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# MONITORING AND REPORTING OF ADVERSE DRUG REACTIONS WITH ANTIMICROBIAL AGENTS IN A TERTIARY CARE HOSPITAL

**S M. Biradar*, Nikita Katti, N V. Kalyane, Ch. Srinath Reddy., Vinod M. and V Aishwarya.**

Department of Pharmacy Practice, BLDEA's College of Pharmacy, Shri. B M. Patil Medical College Hospital and Research Centre, Bijapur-586103.

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***Correspondence for Author**

**S M. Biradar**

Department of Pharmacy Practice, BLDEA's College of Pharmacy, Shri. B M. Patil Medical College Hospital and Research Centre, Bijapur-586103.

## ABSTRACT

***Background:*** Antimicrobials are the most frequently prescribed drugs among hospitalized patients. Antimicrobial resistance, adverse drug reactions (ADRs) and ADRs in biological systems substantially raises health care costs and increases patient's morbidity and mortality rate. With respect to above perspective, the present research was carried out to study the type of ADRs, severity, preventability, probability and Consequences of ADRs involved with the prescription of antimicrobial agents. The commonest drugs involved in ADRs, features of ADRs and biological systems involved in ADRs also been studied. ***Methods:*** A prospective study was carried out for a period of 9 months from Jan. 2014 to Sept. 2014 with the sample size of 160 patients. ADRs were assessed from the in-patient's case report from, yellow forms, medication chart and through patient interviews. ADRs were evaluated by using different scales, such as Naranjo's Assessment scale for Probability, Modified Hartwig Scale for severity and Modified Shumock & Thoronto Scale for Preventability of ADRs. ***Results:*** A total number of 160 patients were included in to the study population, out of which 92(57.5%) were males and 68(42.5%) were females. The higher number of ADR's were seen in male (28) compared to female patients (23). Majority of ADRs occurred in age the group of 36-45 yrs. Out of 51 ADRs, 21 were during hospital admission, 13 were due to ADR induced hospital stay, 12 were during chart review and 5 were through spontaneous reporting. Among 51 ADRs Type A were 39 and Type B were 12 in number. According to Naranjo's

probability assessment scale most of ADRs were possible 29 and probable were 22. Using the Modified Hartwigscale the ADRs were divided into mild 10 (19.60%), moderate 28 (54.90%), severe 13 (25.49%). According to Modified Shumock & Thoronto criteria Preventability assessment of ADRs were divided into Not preventable 01 (1.96%), probably preventable 41(80.39%) and definitely preventable were 11 (21.56%). The commonest system/organ involved in ADRs were skin accounting for 14 (56.20%), Heamatic 13(41.61%), GIT 9 (34.46%), Hepatobiliary 7 (36.01%), Opthalmic 4 (16.61%), musculoskeletal 2 (7.14%) and CNS 1 (4.34%). In 51 ADRs 10 (19.60%) were of the type anaemia, followed by blurred vision, hepatomegaly.Anti viral agents were found to be major class involved in ADRs around 37.25%. ***Conclusion:*** A wide range of ADRs may be produced with many numbers of prescribed drugs including antimicrobial agents; hence every health care professional must have to update the knowledge drug's ADRs and be cautious while prescribing the drugs. The present study provides the greater possibilities of ADRs of antimicrobials agents, which could be helpful to the prescribers for the selection of antimicrobials agents with least ADRs for better patient compliance.

**KEYWORDS*:*** Prospective study, Antimicrobial Agents, Adverse Drug Reactions.

## INTRODUCTION

Efficacy and safety are the two major concerns of drugs. While efficacy of a drug can be quantified with relative ease, the same cannot be said about safety. Medicines can treat or prevent illness and diseases. However, sometimes medicines can cause problems. These problems are called adverse drug reactions. Anybody can have an adverse drug reaction. However, people who take more than 3 or 4 medicines every day are more likely to have an adverse drug reaction.[1]

The WHO definition of an adverse drug reaction (ADR) is '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 modifications of physiological function'. An Adverse drug event (ADE) is medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related.[2]

