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Original Research Article

An analysis of seriousness, predictability and preventability of adverse drug reactions reported at a tertiary care teaching hospital in Kerala, India: a retrospective observational record based study

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ABSTRACT

Background: Adverse drug reactions (ADR) are the leading cause of mortality and morbidity in all health care systems. Hospital based ADR monitoring and reporting programmes can throw some light upon the profile of ADRs and ways to prevent them, facilitating rational drug use. An attempt has been made in this study to analyse the seriousness, predictability, preventability, severity and outcome of ADRs occurring in a tertiary care hospital.
Methods: This was a retrospective observational study based on the data collected from ADRs reported to an approved ADR monitoring centre (AMC). Data collected was evaluated for seriousness, predictability, preventability, severity and outcome using appropriate scales. Simple descriptive statistics was used for analysis.
Results: The total number of ADRs reported was 300. Among this 39% reactions were serious. The commonest reason for considering as serious reaction was prolongation of hospitalization. The overall predictability was 40.4%. Total preventability was found to be 18.3%. Assessment of severity showed 55.3 %, 41.7%, 3% reactions in mild, moderate and severe grades respectively. 64.3% patients had recovered from the reaction and 30% were recovering at the time of reporting ADR. Only 0.3% ADRs caused death.
Conclusions: Authors hope this study will foster the culture of reporting and analysing ADRs among health care professionals and students. The findings from the study can create awareness among health care professionals regarding the impact of ADRs on the treatment course.

Keywords: Adverse drug reactions, Pharmacovigilance, Predictability, Preventability, Seriousness

INTRODUCTION

Adverse drug reaction (ADR) is defined 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 physiological function.[1]

ADRs are the leading cause of mortality and morbidity in health care and have a significant economic impact on health care resources.[2] The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems is called Pharmacovigilance (PV).[3]

This branch of science not only aims to collect the data, but to use the information to increase the safe and rational use of medicines and to communicate it to the public and health professionals.

Though Pharmacovigilance Program was started in India in 1982, it is still in infancy and the Pharmacovigilance Programme of India (PvPI) like most others around the world suffers from underreporting of ADRs.[4]

The ADR reporting rate is below 1% in India compared to the worldwide rate of 6-10%.[5,6] Hospital based ADR monitoring and reporting programmes can contribute significantly in this regard.

They facilitate the early detection of ADRs and help to quantify the risk associated with the use of drugs. Analysis of ADRs reported in hospitals can throw some light upon the profile of adverse reactions occurring and the ways to prevent them, facilitating rational drug use. Hence, an attempt has been made in this study to analyse the seriousness, predictability, preventability, severity and outcome of ADRs occurring in a tertiary care hospital.

In the current scenario, the adverse consequences of the new drugs are detected during the early stage of drug development. However, it has limitations, even in well-designed clinical trials. This is because of many factors such as number of patients studied, duration of treatment, dosage schedule and use of drug in specially selected population. Thus, safety evaluation can only be possible with long term use of drug in clinical practice and hospital-based ADR monitoring and reporting programmes.[7] 10-20% of hospitalized patients are estimated to suffer from some type of ADR.[8]

About 6.7% of all hospital admissions occur due to serious ADRs 8 with 3.7% of patients having fatal ADRs.[9] They have major impact on public health by imposing a considerable economic burden on the society and the already stretched health care systems.[9,10]

Thus, WHO took initiative to set up a worldwide ADR monitoring programme in 1968, following the thalidomide tragedy. The Uppsala Monitoring Centre (UMC, WHO), Sweden is maintaining the international database of ADR reports from several national centres of different countries. It has been recommended for every country to set up their own Pharmacovigilance Programme. India is one of the participating countries in the program with National centre in Ghaziabad, Uttar Pradesh.

The Nationwide ADR monitoring programme in India is called the Pharmacovigilance Programme of India (PvPI). It operates through ADR monitoring centres (AMC) at grass root level. ADRs reported at AMCs are uploaded through the website Vigiflow, and gradually India is developing its own database for adverse reactions, called Vigibase. As per the pharmacovigilance newsletter the incidence of ADRs reported increased since 2010 in India indicating the progress of reporting.[11]

METHODS

Retrospective, observational, record-based study was conducted in the ADR monitoring centre (AMC) of Travancore medical college, working under Pharmacovigilance Programme of India (PvPI) using suspected ADR monitoring form. The study extended from 01.11.2016 to 31.10.2017. Prior permission had been obtained from Institutional Ethics Committee of the hospital for the study.

Inclusion criteria

- Any ADR reported to the ADR monitoring centre of the institution
- ADR reported by healthcare professionals - doctors, nurses, pharmacists
- ADR reported by MBBS and nursing students of the institution
- ADRs reported in CDSCO-IPC suspected ADR reporting form
- ADR reports which are duly completed.

Exclusion criteria

- Incomplete ADR reports
- ADR reports by non-health care professionals
- ADR reports by patients

The ADR reports were evaluated and data regarding details of the adverse drug reaction, seriousness, status of recovery, details of the drugs, and outcomes were collected. Data collected was entered in Microsoft excel and evaluated for seriousness, predictability, preventability, severity and outcome using appropriate scales. Data analysis was carried out with simple descriptive statistics like percentage.

