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A PROSPECTIVE STUDY ON ADVERSE DRUG REACTIONS ASSOCIATED WITH ANTIBIOTIC USAGE IN TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

Antibiotics are the most common drugs causing adverse events that lead to financial burden and various problems to patients. The aim of the study was to evaluate the occurrence of adverse events associated with the use of antibiotics in inpatients of the hospital. **OBJECTIVES:** The study was conducted to assess the incidence of ADRs associated with antibiotics. To assess the causality, severity and preventability of the ADRs associated with antibiotics. **METHODS:** The study was conducted on IPD patients receiving antibiotics in Kamineni institute of medical sciences, Narketpally. A total of 85 patients (54 males and 31 females)were enrolled in the study with informed consent. Data were collected from Patient case sheets, medication charts, lab reports and through structured interviews with patients. **RESULTS:** A total of 14 adverse drug reactions were observed in 85 patients. Severity of reported ADR's was assessed using modified Hartwig and Siegel and Naranjo Causality assessment scale. Most of the ADR's were mild level 1(9) followed by mild level-2 (5) using modified Hartwig and Siegel and probable (46%) for 7 patients followed by possible-3 (27%) for 4 patients and possible-4 (27%) for 3 patients using Naranjo Causality assessment scale. **CONCIUSION:** Antibiotics comprise the major drug family. Implementation of rational usage of antibiotics guideline for the hospitals and strict adherence to it should be ensured to promote their rational and safe use. Health systems need to promote spontaneous reporting of ADRs to regional pharmacovigilance centers.

INTRODUCTION

Antibiotics are used for the prevention of bacterial infection. They may be informally defined as the subgroups of anti-infective that are derived from bacterial sources and are used to treat bacterial infections. Antibiotics have no effect on viral infections. Originally, an antibiotic was a substance produced by one microorganism that selectively inhibits the growth of another [1]. They may either kill or inhibit the growth of bacteria. A limited number of antibiotics also possess anti protozal activity. Antibiotics are not effective against viruses such as the common cold or influenza, and their inappropriate use allows the emergence of resistant organisms. Drugs which inhibit viruses are termed as antiviral drugs or antivirals rather than antibiotics. Sometimes the term antibiotic (which means "opposing life") is used to refer to any substance used against microbes, synonymous with antimicrobial. Antibiotics revolutionized medicine in the 20th century, and have together with vaccination led to the near eradication of diseases such as tuberculosis in the developed world. However, their effectiveness and easy access leads to overuse, especially in livestock raising, prompting bacteria to develop resistance. This has led to wide spread problems with antimicrobial and antibiotic resistance, so

much as to prompt the World Health Organization to classify antimicrobial resistance as a "serious threat that is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country".

General use: Antibiotics are used to treat or prevent bacterial infections. In most cases, they are prescribed for a short period of time to treat a specific infection. This period may range from 3 to 10 days or more. More serious infections may require longer periods of treatment, up to several months or longer. Lower doses may be usedover a long period of time to prevent the return of a serious infection.

ADVERSE DRUG REACTION:

An adverse drug reaction (ADR) is an unwanted, undesirable effect of a medication that occurs during usual clinical use [3]. A response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for modification of physiological function[7](WHO) ADRs occur almost every day in health care institutions and can adversely affect patient's quality of life, often causing considerable morbidity and mortality. Much attention has been given to identify the patient population which is more prone to risk, drugs most commonly accountable, and the potential causes of ADRs. An increase in the number of drugs in the market, aging population, and an upward trend in polypharmacy are contributing factors to the prevalence of ADRs worldwide. Adverse drug reactions may cause patients to lose confidence or have negative emotions towards their physicians and seek self-treatment options, which may consequently precipitate additional ADRs. Around 5% of all hospital admissions are the result of an ADR, and around 10%–20% of inpatients will have at least one ADR during their hospital stay [4] The actual incidence of ADRs may be even greater because some ADRs mimic natural disease states and may thus go undetected or unreported. Although some ADRs presents minor symptoms, others are serious and may cause death in as many as 0.1%–0.3% of hospitalized patients[5]

