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Original Research Article

Evaluation of Suspected Adverse Drug Reactions and their Causal Associations: Experience of an Adverse Drug Reaction Monitoring Centre of A Tertiary Health Care Unit

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Abstract

Objective: The objective of this study was to evaluate the profile and causality of adverse drug reactions reported from various departments of a tertiary care teaching hospital in North India.

Methods: This was an observational study which was conducted in a 510 bedded tertiary care teaching hospital in New Delhi for a period of 2 years. A retrospective analysis of ICSRs from the Adverse Drug Reaction Monitoring Centre (AMC) was done from the records in the department and the reports submitted by VigiFlow. Patients of all age and either sex were included. The WHO_ UMC scale was used to assess if the AE had any causal relationship to the drug/ drugs administered.

Results: Three hundred and thirty-eight (338) ADRs from 218 patients were obtained during a period of 2 years. The mean age was 43 ± 19 years. Highest number of adverse drug reactions 63(29%) were witnessed in the age group of 26- 40 years. Adult group (18- 60yrs) has experienced significantly higher ADRs (70.6%) than the paediatric (18%) or elderly (10%). Females experienced higher number of ADRs 123 (56.42) as compared to males 95(43.57). The most common organ system that was affected was Skin & Subcutaneous Disorders 80 (23.66%). Most common ADR was hypersensitivity reactions (15.68%) followed by pruritus (10.35%), injection site pain and swelling & rash (~5%). Forty five percent (45%) of ADRs were implicated only due to antimicrobials, which is highest among all other groups of drugs. This was followed by anticancer drugs (11.7%), agents used for gastrointestinal disorders (7.3%) and vaccines (6.5%). On WHO-UMC Probability Assessment Scale, majority (55.04%) of the reports were evaluated as `possible' and 26.14% were evaluated as `unassesssable` due to lack of medical reports which the patient could not produce.

Conclusion: Poor quality of the suspected ADR reports reduces the chances of establishing a causal relationship, as essential information to evaluate the likelihood of an event being caused by a drug may be lacking. Measures to improve detection and quality reporting of ADR by all healthcare professionals should be undertaken, to ensure patient's safety. The involvement of Pharmacologists may greatly improve the quality of ADR reporting and can subsequently help in detecting preventable adverse drug events and reduce the incidence of such ADRs.

Keywords: Suspected Adverse Drug Reaction, Adverse event, WHO-UMC Causality Assessment.

Introduction

Medicines are an integral part of the health care system globally. When prescribed for different medical conditions, the choice of a drug is often based on it`s risk-benefit ratio. Adverse Drug Reactions (ADRs) are the unexpected or harmful effects associated with such use of medicines and can impact the treatment outcomes in a major way which can sometimes overshadow the beneficial effects. Prior to the 1960s, health cautions and health care regulations were liberal and drug efficacy was prioritized over drug safety. Though the Lancet Journal in 1848 reported an incidence of the death of a young girl due to chloroform anaesthesia before removal of an infected toenail, there was no proper system in place to record the adverse drug reaction [1]. But in 1961, the thalidomide tragedy, which was a landmark event, forced the stake holders to consider, develop and establish a system for ensuring drug safety. As a result, The World Health Organization (WHO) initiated the International Drug Monitoring Program in 1968, which globalized and systematized the drug safety issues.

As defined by the WHO, ADR is any noxious, unintended, and undesired effect of the drug which occurs at doses used in humans for prophylaxis, diagnosis, or therapy of a disease or the modification of the physiological state [2]. In other words, the ADR is a harm that is directly caused by the medicine at normal doses during normal use. Monitoring of ADRs is the responsibility of the health care system since it is an important cause of morbidity and mortality.

