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Original Research Article

A prospective study on causality, severity and preventability assessment of adverse drug reactions in a tertiary care hospital in India

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ABSTRACT

Background: The present study was undertaken to evaluate the incidence and pattern of adverse drug reaction (ADRs), causality, severity and preventability of ADRs.
Methods: Data was collected and analyzed with the information such as patients' demographic details, associated co-morbid conditions and detailed drug related information gathered from ADR reporting forms. World Health Organization (WHO) scale was used for assessing causality, modified Hartwig scale was used for assessing severity and modified Schumock and Thorntons scale were used for assessing preventability of ADRs. Data was analyzed using descriptive statistics.
Results: Total 154 ADRs were reported in a period of one year (August 2016-July 2017). Out of 154 ADRs analyzed, 120 (77.9%) were in adults, 33 (21.4%) pediatric and 01 (0.7%) in geriatric patients. The most common ADR recorded was cutaneous reactions (43.5%) and the most common causative class of drugs for the same was found to be antimicrobials (46.7%) followed by non-steroidal anti-inflammatory drugs (15.6%). Causality assessment scale indicated 68.8% ADRs possible and 24% ADRs as probable. Severity assessment revealed that 45.5 % were mild, 50.6% moderate and 3.9% ADRs severe. Preventability assessment showed 84.4% of the cases were probably non-preventable.
Conclusions: In this study it was found that, most of the ADRs were of possible category with mild to moderate severity and majority being non-preventable. Antimicrobial drugs being the most common offending drug class causing ADRs. Strategies targeting appropriate and cautious use of this class of drugs may benefit in reducing the number of ADRs and therefore the cost involved in the treatment.

Keywords: Causality, Preventability, Pharmacovigilance, Severity

INTRODUCTION

WHO defines adverse drug reactions (ADRs) 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] ADR is one of the leading causes for morbidity and mortality worldwide.[2] The overall ADRs rate is estimated to be 6.5% and 28% of these are preventable.[3] Antimicrobials and analgesics are the drugs most frequently responsible for ADRs. However, this pattern and the causative drugs can vary due to different prescribing habits, use of newer drugs and referral bias.[4,5] Identification and reporting of these ADRs is extremely crucial as it may possibly help the treating physicians on being vigilant while prescribing those drugs and achieving a substantial reduction in healthcare cost.[6]

The spontaneous reporting system has resulted in many marketed drugs being withdrawn for safety concerns.[7,8] Compared to western countries where ADR reporting is practiced on a regular basis, in India under-reporting of ADRs is a major problem; reasons include lack of time,

knowledge regarding filling up of the ADR reporting forms and underestimating its importance.[9] Reporting of ADRs is essential and each treating physicians should consider it as their professional conscientiousness so as to safeguard patients' wellbeing and to reduce the cost involved in patient care. Hence, this study was undertaken to analyse the most common drugs causing ADRs, and to assess the causality, severity and preventability of ADRs in a tertiary care teaching hospital.

METHODS

This descriptive, observational study was conducted in the Department of Pharmacology in collaboration with clinical departments like General Medicine, Pediatrics, Pulmonary Medicine, Obstetrics and Gynecology, General Surgery, Psychiatry and Dermatology over a period of one year from August 2016 to July 2017 at a tertiary care hospital.

The study was performed in accordance with the Declaration of Helsinki and was initiated following administrative and ethical approvals. Informed consent waiver was obtained from institutional ethics committee as the required information was collected from ADR reports only wherein patients' identity was not revealed.

Study population

ADR reports of patients from all age groups suspected to be due to medications from the inpatient or outpatient departments of the hospital were included.

Study instrument

The Central Drug Standard Control Organization (CDSCO) ADR reporting forms were used for collection of data. The forms comprised of patient's demographic details, medication details (name, dose, frequency and route of administration of drug), comprehensive adverse reaction details including description of the reaction, time of onset, duration of the reaction and treatment given along with relevant investigations. Causality assessment was done according to WHO Uppsala Monitoring Centre (UMC) scale. Severity was assessed by modified Hartwig and Siegel scale. Preventability was assessed by modified Schumock and Thornton criteria.

