Section: Pharmacology

Original Research Article

A RETROSPECTIVE STUDY OF ASSESSMENT OF ADVERSE DRUG REACTIONS AT ADR MONITORING CENTRE OF A TERTIARY CARE HOSPITAL OF NORTHERN INDIA

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Abstract

Adverse drug reactions (ADRs) is any serious, noxious and unpleasant effect occurring at a therapeutic dose which can either lead to withdrawal of treatment or use of any alternative methods. So, study of these unwanted effects by drugs can help in prevention of any future apocalyptic events. This was an observational and retrospective study, which was based on the data collected from the ADR cases reported to King George Medical University ADR monitoring Centre (AMC) from December 2021 to November 2022. All the suspected ADRs which were either reported to the centre or collected by department of Pharmacology on regular visits in various other departments. The study subjects were assessed for demographic characteristics, causality assessment, system organ class and other parameters. Among the reported 270 suspected ADRs, antimicrobials have recorded maximum no. of ADRs which account for almost half of the overall ADRs reported followed by anticancers and NSAIDs. Our study shows that majority of the ADRs reported were non serious and can be easily preventable, while many of them occurred due to poly-pharmacy. The antimicrobial drugs showed a lot of ADRs which is a serious threat as it can lead to development of resistance which can have a very serious impact both on individual as well as community. This study will contribute in providing a strong base for future prospective studies with more time duration which can benefit more definitive outcomes in ADR monitoring.

INTRODUCTION

Medical system in India has come a long way from traditional, antiquated methods to modern, evidence based and scientific approaches for disease management. On one hand, healthcare facilities are attaining unprecedented heights globally as well as nationally while on other hand, it is still like a dream for many to avail the basic healthcare services. In India, life sciences and pharmaceutical industry is one of the largest markets in the world showing an accelerated growth rate and is expected to reach USD 130 billion by 2030.[1] With over 60,000 generic medications produced in 60 therapeutic categories, India's pharmaceutical business ranks 13th in value and third in volume globally.[2] Majority of drugs routinely prescribed in medical practice for treating various diseases carry the risk of adverse effects, which in turn calls for "Pharmaco-vigilance". Concept of pharmaco-vigilance is not new, since long this important tool is in practise to promote safe and effective use of medications. But, it has been found that there is significant lack in monitoring and reporting of adverse drug reactions (ADRs) which is below 1% in India compared to the worldwide rate of 5%.[3] Therefore, vigilant monitoring throughout the life cycle of drug is crucial and is the need of hour.

World Health Organization (WHO) defines "Pharmacovigilance as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems, including herbal materials".[4] WHO Programme for International Drug Monitoring (PIDM) was formed in 1968. In

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India, a formal ADR monitoring system was started in 1986 with 12 regional centers. Then in 1997, India became the member of WHO Programme for International Drug Monitoring managed by the Uppsala Monitoring Centre (UMC), Sweden. In the starting phase, 6 regional centers were set up in Mumbai, New Delhi, Kolkata, Lucknow, Pondicherry, and Chandigarh for ADR monitoring. But only Mumbai and New Delhi centre were active among those 6 and thus spontaneous reporting of ADRs were poor. Later, National Pharmacovigilance Programme (NPvP) was initiated by the Government of India in November 2004, however, due to a lack of funding, the programme was temporarily halted. In July 2010, the Health Ministry introduced a nationwide ADR monitoring program, Pharmacovigilance Programme of India (PvPI) that had been amended in light of the need for better ADR monitoring in the nation. Initially, All India Institute of Medical Sciences, New Delhi was the National Coordination Centre (NCC) for the programme but in April, 2011, it was shifted to Indian Pharmacopoeia Commission (IPC), Ghaziabad.[5] Till date, PvPI has succeeded in establishing a nationwide network of 395 ADR Monitoring Centres (AMCs) across the country.[6] Each AMC holds the responsibility of collecting ADR reporting forms duly filled by healthcare professionals and from neighbouring regions and uploading them into web based database "vigiflow" and following the same as per standard operating guidelines.[6]

India has a large population with wide variety of geographical condition so different types of disease are prevalent in our nation. There are other clinical practises which are also very common apart from Allopathy such as Ayurveda, Homeopathy, Unani etc., the medications which are used in these practises do not have proper standardizations. When an ADR occurs in which patient gives history that they have consumed such medications along with medically prescribed drugs, it becomes very difficult to find the exact cause of ADR as there is incomplete data and information on these formulations. The causality assessment also becomes very unclear. Therefore, our country needs a larger ADR REPORTING SYSTEM which is robust, voluntary, well organised to maintain such a large database of our ethnic population. Also, ADRs are among the top ten leading cause of mortality & morbidity in both ambulatory and hospitalized patients. Although, there has been a boon in the no. of cases which have been reported nowadays, yet there are still many cases which go unreported. These under-reporting of ADR cases is also one of the biggest challenges.[7]