Many new drugs have been rapidly introduced into the global market as a result of advancements in the field of clinical trials. Drug companies in India have also improved their technology and research skills, at par with the International standards to launch new drugs, speeding up the process further. The rapid introduction of pharmaceutical products raises the challenge of monitoring ADRs in a huge country like India with a population of over 1.2 billion and with vast ethnic diversity, practicing various medical systems [3]. According to studies conducted in various parts of India, the incidence of suspected ADRs among hospitalised patients ranges between 2% and 3%. The median incidence of ADRs that led to the hospitalization and those that emerged during hospitalization, according to a recent systematic study, was 2.85 % and 6.34 % respectively. The overall incidence of serious and fatal ADR is 6.7% and 0.32% respectively in hospitalized patients. ADRs increase the duration of hospital stay, the cost of treatment, and the burden on a country's health system [4]. The overall cost of ADRs in a South Indian hospital was estimated to be INR 1,567,397, and the average management cost for an ADR-patient was approximately INR 5000 (USD 115) [5]. Thus, for a country with an annual per capita health expenditure of around USD 109, the cost of management per ADR is significantly burdensome.

In 2010, the Govt. of India initiated a national Pharmacovigilance program, known as the Pharmacovigilance Program of India (PvPI), to protect the health of the country's citizens and to ensure that the benefits of drugs consumed, outweigh the risks. Pharmacovigilance (PV) is a research practice that monitors the medicine throughout its entire lifetime. The Indian Pharmacopoeia Commission (IPC) and National Coordination Committee (NCC), in collaboration with the Central Drug Standard

Control Organization (CDSCO), govern Pharmacovigilance operations in India. There are currently more than 600 ADR monitoring centres (AMCs) in various medical colleges, governmental and non-governmental institutes, and the number is steadily growing. They assist in the early identification of ADRs and the quantification of the risk associated with medicine/drug use. Individual Case Safety Reports (ICSRs) are collected, analysed, and the completed reports are sent to the National Coordinating Centre (NCC) by these AMCs. The coordinating centres then evaluate the causality and feed the reports into the Pharmacovigilance (PV) database. NCC sends the information to the Uppsala Monitoring Centre, Sweden for processing, identification, and analysis of new signals for adverse reactions associated with the particular drug. The integrated ADR data is transferred to the UMC database using the Vigi-Flow database entry software. As a result, CDSCO has received over 149000 ADRs as of December 2015. India currently contributes 3% of the WHO global ICSR database. In January 2017, PvPI received reports of 5523 ICSRs from various centres [6].

Thus, ADR being one of the major threats in the healthcare system which extensively affects health and the quality of life, there is an enormous need to create awareness among patients and to motivate health care professionals in the hospital to report ADRs so that we can contribute towards safer use of medications by generating evidence-based data to help early detection of signals. Early detection of Signals helps to improve patient safety and reduce economic burden due to escalating cost of medications and unwanted adverse effects associated with it. Therefore, the objective of this study was to evaluate the adverse event profile reported from various departments of a tertiary care teaching hospital in North India and to find out if they had any causal associations with the offending drug/ agent.

Methods & Materials

Study design & study population: A retrospective, cross – sectional, observational study was conducted in a 510 bedded tertiary care teaching hospital in New Delhi, India. Study population consisted of patients visiting OPD, wards or emergency. The study was conducted under the active supervision of the Adverse Drug Reaction Monitoring Centre (AMC) of the medical college and hospital.

Study period: Study was conducted over a period of 2 years and data were collected from January 2019 to January 2021.

Sampling method & sample size: A convenient sampling was used. All patients experiencing adverse events from January 2019 through January 2021 were included in the study.

Techniques of data collection:

A retrospective analysis of ICSRs from the Adverse Drug Monitoring Centre was done from January 2019 to January 2021 from records in the department and the reports submitted by VigiFlow. Each ICSR was scanned for completeness and missing data was filled by going through the medical records. Patients from the OPD were tracked and queried telephonically.

Tools Used: 1. Suspected Adverse Drug Reaction Reporting Form v. 1.2 & 1.3 were used (following receipt of updated SOPs from the Indian Pharmacopoeia Commission) to collect all suspected drug events.

