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Monitoring the incidence and severity of adverse drug reactions at multispeciality hospital

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ABSTRACT

Globally, adverse drug reactions (ADRs) make a substantial contribution to ill health. Introducing a systematic approach to patient surveillance could mitigate these problems. Formalized medication monitoring schedules have been proposed as one strategy to diagnose and action side-effects and the problems emanating from adverse drug reactions. To date, most developments have been linked to antipsychotic medications. Several scales, checklists, and side-effect profiles are available, including the West Wales ADR (adverse drug reaction) profile. However, relatively little work has been undertaken on the clinical validity, reliability, and sensitivity of these instruments. Providing an indirect measure of quality of pharmaceutical care through identification of preventable ADRs (Adverse Drug Reactions) and anticipatory surveillance for high-risk drug or patients. It's a prospective observational study carried out in lifeline mulity specialty hospital, Chennai. Potential ADRs were classified as naranjo's causality assessment scale, which causality assessment scales, a new algorithm to identify the causality of adverse drug reactions. This study showed that most of the population developed ADRs during hospital study.

Keywords: Adverse drug reaction, Naranjos casualty scales.

1. INTRODUCTION

Reporting of an adverse drug reaction (ADR) is a critical parameter of medical treatment. ADRs are one of the leading causes of morbidity and mortality, adding to overall healthcare cost. It is estimated that approximately 2.9–5.6% of all hospital admissions are caused by ADRs and as many as 35% of hospitalized patients experience an ADR during their hospital stay.[1] The overall incidence of serious ADRs is 6.7% and of fatal ADRs is 0.32% in hospitalized patients, making these reactions between the fourth and sixth leading cause of death, respectively.[2] Hence, the impact of ADRs on patient safety, health cost, and improved public health in relation to use of medicines by the provision of reliable and balanced information resulting in more rational use of medicines lead to emergence of a new medical discipline known as pharmacovigilance (PV). PV is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.

The World Health Organization (WHO) defines an ADR as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of a physiological function".[3] There are various methods of ADR monitoring such as prescription event monitoring, case report/case series, etc.; however, spontaneous ADR reporting is the widely used. It is particularly useful in identifying rare and delayed reactions.

At present, the WHO International Drug Monitoring program has 104 countries as official members and 29 countries as associate members.[3] ADR reports from various member nations are forwarded to Uppsala Monitoring Centre (UMC) where they are processed, evaluated, and entered into the WHO International database. However, all member countries have different forms of varied parameters, resulting in ambiguity of the collected ADR. For proper evaluation, assessment and processing of the ADR report and to establish

causal relationship between the suspected drug and the adverse reaction, ADR reporting form should be consistent, comprehensive, and conclusive.

1.1. Classification

The terms "drug allergy," "drug hypersensitivity," and "drug reaction" are often used interchangeably. Drug reactions encompass all adverse events related to drug administration, regardless of etiology. Drug hypersensitivity is defined as an immune mediated response to a drug agent in sensitized patient. Drug allergy is restricted specifically to a reaction mediated by IgE.[4]

Table - 1: Immunological drug reactions

Type	Example
Type I reaction (IgE-mediated)	Anaphylaxis from b-lactam antibiotic
Type II reaction (Cytotoxic)	Hemolytic anemia from penicillin
Type III reaction (immune complex)	Serum sickness from anti-thymocyteglobulin
Type IV reaction(delayed, cell-mediated)	Content dermatitis from topical antihistamine, specific T-cell activation, Morbilliform rash from sulfonamides, Fas/Fas ligand-induced apoptosis, stevens-Johnson syndrome, Toxic epidermal necrolysis.
Other	Drug-induced, lupus-like syndrome Anticonvulsant hypersensitivity syndrome