The criteria for serious ADR have been specified by WHO and US Food and drug administration (FDA) and are adopted by CDSCO in suspected ADR reporting form[12] It includes any untoward medical occurrence at any dose that,

- Results in death
- Life-threatening
- Requires or prolongs hospitalization
- Results in persistent or significant disability
- Required intervention to prevent permanent disability
- Results in congenital abnormality.

Predictability was determined by classifying the ADRs. Aronson classification was followed in this study. According to this adverse drug reactions are classified into six types.[13,14]

- Type A - augmented, dose-related
- Type B - bizarre, non-dose-related
- Type C - chronic, dose and time-related
- Type D - delayed, time related
- Type E - end of use, withdrawal reactions
- Type F - failure of therapy.

In the current study, Type A, C, D, E and F were considered predictable. Type B was considered unpredictable.

Preventability was assessed using modified Schumock and Thornton scale (Table 1). Any answer of "yes" to any question in this scale suggests that the ADR might have been preventable.[2] ADRs are categorized as definitely preventable, probably preventable or not preventable.

Table 1: Modified Schumock and Thornton scale.

	Questions for assessment of preventability
Definitely preventable	
1.	Was there a history of allergy or previous reactions to the drug?
2.	Was the drug involved inappropriate for the patient's clinical condition?
3.	Was the dose, route or frequency of administration inappropriate for the patient's age, weight or disease state?
4.	Was a toxic serum drug concentration (or laboratory monitoring test) documented?
5.	Was there a known treatment for the Adverse Drug Reaction?
Probably preventable	
6.	Was required Therapeutic drug monitoring or other necessary laboratory tests not performed?
7.	Was a drug interaction involved in the ADR?
8.	Was poor compliance involved in the ADR?
9.	Were preventative measures not prescribed or administered to the patient?
Not preventable	
	If all above criteria not fulfilled

Table 2: Modified Hartwig and Siegel scale.

Level	Description
1	The ADR requires no change in treatment with the suspected drug
2	The ADR requires the suspected drug to be withheld, discontinued or otherwise changed. No antidote or other treatment is required. There is no increase in length of hospital stay
3	The ADR requires that the suspected drug be withheld, discontinued or otherwise changed, and/or an antidote or other treatment is required. There is no increase in length of hospital stay
4	Level 4a - Any level 3 ADR that increases the length of hospital stay by at least one day
	Level 4b - The ADR is the reason for admission
5	Any level 4 ADR that requires intensive medical care
6	The ADR causes permanent harm to the patient
7	The ADR either directly or indirectly leads to the death of the patient

Severity grades: mild - level 1,2; moderate - level 3,4; severe - level 5,6,7

Assessment of the clinical impact of an ADR is possible by the analysis of severity. The term severity is often used synonymous with seriousness. But they are technically different. Severity denotes the intensity of any reaction, but the term serious can be used only if the reaction fulfils the WHO criteria for serious ADR. In the current study the modified Hartwig and Siegel scale (Table 2) was used to assess severity. According to this scale there are 7 levels of severity, ranging from 'No change in treatment' in level 1 to 'Death' in level 7. Outcome of reaction was categorized as per CDSCO - IPC suspected ADR reporting form as, recovered, recovering, not recovered, recovered with sequelae, fatal or unknown

RESULTS

The total number of ADRs reported during the study period was 300. Among this 39% reactions were serious, and 69% reactions were non-serious. The commonest reason for considering as serious reaction was prolongation of hospitalization. This happened in 34% cases. In 1% cases there was significant disability, 1.7% adverse reactions were life threatening, and 2% cases needed an intervention to prevent permanent disability. In only 0.3% cases (for 1 patient) ADR resulted in death. There were no reports of congenital abnormalities. Results are detailed in Table 3.

Out of the total 300 reports, 121 reactions belonged to Aronson Type A, and 179 ADRs were type B. All the type B reactions were hypersensitivity reactions, and most were skin rashes. No reactions could be attributed to categories C, D or E. Percentage calculation showed 40.4% and 59.6% occurrence for category A and B respectively. Since, type A reactions were considered as predictable in the study the overall predictability of ADRs reported during the study period was 40.4%.

Table 3: Seriousness of ADRs.

Category	No. of serious ADRs	Percentage
Total	117	39%
Death	1	0.3%
Life threatening	5	1.7%
Requires or prolongs hospitalization	102	34%
Results in persistent or significant disability	6	2%
Required intervention to prevent permanent disability	3	1%
Results in congenital abnormality	0	0

Table 4: Preventability of ADRs.

Category	Number of ADRs	Percentage
Definitely preventable	1	0.3%
Probably preventable	54	18%
Not preventable	245	81.7%

Preventability was assessed based on Schumock and Thornton scale. ADRs were categorized into definitely preventable, probably preventable or not preventable. Number of ADR reports belonged to each category were 1, 54 and 245 respectively. Thus only 0.3% ADRs were definitely preventable, 18% were probably preventable. So, total preventability was found to be 18.3%. Results are detailed in Table 4.