Causality assessment - WHO scale

The causality categories described by the WHO- UMC are; certain means good temporal association, no other cause, withdrawal response plausible, re-challenge is positive and "definitive" association, probable means good temporal association, other cause unlikely, withdrawal, possible means good temporal association, other causes possible, unlikely means poor temporal association, other causes more likely, unclassified means more data is essential for proper assessment, unclassifiable means insufficient or contradictory information is available.[10]

Severity assessment - Modified Hartwig and Siegel scale

This scale divides the ADRs into three categories based on severity assessment as mild, moderate and severe. Mild ADRs were defined as those which does not by itself require prolongation of hospitalization and could be managed by simple measures, moderate were those ADRs which needed prolongation of hospital stay of the patient for treatment of the same and severe were life threatening ADRs.[11]

Preventability assessment- Modified Schumock and Thorntons Scale: Modified Schumock and Thornton's criteria have three sections namely definitely preventable, probably preventable and not preventable.[12]

Statistical analysis

The number of ADR reports and their characteristics were analyzed using descriptive statistics.

RESULTS

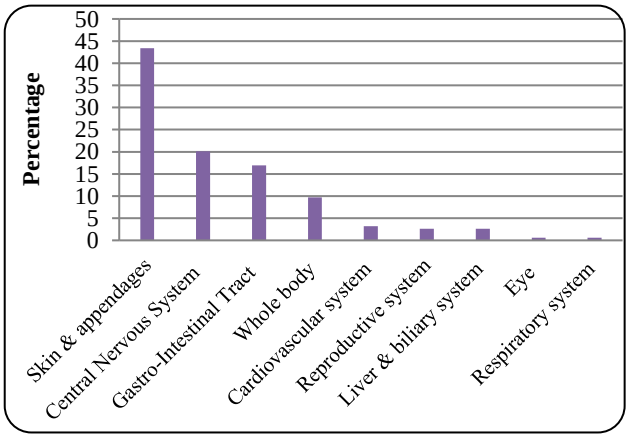

Figure 1: System-wise distribution of ADRs reported in ADR report forms.

Table 1: Distribution of different classes of drugs responsible for causing ADRs.

Different classes of drugs causing ADRs	Number of ADRs N (%)
Antimicrobials	72 (46.7)
Nonsteroidal anti-inflammatory drugs	24 (15.6)
Antipsychotics	14 (9.1)
Hematinics	13 (8.5)
Multivitamins	10 (6.5)
Antiepileptics	5 (3.2)
Antidepressants	4 (2.6)
Antihypertensives	4 (2.6)
Disease modifying antirheumatic drugs	3 (1.9)
Thrombolytics	3 (1.9)
Antihistaminics	2 (1.3)

Among the total 154 ADRs collected 81 (52.6%) were observed in male patients and 73 (47.4%) in female patients. Out of the total patients, 120 (77.9%) were observed in adults, 33 (21.4%) in pediatric and 01 (0.7%) in geriatric age group.

Table 2: Reported ADRs with the suspected drugs causing it.