2. The WHO_ UMC scale was used to assess if the AE had any causal relationship to the drug/ drugs administered. [7]

Evaluation and Verification of Causality Assessment Scale

WHO- UMC scale was used for the causality assessment in this study. The adverse event history and sequence of events along with supporting laboratory parameters was discussed with the reporter (healthcare professionals or nursing staff) by the Pharmacovigilance Associate deputed at the

Adverse Drug Reaction Monitoring Centre (AMC). Detailed history was collected from the Bed Head Tickets or Patient Files from the Medical Records Department after due permission from the Medical Superintendent. Any queries or doubts arising during the process were clarified immediately with the reporter. Subsequently, the narrative was prepared and causality category was evaluated by the Deputy Coordinator and re-checked by the Coordinator, AMC. Each and every ICSR was then discussed at length by the Causality Assessment Committee and report finalized.

Data analysis: Microsoft Excel (MS Office, 2020) was used for data entry and analysis. Descriptive data analysis was used for the analysis of this study. The normally distributed continuous variables are summarized in mean and standard deviation. For categorical variables, frequencies and percentage were tabulated.

Ethical considerations: The study protocol was considered and approved by the Institutional Ethics Committee (IEC) of Jamia Hamdard, New Delhi. The data has been taken from AMC records in the Department of Pharmacology, HIMSR, Jamia Hamdard. This centre has been recognised by the Indian Pharmacopeia Commission, under the aegis of Ministry of Health & Family Welfare, Govt. of India, and functioning as an AMC with effect from 2012.

Results

Three hundred and thirty-eight (338) ADRs from 218 patients were obtained during the period of 2 years with the essential criteria for analysis. The mean age was 43 ± 19 years with a minimum age of 2 months and maximum age of 85 years.

The demographic tendencies toward ADR occurrences are 95 (43.57%) males and 123 (56.42%) females. Some patients suffered more than one ADR. Total number of drugs involved in causing these ADRs was 273.

Highest number of adverse drug reactions 63(29%) were witnessed in the age group of 26- 40 years. On summation, we find adult group (18- 60yrs) has experienced significantly higher ADRs (70.6%) than the paediatric (18%) or elderly (10%). Females experienced higher number of ADRs 123 (56.42) as compared to males 95(43.57). These results are summarized in Table 1.

Reported ADRs were summarized based on MedDRA coding. The most common organ system that was affected was Skin & Subcutaneous Disorders 80 (23.66%) and the preferred term (PT) comprising of pruritus, rash, urticaria, dermatitis, Red Man's syndrome & dry skin followed by Immune System Disorders 69(20.41%) which majorly includes hypersensitivity reactions (53 cases). The most common ADR was hypersensitivity reactions (15.68%) followed by35 cases of pruritus (10.35%), injection site pain and swelling & rash (~5%). Least observed adverse drug reactions were that of renal and reproductive system disorders which includes a single case of acute renal failure and a sexual dysfunction. These results are summarized in Table 2.

Suspected Therapeutic Class of Drugs: Forty five percent (45%) of ADRs were implicated only due to antimicrobials, which is highest among all other groups of drugs. This was followed by anticancer drugs (11.7%) and agents used for gastrointestinal disorders (7.3%), vaccines (6.5%). Surprisingly ADRs reported with multivitamins (4.3%) were nearly as high as those reported with antipsychotics, antidepressants and NSAIDs (4.7%). These results are summarized in Table 3.

Distribution of Antibiotic induced ADRs: Antimicrobials contributed to 45% of adverse drug reactions, out of which nearly 29% were caused by fluoroquinolones like norfloxacin, ciprofloxacin, ofloxacin and levofloxacin. Beta lactam antibiotics like amoxycillin + clavulanic acid, ceftriaxone, piperacillin,

ampicillin, cefpodoxime, cefixime, cefoperazone contributed to 27.6% ADRs. Azithromycin, vancomycin and linezolid possibly related to 8.9% reactions. A significant number of drug reactions were observed with the use of antitubercular agents adding up to 37 (30.83%) cases. The reactions were primarily elevated liver enzymes, pruritus, rash and drug induced liver injury. These results are summarized in Table 4.

