

**REPORTING THE ADVERSE DRUG REACTIONS ASSOCIATED
WITH PREGNANCY WOMENS**

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ABSTRACT

Adverse drug reactions (ADR) are a significant cause of morbidity and mortality, often identified only post-mark tingly. Improvement in current ADR reporting, including utility of underused or innovative methods, is crucial to improve patient safety and public health. Hospital-based monitoring is one of the methods used to collect data about drug prescriptions and adverse events. The aims of this study were to identify the most frequent ADRs recognized by the attending physicians, study their nature, and to target these ADRs in order to take future preventive measures. A prospective study was conducted over a 3-month period in an internal medicine department using stimulated

spontaneous reporting for identifying ADRs. Out of the 300 admissions, 32 ADRs in 37 patients (14.56%) were validated from the total of 36 suspected ADRs inpatients. Female predominance was noted in case of ADRs. Fifty percent of total ADRs occurred due to multiple drug therapy. Dermatological ADRs were found to be the most frequent (68.75%), followed by respiratory, central nervous system and gastrointestinal ADRs. The drugs most frequently involved were antibiotics. The most commonly reported reactions were abdomen pain and vomitings. Out of the 32 reported ADRs, 50% of the reactions were probable, 46.87% of the reactions were possible and 3.12% of the reactions were definite. The most potent management of ADRs was found to be drug withdrawal. Our study indicated that hospital based monitoring was a good method to detect links between drug exposure and adverse drug reactions. Adequate training regarding pharmacology and optimization of drug therapy might be helpful to reduce ADR morbidity and mortality.

KEYWORDS: adverse drug reaction, hospital based monitoring, pharmacovigilance.

INTROUDUCTION

Women's health issues have been defined as “any matter that affects the health of women exclusively, that impacts predominantly on women's health (at any age), or that affects women's health differently from that of men” An effective strategy to support women's health addresses all of these matters, including the approval, use and regulation of prescription drugs.

The paper offers an overview of the current ADR reporting system, including the steps taken to improve both the reporting system itself and the flow of ADR information to health providers, patients and the public at large.

What is adverse drug reaction?

Adverse drug reaction (ADRs) is one of the major problems with medicines. The World Health Organization (WHO) defined as any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy excluding failure to accomplish the intended purpose. ADRs can cause shortened long-term hospitalization and mortality (WHO). It is imperative to monitor ADRs in order to minimize or prevent harm to patients arising from their drugs, to detect ADRs before they are clinically manifested, and to obtain much more knowledge to ensure safe use of drugs.

ADR reporting covers all pharmaceutical products, biological, herbal drugs, cosmetics and medical devices circulating in the India market. For those conducting clinical trials phase 1-4 it is mandatory to report all adverse event encountered to the Authority.

Reported the pharmacists have a reasonable knowledge and are supportive of the yellow card spontaneous ADR reporting scheme. However, education and training are important in maintaining and increasing ADR reporting by pharmacists. Under reporting of ADR is a global issue of major concern. As in most of the pharmacovigilance system around the world. The major weaknesses of Pharmacovigilance program are the lack of awareness among health care professionals regarding pharmacovigilance; under-reporting is another limitation. Other reasons for under-reporting include uncertainty regarding the types of reaction to report, and a lack of awareness about the existence, function and purpose of the national ADR reporting scheme. India, ADRs have recently emerged as leading killers. The

management of drug-induced illnesses requires more than 100 billion US dollars annually⁴. These astronomical figures are currently unmatched by money involved in any single disease management presently. Fortunately, several studies have shown that most ADRs are preventable, provided that the drugs are used rationally.

But unfortunately, the most common system failure has been to disseminate the knowledge of pharmacovigilance to the individuals actually involved in prescribing, i.e. the physicians³.