Type of ADRs	Drugs causing the ADRs
Urticarial rash	Amoxicillin (8), Amikacin (1), Amoxicillin + Clavulanic acid (2), Bromhexine (1), Carbamazepine (3), Cefotaxime (1), Cefpodoxime (1), Ceftriaoxone (1), Cotrimoxazole(1), Diclofenac (1), Tenofovir (3), IV Immunoglobulin (1), Clindamycin (1), Lamivudine (1), Terbinafine (1), Paracetamol (4)Metronidazole (2), Ornidazole (4), Thalidomide(1), Anti TB regimen include [Isoniazid+ Rifampicin+ Ethambutol+Pyrazinamide] (4)
Maculopapular rash	Artemether (3), Haloperidol (1), Paracetamol (1)
Erythematous rash	Ketoconazole (1), Ondansetron (2)
Exenthematous skin eruption	Cotrimoxazole (2)
Angioedema	Tinidazole (1)
Steven Johnson's Syndrome	Dapsone (1), Nevirapine (1)
Fixed drug eruption	Fluconazole (1), Indomethacin (2)
Red man syndrome	Vancomycin (2)
Photosensitivity	Griseofulvin (3), Itraconazole (1)
Periorbital dermatitis	Chloramphenicol (1)
Flushing	Chloramphenicol (1), Tranexamic acid (1)
Itching	Amoxicillin (1), Cefotaxime (1), Lamivudine (1), Paracetamol (6), Anti TB regimen include [Isoniazid+ Rifampicin+ Ethambutol+Pyrazinamide] (1)
Headache	Albendazole (1), Cetrizine (1), Fluconazole (1), Linezolid (1), Kanamycin (1), Imipramine (1)
Giddiness	Phenytoin (3), Ibuprofen (2), Fluconazone (2)
Hypersomnia	Alprazolam (1)
Psychosis	Cycloserine (1)
Extrapyramidal reactions	Haloperidol (3), Trifluperazie (2)
Akathesia	Haloperidol (2)
Orthostatic hypotension	Risperidone (1)
Fever	Kanamycin (1)
Tinnitus	Streptomycin (1)
Nausea and vomiting	Paraaminosalicylic acid (1), Sodium valproate (1), Ibuprofen (2)
Diarrhea	Amoxicillin+ Clavulanoc acid (2), Cefixime (3), Methotrexate (1)
Oral ulcers	Methotrexate (2)
Chills and rigor	Ferrous carboxymaltose (1), Ferrous sucrose (12)
Dry cough	Enalapril (1)
Hyponatremia	Hydrochlorothiazide (1)
Nephrotoxicity	Tenofovir (2)
Jaundice	Anti TB regimen include [Isoniazid+ Rifampicin+ Ethambutol+Pyrazinamide] (10)
Hematuria (3), Petechial hemorrhage (2), Bleeding gums (3)	Warfarin (8)
Anemia	Azidothymidine (3)
Amenorrhea	Risperidone (2)

According to WHO Adverse Drug Reaction Terminology (ART) classification of the organ system involvement and types of ADRs, 67 (43.5%) ADRs involved skin and appendages (cutaneous reactions noted were different types of skin rashes such as maculopapular rash, erythematous rash, urticaria, angioedema, acneiform popular lesions, photosensitivity, Steven Johnson's syndrome and Red Man syndrome). This was followed by symptoms of central nervous system (CNS) involvement such as extra-pyramidal symptoms, giddiness, sedation,

insomnia, 31 (20.1%), ADRs affecting gastro-intestinal tract (GIT) such as nausea, vomiting, gastritis, diarrhoea, oral ulcer, abdominal pain was found to be 20 (16.9%) Other ADRs reported include hypotension, menstrual irregularities, hematuria, bleeding gums, petechial hemorrhage, hepatitis, dry cough which were less than 5% of total ADRs reported (Figure 1).

Most common class of drugs which caused the ADRs was antimicrobial agents responsible for 72 (46.7%) ADRs followed by non-steroidal anti-inflammatory drugs (NSAIDs) for 24 (15.6%) ADRs (Table 1). Reported ADRs with the suspected drugs causing it is shown in (Table 2).

Causality assessment

Causality assessment was done for individual cases by using WHO scale. Causality assessment indicated that 106 (68.8%) ADRs as possible whereas 37 (24%) ADRs were of probable category. The details of the causality assessment are given in the (Figure 2).

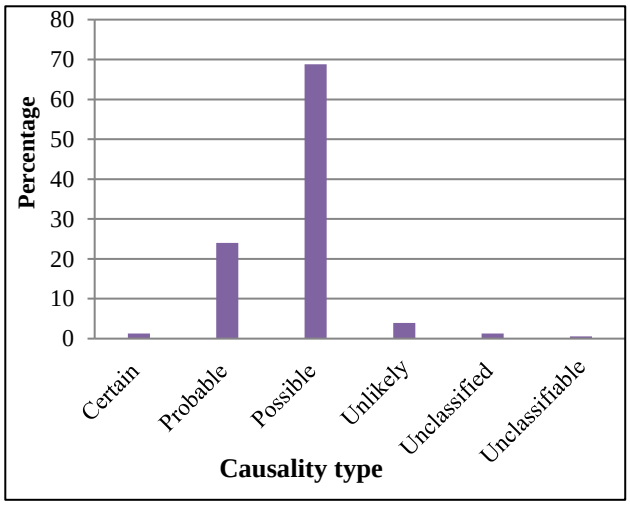

Figure 2: Details of causality assessment using WHO causality assessment scale.