Outcomes attributed to ADRs: Majority (67.7%) of cases were non-serious and did not require hospitalization while in a considerably large number (16.5%) of cases the outcome was not known because either the forms were not filled for outcome or the cases got lost to follow up.

WHO-UMC Probability Assessment Scale: WHO - UMC Scale for causality assessment was applied to 338 adverse events those that were reported to AMC. Majority of reports were evaluated as `possible' 55.04%, followed by `probable' 16.51% and 26.14% were evaluated as `unassesssable' due to lack of medical reports which the patient could not produce. Two events were evaluated as unlikely to be related to the drug. These results are summarized in Figure 1. At least one predisposing factor was present in 55% of the reports and the most common factor associated was co-morbidity or existence of multiple diseases. History of self medication or irrational treatment by local quacks was present in around 30% of cases reported.

Table 1: Demographic Data

Age Distribution (In years)	**Number of ADRs n (%)**
<18	40 (18)
18-25	37(17)
26-40	63(29)
41-60	54(25)
>60	22(10)
Unknown	02(01)
Total	218
Gender Distribution	
Male	95(43.57)
Female	123(56.42)

Table 2: Organ System Affected by ADRs

Organ system affected by ADRS	**No. of ADRs**	**Percentage**
Skin & Subcutaneous Disorders	80	23.66
Immune System Disorders	69	20.41
General Disorders & Administration Site Conditions	41	12.13
GIT & Hepatobiliary System Disorders	41	12.13
Central Nervous System Disorders	28	8.28
Cardiovascular System Disorders	23	6.80
Respiratory System Disorders	18	5.32
Musculoskeletal System Disorders	11	3.25
Renal & Reproductive System Disorders	05	1.4
Others/ Misc	22	6.50

Table 3: Suspected Therapeutic Class of Drugs

Class of drugs causing ADR	No. of ADRS N (%)
Antimicrobials	123(45)
Anticancer	32 (11.72)
GI agents	20 (7.32)
Vaccines	18(6.59)
Analgesics & NSAIDS	13 (4.76)
Antipsychotics & Antidepressants	12(4.39)
Multivitamins	12(4.39)
Antihypertensives & Diuretics	07(2.56)
Antiepileptics	07(2.56)
Bronchodilators	04(1.46)
Anesthetic agents	04(1.46)
Antiseptic agents	04(1.46)
Antidiabetic agents	03(1.09)
Antihistamines	02(0.73)
Others	12(4.39)

Table 4: Distribution of Antibiotics induced ADRs

Antibiotics	No. of ADRs (n=123)
Fluoroquinolones	36 (29.2)
Beta - Lactams	34 (27.6)
Macrolides, Glycopeptides & Oxazolidone	11 (8.9)
Aminoglycosides	2 (1.6)
Others (Anti-TB, Anti- malarial & antifungal)	40 (32.5)
	123

Table 5: Causality Assessment by WHO-UMC Scale

Causality	No. of ADRs	Percentage
Certain	0	0
Probable/Likely	36	16.51
Possible	120	55.04
Unlikely	3	1.37
Conditional/Unclassified	0	0
Un-assessable /Unclassifiable	57	26.14