In India there are very few active ADRs monitoring centers and a lot of effort is required in order to collect ADR data which may generate from safety surveillance of billions of therapeutically active substances either alone or in combinations. [3] Adverse drug reactions

(ADRs) are a great concern in therapeutics. An incidence of 5% to 35% is observed in all age groups among outpatients. ADRs are the fourth leading cause of death ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents and automobile deaths. Serious ADRs account for 6.7% of all hospital admissions. ADRs have an economic burden on the patients as well as on the health care establishment.[4] The leading causal therapeutic class of medicines implicated were antimicrobials followed by anticancer drugs, antipsychotics, and analgesic.[5]

Due to lack of reporting the real picture of ADRs is difficult to estimate. ADR monitoring cell of drug administration should be more active in this regard. We should strengthen the program of pharmacovigilance to ensure the safe use of medicines in the community. It is the preliminary study which tried to evaluate the response of reporting of ADRs among medical practitioners and pattern of ADRs Reported, in order to improve self/spontaneous reporting.[1]

When antibiotics are prescribed to large numbers of persons in a population, resistant bacteria may become the predominant organisms in that community. Appropriate prescribing of antibiotics may slow the rate at which resistance becomes widespread throughout the community.[6]

## MATERIALS AND METHODS

This prospective observational study was carried out for a period of nine months in Inpatients of medicine wards at Shri B.M. Patil Medical College, Hospital and research centre, Bijapur. Total of 160 cases were collected of all ages and either sex from inpatients from medicine department. Patients with over prescription, Excess consumption of medicines, improper administration of the drugs, Medication errors, and accidental & intentional poisonings were excluded from the study. After obtaining approval and clearance from institutional ethics committee, 160 subjects were included in the study after receiving individual informed consent. Data of spontaneously reported ADRs by healthcare professionals was collected through the hospital ADR reporting form (yellow form) made available at medicine wards. For each patient with suspected ADR, a detailed history including drug History, personal history, family history, present and past medical history, and history of previous drug allergy were documented. The pattern of reported ADRs was analyzed for the causality of the reactions using Naranjo's causality assessment scale, severity of ADR using Modified Hartwig scale and preventability assessed by using Modified Schumock and Thornton scale. Statistical analysis carried out by chi square test. A p value $< 0.005$ was considered significant.

## RESULTS

There were 51 suspected ADRs were reported among 160 cases of inpatients from medicine department conducted during the study period and details are as follows.

### Gender distribution

A total number of 160 patients were taken for the study, out of which 92 comprising of male patients constituting 57.5% and 68 were females constituting 42.5%. Males were more in number compared to females (Table 1). The higher number of ADR's were seen in male (28) compared to female patients (23) (Table 2).

### Age distribution of study populations

Of total patients considered, a higher number of patients lying between the age group of 26-35yrs (39.76%), followed by 36-45yr and 46-55yr [37.58%] (Table 3). Majority of ADRs occurred in age group of 36-45 yrs comprising of 14[27.45%] ADRs, followed by age group 26-35yrs constituting 13(25.49%), a few number of ADRs 4 (7.84%) were seen in the age group of 15–25 and >65 yrs(Table 4).

### Correlation of ADRs with duration of treatment

Majority of ADRs occurred within one week of treatment constituting 14 ADRSs (27.45%), followed by more than 1 month (25.49%) and more than 12 months (25.49%) of treatment. ADRs occurred within a day were 7 (13.72%). A very few number of ADRs occurred within a month of treatment constituting 4 (7.84%) (Table 5).

### Detection of ADRs

Detection of ADRs was carried out as, spontaneous reporting, chart review, ADRs during hospital stay and ADRs induced hospital admission. Out of 51 ADRs, 21(41.17%) were during hospital admission, 13 (25.49%) were during ADR induced hospital stay, 12 (23.52%) were during chart review and 5 (9.80%) were during spontaneous report (Table 6).

### Types of ADRs

All the ADR's were divided into two major types: Type A and Type B reactions. Out of total 51 ADR's Type A were 39 (76.47%) and Type B were 12 (23.52%) (Table 7).