So while the exact epidemiological data from government institutions remains to be known in India, a productive, institutional reporting can be instrumental in providing valuable information regarding the potential problems of drug usage in this institution. The main goal of this initiative is to ensure that the benefits of use of medicine should outweigh the risks as drugs are popularly said as a double edge weapon having potential to cause benefit as well as harm.[8,9] Till now there is not a single study available on this important aspect of treatment from our institution. Thus, one of the aims of the study is to create awareness among clinicians of this institution and with this we can move forward to inculcate the culture of ADR reporting. Therefore, this study was planned to evaluate and analyse the incidence and patterns of ADRs with the help of the reports collected from various inpatient and outpatient departments of the hospital as well as to study the drugs and organs involved in ADR and to create awareness of ADR reporting. Regional data generated from this study will also help in planning the institute/ state health policy.[10]

MATERIALS AND METHODS

It was an observational, retrospective, record based study conducted as a part of PvPI and presents the data collected and analyzed from King George's Medical University, Lucknow ADR monitoring Centre (AMC) under PvPI. The Institute is one of the pioneers which caters to the huge population of North India and is recognized as AMC on 15 December 2021. ADR monitoring centre is coordinated by the Institute's Department of Pharmacology. All adverse drug reactions (ADRs) forms received from hospital (In patient & Outpatient departments) from December 2021 to November 2022 were included in the study. The ADRs that were not reported and incomplete were excluded.

Department of Pharmacology has been actively participating in collecting, analyzing and entering data into the Vigiflow database. A total of 270 Individual Case Safety Reports (ICSRs) were reported and their data was entered into the vigiflow. The study focuses on ADRs collected during 1 year study duration, data of suspected medications causing them and the various organs affected as per system organ class. All the suspected ADRs which were either reported to the centre or collected by department of Pharmacology on regular visits in various other departmental wards and OPDs were recorded and finally uploaded on the vigiflow database. ADRs comprised of over-the-counter medications taken by the patients, prescribed medications from the physicians, referral cases, ADRs occurring due to suspected Ayurvedic or any other herbal medications. Some serious ADRs such as life threatening conditions, required hospitalization or pro-longed hospitalization, leading to congenital anomaly, permanently disabling or leading to death were also reported. Our departmental causality assessment committee used the WHO-Uppsala Monitoring Centre Causality Scale for doing the causality assessment for all the reported ADR cases. The number, pattern, type and seriousness of the reported ADRs as per SOC (system organ class) and the suspected medications causing such ADRs were studied and recorded. All the data collected

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from the patient population was expressed as percentage of patient population. P value <0.005 was considered statistically significant.

The personal identification variables were masked before analyses, and analyses were conducted in groups to maintain full confidentiality. Since the results do not contain any personal information, taking consent from the patients was exempted. This was a non-interventional study where no influence was imposed on the treatment or medical care. Treating consultants were not approached regarding the reported ADRs as this was not the aim of the study. Full confidentiality was maintained throughout the analyses, and the analyses were performed in groups to affirm patient's confidentiality. Necessary communication was accomplished with PvPI for permission to use the data for publication.

RESULTS

In the entire period of study duration, the total number of patients visiting the institution was around 4000 patients per day (hospital medical record department) this data included both inpatient and outpatient departments, amid them 270 ADRs were seen.

Figure 1 shows monthly distribution of ADRs. Maximum no. of ADRs has been seen in the month of April 2022 while February 2022 has the lowest no. of ADRs.

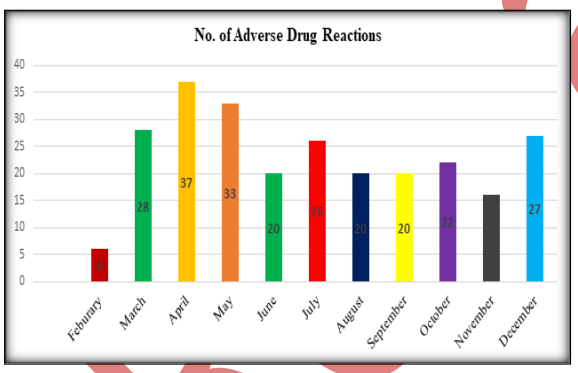

Figure 1: Month wise distribution of ADRs since December 2021 to November 2022

Among 270 ADRs, 36 reactions were serious (13%), 43 reactions can be prevented by the intervention (37%), patients with 22 reactions were hospitalized (18.9%) and 5 were other medically important (4.3%), and 3 were life threatening (2.5%) Figure 2.

