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Incidence of adverse drug reaction and its outcome among patients in tertiary care hospital, Uttar Pradesh

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Abstract---Introduction: World Health Organization defines adverse drug reactions (ADRs) as any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. For evaluating the incidence and outcome of adverse drug reactions (ADRs) to assist in minimizing the deleterious effects, the present study was planned to find the incidence of ADR, its severity, and outcomes among patients. Material and Methods: The spontaneous ADR reporting technique and the Suspected Adverse Drug Reaction Reporting Form were used for the data collection and reporting. All patients who developed an ADR during the study period has included. By using Expanded Rawlins and Thompson's classification, all patients were categorized into types A to F and classified according to the severity levels (mild, moderate, severe) by applying the Modified Hartwig severity scale. The classification of outcomes of the ADRs was done as per WHO criteria as fatal, continuing, recovering, recovered, unknown, or any other.

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Results: Type B (Bizarre) ADRs were found to be the most frequently occurring ADRs (51%) followed by type A (Augmented) 29%. Maximum ADR cases were found in the 12-45 years age group (58%). On the severity scale, the majority of ADRs were found of moderate severity (64% moderate v/s 35% mild). Only 15 % of reactions were serious in nature and the maximum burden (61%) of serious ADRs was found with type B. The best outcome has been found in type B ADRs while type-D and type-C ADRs have more protracted courses. Conclusion: In the present study the incidence of ADRs was clinically significant among study patients. ADRs increase patients' morbidity, mortality, cost of health care, and duration of hospital stay. Although, further studies are needed with a more focused approach.

Keywords---adverse drug reactions, incidence, outcome, patients.

Introduction

The history of adverse drug reactions is over 2000 years old. In the 10th century AD, the medical school of Salerno in Italy was empowered to hang offending druggists if they were found to have sold a poison or noxious drug. In 1937, at the dawn of the antimicrobial era, 105 people died after ingesting a sulfanilamide preparation known as Elixir Sulfanilamide. However, the seminal moment in drug safety was the thalidomide case in the 1960s when a large number of children were born with limb deformities. Following this incident, a major change occurred in the monitoring of the ongoing safety of medicines. [4] Since then, pharmacovigilance has been considered a critical activity by medical and drug manufacturing personnel. During the last few years, pharmacovigilance has been more visible and talked about for the reason of patient safety. Medical science has progressed a lot in recent years, but this development has led to a new group of diseases called iatrogenic diseases. While most patients derive far more benefit than harm, a proportion of them experience adverse drug reactions (ADRs) from the use of the medicines at recommended doses and frequencies.[9]

World Health Organization defines adverse drug reactions (ADRs) as any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. For evaluating the incidence and outcome of adverse drug reactions (ADRs) to assist in minimizing the deleterious effects, the present study was planned to find the incidence of ADR, its severity, and outcomes among patients. the present study was planned at GSVM Medical College and associated hospitals, Kanpur, Uttar Pradesh. This study has been conducted the keeping following objectives in mind;

- To estimate the incidence of ADRs in patients
- To determine the pattern of the severity of ADRs.
- To find the outcome of reported ADRs.

Materials and Methods

Study type, population, and area

A prospective study was conducted among patients who developed an ADR during12-months the study period in the LLR & Associated Hospitals, GSVM Medical College, Kanpur, Uttar Pradesh.

Exclusion criteria

Patients who developed an ADR due to intentional or accidental poisoning, ADRs due to fresh blood/blood products, and patients with drug abuse and intoxication.

Methodology

All patients who developed an ADR during the study period has included in the study. The spontaneous ADR reporting technique and the Suspected Adverse Drug Reaction Reporting Form were used for the data collection and reporting of ADRs. All cases were properly assessed and discussed with treating clinicians and were further analyzed for types of ADR. By using expended Rawlins & Thompson's classification, there are six types of ADRs namely Type A (augmented pharmacologic effects), Type B (bizarre effects), Type C (chronic, cumulative effects), Type D (delayed effects), Type E (end-of-treatment effects), and Type F (failure of therapy) [10]. Assessment of the severity levels (mild, moderate, severe) was done by applying the Modified Hartwig severity scale. The classification of outcomes of the ADRs was done as per WHO criteria as fatal, continuing, recovering, recovered, unknown, or any other.

Statistical analysis

All the above variables were recorded in MS excel and SPSS 23 Version software simultaneously. Data has been presented in form of tables and charts and statistical analysis was carried out using an appropriate test. Nominal data were analyzed using the Chi-square or Fisher's exact test. Statistical significance was accepted as $P < 0.05$.