1.2. Non – immunological drug reaction

Drug reactions can be classified into immunologic and non immunologic etiologies (Table 1). The majority (75 to 80 percent) of adverse drug reactions are caused by predictable, non immunologic effects[6]. The remaining 20 to 25 percent of adverse drug events are caused by unpredictable effects that may or may not be immune mediated. Immune-mediated reactions account for 5 to 10 percent of all drug reactions and constitute true drug hypersensitivity, with IgE-mediated drug allergies falling into this category. [4]

Table - 2: Non – immunological drug reaction

Type	Example
Predictable	
Pharmacologic side effect	Dry mouth from antihistamines
Secondary pharmacologic side effect	Thrush while taking antibodies
Drug toxicity	Hepatotoxicity from methotrexate
Drug-Drug interaction	Seizure from theophylline while taking erythromycin
Drug overdose	Seizure from excessive lidocaine (Xylocaine)
Unpredictable	
Pseudoallergic	Anaphylactoid reaction after radiocontrast media
Idiosyncratic	Hemolytic anemia in a patient with G6PD deficiency after primaquine therapy
Intolerance	Tinnitus after a single, small dose of aspirin

G6PD = glucose-6-phosphate dehydrogenase.

The Gell and Coombs classification system describes the predominant immune mechanisms that lead to clinical symptoms of drug hypersensitivity (Table 2). This classification system includes: Type I reactions (IgE-mediated); Type II reactions (Cytotoxic); Type III reactions (immune complex); and type IV reactions (delayed, cell- mediated). However, some drug hypersensitivity reactions are difficult to classify because of a lack of evidence supporting a predominant immunologic mechanism. These include certain cutaneous drug reactions (i.e., maculopapular rashes, erythroderma, effoliative dermatitis, and fixed drug reaction) and specific drug hypersensitivity syndromes (Table 3) [4,7]

1.3. Specific Drug Hypersensitivity Syndromes Caused by Non-IgE Immune Mechanisms [11]

Unpredictable, non immune drug reactions can be classified as pseudo allergic,

Table - 3: Gell and coombs classification of drug hypersensitivity reactions

Immune reaction	Mechanism	Clinical manifestations	Timing of reaction
Type II (Cytotoxic)	Specific IgE complex binding to mast cells with release of histamine, mediators	Uricaria, antioedema, bronchospasm, inflammatory pruritus,vomiting, diarrhea, anaphylaxis	Minutes to hours after drug exposure
Type II (Cytotoxic)	Specific IgE or IgM antibodies directed at drug-hapten coated	Hemolytic anemia, neutropaenia, thrombocytopenia	variable
Type III (immune complex)	Tissue deposition of drug-antibody complexes with compliment activation and inflammation	Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis	1 to 3 weeks after drug exposure
Type IV (delayed, cell-mediated)	MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release	Allergic contact dermatitis, maculopapular drug rash	2 to 7 days after cutaneous drug exposure

Table - 4: Specific Drug Hypersensitivity Syndromes Caused by Non-IgE Immune

Causative drug	Syndrome
Hydralazine, Procainamide	Lupus-like syndrome
Carbamazipine, Phenytoin	Anticonvulsant hypersensitivity syndrome
Sulfonamides, Anticonvulsants	Stevens-Johnson syndrome, toxic epidermal necrolysis

idiosyncratic or intolerance. Pseudo allergic reactions are the result of direct mast cell activation and degranulation by drugs such as opiates, vancomycin (Vancocin), and radio contrast media. These reactions may be clinically indistinguishable from type I hypersensitivity, but do not involve drug-specific IgE. Idiosyncratic reactions are qualitatively aberrant reactions that cannot be explained by the known pharmacologic action of the drug and occur only in a small percent of the population. A classic example of an idiosyncratic reaction is drug-induced hemolytic in persons with glucose-6-phosphate dehydrogenize (G6PD) deficiency [8]. Drug intolerance is defined as a lower threshold to the normal pharmacological action of a drug, such as tinnitus after a single adverse dose of aspirin. [4]

