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SURVEILLANCE AND ASSESSMENT OF ADVERSE DRUG REACTIONS AND COMPARISON WITH THE RETROSPECTIVE STUDIES IN A SECONDARY CARE HOSPITAL

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ABSTRACT: Adverse drug reactions are considered to be among the leading causes of morbidity and mortality. Approximately 5-25% of hospital admissions are due to ADR's, and 6-15% of hospitalized patients experience serious adverse drug reactions (SADR's), causing significant prolongation of hospital stay. The adverse drug reactions reported were classified based on Wills and Brown classification, Causality assessment by the Naranjo's causality assessment scale, the severity of the adverse drug reactions was assessed using modified Hartwig and Siegel severity assessment Scale. Preventability of the adverse drug reactions was assessed using Schumock and Thornton preventability scale. A total of 108 suspected adverse drug reactions (ADR) were reported during the study period. Highest percentages of ADRs were seen in adults (62.03%) than geriatrics (24.07%) followed by pediatrics (13.89%). The present study concluded that continuous ADR monitoring Programme was found to be useful and beneficial in identifying the percentage of ADR occurrence on an annual basis in the hospital and also helpful to the patient and health care professionals for a better therapeutic outcome.

INTRODUCTION: Adverse drug reactions are considered to be among the leading causes of morbidity and mortality. Approximately 5-25% of hospital admissions are due to ADR's [1], and 6-15% of hospitalized patients experience serious adverse drug reactions (SADR's), causing significant prolongation of hospital stay [2]. Moreover, fatal ADR's are estimated to occur in 0.13% of hospitalized patients, and complications from drug therapy constitute the most common adverse events in them [3].

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The detection and reporting of SADR's have become important components of monitoring and evaluation activities in hospitals [4]. The World Health Organisation [5], The United States Food and Drug Administration [6] (USFDA) and the European Medicines Agency [7] (EMA) have recognized the need to evaluate the beneficial and harmful effects of drugs and to continually improve their use to provide appropriate, safe and effective drug therapies.

Advantages of Pharmacovigilance Program from Laboratory Signals are

A. Detection and reporting of SADR's would be increased.
B. Development of systems to improve the detection, reporting, and prevention of SADR's by methods other than spontaneous reporting.

C. The availability of clear denominators would allow calculation of the in-hospital incidence rates for specific ADR's.

Most of the hospitals conduct pharmacovigilance program through the spontaneous reporting system. But spontaneous reporting systems have limitations such as difficulties of recognizing ADR's, the uncontrolled nature of the reporting method, and underreporting. So, retrospective and prospective surveillance methods are considered to be effective than spontaneous reporting systems [8]. Retrospective systems tend to underestimate the burden of the ADR's in hospitals due to the poor documentation of ADR's in medical case sheets and incomplete information available in ADR reports. The main advantage of a prospective system which is unavailable in the retrospective system is: it provides high-quality information regarding an adverse event and early identification of a potential ADR before it exacerbates the clinical condition of an individual patient. Methods used by various pharmacovigilance programs differ greatly because they must be adapted to the specific characteristics of each hospital.

The study was conducted in Government Head Quarters hospital, a 420 bedded hospital providing secondary healthcare to people for the various parts of The Nilgiris district. On an average of 180 out-patients and 20 in-patients are treated and admitted per day, respectively. The hospital has various wards *viz*., intensive care unit, medical wards, surgical wards, pediatric wards, and gynecology department. The study was conducted for a period of 6 months from October 2013 to April 2014 for which a prospective Spontaneous Adverse Drug Reaction reporting method was followed. It was approved by the Institutional Ethical Committee, JSS College of Pharmacy, Ooty (JSSCP/DPP/IRB/ 017/2013-14).

Following were the inclusion and exclusion criteria:

Inclusion Criteria:

- All the patients admitted in Government Head Quarters Hospital (GHQH) were included in this study.
- Patients with ADR reports by healthcare professionals and themselves.
- ADR detected based on drug knowledge and patient interview.

Exclusion Criteria:

- Patients with intentional or accidental poisoning with the drug (Overdose).
- Patients with drug abuse.