Principles and practice of pharmacovigilance seem to be more often discussed in an academic manner, rather than in a pragmatic or applied sense. Several times, such discussion is held amongst pharmacologists and pharmacists who are not directly involved in patient care; and physicians who treat cases and use drugs generally keep themselves uninvolved. Drug safety has been included in curriculum guidelines of Indian medical undergraduates, but little is done in this regard. Prevention is considered to be better than cure, as elsewhere in medicine; application of the same principle has given a new dimension to the study of pharmacovigilance.

Why is ADR monitoring needed?

One of the most frequently asked questions in pharmacovigilance is: What is the need to monitor the adverse reactions to drugs, if their safety profiles have already been studied adequately before their commercial release?

The answer is simple: To make the drugs safer. The next obvious question would be: How would drug monitoring for adverse reactions make the drugs safer, when, according to the general perception, safety is something that is inherent in the physiochemical properties of the drug molecules under consideration? This is because in the formal evaluation of the drug by clinical trials, many of the drug issues related to the safety are inadequately studied. In addition, the formal therapeutic trials are conducted in carefully controlled conditions; in highly selected and limited number of patients, so that the exact safety profile of the drug in the real life situations is not known. Moreover, prior to its release, a drug is studied in just 4,000 cases. Therefore, adverse reactions having frequency less than 0.5 to 1% are missed⁴. Children, pregnant women, and elderly are not included in clinical trials for ethical reasons. Therefore, the safety of the drug in these cases remains unknown until its release⁶. Another important drawback of clinical trials is that they can only report adverse reactions that appear within the Finite duration of trial.

Delayed reactions would be missed. Reporting of adverse drug reactions is done by mainly two methods: spontaneous and intensive. Though plagued by numerous problems like low yield of reports, sub-optimal quality and imperfect nature, these have often served to be a useful source of data or provided early warning signals for the drug related regulatory actions.

Aims of pharmacovigilance

1. Detection of severe and unexpected adverse drug reactions to the established drugs and even the minor ones to newer drugs.
2. Identification of the risk factors associated with the development of adverse drug reactions and mechanisms of their causation like Type A, Type B, Type C, etc.
3. Quantitative estimation of the risk factors, incidence, and prevalence of adverse drug reactions. Estimation of the pharmacy economic data related to ADRs, e.g. How much is the hospital stay prolonged by ADRs? How much is the total cost (direct and indirect) involved in the management of ADRs and what is the cost incurred by the hospital and the nation? To what extent ADRs are the cause of hospital admissions? What is the total extent of morbidity and mortality caused by adverse drug reactions?
4. Systematic analysis of the obtained data and dissemination to the health agencies, regulatory authorities, pharmaceutical companies, physicians, and other members of the health care system (e.g., nurses, dentists, and paramedics, etc.), so that the safety of drugs and modification of the prescribing patterns can be ensured. Journal, Indian Academy of Clinical Medicine

Type-A (Augmented)

Commonest (up to 70%) - Dose dependent, severity increases with dose. Preventable in most part by slow introduction of low dosages. Predictable by the pharmacological mechanisms, e.g., hypotension by beta-blockers, hypoglycemia caused by insulin's or oral hypoglycemic

Type-B (Bizarre)

Rare, idiosyncratic, genetically determined, unpredictable, mechanisms are unknown, serious, can be fatal; unrelated to the dose, e.g., hepatitis caused by halothane, a plastic anemia caused by chloramphenicol, narcoleptic malignant syndrome caused by some anesthetics and antipsychotics.

Type-D (Delayed)

Delayed occurrence of ADRs, even after the cessation of treatment, e.g., corneal opacities after thioridazine, ophthalmopathy after chloroquine

Type-E (End of dose)

Withdrawal reactions. Occurs typically with the depressant drugs, e.g., hypertension and restlessness in opiate abstainer, seizures on alcohol or benzodiazepines withdrawal; first dose hypotension caused by alpha-blockers (Prazosin) or ACE inhibitors.

Type-F (Failure of therapy)

Results from the ineffective treatment (previously excluded from analysis according to WHO definition), e.g., accelerated hypertension because of inefficient control.