Epidemiology of ADRs: The frequency of adverse drug reactions and drug related problems in society is not known. Many studies have been carried out in several parts of the world on incidence in hospitalized patients and of hospital admissions that result from adverse drug reactions and drug related problems. In recent analysis of 25 different studies of admissions to internal medicine departments, 4.2-6.0% of admissions were due to adverse reactions with median of 5.8%. A study from the USA demonstrated that the incidence of serious adverse drug reactions among hospitalized patients was 6.7% and 0.3% outcome was fatal. This makes ADRs between the 4th and 6th leading causes of death in the USA. A detailed study from the UK showed that 6.5% of hospital admissions were related to ADRs. These patients accounted for 4% of the hospital bed capacity. Approximately 70% of the reactions were considered avoidable. A similar study in 2007 carried out in Mumbai, India, demonstrated that 6.9% of the hospital admissions were caused by ADRs, 60% deemed avoidable. The average hospital cost was calculated to be Rs 6197/patient.[3] In an older Indian study assessed 4764 consecutive visits to the medical emergency department at the Postgraduate Institute for Medical Education and Research, Chandigarh for adverse drug events. They reported that 5.9% of all such visits were deemed to be drug related. Adverse drug reactions accounted for 45% of events. **Types of ADRs:** Adverse drug reactions were originally classified into two subtypes. **Type-A:** ADRs are dose-dependent and predictable; they are augmentations of known pharmacologic effects of the drug, such as orthostatic hypotension with antihypertensive medications. Type A reactions were later called **Augmented**.

Type-B: ADRs are uncommon and unpredictable, depending on the known pharmacology of the drug; they are independent of dose and affect a small population, suggesting that individual patient host factors are importantHypersensitivity (allergic) reactions to drugs are examples of type B ADRs. Type B reactions were called **Bizarre**.

Two further types of reactions were eventually added: **Chronic** reactions, which relates to both dose and time (type C), and **Delayed** reactions (type D). **Withdrawal** later became the fifth category (type E), and most recently, **unexpected failure of therapy** became the sixth (type F) about 80% of ADRs in the hospital setting or causing admission to a hospital are Type "A" ADRs. These ADRs are potentially avoidable and often predictable.[10] The drug classes most commonly responsible for ADRs in adults are adrenal corticosteroids, antibiotics, anticoagulants, anti neoplastic and immunosuppressive drugs, cardiovascular drugs, nonsteroidal anti-inflammatorydrugs, and opiates. For children, the most prevalent drug classes for ADRs are anti-infective drugs, respiratory drugs, and vaccines [9] **Causality Assessment of Suspected ADRs:** Although several methods for assigning ADR causality probability have been developed, no system has been able to produce a

definitive estimation of relationship likelihood. Regardless, causality assessment is a routine practice in pharmacovigilance. Although causality assessment cannot change possibility into certainty, it can provide a degree of likelihood to the relationship between a drug and an adverse reaction. One scheme used in the United States is the World Health Organization - Uppsala Monitoring Centre (WHO-UMC) Causality Categories scheme, This scheme classifies the ADR into one of six category terms: certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable[10] (WHO 2014). Determining the cause of a suspected ADR is a complex process. Because many patients take more than one drug, it can often be difficult to distinguish which agent caused the ADR. Furthermore, the suspected ADR may in fact be a manifestation of the patient's underlying disease state. An important step in identifying an ADR and determining causality is to obtain an accurate patient drug list. Not only is this an opportunity to screen for ADRs that could have led to the hospitalization, but maintaining an updated, accurate medication history for each patient can also help prevent future ADRs. If the inpatient prescriber is unaware of the patient's home drug regimen on admission, duplicate therapy may be prescribed. If admission and discharge reconciliation are not done, discharged patients may resume taking their home medication in addition to the newly prescribed therapy; this could result in an ADR might result or lead to

Re- hospitalization. Assessing the timing between administration of the drug and development of the reaction is important. Does the reaction worsen with repeated or increased dosing?