For this study, the materials were used as Patient Case Sheets, Patient Medical Records, Adverse Drug Reaction Documentation Formanddifferent ADR assessment scale. Study procedure created awareness about adverse drug reaction and spontaneous reporting among the health care professionals like doctors, nurses, pharmacists, laboratory technicians, nursing students, and pharmacy students. Health Care Personnel were encouraged for ADR reporting through the email, telephonic messages, and direct access during the ward rounds to the pharmacists. The ADR notification forms in the ADR boxes were kept in each ward. Patient's demographic data; presenting complaints; past medical history; drug therapy details including over the counter drugs, current medications and medications on admission were collected. Details of the suspected adverse drug reactions such as time of onset and duration of action, nature and severity of reaction; details of the suspected drug including dose, frequency, time of administration, duration of treatment; previous report on reported reaction; data on any other causes including risk factors and predisposing factors were collected and documented in a suitably designed 'ADR Documentation Form'.

Patients who developed ADR were interviewed daily throughout their hospital stay, from the day the ADR was reported.

The list of the commonly prescribed drugs and the potential spontaneous signals was prepared. These drugs were especially monitored for spontaneous signals along with the routine ADRs. All the drugs prescribed that had Spontaneous adverse Drug Reactions were reported.

- The information was passed to the physician-in-charge.
- In case of management steps that had to be taken, were informed, and the outcomes were monitored.

- The ADR was classified based on Wills and Brown classification.
- The probability of ADR was assessed by using Causality Assessment Scales.
- Preventability of ADR was categorized into Definitely Preventable, Probably Preventable and Not Preventable using the criteria of Schumock and Thornton modified by Lau *et al.*
- Depending upon the severity, ADR was classified into mild, moderate, and severe reactions using Modified Hartwig and Siegel Severity scale. Drug Alert Cards were provided for the patients in case of high morbid and mortal ADRs to prevent the recurrence of a similar ADR in the same patient.
- Feedback to each reporter was given using a "Thank You Note."
- The ADR surveillance report was disseminated in the quarterly bulletin of the Drug Information Centre.

Data Collection Procedure:

ADR Documentation Form: ADR documentation form was suitably designed with all the relevant data's of patient such as patient details including name, age, sex, ward, In-patient or out-patient number, date of admission, diagnosis, patient's allergy status to drugs and food, laboratory data, medication history, description of reaction, onset of action, and prescription details such as generic name, strength, manufacturer, batch number, dose, route of administration, frequency, therapy duration, predisposing factors, dechallenge, rechallenge, seriousness of the reaction, management and treatment of the adverse drug reactions, outcome of management and details of reporter and clinician.

Wills and Brown Classification:

ADR classified as

- Type A (Augmented)
- Type B (Bugs)
- Type C (Chemical)
- Type D (Delivery)
- Type E (Exit)
- Type F (Familiar)
- Type G (Genotoxicity)
- Type H (Hypersensitivity)
- Type U (Unclassified)

Causality Assessment Scales: Causality assessment [9] aims at determining the probability that a specific drug is responsible for the adverse drug event. Adverse events with the high causal association (probable and certain) with the drug are likely to recur. Thus, providing information on this causal link may be useful in preventing future recurrences. Many methods have been developed for a structured and harmonized assessment of causality, but none of the available methods have been shown to produce a precise and reliable quantitative estimation of a relationship likelihood. Some of the available methods are too complex, and time-consuming that their application in routine clinical practice has been limited. Naranjo probability scale and World Health Organisation – Uppsala Monitoring Centre (WHO-UMC) causality assessment method, the two main approaches to causality assessment are discussed. These scales represent convenient, practical tools for assessing the probability that a given reaction can be attributed to a specific drug.

Naranjo's Algorithm: The Naranjo's causality assessment scale consists of 10 questions addressing different issues related to alleged adverse drug reactions, which can be answered with 'yes,' 'no' or 'do not know.' Prefixed numerical scores are attached to the answers, and these scores result in a cumulative value, which can be translated into a causality category. Each question is weighed, with the total at the end of the question categorizing the adverse event as a definite (≥9), probable (5-8), possible (1-4) or doubtful (0) related to the suspected medication.