Results

During the study period, 185 reported ADR cases were reported and assessed. Out of 185 ADRs, 105 (57%) were in male patients and 80 (43%) were in female patients. [Figure1]

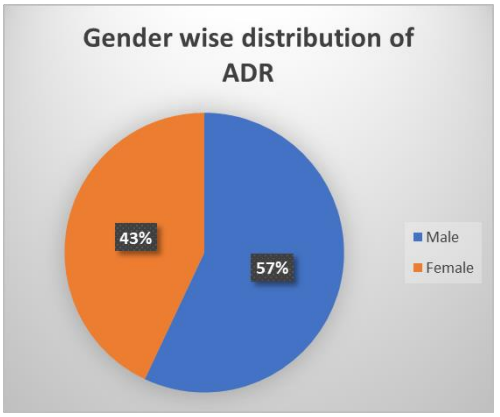

Figure 1

Out of the total 185 ADRs, Type B (Bizarre) ADRs were found to be the most frequently occurring ADRs 94 (51%) followed by type A (Augmented) 29%. Twenty-seven (15%) patients were of type C and 10 (5%) were of type D. There were no type E and type F ADRs reported. [Table 1]

Table 1
Distribution of Types of ADR among study subjects

ADR Type	Frequency (n=185)	Percentage (%)
A	54	29
B	94	51
C	27	15
D	10	5
E	0	0
F	0	0

Table 2 shows the gender distribution of ADRs. There was the same gender distribution of patients in type A, 27(50%) each. Among type B, 53(56%) of ADRs were in males and 41(44%) in females while type C 18(67%) were in males and 9(33%) in females. Among type D 7(70%) of ADRs were in males and 3(30%) were in females.

Table 2
Distribution of Types of ADR by Gender of study subjects

ADR Type	Gender			
	Male		Female	
	Frequency (n=105)	Percentage (%)	Frequency (n=80)	Percentage (%)
A	27	50	27	50
B	53	56	41	44
C	18	67	9	33
D	7	70	3	30

E	0	0	0	0
F	0	0	0	0

Chi-square value = 2.80 p>0.05, Inference- Not significant

Maximum ADR cases were found in the age group 12-45 years, 107 (58%) followed by 25 (13%) cases below 12 years of age, and 53 (29%) cases were in the less 45 years age group. Among the less than 12 years age group, the majority (92%) of type B ADRs followed by 4% of ADRs of type A and type C each. In the 12 – 45 years age group 30% of ADRs were of type A, 50% of type B, 17% of type C and 3% were of type D. In > 45 years age group 40% of ADRs were of type A, 34% of type B, 13% of type C and 13% were of type D. Among type A ADRs, 2% were found in <12 years age group, 59% in 12 – 45-year age group and 39% in > 45 years group. Among type B ADRs 25% were in the < 12 years age group, 56% in the 12 – 45 years group, and 19% in the> 45 years group. Among type C ADRs 4% were found in the < 12 years age group, 70% in the 12 – 45 years age group, and 26% in the> 45 years age group. Among type D ADRs 30% were found in the 12 – 45 years age group and 70% in the> 45 years age group. On applying the chi-square test for the association between ADR and age groups, these findings were statistically significant (χ^2= 17.05, p<0.05). [Table 3]

Table 3
Distribution of types of ADR by Age Groups of study subjects

ADR Type	Age						Total
	<12 Years		12 to 45 Years		>45 Years		
	Frequency (n=25)	Percentage (%)	Frequency (n=107)	Percentage (%)	Frequency (n=53)	Percentage (%)	
A	1	4	32	30	21	40	54
B	23	92	53	50	18	34	94
C	1	4	19	17	7	13	27
D	0	0	3	3	7	13	10
E	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0

On the severity scale, the majority of ADRs were found of moderate severity, 119 (64%) and 65 (35%) mild in form. In type A, 41% were mild, 57% moderate, and 2% severe. Among type B, 23% were mild and 77% moderate. Among type C, 78% were mild and 22% moderate. Among type D ADRs, all (100%) were of moderate severity. On applying the chi-square test for the association between ADR and severity, these findings were statistically significant (χ^2= 16.35, p<0.05). [Table 4]

Table 4
Distribution of Types of ADR by Severity condition

ADR Type	Mild		Moderate		Severe		Total
	Frequency (n=65)	Percentage (%)	Frequency (n=119)	Percentage (%)	Frequency (n=1)	Percentage (%)	
A	22	41	31	57	1	2	54
B	22	23	72	77	0	0	94