If adverse drug reactions are considered as any other medical illness and approached in the same way, then many questions would appear like

What is an adverse drug reaction (Definition)?

What is its importance in the current medical practice (Epidemiology)?

What are the factors related to its occurrence (Etiology)?

What are the mechanisms of its causation (Pathogenesis)?

What can be done to prevent it (Prevention)?

The last question is indeed the most important one. Many studies from different parts of the world have shown that with timely intervention, many of the adverse drug reactions can be prevented. Focus of the studies in the pharmacovigilance has now shifted from knowing the incidence, patterns, severity, and predictability to prevention. Type-C (Continuous drug use) : Occurs as a result of continuous drug use. May be irreversible, unexpected, unpredictable, e.g., tardive dyskinesias by antipsychotics, dementia by anticholinergic medications.

Many programmes and approaches are being tried in the western countries to know what can be done to prevent the adverse drug reactions. This has made the study of pharmacovigilance more relevant than ever before.

Spontaneous adverse drug reaction monitoring is the structured countrywide system of reporting of suspected effects of the drugs. This has at many times served to be the early warning system for regulatory action related to the particular drug. The vigilant clinicians

during their routine clinical work might encounter many adverse drug reactions worth reporting. Publications of series of cases or individual case reports in the medical journals are examples of spontaneous drug monitoring. Intensive adverse drug monitoring on the other hand, is a systematic method of data collection of reports of ADRs in the hospital setting.

Several studies relevant to knowledge, attitudes, perception (KAP) towards pharmacovigilance activity among medicine or pharmacy students in different Universities have been reported in various hospitals. The effectiveness and success of any Pharmacovigilance system depends highly on the participation of all health care professionals and thus, physicians, and pharmacist are important healthcare professionals responsible for the pharmacovigilance activities and ADR reporting during their practice and also to increase awareness among public pharmacovigilance. Studies indicate that inadequate knowledge and lack of awareness about ADR reporting among healthcare professional as well as attitude is associated with a high degree of under-reporting.

What constitute an ADR report?

All adverse drug reactions to both older and newer drugs

- a) Unexpected, severe, and serious reactions to established drugs and minor ones to the newer ones.
- b) ADRs to established drugs: Chloramphenicol induced plastic anemia. ACE inhibitor induced ARF in bilateral renal artery stenosis. NSAID induced hepatitis or nephritis (analgesic nephropathy). Antithyroid drugs induced granulocytopenia. Cisapride induced cardiac rhythm disturbances. Phenylpropanolamine induced cerebral hemorrhage.
- c) ADRs to newer drugs: Upper gastrointestinal hemorrhage to COX2 selective NSAIDs.

Hepatitis by insulin receptor sensitizers e.g. troglitazone. Adrenal suppression and growth retardation by budesonide. Reduced libido by newer selective serotonin reuptake inhibitors like fluoxetine, paroxetine, or sertraline. Complete spectrum of ADRs including minor ones like rashes or gastrointestinal upset by herbal antidepressant St John Wort. Hypersensitivity reactions (Churg-Strauss syndrome) with montelukast and zafirlukast.

1. Teratogenesis by both newer and older drugs and their safety in pediatric and geriatric population should be reported whenever encountered or systematically studied.