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

1.4.1. Cause

- Type A: Augmented pharmacologic effects
- Type B: Bizarre effects (or idiosyncratic)
- Type C: Chronic effects
- Type D: Delayed effects
- Type E: End of treatment effects
- Type F: Failure of therapy

Types A and B were proposed in the 1970s, and other types were proposed subsequently when the first two proved insufficient to classify ADRs [4]

1.4.2. Seriousness and severity

The American Food and Drug administration defines a serious adverse event as one when the patient outcome is:

- Death
- Life-Threatening
- Hospitalization (initial or prolonged)
- Disability – significant, persistent, or permanent chance, impairment, damage or disruption in the patient's body function/ striation, physical activities or quality of life [9].
- Congenital Anomaly
- Requires Intervention to prevent permanent Impairment or Damage.[4]

An ADR is a particular type of adverse effect. 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.[5]

2. METHODOLOGY

The study was carried out at life line multispeciality hospital. Life line multispeciality hospital is a 500 bedded. The hospital has more than 40 medical disciplines managed by highly qualified and trained full time medical specialists.The hospital includes Anesthesiology, critical care, cardiology with cathlab. Dermatology, Endocrinology, Gastro- enterology, Geriatric medicine, General medicine, Haematology and Haemato-oncology, Nephrology, Neurology, Neonatology and paediatrics, psychological Medicine and De-addiction, pulmonology, Rheumatology, General surgery, vascular surgery, Laparoscopic surgery, Cardio vascular and thoracic surgery, Dentistry, ENT, Head and Neck surgery, Neurosurgery, Obstetrics and gynecology, Ophthalmology, Orthopedics, Plastic and cosmetic surgery, Pediatric surgery, Urology, Physical Medical and Rehabilitation, Diabetic clinic, stem cell therapy, Master health check Up, Over 1000 in-patients and out-patients are treated every day in the hospital.

2.1. Study period

This study was a spontaneous reporting system carried out for a period of 6 months (November 2010- April 2011) by a clinical pharmacist on both in-patients and out-patients.

2.2. Study procedure

All the necessary and relevant data collected from patient case notes, treatment charts, laboratory data reports, ADR notification forms, patient interview and reporter interview. ADR alert form was formed and implemented in hospital. When doctors on their routine ward round, if they come across any ADR in their patient it will be noted in the ADR alert form, kept in each patient medical chart. The clinical pharmacist will be visiting the different ward and go through the ADR alert form by the doctor or the nurses it will be noted and the data regarding ADR is collected from patient medication record and documented.

ADRs were defined in accordance to the World Health Organization definition of an adverse drug reaction. A suitable 'ADR Reporting Card' was designed based on a format similar to the 'Blue card' (Australian Adverse Drug Reaction Advisory Committee) with necessary changes to suit the present study.

2.3. Inclusion criteria

Patients of either sex of any age, who developed ADR due to drugs, were included in the study

2.4. Exclution criteria

Allergic reactions due to pollen, dust, and insect are excluded from this study.

2.5. Documentation of ADR

ADR monitoring form was designed and implemented. If a suspected ADR was reported and had met the inclusion and exclusion criteria, data on that particular suspected drug and reaction were collected and documented in a suitably designed 'ADR Documentation form'. Oral consent was taken from patients, their relatives and consent doctors for further interviewing, to collect data such as description of ADR and also permission to take photograph. All relevant data which included drugs that the patient received prior to onset of reaction, their respective dosage, route of administration with frequency, data of onset of reaction and the patient's allergy status were noted. The permission to conduct the study was granted by hospital and ethical committee prior to state the study. The relevant data of drugs which were taken by the patient's prior to start the study. The relevant data of drugs which were taken by the patients prior to onset of reaction, like dosage, route of administration, and its frequency were collected.

2.6. Assessment of ADRs

ADRs are assessed through Naranjo's causality assessment scale, new algorithm to identify the causality of ADRs, and WHO causality assessment scale. Depending on the questionnaire in the assessment form, ADR is categorized as definite, probable, possible and unlikely. In case of Naranjo's, new algorithm scale and in the case of WHO probability scale depending on the questionnaire it is categorized as certain, probable, possible, unassessable/ unclassified, unlikely, conditional/unclassified.