### Naranjo's Assessment scale for Probability of ADRs

According to Naranjo's probability assessment scale most of ADRs were possible 29 (56.86%) and probable were 22 (43.13%) (Table 8).

**Modified Hartwig Scale for severity of ADRs**

Using the Modified Hartwig scale the ADRs were divided into mild 10 (19.60%), moderate 28 (54.90%), severe 13 (25.49%) (Table 9).

**Modified Shumock & Thoronto Scale for Preventability of ADRs**

According to Modified Shumock & Thoronto criteria Preventability assessment of ADRs were divided into Not preventable 01 (1.96%), probably preventable 41(80.39%) and definitely preventable were 11 (21.56%) (Table 10).

**ADRs affect the Biological systems**

The commonest system/organ involved in ADRs were skin accounting for 14 (56.20%), Heamatic 13(41.61%), GIT 9 (34.46%), Hepatobiliary 7 (36.01%), Opthalmic 4 (16.61%), musculoskeletal 2 (7.14%) and CNS 1 (4.34%) (Table 11).

**Chief complaints of ADRs**

Anaemia is major presenting complaint of patients. In 51 ADRs 10 (19.60%) were of the type anaemia, followed by blurred vision, hepatomegaly and thereof. The details are given in Table 12.

**Therapeutic drug classes involved in ADRs**

Anti viral agents were found to be major class involved in ADRs around 37.25%, then it was followed by anti-tubercular agents 17.64%, details are given in Table 13. Some of important individual drugs effects on ADRs profile (Table 14).

**Consequence of ADR**

Patients continued with the same drug 13 (25.49%) with mild ADRs on risk/benefic ratio, 23 (45.09%) ADRs were need to stop the drug administration, 15 (29.41%) ADRs were needed other drugs treatment to stop the ADRs occurred (Table 15).

**Table 1. Gender distribution.**

| GENDER | NUMBER WITH ADRs | NUMBER WITHOUT ADRs | TOTAL | PERCENTAGE |
|---|---|---|---|---|
| Male | 28 | 64 | 92 | 57.5% |
| Female | 23 | 45 | 68 | 42.5% |
| Total | 51 | 109 | 160 | 100.0% |

**Table 2. Correlation between Gender and ADRs.**

| GENDER | NUMBER OF ADRs | PERCENTAGE |
|---|---|---|
| Male | 28 | 54.90% |
| Female | 23 | 45.09% |

**Table 3. Age distribution of study populations.**

| Age Group (in years) | MALE | | FEMALE | | TOTAL | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| 15- 25 | 8 | 8.69% | 11 | 16.17% | 19 | 24 .86% |
| 26- 35 | 19 | 20.65% | 13 | 19.11% | 31 | 39.76% |
| 36-45 | 17 | 18.47% | 13 | 19.11% | 30 | 37.58% |
| 46- 55 | 19 | 20.65% | 11 | 16.17% | 30 | 37.58% |
| 56- 65 | 15 | 16.30% | 14 | 20.58% | 27 | 36.88% |
| ≥ 65 | 14 | 15.21% | 6 | 8.82% | 19 | 24.03% |
| Total | 92 | | 68 | | 160 | |

**Table 4. Correlations between Age and ADRs.**

| AGE | NO. Of ADR's | PERCENTAGE |
|---|---|---|
| 15 – 25 | 4 | 7.84% |
| 26 – 35 | 13 | 25.49% |
| 36 – 45 | 14 | 27.45% |
| 46 – 55 | 8 | 15.68% |
| 56 – 65 | 8 | 15.68% |
| ≥ 65 | 4 | 7.84% |

**Table 5. Correlation of ADRs with duration of treatment.**

| DURATION | NO | % |
|---|---|---|
| Within a day | 7 | 13.72%. |
| Within 1 week | 14 | 27.45% |
| Within 1 month | 4 | 7.84% |
| ≥1 month | 13 | 25.49% |
| ≥ 12 months | 13 | 25.49% |

