ADR ASSESSMENT AND PREVENTION IN TERTIARY HOSPITAL OF INDIA

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Abstract

Drug is beneficial for the treatment, prevention or diagnosis of disease. However, adverse drug reactions (ADRs) associated with the use of drugs are also very common. Due to the lack of knowledge and awareness, many adverse incidents due to a drug remain unnoticed. Present study was conducted to evaluate the prevalence of adverse drug reactions in a tertiary care hospital. In order to ensure a better treatment regimen and improve patients' compliance, it is essential to reduce and prevent adverse drug reaction. Implementation of pharmacovigilance programs in the hospitals is thus essential to enhance the awareness regarding early detection, reporting, management and further prevention of Adverse Drug Reactions. 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. 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.

Keywords: *Drug, adverse drug reactions, pharmacovigilance, department of general medicine, multi-specialty, monitoring system*

Introduction

Adverse drug events (ADEs) or adverse drug reactions (ADRs) are hazardous to patients and contribute to an increase in morbidity and overall mortality. ADRs are difficult to identify as they are seen in certain groups of people in some conditions and may be seen after long-term exposure. This is why all drugs, before their release into the market, undergo rigorous clinical trials to discover potential ADRs before selling the products but are limited in numbers. As a result, post-marketing surveillance is required to help discover adverse drug reactions after the drugs are available on the market. The per-hospital admission prevalence for adverse events varies from 2.9% to 16.6%. There is a need to identify interventions for detecting and reducing medical errors and adverse events. The traditional ADR classification includes type A (pharmacologic) or type B (idiosyncratic) reactions. The former makes up to 90% of all ADRs and is known due to the drug's pharmacological properties. The latter is related to hypersensitivity reactions and can account for 10-15%. As per expert opinion, most of this could be related to inflammation or immunologic mechanism. The onset of action needs to be studied (immediate vs delayed).

Immunologic drug reactions are classified as Type I, II, III and IV. Type I reactions usually start within an hour and are related to IgE antibodies. But some reactions can appear after an hour if the drug is given orally, and food also affects the absorption of the drug. Among delayed reactions are those that arise after an hour, most of which begin after six hours and some after many days of treatment. Here, antibodies (IgG or IgM) are directed against cellular antigens, resulting in cellular destruction and tissue damage. Type I reaction signs can be due to vasoactive mediators released by mast cells [3]. The most typical reaction is a rash, and the most severe is anaphylaxis. The timing of onset of Type 1 reaction is rapid but varies with the presentation. Type II and Type III are rare and are mediated by IgG/IgM. Type III reactions are mediated by antigen-antibody complexes and can present as drug fever. Type IV reactions are not mediated by antibody response and are delayed; hence are termed delayed-type hypersensitivity reactions

Adverse Medication Reaction Terms and Definitions

Adverse Medication Reaction (ADR)

A reaction to a medication that is noxious and unintended and happenss at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for modification of physiological function (WHO)

An appreciably harmful or unpleasant reaction, affected by an intervention related to the use of a medicinal product, which predicts hazard from future administration and war- rants prevention or specific managment, or alteration of the dosage regimen, or withdrawal of the product (Edwards)

Any unexpected, unintended, undesired, or excessive reaction to a medication that requires discontinuing the medication (therapeutic or diagnostic), requires changing the medication therapy, requires modifying the dose (except for minor dosage adjustments), necessitates admission to a hos- pital, prolongs stay in a health care facility, necessitates supportive managment, importantly complicates diagnosis, negatively affects prognosis, or outcomes in temporary or permanent harm, disability, or death (ASHP)

Harm directly affected by a medication at normal doses (Ed- wards)

Adverse Medication Event (ADE)

Any untoward happens rence that may present in the course of management with a pharmaceutical product but that does not necessarily have a causal relation to the management (WHO)

Injuries affected by medical interventions related to a medication.

Adverse medication events may outcome from medication faults or from ADRs in which there was no error (Bates)

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or expected from characteristics of the medication (Cobert)

Serious Adverse Effect

Any untoward medical happens that at any dose outcomes in death, requires hospital admission or prolongation of existing hospital stay, outcomes in persistent or important disability/incapacity, or is life threatening (Edwards)

Signal

Reported information on a possible causal relation between an adverse event and a medication, the relation being previously unknown or incompletely documented.

Medication Error

Any preventable event that may cause or lead to in-appropriate medication use or sufferer harm while the medi- cation is in the control of the health care professional, sufferer, or consumer (NCC MERP)

Faults in the process of ordering or delivering a medication, regardless of whether a damage happens or the potential for damage was present (Bates)

Inappropriate use of a medication that may or may not outcome in harm

PREVENTION

Prevention of adverse medication reactions requires familiarity with the medication and potential reactions to it. Computer-based analysis should be used to check for potential medication interactions; analysis should be repeated whenever medications are changed or added. Medications and initial dosage must be carefully selected for the elderly If sufferers develop nonspecific symptoms, ADRs should always be considered before beginning symptomatic management

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 antidiabetic medication reduces the blood sugar level too much. This type of adverse medication reaction is commonly predictable but sometimes unavoidable. It may happen if a medication dose is too high, if the person is uncommonly 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 commonly 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 outcome 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 happens in a very small number of people. Affected people may have genetic differences in the way their body metabolizes or responds to medications.