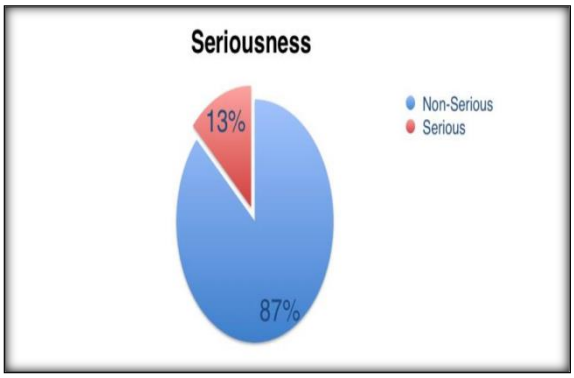

Figure 2: Severity of ADRs submitted since December 2021 to November 2022

Demographic characteristics collected from various ADRs shows that 33.72% of females and 44.31% of males have reported ADRs [Table 1].

Causality assessment of ADRs has been shown in [Table 2]. Most of the ADR cases belong to the Probable category – 120 cases (44.4%).

Department wise distribution of ADRs has been shown in [Table 3].

Various ADRs caused by different pharmacological classes of drugs were analyzed and summarized in Figure 3.

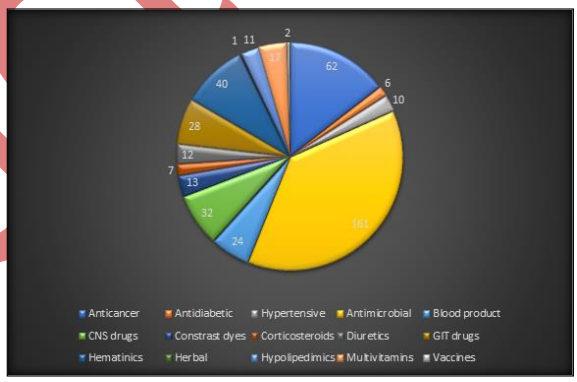

Figure 3: Adverse drug reactions caused by various pharmacological classes of drugs

The frequency of ADRs in various clinical departments was calculated and found that 52(19.4%) ADRs were reported from the Department of dermatology and venerelogy followed by cardiology and radiotherapy department i.e. 40(14.8 %) and 34 (12.5%) respectively as shown in [Table 4].

Antimicrobials have recorded the maximum no. of ADRs which account for almost half of the overall ADRs reported followed by anticancer drugs and NSAIDs. The system organ system (SOC) for the ADRs describing the pattern, number, type and seriousness of the cases have been described in. [Table 5].

There has been a total of 117485 ICSRs in one-year period which has been reported from 534 AMCs operating nationwide as well as the pharmaceutical companies. This data has been collected from the vigiflow database. Compared to other institutions as our AMC is a newly appointed centre it has reported

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270 ICSRs which accounts for around 0.30% of ICSRs reported in the vigilow which is our Indian database.

Table 1: Demographic Characteristics

Gender wise distribution of ADRs		
Male	178	44.31%
Female	92	33.72%

Table 2 : Causality Assessment of ADRs

	Causality assessment	
Certain	4	24.12%
Probable	120	44.4%
Possible	85	34.48%

Table 3: Adverse drug reactions reported by various departments

Department Reported ADR in the AMC	
Anaesthesia	Cardiology
Clinical haematology	Critical Care Medicine
CTVS	Dermatology
Surgery	Internal medicine
METC	Neuro-Surgery
Neurology	Obs & Gynae
Orthopaedics	Paediatrics
Plastic surgery	Psychiatry
Respiratory Medicine	Radiotherapy
Thoracic surgery	Surgical oncology
Vascular surgery	

Table 4: Maximum no. of Adverse drug reactions reported by various departments

Maximum No. of ADR Reported – 2021 – 2022 (above 20)
Dermatology & Venereology – 52
Cardiology - 40
Radiotherapy - 34
Respiratory Medicine - 21

Table 5: Pattern and frequency of various type of ADRs reported according to system organ class