**Table 6. Detection of ADRs**

| DETECTION METHOD | NO. OF ADRS | PERCENTAGE |
|---|---|---|
| Spontaneous report | 5 | 9.80% |
| Chart review | 12 | 23.52% |
| ADRs during hospital stay | 21 | 41.17% |
| ADRs induced hospital admissions | 13 | 25.49% |

**Table 7. Types of ADRs**

| TYPES OF ADR* | MALE | | FEMALE | | TOTAL |
|---|---|---|---|---|---|
| | Male | % | Female | % | % |
| **Type A** | 22 | 43.13% | 17 | 33.33% | 39 (76.47%) |
| **Type B** | 5 | 9.80% | 7 | 13.72% | 12 (23.52%) |
| **Total no of ADRs** | 27 | 52.93% | 24 | 47.05% | 51 (100.0%) |

**Table 8. Naranjo's Assessment scale for Probability of ADRs**

| PROBABILITY SCALE* | NO. OF ADRS | PERCENTAGE |
|---|---|---|
| Definite (9-10) | 0 | 0.00% |
| Probable(5-8) | 22 | 43.13% |
| Possible(1-4) | 29 | 56.86% |
| Doubtful (0) | 0 | 0.00% |

**Table 9. Modified Hartwig Scale for severity of ADRs**

| SEVERITY SCALE* | NO OF ADRS | PERCENTAGE |
|---|---|---|
| Mild (1-2) | 10 | 19.60% |
| Moderate (3-4) | 28 | 54.90% |
| Severe (5-6) | 13 | 25.49% |
| Fatal 7 | 00 | 00.00% |
| Total No. of ADRs | 51 | 100% |

**Table 10. Modified Shumock & Thoronto Scale for Preventability of ADRs**

| PREVENTABILITY SCALE* | NO OF ADRs | PERCENTAGE |
|---|---|---|
| Definitely Preventable | 11 | 21.56% |
| Probably Preventable | 41 | 80.39% |
| Not Preventable | 01 | 1.96% |
| Total No. of ADRs | 51 | 100.0% |

**Table 11. ADRs affect the Biological systems.**

| ORGAN SYSTEM | MALE | | FEMALE | | TOTAL | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Skin | 6 | 21.42% | 8 | 34.78% | 14 | 56.20% |
| Haematology | 8 | 28.57% | 3 | 13.04% | 13 | 41.61% |
| Ophthalmology | 1 | 3.57% | 3 | 13.04% | 4 | 16.61% |
| Hepatobiliary system | 4 | 14.28% | 5 | 21.73% | 7 | 36.01% |
| Metabolic | 1 | 3.57% | 0 | 0.00% | 1 | 3.37% |
| Gastrointestinal system | 6 | 21.42% | 3 | 13.04% | 9 | 34.46% |
| Musculoskeletal | 2 | 7.14% | 0 | 0.00% | 2 | 7.14% |
| Central nervous system | 0 | 0.00% | 1 | 4.34% | 1 | 4.34% |
| Total | 28 | | 23 | | 51(100.0%) | |

**Table 12. Chief complaints of ADRs.**

| COMPLAINTS | MALE | | FEMALE | | TOTAL | |
|---|---|---|---|---|---|---|
| | NO | % | NO | % | NO | % |
| Anaemia | 6 | 11.76% | 4 | 7.84% | 10 | 19.60% |
| Blurring vision | 1 | 1.96% | 3 | 5.88% | 4 | 7.84% |
| Hepatomaegaly | 2 | 3.92% | 2 | 3.92% | 4 | 7.84% |
| Diarrhoea | 2 | 3.92% | 2 | 3.92% | 4 | 7.84% |
| Hypersensitivity reaction | 0 | 0.00% | 3 | 5.88% | 3 | 5.88% |
| Erythroderma | 1 | 1.96% | 2 | 3.92% | 3 | 5.88% |
| Echymatous patches | 1 | 1.96% | 2 | 3.92% | 3 | 5.88% |
| Uticaria | 3 | 5.88% | 0 | 0.00% | 3 | 5.88% |
| Vomiting | 2 | 3.92% | 2 | 3.92% | 4 | 7.84% |
| Melanonychia | 2 | 3.92% | 0 | 0.00% | 2 | 3.92% |
| Facial puffiness | 0 | 0.00% | 2 | 3.92% | 2 | 3.92% |
| Liver enzymes increased | 2 | 3.92% | 0 | 0.00% | 2 | 3.92% |
| Blood urea nitrogen | 0 | 0.00% | 1 | 1.96% | 1 | 1.96% |
| Gastritis | 1 | 1.96% | 0 | 0.00% | 1 | 1.96% |
| Thrombocytopenia | 1 | 1.96% | 0 | 0.00% | 1 | 1.96% |
| Neutropenia | 1 | 1.96% | 0 | 0.00% | 1 | 1.96% |
| Achill tendonitis | 1 | 1.96% | 0 | 0.00% | 1 | 1.96% |
| Peripheral neuropathy | 0 | 0.00% | 1 | 1.96% | 1 | 1.96% |
| Metabolic alkalosis | 1 | 1.96% | 0 | 0.00% | 1 | 1.96% |

