were probably medication-related, whereas 30% were classified as certainly related to medication. Assessment by Naranjo scale showed that 59% of ADRs were possibly medication-related, whereas 37% were classified as probably or definitely related to the medication. These results matches with Davies et al[15] trail which had assessed the feasibility and

established the methodology for conducting a large prospective trail to fully assess the impact of ADRs on inpatients. Causality assessment showed that 59% of ADR were possibly medication-related whereas 37% were classified as probably or definitely related to the medication 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 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 trail conducted by Suh et al, which revealed that the system most badly affected was the dermatological and gastrointestinal system. The medication class mostly related with ADR was antibiotics in 23% of cases, followed by NSAIDs in 19% in the present trail. 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 trail revealed that the most common adverse reactions were rash; and antibiotics were the most commonly implicated medication class [15]. The results were also comparable with other studies like one done by Classen et 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 trail 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 medication kinetics and response were essential if we are to promote safe prescribing practices.

The provision of "alert card" was aimed at preventing the causerence of the similar ADR to the same medication and/or other medication(s) belonging to similar class or other classes of medications which shows cross sensitivity reaction with suspected medication(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.

CONCLUSION:

This trial 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 trial 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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