Methodology

The population of India is too large to study in its entirety, so an attempt was made to select the representative sample of our total population. So instead of every unit of the population

only a part of the population was studied and the conclusions were then extrapolated to the entire population.

Estimating a statistically valid sample size, in absence of any past data on similar studies at National level was very challenging especially for a country like India with a very huge population. Hence it was decided to label this study as a pilot exploratory study. In this highly populated country, to estimate number of people with at least one disease was again a challenge. Hence it was decided to estimate the sample sizes for group of Medical Practitioner, Patients and Experts as follows:

(a) Medical Practitioners

Following assumptions were used to estimate the size of MPs to be included in the survey:

1. ADR reporting rate in India = 20%
2. Accepted Error Margin = 5%
3. Level of significance@ (a) = 5%
4. Power$ of test/ study= (1-13) = 80%

@ = Level of significance is probability of making type I error that is rejecting the null hypothesis (hypothesis of no difference) when in reality it is true (that is when really there is no difference). This level is denoted by Greek letter (a) and generally the accepted level of significance is 5% that is a= 0.05 $ = Power of test I study is probability• _of accepting false the null hypothesis (hypothesis of no difference) when in reality it is not true (that is when really there is a difference). This power is denoted by an expression (1- 13) and generally the accepted power is 80%. ~ is the probability of making type II error accepting false null hypothesis which is _generally kept at minimum at 20% or below.

Sample size results

Assumptions :

Precision = 5.00%

Prevalence = 20.00%

Population size =1000000000

95% Confidence Interval specified limits [15% -- 25%] (these limits equal prevalence plus or minus precision)

Estimated sample size:

n = 246

The sample size of medical practitioners estimated works out to 246 - 250 per region. It is planned to contact 1000 doctors from 4 regions, namely north, east, west and south.

(b) Patients

For the ease of logistics, it was pla.rined to contact about 6 patients at the clinic of each medical practitioner included in MPs survey to make size of 6000 valuable patients.

Methods of Sampling

Based on the list of medical practitioners available from contacts of researcher and guide, in pharmaceutical industries and in associations of medical practitioners, lists of potential medical practitioners from each of the four regions of India were prepared. From these lists of medical practitioners for each region about 400 medical practitioners were randomly selected from within each region with an idea to contact maximum possible but not less than at least 250 MPs as estimated above from each region.

(a) Medical Practitioners

The list of these 1600 MPs was subjected to IT program I code for identifying duplicate names, if any. The repeat I duplicate names were excluded. This exclusion resulted in providing a list of 1365 unique MPs from 4 zones. These MPS were not evenly distributed in 4 zones, hence names of some MPs were deleted from 2 zones where the number of MPs was above 300. Thus, a total of 1200 doctors with a distribution of 300 from each zone were included in the survey.

(b) Patients

• About 6 patients were targeted for survey of patients. from each clinic for ease of having captive patient population. These 6 patients were identified during visit to MP'sclinic. However, by the time the interview with•MP used to get over, about 4-5 patients were available for interview.

The available number of patient$ during the visit to clinic was interviewed immediately after the completion of MP'sinterview.

(c) Experts- ADRIPV Centres or others

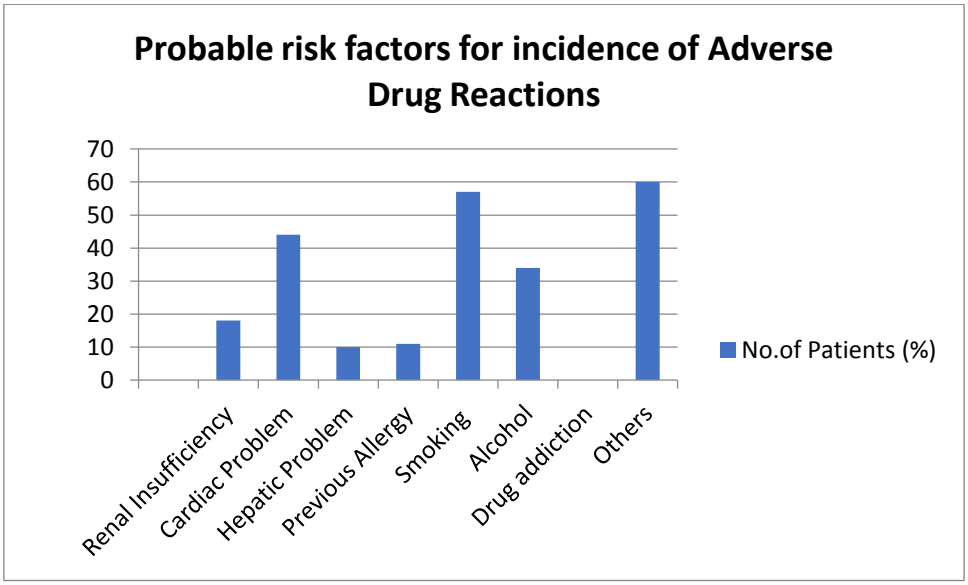
It was planned to contact at least one expert from each of 32 centres involved in Pharmcovigilance. However, during the study period we could contact experts from only 15 centres (about 50%)

Results and discussions

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: 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. The severity of 45% of reactions (using Hartwig scale) was reported as moderate and 14% considered as severe. On the basis of Modified Schumock and Thornton scale, 46 (28%) and 13 (8%) reactions of the suspected ADRs.