The various forms for assessing ADRs were

- Naranjo's causality assessment scale. (Annexure-IV)
- WHO causality scale. (Annexure-V)
- New algorithm to identify the causality of ADRs. (Annexure-VI)

2.7. Panal of judges

The patient's case notes were reviewed independently by the doctors and clinical pharmacists. The panel of reviewers consisted of 2 doctors and 2 clinical pharmacists. The evaluation of ADR monitoring and assessing causality was done by the panel. During the ward rounds if

required the physician in consultation with other members of the healthcare team could make decisions regarding patient diagnosis and management. On certain occasions the pharmacist's suggestions were recommended.

The recommendations were as follows:

- Provision to drug information relevant to the suspected ADR to the notifying doctor as a part of primary patient care
- Educate the patient about the event of ADR and prevention of further reactions recommendation of alternative therapy and identification of drug interaction
- "Systems error" and drug allergy.

3. RESULTS AND DISCUSSION

ADR was slightly higher in males (58.3%) compared to females (41.7%) , Out of the 60 ADR, 50 ADR (83.3%) were reported from in-patient department, in which 33 ADR (66%) were males and 17 ADR (34%) were females, ADR affected individual were classified as per the age group in the range of 0-20, 21-40, 41-60, 61& above years of age. Maximum number of ADR was found in the age group of 41-60. Out of 60 reported ADR about 47 patient's (78.3%), drug reactions were managed by withdrawing the drug, only in 6 patients (10%) doses were altered, for about 7 patient (11.7%) no change in the treatment was made especially in those patient undergoing chemotherapy. Out of 60 reported ADR from both in-patient and out-patient department in the hospital, of which 35(58.3%) patients with ADR were given specific treatment, 18(30%) patients with ADR received symptomatic treatment and 7(11.7%) patients with ADR received no treatment. Out of the 60 reported ADR 26 (43.3%) cases were moderate, 26 (43.3%) were 'mild' and 8 (13.3%) were severe. The ADR were highly prevalent in neurology department. About 11.6% of ADR were noted in neurology department. Other departments such as Dermatology 1.7% cases, pulmonology 3.3%, and cardiology 12%, oncology 8.3%, obstetrics and gynecology 1.7%, Endocrinology 8.3%, orthopaedics 2%, General medicine 10%, psychiatry 5%, Gartroenterology 13.3% and nephrology 5%. Majority of the ADR from various department were associated with skin reaction 30%, and other suspected ADR noted in the hospital include peripheral neuropathy (5%), urticaria, fixed drug eruption, hematuria, hyperglycemia, erythroderma, elevated hepatic enzymes (3.3%) Cushing's syndrome, angioedema, myalgia, ear ache, constipation, gastritis, hypotension, hyponatremia, hepatitis, steroid psychosis, xerosis with prurigo, abdominal upset, anaphylaxis, gingival hyperplasty, toxic epidermal necrolysis, angioedema, exfoliative dermatitis, phototoxic reaction, periarticular rash, malaena, scalintiform eruption, toxic erythema multiform, lichenified skin lesion, eczematous skin lesion, vomiting (1.7%). Anticancer drugs were also having their share of ADR. Surprisingly peripheral neuropathy was the only reported ADR in this group. Corticosteroids induced hyperglycemias, steroid psychosis, Cushing's syndrome were reported. Hepatitis, hypersensitivity reactions, erythroderma were the ADR reported for Antitubercular drugs.