2. Previously obscure adverse reactions, e.g. Hallucinations caused by fluoroquinolones. Constipation by clozapine. Oculogyric reactions by antipsychotics haloperidol. Pedal edema by selective COX-2 inhibitors; tracheoesophageal fistula caused by conventional NSAIDs. Hyperthyroidism and hypothyroidism by lithium in the same patient. Unexpected therapeutic benefits that can occur to either newer or established drugs and can accidentally be discovered by careful clinical observations.
3. Lipid lowering effects of paracetamol. NSAIDs reduced the risk of Alzheimer's disease. Amantidine reduced the manifestation of Parkinson's disease. Monoxide produced hair growth. Sildenafil caused penile erection. Lithium increased neutrophil counts in the patients with bone marrow suppression.
4. Proof positive ADRs (ADRs that not only occur once a drug is given and subside on discontinuation, but reappear on read ministration – positive re-challenge) e.g. : Cotrimoxazole induced urticarial rashes. Penicillin or cephalosporin allergy. Bronchial asthma by NSAIDs in susceptible patients. Extra pyramidal disturbances by antipsychotics. Jaundice by barbiturates in patients with acute intermittent porphyria
5. Experiences of educational value, e.g. : Ampicillin induced rashes in patients with infectious mononucleosis.
6. NSAIDs may reduce the control of blood pressure by antihypertensive. Megaloblastic anemia and reduced fertility can occur in female health workers exposed to nitric oxide in anesthetic care units.
7. Indians are less prone to the bone marrow suppressing actions of thioacetazone. Asians require lesser doses of antipsychotics than their Caucasian counterparts in the management of schizophrenia. Moreover, adverse effects of antipsychotics in Asians appear at lower dosages than Caucasians.

Causality is assessed using WHO criteria. These ensure that the drug has caused the suspected reaction. There should be a temporal association between drug use and the appearance of an adverse reaction. It should disappear (maybe partially), once the drug is stopped (de-challenge). It should reappear when the drug is reintroduced (rechallenge). However, performing this de-challenges and rechallenge is not always possible in real clinical situations. In these cases, one should use the best judgment about the adverse effect profiles of the drug, underlying disease, concomitant medications, and pattern after removing the most likely offender.

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SUBJECTS AND METHODS

This study was a concurrent, spontaneous reporting, involving both active and passive methods. Active methods include physicians, pharmacists and nurses actively looking for

suspected ADRs and passive methods include stimulating prescribers to report suspected ADRs. The study was conducted in a 35-bed internal medicine ward of the Rural Government Hospital, Nalgonda. over a period of 3 consecutive months, starting from Feb 2016 to March 2016.

All the physicians in the ward were informed about the study, outlining the ADRs' negative impact and were asked to report all observed adverse events. In order to ensure that the rate of notifications remains constant during the whole study period, the physicians were regularly reminded about the study taking place.

An Adverse Drug Reaction Reporting Form was designed and made available at all nursing stations of the ward of the hospital for easy access to all healthcare professionals. The Adverse Drug Reaction Reporting Form was prepared with reference to the ADR reporting form of the Indian Pharmacopoeia Commission (IPC). which includes information about the patient, like name, age, sex, medication history, diagnosis history, name of the suspected drug along with batch number, lot number manufacturing date and expiry date. The route of drug administration, frequency and dose is also mentioned in the form. Basic information of adverse reaction caused by the suspected drug was also included. We defined adverse drug reactions according to the World Health Organization definition, as being all "noxious and unintended drug response, which occur at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function (WHO, 1972). By this definition, ADRs primarily include allergic reactions and adverse effects. Therefore, we excluded all the intentional overdoses, poisonings and therapeutic failures.

In addition, the patient's medication history was also taken and any co-morbidity identified to assess the causality relationship between the suspected drug and reaction. Patients who developed an ADR were interviewed daily from the day the ADR was reported with regard to consumption of any other medication. The relationship between ADR and the suspected drug was assessed. The severity of the ADRs was also assessed in different categories as mild, moderate and severe for each ADR. All the reported ADRs were assessed for their preventability criteria. Personalized letters and circulars signed by the director of the hospital were circulated to all residents and practitioners, visiting practitioners and nursing stations. These letters contained information on the number of suspected ADRs that had been reported till date, need for continuing reporting of ADRs and a request to maintain a high degree of

suspicion for the ADRs. The data observed were analyzed in order to study the characteristics of the ADRs and to determine the nature and pattern of ADRs related to hospital admission and difference in the severity of ADRs and management and outcome of management of the reported ADRs. Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established. The assessment of causality relationship is often subjective, based upon an individual clinician's assessment. One clinician's judgement may appear unlikely to another clinician. If an ADR is suspected, the assessment starts with collection of all the relevant data pertaining to patient demographics, medications, including non-prescription (OTC) drugs, comprehensive ADR details including a description of the reaction, time of onset and duration of the reaction, complications and/or sequelae treatment of the reaction and outcome of the treatment and further relevant investigation reports. The collected data were used to correlate and categorize the relationship between the suspected drug and the adverse drug reaction. The data were also analyzed as per severity (Mild, Moderate and Severe) of the suspected adverse drug reaction and categories as death, life threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention to prevent permanent impairment or damage, not serious, and others.