C	21	78	6	22	0	0	27
D	0	0	10	100	0	0	10
E	0	0	0	0	0	0	0
F	0	0	0	0	0	0	0

Overall, 28 (15%) ADRs were serious and the maximum burden of 17(61%) serious ADRs was found with type B followed by 6 (21%) of type A, 2 (7%) type C, and 3 (11%) type D. [Figure 2]

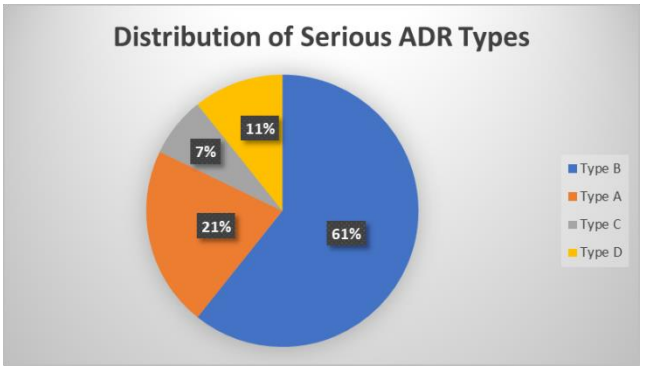

Figure 2

Overall, out of the total 185 cases, 118 (63%) ADRs were recovered, 55 (30%) were recovering, 9 (5%) were continuing, 0 (0%) were fatal and 3 (2%) outcome was unknown. Among type A, 35(65%) ADRs were recovered, 12 (22%) were recovering, and 7 (13%) were continuing. Outcome among type B ADRs; 70 (74%) recovered, 24 (26%) recovering. Outcome among type D ADRs; 3 (30%) recovered, 7 (70%) recovering. [Table 5]

Table 5
Distribution of types of ADRs by Outcomes

ADR Type	Recovered		Recovering		Continuing		Fatal		Unknown	
	Frequency (n=118)	(%)	Frequency (n=55)	(%)	Frequency (n=9)	(%)	Frequency (n=0)	(%)	Frequency (n=3)	(%)
A	35	65%	12	22%	7	13%	0	0%	0	0%
B	70	74%	24	26%	0	0%	0	0%	0	0%
C	10	37%	12	45%	2	7%	0	0%	3	11%
D	3	30%	7	70%	0	0%	0	0%	0	0%
E	0	0%	0	0%	0	0%	0	0%	0	0%
F	0	0%	0	0%	0	0%	0	0%	0	0%

Discussion

We conducted this study at GSVM Medical College and associated hospitals, Kanpur, Uttar Pradesh which is a tertiary care center and covers a large population of both urban and rural back ground. We adopted a spontaneous reporting method for ADR collection. The spontaneous reporting method has the advantage of covering a large number of patients i.e., the entire population and all

drugs simultaneously. This method does, however, have several limitations. Data from spontaneous reporting when taken alone, do not accurately quantify the incidence of ADRs and the risk factors associated with them. Different studies showed that there is gross underreporting in the spontaneous reporting method. [17, 1] Even though 185 suspected ADRs were reported during the twelve months of the study period. There are many factors responsible for underreporting among them lack of knowledge about ADRs and attitude to ADRs are major causes of underreporting. [5,12]

During this study, we found that the maximum ADRs were of type B (51%) followed by type A (29%), type C (15%), and type D (5%). This is in contrast to higher incidences of type A (82%) reactions, reported worldwide [11]. This may be due to better awareness of physicians to ADRs and improving the educational status of society, as they knew the augmented effects of drugs already. Selective reporting of Type B reactions may also be a cause as type B ADRs seek the attention of clinicians more frequently than other types of ADRs. While a South Indian study supports this pattern stating that 68% of ADRs in their study were of type B. [14]

On age distribution maximum ADRs were found in the 12 – 45 years age group (58%), followed by the> 45 years age group (29%) and the least occurrence was in the < 12 years age group (13%). This distribution is in comparison to the international scenario. In a Brazilian study [8 10] highest rate (75.8%) was found in the adult age group (15-50 years) and the lowest rate (7.4%) was found in children (3 – 13 years). When we analyzed the pattern of ADRs among different age groups, we found that in < 12 years, maximum ADRs were of type B (94%) than other types (type A 4% and type C 4%). Among 12 – 45 years also, type B ADRs were more (50%) than other types (type A 30%, type C17%, and type D 3%). Among > 45 years, the maximum ADRs were of type A (40%) followed by type B (34%) then type C (13%), and type D (13%). This pattern of ADRs is supported by a study conducted at Kasturba Hospital, Manipal. [7] On Applying the chi-square test association between different age groups with different types of ADRs is significant.