System Organ Class		Reactions
Blood and lymphatic system disorders	10	Leukopenia, Anaemia
Cardiac disorders	6	Tachycardia, Palpitations
Eye disorders	2	Ocular hyperaemia, Periorbital swelling
Gastrointestinal disorders	33	Abdominal discomfort, Abdominal distention, Abdominal pain, Constipation, Diarrhoea, Dry mouth, Dyspepsia, Gastrointestinal haemorrhage, Gingival hypertrophy, Lip swelling, Mouth ulceration, Tongue discolouration, Tongue
General disorders and administration site conditions	62	Chest pain, Chills, Condition aggravated, Inflammation, Injection site inflammations, Injection site pain, Injection site swelling, Oedema peripheral, General physical health deterioration, Peripheral swelling, Pyrexia, Swelling, Swelling face
Hepatobiliary disorders	6	Hepatitis, Drug induced liver injury
Immune system disorders	2	Anaphylactic reactions, Anaphylactic shock
Infections and infestations	1	Pulmonary tuberculosis
Injury, poisoning and procedural complications	4	Off label use, Overdose, Exposure during pregnancy, Toxicity to various agents
Metabolism and nutritional disorders	2	Hyponatremia, Hypokalaemia
Musculoskeletal and connective tissue disorders	2	Muscle spasms, Pain in extremity
Nervous system disorders	14	Neuropathy peripheral, Speech disorder, Somnolence, Depressed level of consciousness, Dizziness, Paraesthesia, Loss of consciousness, Amnesia, Seizure, Headache, Burning sensation
Psychiatric disorders	16	Agitation, Anxiety
Renal and urinary disorders	1	Chromaturia
Respiratory, thoracic and mediastinal disorders	15	Tachypnoea, dyspnoea
Skin and subcutaneous tissue disorders	132	Acute generalised exanthematous pustulosis, Alopecia, Blisters,

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		Dermatitis bullous, Rash, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Eczema, Erythema, Erythema multiforme, Fixed eruptions, Generalised bullous fixed drug eruptions, Lichen planus, Nail disorders, Papule,Petechiae, Post inflammatory pigmentation change, Pruritis, Purpura, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Skin lesions, Stevens- johns syndrome, Toxic epidermal necrolysis, Urticaria

DISCUSSION

Pharmacovigilance programme is a worldwide effort of more than 100 member nations which helped to create a global database of such drugs which cause suspected ADRs in healthy as well as susceptible individuals on regular intake of such medications for chronic diseases as well as such medications which lead to reactions even on single intake.[11] This helps Health care professionals (HCPs) to carefully prescribe such medications and helped to create a database of such ADRs called Vigibase. The information in this database has reached closer to 14 billion with the help of prompt reporting of such drugs via ICSRs. Vigiflow, is the Indian database where all the information of the suspected ADRs occurring nationally is reported in the form of ICSRs and then this information is shared to Vigibase and Uppsala monitoring centre which is the apex centre of ADR reporting globally.[12,13] Currently, 117485 ADRs have been reported in this form around 534 ADR Monitoring Centre and pharmaceutical companies operating nationwide for the year 2021-2022. Our AMC which was recognised on December 15, 2021 has reported 270 suspected ADRs in the Vigiflow for the year 2021-2022 which accounts for around 0.30% of whole ICSRs reported that year nationally. The reporting of data from our AMC is currently less as compared to other institutions which have been functional for quite some time like AIIMS, Delhi, KEM Mumbai which have reported majority of ADRs apart from the pharmaceutical companies.[14] There are currently 534 AMCs which have been recognised under the Pharmacovigilance Programme of India but most of them have been reporting far less ADRs compared to other centres.[15] There are multiple contributory factors for this underreporting of ICSRs like – lack of awareness among individuals and health care professionals, lack of initiatives as well as infrastructure, underdeveloped health care system, limited literacy, and lack of basic health care needs owing to high poverty. In such areas, we need to create more awareness by regular training programmes to health care professionals and public and other efforts to increase ADR reporting. These efforts will help us in creating a database for all such drugs which carry hazards and will help the clinicians in practising rationale use of drugs.[16,17]

It has been seen that globally among various researches, the incidence of reporting of ADRs is around 5%-20%. Our institution has a per day OPD and IPD of around 4000 patients/day while the incidence of the ADR reporting by our AMC is 270 ICSRs in the year 2021-2022 which amounts to around 0.33%.[18]

In a study conducted by a tertiary hospital in Chhattisgarh, the incidence of ADR was 0.22% in a 6month period study while another study conducted by Gor and Desai reported the incidence rate of 3% ADR in their study in a 1year study. Since our AMC, has recently been recognised due to which our ADR reporting is low as compared to other centres. There is still more awareness need to be created for dynamic ADR reporting from the already overburdened physicians and other HCPs.[19]