- Does the reaction decrease in intensity when the dose of the drug is reduced or

Discontinued?

Has the patient previously been exposed to the drug, in cases of allergic reaction?

- Is the reaction known to occur with long-term use of the medication?
- Did symptoms appear or worsen when a drug was discontinued?

Answering such questions can help the pharmacist determine causality. The next step is to identify patterns in ADR symptoms. Do the symptoms fit the normal pharmacology or allergy profile of the drug? Is this a known adverse reaction associated with this drug, or is it unique? Have case reports been published on this reaction? Particularly with new medications, much of the information about associated adverse reactions is unknown. By the time a drug has been approved for marketing in the United States, only about 1500 people have been exposed to the drug [8]. Post marketing surveillance and case reports are important tools that should be used when assessing ADRs for newly marketed drugs. Reporting a suspected ADR to the drug manufacturer and/or the U.S. Food and Drug Administration (FDA) will help identify a causal relationship between the drug and the adverse reaction, if one exists. This, in turn, will provide valuable information or warnings to other health care practitioners and potentially prevent further ADRs in their patients. Several algorithms and probability scales have been developed to assist with causality determination. Among those published are the Jones algorithm, the Yale algorithm, the Karch algorithm, the Begaud algorithm, and a quantitative approach algorithm .Two others are more commonly used because of their simplicity and time efficiency; one is the Naranjo ADR Probability Scale shown[11]

By answering 10 questions about the ADR and assessing numeric score to each answer, the ADR probability classification can be determined.

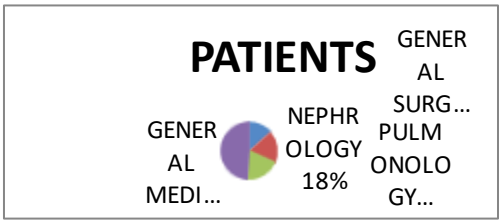
The General Adverse Drug Reactions Caused By Antibiotics as Follow:

Penicillins : Hypersensitivity- rashes, anaphylaxis, fever, joint pains, angioedema, serum sickness like reaction, blood disorders, C.N.S. toxicity in high doses; colitis and diarrhea

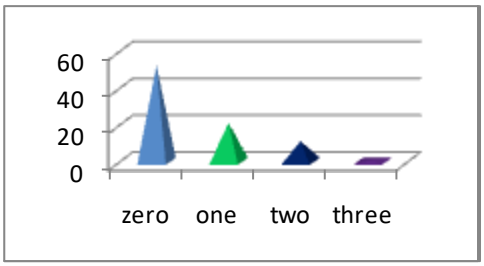
Cephalosporin : Hypersensitivity rashes, joint pains, rarely anaphylaxis; abdominal discomfort,colitis,erythema,reversible interstitial nephritis; transient hepatitis; blood disorders, dizziness etc.

Aminoglycosides: Ototoxicity, nephrotoxicity, more common in the elderly and in renal failure; may impair neuromuscular transmission and may cause transient myasthenia

Tetracyclines: Nausea vomiting diarrhea, erythema, benign intracranial hypertension; colitis Nausea, vomiting, abdominal discomfort, diarrhea, rashes, arrhythmias; cholestatic jaundice



Fluoroquinolones: Nausea, vomiting, diarrhoea, headache, dizziness, sleep disorders, rash, pruritus, anaphylaxis, increase in urea, creatinine and liver enzymes, arthralgia and myalgia, blood disorders, restlessness, hallucinations, depression, tendon damage[12]



METHODOLOGY

STUDY SITE: The study was conducted in the inpatient Department (IPD) of Medicine; Kamineni institute of medical sciences, a 1500 bedded multispecialty tertiary care teaching hospital.

