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An Evaluation of Causality, Severity, and Preventability of Adverse Drug Reactions Reported by Undergraduate Medical Students in a Tertiary Care Hospital

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Abstract

Adverse drug reactions (ADRs) have become a major clinical problem that causes mortality and morbidity, besides causing an additional burden on the total cost of patient treatment worldwide. Therefore, this study aimed to assess ADRs' causality, severity, and preventability and sensitize undergraduate medical students to reduce underreporting of cases. It was a retrospective observational study conducted in a tertiary teaching hospital of J&K India. The study was conducted after sensitizing the students about Pharmacovigilance and guiding them to collect and submit individual case safety reports (ICSRs) of ADRs during their clinical postings over a period of 10 months, from May 2020 to February 2021, as a part of their internal assessment followed by evaluating the data using simple descriptive statistics. We analyzed a total of 124 reports over the stipulated time. The most common ADRs reported were related to skin and appendages and antibiotics accounted for a maximum number of cases. Causality assessment showed that most ADRs were possible (61.1%) and probable (38.8%). Severity and preventability assessment revealed that most reported ADRs were moderate (67.9%) and mild (32.0%), while most ADRs were preventable, with only 30.0% of them not preventable. Students reported valuable and clinically relevant ADRs. This study will foster the culture of reporting and analyzing the impact of ADRs among undergraduate students. Furthermore,since most ADRs in this study were preventable, managing such ADRs through therapeutic intervention would benefit better patient care.

Keywords: Adverse drug reactions (ADRs), Undergraduate medical students, Pharmacovigilance, Causality, Severity, and Preventability.

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Introduction

Adverse drug reactions (ADRs) are a major health concern[1] and a leading cause of mortality and morbidity in healthcare that significantly impacts healthcare resources.[2] According to the World Health Organisation (WHO), "ADR is a noxious and unintended response that occurs at doses normally used in humans for prophylaxis, diagnosis or therapy of a disease or the modification of physiological function."[3]

This definition eliminates therapeutic failure, overdose, medication abuse, noncompliance, and medication error.[4,5] Lazarou et al. reported ADRs were ranked fourth and sixth leading causes of death in the USA in a meta-analysis study of 39 epidemiological students.[6] In India, the incidence of serious ADRs occurred in 6.7% of cases approximately. It has also been reported that 2.4-6.5% of hospital admissions are due to adverse reactions, many of which are preventable.[7,8] Preventable ADRs sometimes can be considered as a form of medication error[9] and a meta-analysis by Hakkarainen et al. observed that preventable ADRs are significant causes of morbidity in outpatients.[10]

Half of the ADRs cases are preventable due to contraindications, inappropriate dose or lack of monitoring, interactions, ignoring toxic serum drug concentration, allergic reactions, and non-compliance. Thus, ADRs need definite strategies for prevention to reduce the burden of ADRs and treatment costs. Although many regulatory agencies obligate ADRs monitoring, it is not extensively accomplished in Indian hospitals as the ADRs reporting rate is below 1% in India compared to the worldwide rate of 6-10%.[11,12]

Since the number of medications and their usage has increased recently the early detection of ADRs is essential to monitor both known and unknown effects of medication.[13] Voluntary reporting of ADRs by healthcare professionals is considered the cornerstone of managing ADRs. Hospital-based ADR reporting programs can provide valuable information about the potential issues associated with medication usage in that institution.

In addition, the ability to detect rare ADRs and generate new signals would enhance a sound Pharmacovigilance system in the country by revealing unusual or rare ADRs to the Indian population. However, physicians are still unaware of ADR reporting and monitoring services, as many untoward adverse incidents are unrecognized in an Indian hospital setting.[14] One method to reduce the under-reporting of ADRs is the exposure of medical students to ADR cases during their undergraduate study period by checking medical records. This can cultivate ADR reporting habits, thereby increasing awareness about the detection, reporting, management, and prevention of ADRs among healthcare providers and the general population.

Hence this study was planned to assess the causality, severity, and preventability of ADRs. In most of the earlier studies, students evaluated only the causality. However, this present study is the first in this 800-bedded tertiary care institute in the union territory of Jammu and Kashmir and students have assessed the causality, severity, and preventability of ADRs.

Methods

This retrospective observational study was carried out in the Postgraduate Department of Pharmacology, Government Medical College, Srinagar (J&K), a teaching postgraduate medical institute from May 2020 to February 2021. As no ethical issues were involved in this study, no ethical clearance was obtained. However, permission from Adverse

Drug Reaction Monitoring Centre (AMC) coordinator was obtained for this study.

Undergraduate medical students reporting of ADRs was part of their internal assessment during regular classes in which the students were taught and sensitized about Pharmacovigilance and ADR reporting. The ADR reporting form designed by the Indian Pharmacopoeia Commission (IPC), Pharmacovigilance Programme of India (PvPI) was used to report ADRs. As our institute has a registered Pharmacovigilance centre through which all ADRs by clinicians, postgraduates and faculty members are reported which are further transmitted to "Vigiflow Software" of WHO-UMC for global monitoring of ADRs provided by the Indian Pharmacopoeia Commission, Ghaziabad, India.