The elements considered in this algorithm are as follows: previous conclusive report on this reaction, time frame of the occurrence of ADR (after the administration of the suspected drug), improvement in patient after discontinuation of therapy or after administering specific antagonist, patient response with rechallenge, alternative causes for the reaction (other than the drug), recurrence of ADR with placebo, drug detected in the blood (or other fluids) in concentrations known to be toxic, change in severity with increasing or decreasing dose, occurrence of similar reaction to

the same or similar drugs in any previous exposure and availability of objective evidence.

Severity Assessment Scale: Modified Hartwig and Siegel Severity Scale: This scale is used for severity assessment. Depending upon the severity of the suspected reaction, this scale is divided into three categories. They are mild, moderate, and severe. They also have 7 levels. In the 'mild' type reaction level 1 requires no change in treatment with the suspected drug. Whereas in level 2 the ADR requires that the suspected drug be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no increase in the length of stay. For moderate reactions, level 3, the suspected drug should be withheld, discontinued or otherwise changed, and an antidote or other treatment is required. There is no increase in the length of hospital stay for these patients. But level 4(a) is level 3 reactions that increase the length of stay by at least one day, whereas level 4(b) the ADR is the reason for the hospital admission. In the severe type of ADR, level 5 are reactions which require intensive care unit attention. Level 6 reactions cause permanent harm to the patient, whereas in level 7, ADR leads to the death of the patient either directly or indirectly.

Preventability Assessment Scale: Schumock and Thornton Preventability Scale: Schumock and Thornton Preventability scale used to categorize the ADR into Definitely, Probably and Not preventable. In section 'A' an ADR is definitely preventable if there was a history of allergy or a previous adverse reaction to that drug, or if the drug involved was inappropriate for the patient's clinical condition, or if the drug dose, route, and frequency of administration are inappropriate for the patient's age, weight or disease state. In section B, an ADR is considered to be probably preventable if required therapeutic drug monitoring or other necessary tests not performed or if there was a drug interaction or compliance problem, or appropriate preventable measure was not taken, or if the preventative measure is inadequate. If ADR occurs, even after all necessary prevention, it is considered as 'not preventable.'

RESULTS AND DISCUSSION: Ethical approval was obtained for the study from the Institutional Review Board of JSS College of Pharmacy, Ooty and the study were conducted in the Government Head Quarters Hospital, a 420 bedded hospital providing secondary health care for the people of The Nilgiris District.

Evaluation of Data: A total of 108 suspected adverse drug reactions (ADR) were reported during the study period (6 months).

Majority of the ADRs were observed through spontaneous reporting among adults *i.e.* 61.68% (n=66) than the paediatrics 14.95% (n=16) and geriatrics 23.364% (n=25). It showed similarity to the results obtained in the studies conducted in the year 2013-14 and 2008-09.

Suspected Adverse Drug Reactions Reported from the Study Wards: Adverse drug reactions were obtained from 5 medical wards of the hospital (Female ward, Male ward, Gynaecology, ICU (Intensive care unit) and Paediatric ward.

Table 1 represents the ADRs reported from the different wards of the hospital. From female medical ward about 39.25% (n=42) ADR's were reported followed by male medical ward 25.23% (n=27), ICU 20.56% (n=22), paediatrics & NICU 12.14% (n=13) and Obstetrics & gynec 2.80% (n=3). The results found to be comparable to that obtained from a study conducted in 2008-09 were also the higher incidences of ADRs was reported in the female ward (29.52%) and ICU (31.93%) although the incidence of ADRs in the respective wards was found to be decreased in this study.

TABLE 1: ADVERSE DRUG REACTIONS REPORTED IN THE DIFFERENT UNITS

Medical/Surgical Ward	Spontaneous ADR (%)
Male medical ward	27 (25.23%)
Female medical ward	42 (39.25%)
Intensive care unit	22 (20.56%)
Pediatrics and NICU	13 (12.14%)
Obstetrics and gynaec	3 (2.80%)
Total	108 (100%)

Classification of Adverse Drug Reactions Reported using Wills and Brown Classification: The adverse drug reactions reported were classified based on Wills and Brown classification and it is reported in **Table 2**. Majority of ADRs through spontaneous reporting was of Type A 75.70% (n=81) followed by Type H 18.691% (n=20) reactions.