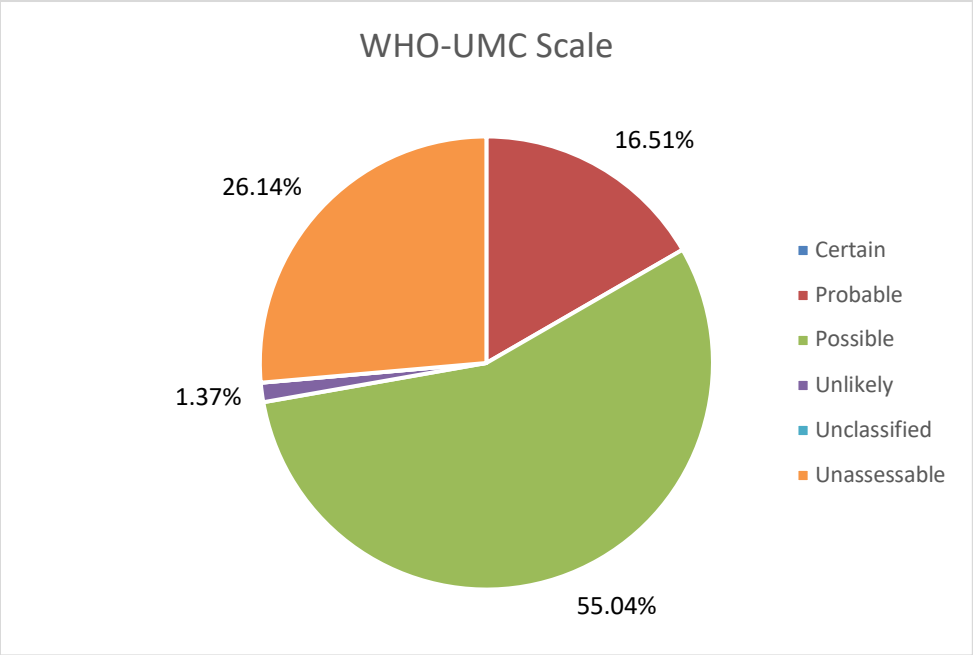

Figure 1: Causality Assessment and percentage of causal relationship

Discussion

Adverse drug reaction (ADR) is a major burden for patients and healthcare industry. A timely detection of either new ADRs or an increase in the frequency of ADRs which are already known to be associated with the drugs involved, and an accurate detection of potential ADRs can help improve drug safety and reduce financial costs to patients.

Real-life uses of medicines/drugs are very different from the controlled clinical trial environment because in the latter case, the duration of exposure is short and vulnerable individuals such as the elderly, women of child-bearing age, children, and those with concurrent illnesses, are not included. Therefore, when a drug is marketed, not all of its adverse effects may be known and close monitoring of adverse drug reactions (ADRs) remains necessary [8].

Pharmacovigilance embraces risk- benefit assessment, thus dealing with multiple types of evidence emerging along the life cycle of each drug for continuous reassessment of its place in therapy, both in clinical and in regulatory terms. This is done through spontaneous reporting system (SRS) and every national Drug Licensing Authority maintains it's specific SRS to collect all suspected AE reports and routinely use data-mining algorithms to process data. The aim is to identify possible signals of unknown drug – effect relationships [9]. Post-marketing spontaneous reporting of ADRs thus remain a cornerstone of Pharmacovigilance and a series of drug safety signal detection methods play an important role in providing drug safety insights. This crucial role is played by AMCs in improving patient's safety and the quality of life.

In the present study, analysis of the age wise distribution shows the predominance of ADRs in the adult age group which amounts to 70%. Singh *et al*. found the mean age for ADR as 35 years, whereas Yu *et al*. observed median age for ADR as 58 years, while the mean age of our population was 43 ± 19 years. The most common occurrence of ADRs in adult population was also reported by Singh et. al. [10,11]. The probable reason of young adults (mean age.) experiencing highest frequency of

ADRs could be higher exposure to various medications. While better accessibility of young adults to health care system cannot be ignored, the involvement of patients in their fourth & fifth decade indicates vulnerability of this age- group.

We identified female gender has a higher risk factor with ADRs. Gender predominance for females experiencing higher ADRs is in sync with various other studies. Singh *et al.* [10] Vervloet and Durham [12] and Tran *et al.* [13] observed that ADR experienced were more common in females as compared to men. They attributed this difference to more weight and body mass index, hormonal changes, which are unique to this gender such as during puberty, menstrual cycles, and menopause, and the effect of these changes on drug metabolism. They also concluded that genomic constitutional differences can influence drug metabolising enzymes among the females [10] Kunnoor *et al.* [14] found that although polypharmacy was more common in males but ADRs were 1.5- to 1.7-fold more common in females. On the other hand, Gor and Desai (2008) [15] found no influence of age and gender in the incidence of ADRs. The differences observed by Kunnoor *et al*. were thought to be due to different pharmacokinetic, pharmacodynamic, immunological, and hormonal factors in females as well as differences in the pattern of use of medications in them [14].