RESULTS

TABLE-1 Age Wise Distribution of No. Of ADRs

Age	No. Of ADRs	Percentages (%)
15-25	52	88%
26-35	4	6%
36-45	3	5%

TABLE-2: Sex wise Distribution of ADRs

Female	No. Of ADRs	Percentage (%)
59	59	100%

TABLE-3 Top 10 Drug causing ADRs

Drug	No.of. ADRs	Percentage (%)
1.Ranitidine	9	15%
2.Elemental iron	5	8%
3.Ceftriaxone	3	5%
4.cefotxime	15	25%
5.Dicofenac	8	13%
6.Pantoprozol	4	6%
Others	15	25%

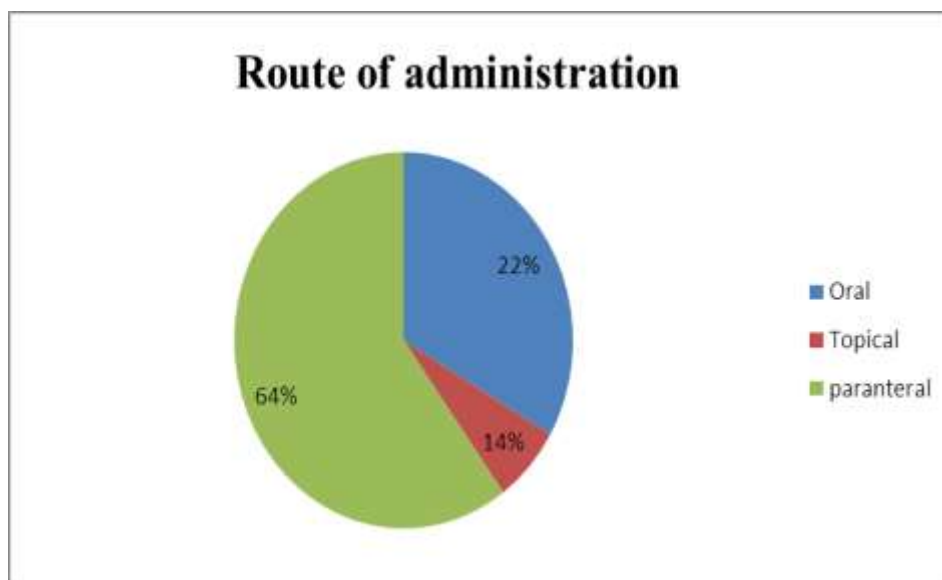
TABLE4: Anatomical main Groups of ADRs

Anatomical main groups	No.ofADRs	Percentage%
1.Alimentary tract and metabolism	8	13%
2.Blood and blood forming organs	12	20%
3.Systemic hormonal preparation(Excluding sex Hormones and Insulin)	8	13%
4.Nerves system	4	6%
5.Others	28	47%

The primary search resulted in 59 cases, of which 40 cases were ruled out by the exclusion criteria. Of the resulting cases, 19 were excluded as they were incorrectly classified. Another six cases were excluded because they were double reports.