The results were different from the study conducted during the year 2012-2013 which showed that 51.06% ADRs were of Type H followed by Type A (40.42%), and the results were similar as compared from the study conducted during the year 2008-2009 showed that 45.48% ADRs were Type A(n=75) followed by Type H (17.46%) n=21

TABLE 2: WILLS AND BROWN CLASSIFICATION FOR THE ADVERSE DRUG REACTIONS REPORTED

Classification	Spontaneous ADRs (%)
Type A	81 (75.7009%)
Type D	1 (0.9%)
Type H	20 (18.691%)
Type U	5 (4.67%)
Total	107 (100%)

Causality Assessment: The suspected adverse drug reactions were assessed using Naranjo's Causality assessment scale to establish the extent of the relationship between the suspected drug and the reaction. According to Naranjo's Algorithm majority of the ADRs through spontaneous reporting were probably 70.09% (n=75), followed by Definite 16.822% (n=18) and possible 13.084% (n=14). The result showed similarity with the study conducted during the year 2012-2013 and 2008-2009.

Severity Assessment: Severity of the adverse drug reactions was assessed using modified Hartwig and Siegel severity assessment Scale. Majority of the ADRs through spontaneous reporting were mild: Level 1 (n=73), Level 2 (n=24) with a total of 90.65 % (n=97) followed by moderate: Level 3 (n=7) and level 4 (a) (n=1) with a total of 7.47% (n=8) and severe: Level 5 (n=2) with a total of 1.86%. This result was similar to the study conducted during the year 2012-2013 and 2008-2009.

Preventability Assessment: Preventability of the adverse drug reactions was assessed using Schumock and Thornton preventability scale. Majority of the ADRs through Spontaneous reporting were not preventable 76.63% (n=82) followed by probably preventable 19.62% (n=21) and definite preventable 3.73% (n=4) and is presented in **Table 3** which was similar to the results in the study conducted during the year 2012-2013 and no results were obtained in the year 2008-2009 using this scale.

TABLE 3: PREVENTABILITY OF THE REPORTED ADVERSE DRUG REACTIONS BASED ON SCHUMOCK AND THORNTON PREVENTABILITY SCALE

Preventability	No. of spontaneous ADRs (%)
Definite preventable	4 (3.73%)
Probably preventable	21 (19.62%)
Not preventable	82 (76.63%)
Total	107 (100%)

CONCLUSION: The present study made observations on the suspected adverse drug reactions through prospective spontaneous reporting. The study was conducted in a secondary care hospital for over six months (October 2013 to April 2014). It came across with the various factors such as the patient demographics, most commonly involved drug classes, most commonly affected organ system, type of ADRs, management, and outcome related to ADR, seriousness, causality, preventability and severity assessment of ADRs. The ADR reporting programs are required to educate and increase awareness about reporting of ADRs among health care professionals that helps to improve the quality of patient care.

A total of about 108 ADRs were identified through spontaneous reporting. Highest percentages of ADRs were seen in adults than pediatrics and geriatrics. Type A reactions accounted for the majority of reports based on spontaneous reporting. The dermatological system was the most commonly affected organ system. Antibiotics were the drug class most commonly involved in spontaneous reporting ADRs. Most of the ADRs were reported from the medical wards compared to other wards in the hospital. Majority of the reports were rated as probable, not preventable and mild Level - 1 according to the Naranjo's causality scale, Schumock and Thornton Preventability Scale, Modified Hartwig and Siegel Severity Scale respectively.

Compared to the previous studies conducted during the year of 2008-09 and 2012-13 the results were found to be comparable with some differences like the high prevalence of type A reaction, unlike the previous studies where type H reactions were more prevalent. Although antibiotics are the main source of ADRs in all the 3 studies but in the present studies it was found to be increased almost by 20%. Monitoring of ADRs is an ongoing and continuing process, in which clinical pharmacist and other

health care professionals play a vital role to enhance effective patient care. The study concluded that ADR monitoring program was found to be useful and beneficial to the patient and health care professionals for a better therapeutic outcome.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

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