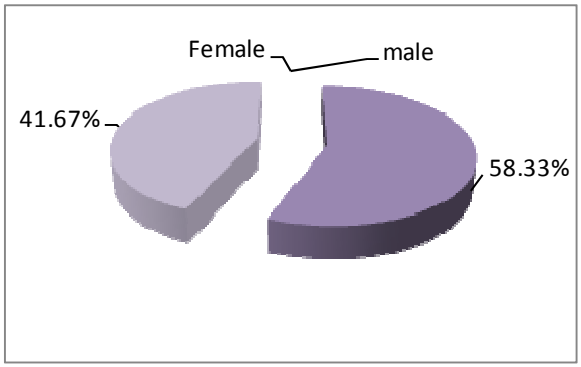

Figure - 1: Figure showing the incidence of ADRs in both genders

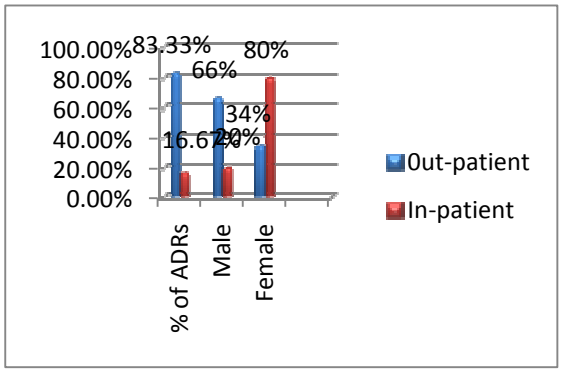

Figure - 2: Figure showing weight distribution of ADRs in both genders.

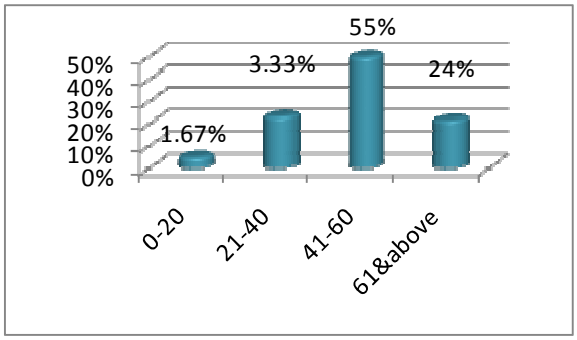

Figure – 3: Table showing age wise distribution of ADRs in both genders.

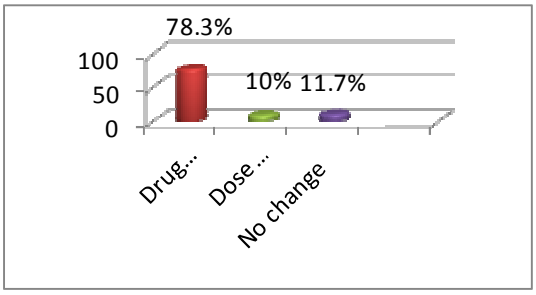

Figure – 4: Showing management of ADRs in the hospital.