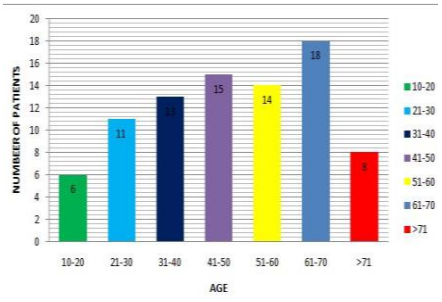
STUDY DESIGN: Prospective and observational study. **STUDY PERIOD:** The study was conducted for a period of 6 months, from October 2016 to March 2017. **RESULTS:** A total of 85 patients were enrolled in the study. Among 85 patients, 14 ADRs were reported during the study period. 6 patients were between the age group of 10-20 years, 11patients 21-30 years,13 patients 31-40 years, 15 patients 41-50 years, 14 patients from 51-60years, 18patients from 61-70 years and 8 patients were above 71years as shown in Graph-1

Graph-2 shows the number of patients using antibiotics in Kamineni hospital admitted in different wards depending on the severity of their condition. This shows most of the patients using antibiotics were admitted to general medicine (49%), followed by Pulmonology i.e.,(20%) nephrology i.e.,(18%) and general surgery i.e.,(13%).

COMORBIDITIES

Graph-3 shows that the number of patients with co morbidities who were received antibiotics in Kamineni hospital admitted in different wards depends upon the severity of their condition. Mostly 61% of the patients (52) doesn't have any kind of co morbidities , 24% of the patients (21)with one co morbidity , 12% of the patients (11) with two co morbidities and 1.17% of the patients (1) ware founded with three co morbidities. As shown in above table employment status of patients was found to be 27 patients had an educational qualification of primary school and 24 patients were found to be secondary school followed by uneducated (31) this states that the most of the reported. Incidence of ADR's had shown an increase among the patients who were uneducated due to lack of awareness about usage of antibiotics. Marital status was found to that 76 were married and 9 were unmarried.

Category	No Of Patients
➢ **Educational Status:**	
None	31
Primary School	24
Secondary School	27
Puc	3
➢ **Employment Status:**	
Employed	14
Unemployed	69
Retired	2
➢ **Marrital Status:**	
Married	76
Unmarried	9
➢ **Social Hystory:**	
Alcoholic	29
Non Alcoholic	39
Past Alcoholic	1
Social Drinker	16
➢ **Diet:**	
Veg	7
Mixed Diet	78
➢ **Allergic Reactions:**	
Nill	84
Rashes	1



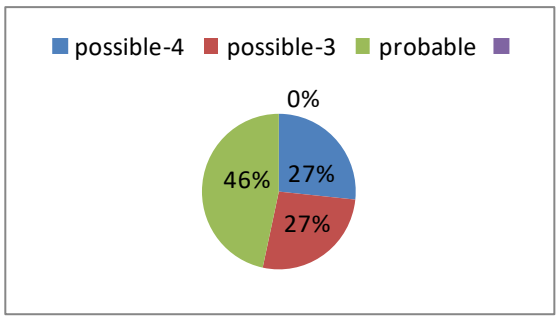
ADVERSE DRUG REACTION:

The reported adverse reactions were listed below based on their causality parameters which are assessed by Naranjo scale.

DECHALLENGE: 14

Graph-4

ASSESSMENT BY NARANJO SCALE:



Causality parameters	No.of ADRs	Percentage
Probable	7	46%
Possible-4	3	27%
Possible-3	4	27%

SEVERITY:

Level of severity	No.of ADRs
Mild level-1	9
Mild level-2	5

As shown in graph-4, Severity of reported ADRs were assessed using modified Hartwig and Siegel. Most of the ADRs were mild level 1(9) followed by mild level-2 (5). In this study, ADRs were assessed based on Naranjo Causality assessment scale. Most of the reported ADR's were probable (46%) for 7 patients followed by possible-3 (27%) for 4 patients and possible-4 (27%) for 3 patients.