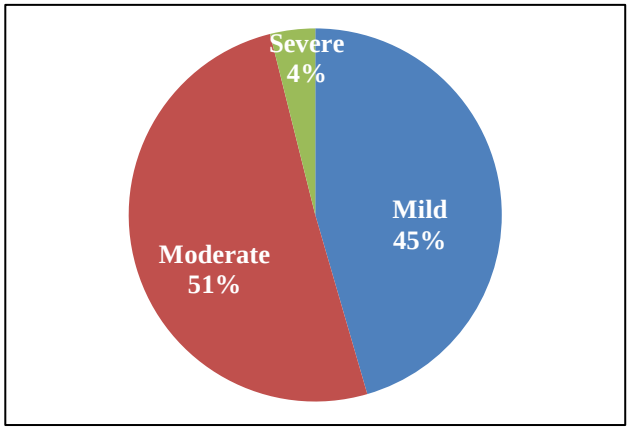

Figure 3: Details of severity assessment by Modified Hartwig and Siegel scale.

Table 3: Details of preventability assessment ADRs using modified Schumock and Thornton scale.

Preventability assessment	Number of ADRs (%)
Definitely preventable	47 (30.5)
Probably preventable	24 (15.6)
Not preventable	83 (53.9)
Total	154

Severity assessment

On evaluation of the severity of ADRs by Modified Hartwig and Siegel scale, it was evident that most of the ADRs reported in the study, were of moderate severity followed by mild and severe. Details of the severity assessment are given in the (Figure 3).

Preventability assessment

On evaluation of the chances of preventability of ADRs using modified Schumock and Thornton scale, it was evident that most of the ADRs reported were not preventable (Table 3).

DISCUSSION

Spontaneous ADR reporting activity is important to monitor known and unknown adverse effects of medicines. It has played a most important role in the detection of serious and unusual ADRs after marketing when the drug is actually being prescribed by the clinicians. This activity of continuous vigil on the drug related adverse drug reactions has resulted in withdrawal of quite a few drugs in the past such as rofecoxib, cisapride, terfenadine, etc. ADRs have to be considered as one of the major causes of iatrogenic disease with detrimental effect on patient's wellbeing and over-all healthcare system.[13] The Pharmacovigilance Program of India (PvPI) was launched in the year 2010 with a broad objective to safeguard the health of 1.27 billion people of India. Adverse drug Reactions (ADRs) are reported from all over the country to National Coordinating Centre (NCC)-PvPI, which also work in collaboration with the global ADR monitoring centre (WHO-UMC), Sweden to contribute in the global ADRs database. NCC-PvPI monitors the ADRs among Indian population and helps the regulatory authority of India, Central Drugs Standard Control Organization (CDSCO) in taking decision for the safe use of medicines. Authors conducted this present study at an ADR Monitoring Centre (AMC) of a newly started municipal medical college. With the active involvement from authors' departmental faculty, the clinicians were asked daily about the occurrence of the ADRs in their respective outpatient departments or wards and then the details of the ADRs and the drugs were elicited to gather complete information as asked in the ADR reporting form. This indirectly helped us in increasing awareness and sensitizing the clinicians on reporting of the ADRs noted.