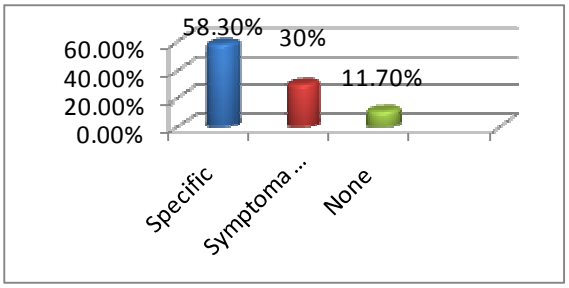

Figure – 5: Showing treatment given for reported ADRs

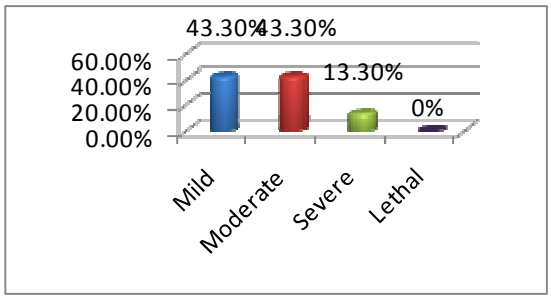

Figure – 6: Showing severity of reported ADRs

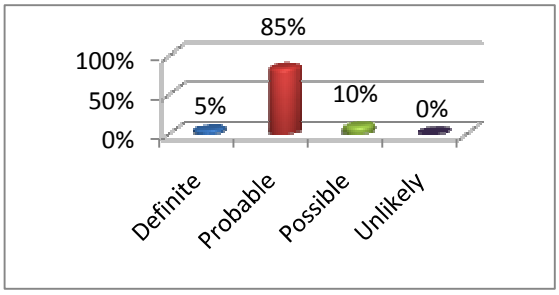

Figure - 7: Showing Naranjo's causality assessment of ADRs

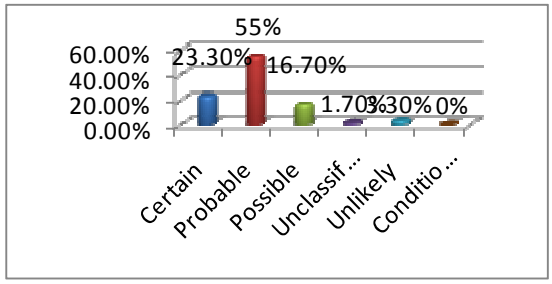

Figure - 8: Showing WHO probability assessment of ADRs

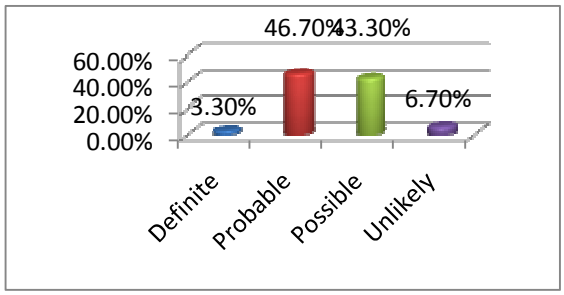

Figure - 9: Showing assessment of ADRs through new algorithm

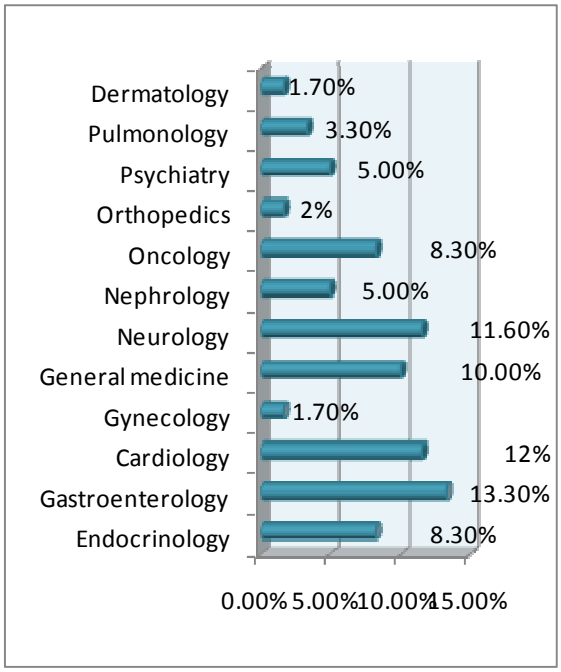

Figure - 10: Showing clinical classification of reported ADRs as per the department

4. CONCLUSION

This study was concluded more number of ADRs was seen in in-patient department. In general ADRs are mostly seen in female population when compared to the male population, in the contrary, my study revealed a male predominance over female. In general geriatric and pediatric population is mostly affected with ADRs. In my study adult population were mostly affected with ADRs. My study showed that most of the population developed ADRs during hospital study. Most of the ADR were managed by drug withdrawal and dose altered. In my study ADRs were commonly seen in the neurological drugs and antibiotics. The simplest way to prevent most ADR is to use the minimum dose of drugs. The simplest principle of "STRAT LOW and GO SLOW" should be followed. This study highlights the need for a

greater awareness of the potential for drug related admissions.

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