PREDICTABILITY OF ADVERSE DRUG REACTION: 14

FATE OF DRUG: WITHDRAWN: 14

Treatment	
Specific	Symptomatic
2	1

It discusses the fate of drug i.e., the antibiotics that caused ADR's were withdrawn in patients and were treated with other alternative medications, finally the 14 patients in our study were recovered from adverse drug reactions.

DISCUSSION: Treatment of infections always includes antibiotics, as the drug resistance incidence is on the raise there is a huge need for taking steps to promote rational use of antibiotics. Antibiotics are considered as the second most prescribed drugs in the world. This study was an attempt to figure out the ADRs associated with antibiotics. ADR's can have a determinant effect on a patient's wellbeing and the overall health care system. A comprehensive daily ADR program in a hospital can help to complement organizational risk management activities, assess the safety of drug therapies, ADR incidence rates over time and educate health care professionals of drug effects and increase their level of awareness regarding ADR's of new and old drugs. Overall 14 patients with ADR were reported from 85 patients in the study. Incidence of ADR's among 6 patients were from 10-20 years, 11patients from 21-30 years,13patients from 31-40 years,15 patients from 41-50 years,14 patients from 51-60years,18patients from 61-70 years and 8 patients from age above 71years. Based on Naranjo algorithm, adverse reactions were considered probable concerning their causality, adverse drug reactions occurred in young patients which contrasts with other studies where the elderly were prone to these reactions because of changes in the intrinsic pharmacodynamics and pharmacokinetics caused by advanced age and loss of functional body reserve requiring prescription adjustments. Antibiotic protocol availability and high adherence in certain instances at the hospital studied did not prove to be enough to prevent all adverse events, in addition to protocols, other approaches are required such as prescribers education, educating nursing staff and giving sufficient knowledge to the patients taking antibiotics as candies. Kavitha Dhar et al.. in a study pattern of adverse drug reactions to antibiotics commonly prescribed in department of medicine and pediatrics in a tertiary care teaching hospital, Ghaziabad states that adverse drug reaction are an important cause of mortality and morbidity and constitute an enormous burden on the society. Many studies have implicated that the antibiotics are among the major group of drugs, which cause adverse drug reactions. This retrospective, non-interventional study was undertaken in Medicine and Pediatrics unit from November 2013 to April 2014 to monitor adverse drug reactions of antibiotics prescribed by physicians and pediatricians in a tertiary care hospital, Ghaziabad, to establish ten most common antibiotics which caused ADR's to determine most commonly affected

organ system and assess their causality. A total of 126 ADR's were identified in 80 patients, out of which 42(52.5%) occurred in male patients and 38(47.5%) in female patients.[13] Estela louro et al., in a study of Adverse events to antibiotics in inpatient of a university hospital states that antibiotics are the most common drugs causing adverse events and they lead to problems to patients and additional costs of the health system. In this study 87 patients were studied and 91 adverse events were identified,3 adverse drug reactions, 7 medication errors were found. As our study is completely adhered to adverse drug reactions with antibiotics, we hooked only to adverse reactions rather than adverse events and medication errors etc. The results indicate that an in adequate knowledge of antibiotics is the major factor for causing adverse drug reactions.

CONCLUSION:

The study concludes that the prescriptions of antibiotics in general medicine ward is increasing day by day and gastrointestinal tract (GIT) was more vulnerable to ADRs. The prospective study on adverse drug reactions associated with antibiotics usage in tertiary care teaching hospital, which was conducted in Kamineni institute of medical sciences in the period of 6 months time 14 ADRs are reported out of 85 suspected patients. The percentage of ADRs is 16.45%. Most of the reactions are related to gastro intestinal system (diarrhea) then followed superficial contentious such as skin rash. Super vision of antibiotics usage is necessary for preventing from adverse drug reactions caused by antibiotics. The spontaneous reporting of ADRs and making standard guidelines of issuing of antibiotics to patients are very much helpful for good clinical practice.

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