This study also found that antimicrobial agents (fluoroquinolones and beta - lactams) were the major contributors of ADRs and mostly involved skin and subcutaneous tissue which was in concordance to the findings of Arulappen *et al* [16] but varied in the therapeutic class of antibiotics (vancomycin and co-trimoxazole). For example, in one case, that was considered medically important, the patient experienced generalized pruritus, facial edema, mouth ulceration and difficulty in breathing when 1.2g amoxicillin + clavulanic acid were used IV for urinary tract infection. The drug was withdrawn and patient improved. Allergic reactions to amoxicillin are not uncommon, including anaphylactic reaction [17] and hypersensitivity reactions. Clavulanic acid, which is prescribed along with amoxicillin, is also found to cause allergic reactions [18,19]. Hence Salas *et al*. recommended that if the patient is sensitive to amoxicillin, they should also be evaluated with skin test regarding the sensitivity of the clavulanic acid [20].

The highest number of ADRs in the present study were found to be with antitubercular drugs. Gor and Desai (2008) [15] observed antimicrobials as the topmost group of drugs, among which chloroquine, amoxicillin, and antitubercular drugs topped the list. Preeti *et al*. (2017) [21] and Salvo *et al*. (2013) [22] also had similar types of findings, in which antimicrobials were the main drugs leading to ADRs. Another study [23] found the most common ADRs with antitubercular drugs, which were neuropathy followed by skin rash, whereas, Abhijeet *et al*. (2017) [24] observed allergic skin reactions as the fourth most common type of ADRs with antitubercular drugs.

Notable drugs other than antimicrobials that were responsible for hypersensitivity reactions were diclofenac, ibuprofen, enlapril, telmisartan, amlodipine, ondansetron hydrochlorthiazide, drotaverine, dicycloverine, loperamide and metoclopramide. NSAID-induced ADRs were found in almost 1.6% of patients in previous studies [25,26]. NSAID-induced hypersensitivity reactions were observed in almost 20% of all ADRs to NSAIDs in earlier data. These are unpredictable “bizarre” (type B) ADRs and are due to inter-individual differences [27]. Although the exact mechanism behind NSAID-induced hypersensitivity reactions is not fully understood, it is proposed that NSAID-induced blockade of the enzyme cyclooxygenase results in excessive prostaglandin E_2 production in the affected persons [28,29].

In the causality assessment studies, majority (55%) of the cases were considered as `possible` in the WHO-UMC probability scale. The possible reasons are, drug events or laboratory test abnormality followed reasonable time after the use of that particular drug but the event could also be explained by disease or other concomitant drugs taken around the same time. The suspected drug was either not withdrawn or the informati lacking in most of the cases. A total of 15.8% reactions that occurred due to the use of antitubercular drugs were considered as probable, as the event or laboratory test abnormality followed reasonable time relationship to the intake of drug and was unlikely to be attributed to disease or other concomitant drugs. Thus, the response to withdrawal was clinically reasonable ie. patient's condition improved on withdrawing the suspected drug.

Conclusion

No drug is completely safe and devoid of adverse effects. The probability of occurrence of Adverse Drug Reactions should always be taken into account in the management of any medical condition because ADRs have substantial impact on the course of treatment. Fifty five (55) percent of our cases reported were possibly related to the adverse drug reaction and 26% were unassesssable which strongly suggests that there is a greater need for spreading awareness amongst healthcare professionals to improve the quality of reporting.

Poor quality of the suspected ADR reports reduces the chances of establishing a causal relationship, as essential information to evaluate the likelihood of an event being caused by a drug may be lacking. Measures to improve detection and quality reporting of ADR by all healthcare professionals should be undertaken, to ensure patient's safety. The involvement of Pharmacologists may greatly improve the quality of ADR reporting and can subsequently help in detecting preventable ADRs and reduce the incidence of such ADRs.

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