Table 5: Preventability of ADRs.

Category	No. of ADRs	Percentage
Mild (level 1,2)	166	55.3%
Moderate (level 3, 4)	125	41.7%
Severe (level 5,6,7)	9	3%

Modified Hartwig and Siegel scale was used for assessment of severity. Majority of the reactions (142, i.e. 47.3%) had level 2 severity. There were 81 reactions (27%) belonging to level 3 severity. The number of reactions belonging to other levels were 24 (level 1), 44 (level 4), 5 (level 5), 3 (level 6) and 1 (level 7). Assessment of severity showed 55.3%, 41.7%, 3% reactions in mild (level 1 and 2), moderate (level 3 and 4) and severe (level 5, 6 and 7) grades respectively. Percentages of reactions in each level are detailed in Table 5.

Assessment of outcome showed 64.3% patients recovered from the reaction and 30% were recovering at the time of reporting ADR. In 3% reports, patients had not recovered from ADR and in 1.7% cases recovery happened with some sequelae. In 0.7% reports outcome was unknown due to loss of follow up. Only 0.3% ADR (1 case out of 300) were fatal. Details are provided in Table 6.

Table 6: Outcome of ADRs.

Category	Number of ADRs	Percentage
Recovered	193	64.3%
Recovering	90	30%
Not recovered	9	3%
Recovered with sequelae	5	1.7%
Fatal	1	0.3%
Unknown	2	0.7%

DISCUSSION

Total 300 ADR reports were eligible to be included in present study during the concerned period. Among this 39% reactions were considered serious and the commonest reason for seriousness was prolongation of hospitalization (34%). Similar results could be seen in Badyal DK et al, study with 41.5% serious cases.[10]

In most of reference studies considered the most common reason for seriousness was prolongation of hospitalization and it contributed to an extend of 72.71% serious cases in Raut A et al, study.[2,8,10] In that study all reactions included were serious and that might be the reason for high incidence of hospitalization. In present study ADRs contributed to death in 0.3% cases and similar incidence could be seen in Lazarou J et al, study (0.32% fatality).[8]

In the current study 1.7% reactions were life threatening and similar pattern was seen in Raut A et al, study with 2.1% life-threatening reactions.[2] In the current study and Raut A et al, and Lazarou J et al, studies there were no reports of congenital abnormalities.[2,8]

The pattern of predictability was different in current study compared to Raut A et al, study.[2] In the current study, the overall predictability of ADRs reported during the study period was 40.4%. But in Raut A et al, study 69% reactions were predictable.[2] The differences observed may be due to due to the difference in the type of reactions included. Hypersensitivity reactions were the major contributor in the current study, which belong to type B and are considered not predictable.

In the current study, only 0.3% ADRs were definitely preventable, 18% were probably preventable and 81.7% were not preventable. In Raut A et al, study the pattern is different with 34%, 21%, 45% in each category respectively.[2] The differences observed may be due to due to the difference in the type of reactions included and the attitude of health care professionals towards ADR reporting.

In the current study reports from all health care professionals and students were included and there was

more incidence of hypersensitivity reactions which have less chances for prevention. In the Raut A et al, study most reports were given by pharmacists and the patient group considered belonged to inpatient areas and ICUs of Internal medicine department.[2] Dose related type A reactions were more included, and all the reactions considered were serious. In the Geer MI et al, study also, preventable reactions contributed the bulk (81.57%) of total reports, against 18.3% preventability in current study.[7]

Severity assessment showed 55.3%, 41.7%, 3% reactions in mild, moderate and severe grades respectively. In the Geer MI et al, study the pattern was 23.68%, 69.29% and 7.01% in respective grades.[7] In both studies less number of reactions belonged to severe grade. The more number of reactions of mild severity grade in current study might be due to the major contribution of hypersensitivity reactions like skin rashes.

Assessment of outcome showed 64.3% patients recovered from the reaction and 30% were recovering at the time of reporting ADR. In Vora MB et al, and Badyal DK et al, studies 87.23% and 95.5% cases respectively had recovered from the reaction at the time of report.[9,10] The difference may be due to two factors.

Inclusion of inpatient ADR reports only in the reference studies and the reactions might have been carefully treated for such patients even before they were reported. Only 0.3% ADR (1 case out of 300) were fatal in the current study. In the reference studies 9 and 10 also fatal reactions were less common (4.25% and 1% respectively).

CONCLUSION

This was a retrospective observational study based on the ADR reports collected at AMC of Travancore medical college during one year period. Authors' institution is an approved AMC under PvPI and there is a well-established system for reporting, analysing and preventing ADRs.

Authors have tried to include maximum number of reports and analyse all reported ADRs as precisely as possible. However, since there was a spontaneous reporting system the actual incidence of ADRs could not be estimated. Authors think, still there is underreporting of ADRs, considering the number of patients taking treatment from our institution and the number of drugs available. Authors hope this study will foster the culture of reporting and analysing ADRs among health care professionals and students. The findings from the study can create an awareness among health care professionals that chances of ADRs should always be kept in mind, while managing any medical condition, as the development of ADRs has significant impact on the treatment course.

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