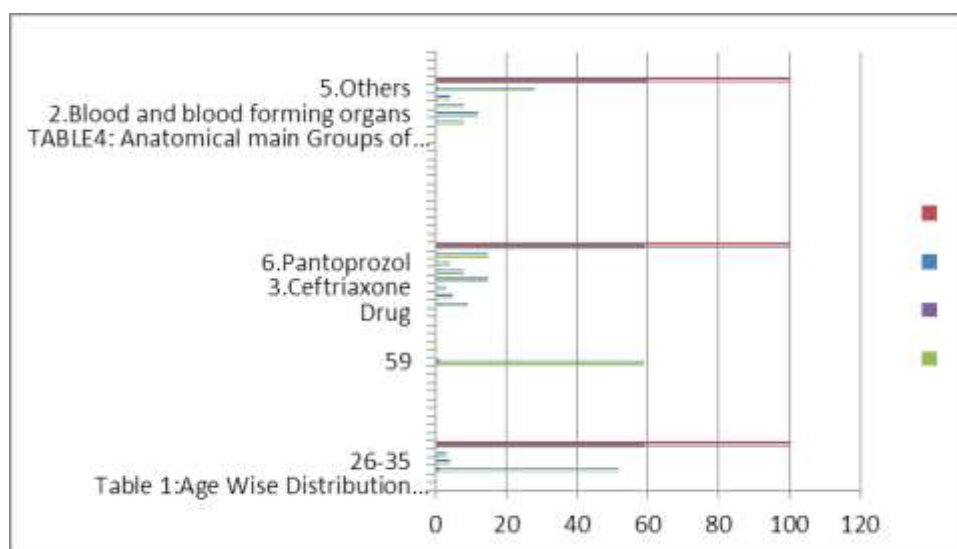
The final study group, as defined by the inclusion criteria, therefore included a total of 59 ADR reports from the Nalgonda Government hospital ADR database from February 2 to march 18 with sufficient information on at least one negative fetal outcome of the reaching a maximum in 2016 with 31 reports about fetal disorders.

shows that in the general population also, the number of ADR reports sent per month has increased during the last 20 years Most ADR reports were sent by the pharmacy students(38.6 %) other senders played only a minimal role (2.0 %). Sufficient quality (as defined above) was provided for 59 of the reported drugs (87.3 %) followed by the missing route of administration (3.6 %). Within the study group, 78.7 % of the reports were classified as “ serious ” and 21.3 % as “ not serious ” . The most frequent special reasons for a report to be classified as serious were “congenital anomaly” (28.3 %) and “ death ” is not seen. Majority of ADRs were noted with Oral route of administration (64%). Drugs administered by parenteral route accounted for 22% Of ADRs, while 14%of the drugs given topically caused ADRs.

**Figure-1**

NOTE: From the above data Oral 22% Topical 14% Parenteral 64%.

Causality

**Figure-2**

NOTE: From the above data the drug cefotxime is more affect on blood and blood forming

DISCUSSION

The first study about ADR reports in focusing on the WHO-ART SOC category includes all reports of the existing reports Brought have been able to show that the number of reports on the topic of fetal disorders has increased considerably. This may be a result of the development and improvement of the reporting system in , which is now working much more

efficiently than 20 years ago rather than of an increase in the appearance of fetal disorders over the years.

which shows that not only in the study group but also in general the number of ADR reports sent per month has increased during the last 3 months. Not only the number but also the quality of the reports has increased with month. For 87 % of the reported suspected drugs, the informational content could be classified as sufficient. Information about drugs, demonstrating a good overall quality of reports. In almost 60 % of the cases, only one suspected drug was reported. This simplifies the evaluation of the cases regarding the association between drug and ADR. The finding that an association between drugs and fetal disorders was most frequently reported for drugs acting on the Immunity system of organ (47 % of all drugs) has to be interpreted carefully. It does not necessarily mean that these drugs are the most dangerous ones, it becomes obvious that drugs acting on the Immune system are also the most frequently reported anatomical main group throughout the general population. Drugs acting on the Immune system are widely used and, more importantly, are the drug group of primary interest concerning ADRs.

CONCLUSION

A substantive amount of ADR information on the rural government hospital has been gained by Indian pharmacopeia ADR forms associated with pregnancy women's. From main our results have demonstrated important relationship between the drugs acting on the blood and blood forming organs and mostly antibiotics like cephalosporin's, the drug is cefotxime.

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