**Table 13. Therapeutic drug classes involved in ADRs**

| CLASS | No. OF ADRS | SUSPECTED DRUGS | NO. OF ADRs | PERCENTAGE |
|---|---|---|---|---|
| **ANTIBIOTICS** | 7 | Magnamycin | 1 | 13.72% |
| | | Ceftazidime | 1 | |
| | | Cefixime | 1 | |
| **Cephalosporin** | | Ceftriaxone+salbutamol | 1 | |
| | | ceftriaxone | 3 | |
| **Fluroquinoles** | 5 | Levofloxacin | 2 | 9.80% |
| | | Ofloxacin | 1 | |
| | | Ofloxacin+ ornidazole | 2 | |
| **Oxazolidones** | 4 | Linezolide | 4 | 7.84% |
| **Macrolides** | 2 | Azithromycin | 1 | 3.92% |
| | | Tobramycin | 1 | |
| **others** | 1 | Amphotericin B | 1 | 1.96% |
| **ANTI VIRAL** | 19 | Zidovudine | 8 | 37.25% |
| | | Lamivudine | 3 | |
| | | Efaverinz | 4 | |
| | | Z+L+N | 3 | |
| | | Tenofovir + Lamivudine | 1 | |
| **ANTI TUBERCULAR** | 9 | Ethambutol | 4 | 17.64% |
| | | H+R+Z+E | 3 | |
| | | Isoniazide | 1 | |
| | | Rifampcin | 1 | |
| **ANTI MALARIAL** | 4 | Chloroquine | 1 | 7.84% |
| | | Artether | 2 | |
| | | Artesunate | 1 | |

**Table 14. Individual drugs effects on ADR profile.**

| Class | Drug | Type of ADRs | Probability | Severity |
|---|---|---|---|---|
| **Cephalosporin** | Magnamycin | Type B | Possible | Mild |
| | Ceftazidime | Type B | Possible | Moderate |
| | Cefixime | Type B | Possible | Moderate |
| | Ceftriaxone+salbutamol | Type B | Probably | Moderate |
| | Ceftriaxone | Type A | Possible | Mild |
| **Fluroquinoles** | Levofloxacin | Type A | Possible | Moderate |
| | Ofloxacin | Type B | Possible | Mild |
| | Ofloxacin+ ornidazole | Type B | Probably | Mild |
| **Oxazolidones** | Linezolide | Type A | Probably | Mild |
| **Macrolides** | Tobramycin | Type B | Probably | Mild |
| | Azithromycin | Type B | Probably | Mild |
| | Amphotericin B | Type A | Probably | Mild |
| **Anti viral** | Zidovudine | Type A | Probably | Moderate |
| | Lamivudine | Type A | Probably | Moderate |
| | Efaverinz | Type A | Possible | Sever |
| | Z+L+N | Type A | Possible | Moderate |
| | Tenofovir +Lamivudine | Type A | Probably | Sever |
| **Anti tubercular** | Ethambutol | Type A | Possible | Moderate |
| | H+R+Z+E | Type A | Possible | Moderate |
| | Isoniazide | Type B | Possible | Mild |
| | Rifampcin | Type A | Possible | Mild |
| **Anti malarial** | Chloroquine | Type B | Possible | Moderate |
| | Artether | Type B | Probably | Mild |
| | Artesunate | TypeA | Possible | Mild |