It was observed that the incidence of ADRs was same in both males and females, finding similar to Jose et al, who reported similar incidence for both genders, though other spontaneous reporting studies in our country had observed high percentage of ADRs in females.[13-17]

In the present study the incidence of ADRs was more in adults which was comparable to the findings reported by various studies, such as Pudukadan et al, Shah et al, Venkatesan et al, Rajkannan et al, and Rao et al, however, contrary to these finding, studies conducted by Ramesh et al, and Arulmani et al, mentioned more incidence of ADRs in elderly patients.[14-20]

Most commonly reported ADRs involved the skin in the form of rashes such as urticaria (N=42, 62.7%) which was similar to the findings reported in previous studies.[15,17,21] This was followed by ADRs related to CNS (20.1%) and GIT (16.9%). This finding was comparable to a study by Ramesh et al and Bhabhor et al, and which also showed ADRs involving similar systems.[15,22] The other system which was found to be involved with regards to the ADR occurrence was gastrointestinal as reported by previous several studies.[15,16,19,20] In a study conducted by Doshi et al, the author has mentioned that gastrointestinal symptoms occurred most commonly during hospitalization while cutaneous reactions were the most common cause of hospitalization.[6] No such correlation was observed in this study. Among the cutaneous reactions, urticarial rash was found to be most common ADR in this study, the same has been reported by Doshi et al. Most reactions had sub-acute and latent onset which was similar to the findings reported in previous study.[20]

The major causative class of the drugs responsible for causing ADRs was antimicrobials (46.7%) followed by NSAIDs (15.6%). Other epidemiological studies also have reported ADRs due to the same class of drugs.[5,13,18,21,23-26] Authors observed that among different classes of drugs prescribed, β- lactams and fluoroquinolones were most common classes of drugs that caused ADRs. Similar findings were reported by Thong BY et al, and Shamna et al.[27,28]

Causality assessment

As per WHO causality assessment scale, in present study, it was evident that majority of ADRs belonged to possible category; and seen as those patients were treated with more than five drugs. The multiple medications are important risk factors for drug interactions and ADRs to occur.[29]

Severity assessment

On evaluation of the severity of ADRs by Modified Hartwig and Siegel scale, it was evident that most of the ADRs reported were of moderate severity (50.6%) followed by mild (45.5%) and very few were severe (3.9%). Other study by Ghosh S et al, reported majority (53%) of ADRs as moderately severe in nature, but the ADRs in severe category were higher (25%).[25]

Preventability assessment

On evaluation of the chances of preventability of ADRs using modified Schumock and Thornton scale, it was evident that 53.9% ADRs were not preventable, 30.5% ADRs were definitely preventable and 15.6% were probably preventable. In present study, a total 46.1% of the reported ADRs were preventable, which is more than the figures mentioned (15-37%) in previous Indian studies.[6,17,20] Though 54% of ADRs belong to non-preventable category, efforts in the direction of precautious and judicious use of antimicrobials and NSAIDs, the most common offending classes of drugs in present set up, perhaps help in substantially reducing the number of preventable ADRs in patients.

CONCLUSION

The common organ systems showing ADRs with drug use were skin and appendages and central nervous system. The most commonly implicated classes of drugs were found to be β-lactam group of antibiotics, fluoroquinolones and NSAIDs. The most implicated class of drugs for serious reactions was antimicrobials. Strategies targeting cautious use of these drug classes may help in reducing the number of ADRs and perhaps the associated costs of treatment. Most of the ADRs were of possible category with mild to moderate severity and were non-preventable.

The study had limited number of patient data from tertiary care teaching municipal hospital. Hence, the findings cannot be generalized. Further, in patients on multiple drug prescriptions/polypharmacy, skin allergen tests and oral drug provocations were not performed to confirm the causality and to look safer alternatives.

Future prospects

The success of a pharmacovigilance program depends upon the active involvement of the healthcare professionals such as doctors, pharmacist, and nurses. Being the key healthcare professionals, providing information on suspected ADRs is as much a moral duty for the doctor as other aspects of patient care. This particular activity helped us in sensitizing the clinicians of authors' institute in reporting of ADRs encountered and above all provided information related to drugs most commonly involved in causing the ADRs, their category and severity. To transform the pharmacovigilance activity into practice, treating physicians need to be educated with regards to importance of reporting predictable as well as unpredictable ADRs. The purposeful pharmacovigilance activity not only will help in identifying some exceptional ADRs not reported in the literature but will also help in generating Indian data on commonly encountered ADRs with specific drugs.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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