There has been a lot of ADRs which are reported from Antimicrobials which account for more than 50% of the cases, which can be an alarming situation as it can lead to antibiotic resistance.[20] Anticancer drugs also lead to a lot of ADRs in our study which can cause additional economic burden on the patients due to prolonged hospital stay and may cause more complications.[21] Other aspect is Polypharmacy which is yet another leading cause of ADRs as it may cause more drug-drug interactions. In various studies, it has been seen that prescribing more than 2 drugs at a time may increase the risk of avoidable ADRs but prescribing multiple drugs has become a very common practise everywhere including our institution as well as worldwide.[22]

Our AMC has been conducting regular training programmes among various departments to educate them about the implications of ADRs and encourage them for active reporting but it has been noted that a lot of ADRs happening in our institution goes unreported.[23] The majority of ADRs are reported by the clinicians (83.22%) followed by other HCPs and least of them are reported by the patients or their attendants. This has been seen in another study conducted in South India.[24] The reasons can be poor literacy rate, lack of initiative, ignorance towards its impact on quality of life etc. Among the health care workers, the most important reason could be overburdened workload and ignorance.[25] Fear of any legal obligations has also been observed as a major roadblock in the drive for reporting ADRs especially among HCPs while it has been always stressed upon that confidentiality is utmost among the patient and reporter in ADR cases and there are no legal consequences for reporting of an ADR.[26]

According to the pattern and frequency of various type of ADRs reported according to system organ class, it was seen that majority of ADRs were reported from skin and subcutaneous tissue disorders 132 followed by general and administration site conditions 62 and gastrointestinal disorders 33 respectively. These observations have also been

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supported by other studies where the ADRs due to skin and subcutaneous tissue disorders are the highest. Majority of the ADRs which were reported were already know reactions from the particular drug and very few among them were any new reactions namely – we encounter 1 ADR of bronchospasm occurring from multivitamins. Some specific ADRs such as systemic lupus syndrome and Stevens–Johnson syndrome were also reported to our AMC by drugs such as carbamazepine, option, levetiracetam, heparin respectively.

The Pharmacovigilance programme of India aims at raising awareness among common people through HCPs or other sources to avoid potential ADRs from routinely prescribed medications. This body ensures periodical reporting of ADRs occurring in any health care system whether it's a government institution or a private health care setup. The main motive is to safeguard the health of Indian citizens.[27] The information which are collected from the various organisations are dispensed periodically to create a safety information database. PvPI is now also starting initiatives for local public involvement in the reporting of ADRs through toll-free helpline numbers, mobile applications and other initiatives, still there are lot of challenges that need to be faced- Unawareness – people are not much aware of the ADRs and confuse it with the side effects associated with medications, they need to be made aware that these are avoidable reactions (2) negligence – the common ADRs are not paid much heed and only serious and life threatening ADRs are considered important enough to be reported (3) doubtfulness – whether an ADR has occurred by a single drug or other factors, such ADRs go unreported (4) polypharmacy – prescribing multiple drug to patients especially for symptomatic reliefs can lead to unnecessary drug – drug interactions and can cause ADRs (5) legal complications – many HCPs are worried about the legal factors associated with reporting of an ADR which also contributes to the underreporting of the ADRs in our country (6) other factors – lack of interest, overburdened medical staff, ignorant attitude of public are other reasons for lack of proper ADR reporting. These are the most common problems we encountered in our institution for spontaneous reporting of the ADRs.[28] We are trying to make people realise the gravity of situation and understand the health benefits associated with the proper reporting of ADRs. Some other measures can also be taken like making ADR reporting compulsory especially for clinicians as well as other HCPs, acknowledging those health personnel who take effort in reporting these ADRs through felicitations etc., organising more hands- on training programmes and lectures to educate undergraduates or other masses regarding the importance of reporting of ADRs and how to report it via ICSRs to vigiflow.[29] Help the public to report ADRs by making it more accessible to them through telephonic conversations or mobile apps. Pharmacovigilance is an important tool in making the drug regimenssafer and ensure rational use of medicines.[30] Our study has some limitations, but it provides a strong base for future prospective studies with more time duration which can benefit more definitive outcomes in ADR monitoring.

CONCLUSION

There has been a tremendous rise in the ADR reporting all across the country through the active training programmes and other initiatives by PvPI. This has helped in garnering large data on the safety information for all the medical products used in our country which is made available to the public from time to time. Overall, the frequency of ADR reporting in our nation is still less than other nations which is around 6% - 10%. In India, the incidence of ADR reporting is still around 3 %, whereas in our AMC it is around 0.30%. The prime reason for this is that our centre is a newly recognised AMC so sensitising the HCPs for active reporting of ADRs is a major task. Other measures also needed to be taken to increase reporting from the common public.

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