**Table 15. Consequence of ADR**

| Consequence of ADR | NO. | Percentage |
|---|---|---|
| Patients continued the drug | 13 | 25.49% |
| Drug had to be stopped | 23 | 45.09% |
| ADR developed after stopping the drug | 00 | 0.00% |
| ADR needed treatment with other drug | 15 | 29.41% |
| Total | 51 | 100% |

## DISCUSSION

As concern with ADRs prevalence, males were more predominance than female. Majority of study reveals that males have higher incidence of ADRs than females. This needs to be interpreted in the light of higher number of male admissions. There are various factors affecting the ADR incidence, such as age of patients, gender, number of drug exposure, length of hospital stay, genetic factors, ethnicity, dietary, and environmental factors.[7]

In the present study the majority of ADRs were from the age 36-45 years, this observation is in contradiction with the earlier studies, where incidence of the ADRs have been observed

with the increase in age, suggesting age is a risk factor for the occurrence of the ADRs. However the results that the present study has revealed could be due to less number of geriatric patients attending the study site.[8]

According to correlations of ADRs with duration of treatment, Majority of ADRs occurred within one week of treatment. Based on Thompson's and Rawlins classification, it was observed that, maximum were Type A reactions.[9]

Majority of ADRs were detected during hospital stay, from the above results, it is evident that the number of ADRs reported by spontaneous reporting method were very less when compared to the overall ADRs detected during the study period. Also, a large number of ADRs were not reported spontaneously were detected during the chart reviews by clinical pharmacists.[10] Which highlights the importance of pharmacists as manual chart reviewers in ADRs detection the less number of ADRs detected by spontaneous reporting method highlighted the problem of under-reporting of ADRs.[11]

The causality assessment of the ADRs was carried out using Naranjo's scale. Possible were more.[12] Thus a majority of the ADRs detected were of moderate severity. [13] Preventability of ADRs was assessed by using Modified Shumock and Thornton criteria. Majority of ADRs encountered were found to be probably preventable, ADRs coming under the class of "probably preventable" and definitely preventable" highlights the importance of pharmacovigilance program, regularly updating the clinicians and educating the patients on ADRs. In this study there were no reporting found from nursing department, this may be due to lack of awareness among nurses on ADR monitoring.[14]

Drugs can affect any organ system of the body, again it depend on nature of a drug. It is observed that the most of ADRs were reported with skin. The data collected on the ADRs during the study Period was analyzed to detect the various therapeutic classes of drugs implicated in ADRs, majority of drugs were Anti-Viral followed by Anti-Tubercular, Cephalosporins, other classes of drugs were found to be very less. Consequence of ADR classified as, patient continued the drug, drug had to be stopped, and ADR developed after stopping the drug and ADR needed treatment with other drugs. Majority of consequence of ADR resulted to stop the drug.

## CONCLUSION

Hospital based ADR monitoring and reporting programs aims to identify and quantify the risks associated with the use of drugs. This information may be useful in identifying and minimizing preventable ADR while generally enhancing the knowledge of the prescribers to deal with ADRs more efficiently. Monitoring adverse effects of drugs is important aspect of health care setup as very less is known about the safety profile of the drugs from its preclinical and clinical data before the product is marketed. Among all the reported ADRs, most of them were preventable. By the implementation of a successful ADR surveillance system there can be a positive impact on the medication use which will ultimately lead to a better patient care and in reducing the excess length of stay in hospital, extra costs involved, and attributable mortality.

The pattern of ADRs reported in our hospital is comparable with the result of previous studies conducted in different hospital setup elsewhere. This study provides data base of ADRs due to common drugs in our hospital, which will help clinician for optimum and safe use of drugs. Hence strict vigilance is required for the use of these likely drugs and their safety assessment.

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