Gender is not found a risk factor for ADRs. In our study, we found that male is slightly more vulnerable to ADRs (53% male, 43% female). In a Brazilian study [11], there was also slight preponderance of ADRs in males(55% male and 45% female). This pattern is also supported by a study done in Nepal [3] stating male preponderance (58.5% male, 48.5% female) of ADRs, while a British [13] study states that ADRs in females are 60% more common than in males. One study conducted at Kasturba Hospital, Manipal found no significant difference in the overall incidence of ADRs in males and females. [3] On the severity scale, the majority of ADRs were found of moderate severity (64% moderate v/s 35% mild). Only one case of type A was found severe on a severity scale. Among type A, moderate cases (57%) were found slightly more than mild cases (41%).

Type B ADRs were moderate on maximum occasions (77% moderate v/s 23% mild), while type C ADRs were found of mild severity (78%) on maximum occasions. All type D ADRs were found of moderate severity. The overall pattern of severity is supported by a south Indian study [16] stating that the majority of

reactions (47%) were of moderate severity, while another study done in a south Indian hospital [2] showed results against our results, stating that majority of the reactions (53.7%) were mild followed by moderate (35.4%). However, the majority of cases were found of mild and moderate severity in maximum published studies, as in ours.

Overall, only 15 % of reactions were found serious in nature rest were not serious (85%). Various other published studies have quoted an incidence of serious ADRs from 0% to 20%. [9] Maximum burden (61%) of serious ADRs was found with type B. On analyzing patterns among different types of ADRs it was found that type D ADRs were serious on more occasions (30% serious v/s 70% not serious) than other types, followed by type B ADRs (18% were serious and 82% were not serious). This pattern among different types of ADRs can be easily explained by the description given for the classification of ADRs, as type B ADRs have no relationship to doses and functions of drugs and include idiosyncratic, anaphylactic reactions which are serious on most occasions. Among type D ADRs also, there is more chance of seriousness (e.g., neutropenia/pancytopenia after a single dose of the cytotoxic drug – delayed effects of drugs). Like severity, addiction to alcohol or tobacco is, also not found a risk for the seriousness of ADRs.

By the time ADRs were reported, maximum ADRs were either recovered (63%) or recovering (30%). The best outcome was among type B ADRs (74% recovered and 26% recovering). As type B reactions are hypersensitivity/anaphylaxis reactions most of the time, they recovered on a drug withdrawn and by giving treatment. Type D (70% recovering) and type-C (45% recovering) ADRs were found to have a more protracted course. Among type A ADRs 13% of reactions were continuing, these were those reactions in which reactions were mild and the drug was not withdrawn. One south Indian study also found results as ours for the outcome of ADRs, stating that 72.6% of patients recovered from the drug reaction. [2]

In our study, we found that antimicrobials are causing type B reactions on maximum occasions (94% type B ADRs & 6% type A ADRs) and antimicrobials are also responsible for maximum ADRs (34% of all ADRs). Among the second largest group of cytotoxic/immunosuppressant drugs, maximum ADRs were of type A (54%) followed by type D (20%) then type C (18%) and type B ADRs were only 8%. Among antihypertensives and antipsychotics, type A ADRs were far more than type B. As we discussed earlier that type B ADRs was maximum (51%) in our study, while several studies done in western countries state that type A ADRs are the most commonly occurring ADRs, this pattern of more type A ADRs in western studies may be due to more use of other class of drugs than antimicrobials in the west. [8, 15] In our study, in maximum cases we found those ADRs which were previously well-reported and documented in the literature. However few cases were those, whose exact incidence was not known or which were not included in the literature. From the above observation it may be concluded that when we use a fixed dose combination of quinolone and nitroimidazole, the chance of ADR is more. Many studies state that fixed dose combinations cause more ADRs than solo drugs and fixed dose combinations of nitroimidazoles and quinolones are a common cause of cutaneous reactions. [6, 18]

Conclusion

Type B (Bizarre) is the most frequently occurring ADR and most commonly found in the 12-45 years age group (58%). The incidence of ADRs among males (57%) was slightly higher than in females. On the severity scale, the majority of ADRs are found with moderate severity, and the maximum was found with type B. In the present study, the incidence of ADRs was clinically significant among study patients. ADRs increase patients' morbidity, mortality, cost of health care, and duration of hospital stay. Although, further studies are needed with a more focused approach method (cohort event monitoring, targeted spontaneous reporting) and further analytical studies can be designed.

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