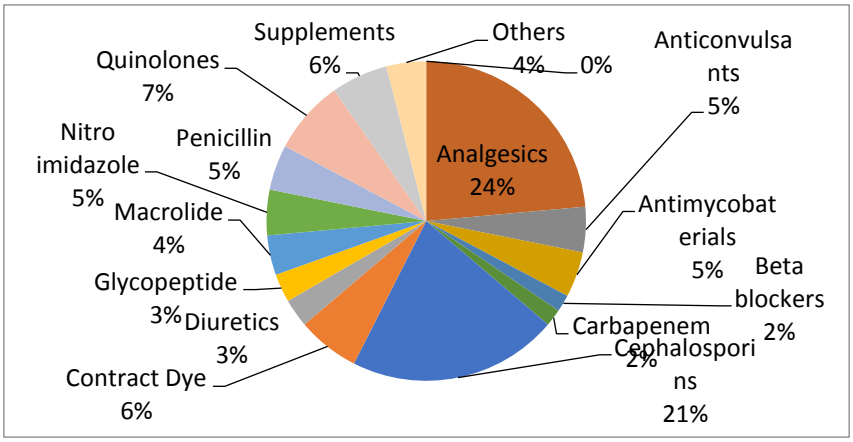
were definitely and probably preventable, respectively. In 57 (35%) of cases the ADR was managed by withdrawal of drug and in 41 (25%) patients the dose of drug was altered. While in 41 (25%) of cases the severity of ADR was safely decreased, 118 (72%) patients recovered from the reaction. No fatal cases were reported. Dechallange was done in 52 (32%) and the affected patients were not subjected to rechallenge. Multiple drug therapy, age and comorbid diseases were identified as the major predisposing factors for occurrence of ADRs. The major risk factors for causing ADRs were identified as cardiac problems, smoking, alcohol intake, etc.

Table: 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: Class of Drugs Associated with ADRs

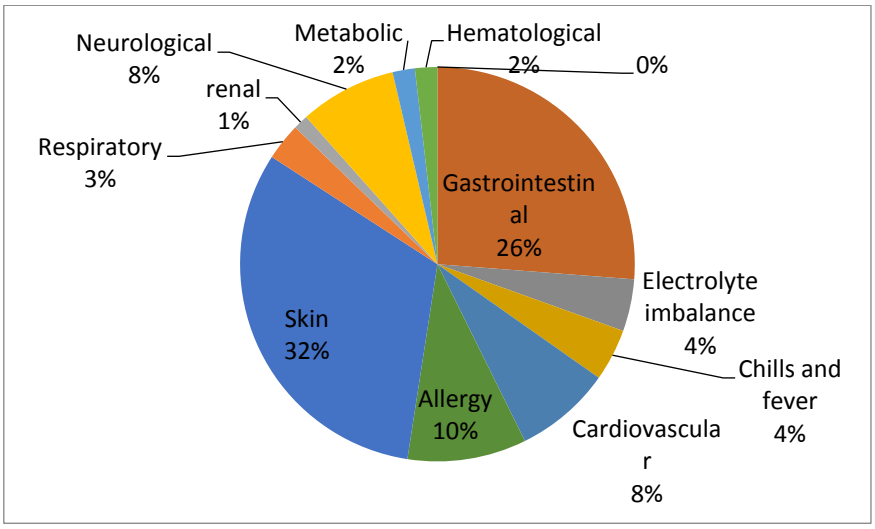


In our retrospective study ADRs were commonly associated with Analgesic (25%) followed by Cephalosporins (23%), Quinolones (7%) and Contrast Dye (6%). Our prospective study shows that ADRs were most common in Chemotherapy (33.3%) followed by Fluroquinolones and Sympatholytics (11.1%).

Table: 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: 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

Conclusion

Adverse events can be minimized by active monitoring, but it is challenging to eliminate them from practice. Optimizing patient safety requires the reduction of potential harm before and after the marketing of a drug. Identifying the exact benefit-to-risk ratio in a drug is necessary, and those drugs in which risks outweigh benefits should be reserved only for specific diseases or populations. The post-marketing of drugs needs to include doctors and patients to make informed decisions. The drug development process cannot study all the adverse events and ADRs of drugs. This needs separate trials specifically designed to detect ADRs, preferably involving randomization with adverse events of concern as the primary outcome measure. Reporting of ADRs has become common practice worldwide, and future studies must focus on implementing new ideas and perhaps develop AI-based models for easy detection of adverse events.

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