ADR reporting form noted demographic details of patients, detailed clinical history including pre-existing medical conditions, and relevant laboratory data. Other drugs used for treating patients and patients with ADRs were noted in the ADR reporting form at the time of collection of ADRs. The suspected drug, as well as concomitant drug history, was taken in terms of dosage, route of administration, indication, improvement after discontinuation of the drug, history of any over-the-counter formulation and drug allergy were noted in the ADR reporting form, and only those ADRreports were included in the study which met the minimum criteria as per PvPI guidelines.

Some ADR reports were excluded based on duplication and paucity of the required information. ADRs were assessed for causality with World Health Organisation-Uppsala Monitoring Centre (WHO-UMC) scale for causality,[15] Modified Hartwig and Seigels scale[16] for severity assessment and Modified Schumock and Thornton scale[17] for preventability assessment.

Results and Discussion

The present study has been conducted to sensitize second-professional undergraduate medical students who are future doctors and healthcare professionals to explore the causality, severity, and preventability of ADRs among hospitalized individuals. The sensitization was to reduce the wide gap between the occurrence and reporting of ADRs in India and worldwide, generate signals and alerts, and identify and manage ADRs early, thereby improving patient safety and quality of life and reducing the cost of treatment. Further reporting and labeling of new ADRs will help prepare the prescribing policies, modify the prescribing pattern and decrease the prescribing of the flagged drugs, eventually reducing the prevalence of ADRs.

During the study period, data was collected by undergraduate medical students by checking medical records and a total of 124 reports were submitted. After analyzing the reports 9 were excluded due to duplication and 12 were rejected due to a paucity of the required information making 103 reports eligible for the study.

The maximum number of cases i.e. 82 (79.6%), fell between the ages of 19 to 65, which may be due to the reason that this age group constitutes the bulk of the population. This is also similar to a study conducted by Daulat et al[18] and Thakare et al[19], which may be due to the wide age range. Moreover, about 60 ADRs (58.25%) were reported in females, which may be incidental and other factors like body size, genetic factors, etc. However, the literature states that female anatomical and physiological differences alter the drug pharmacokinetics and pharmacodynamics and predispose them to more ADRs.[23]

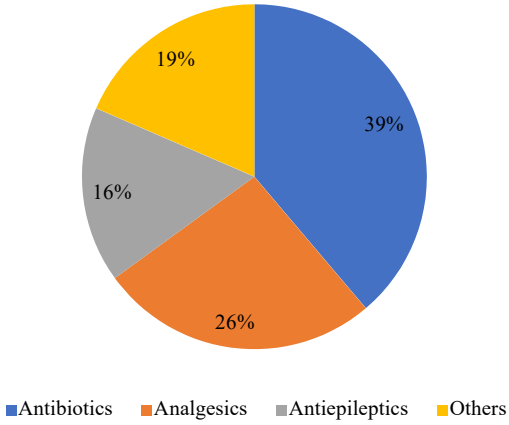

Figure 1. ADRs Percentage based on Drug Classes

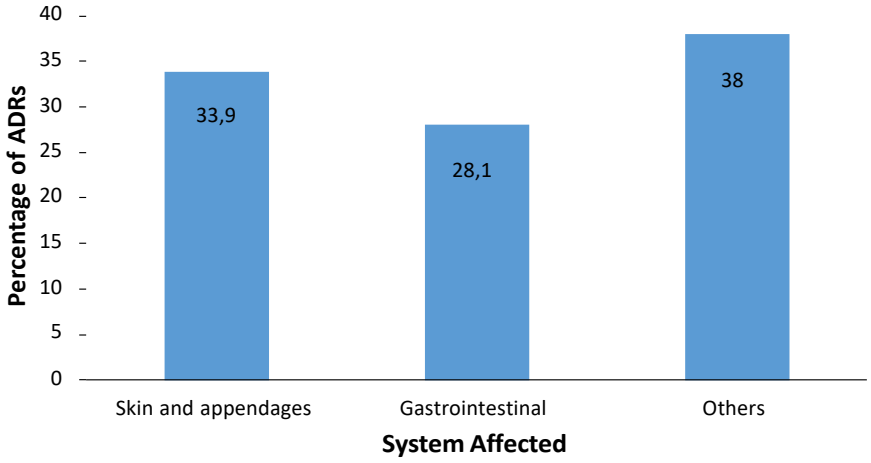

Figure 2. ADRs Percentage based on System Affected

Among the groups of drugs most commonly associated with ADRs were antibiotics (38.8%), analgesics (26.2%) and antiepileptics (16.5%) with antihypertensives, hypoglycaemics, diuretics and anticancer drugs constituting the rest (Fig. 1). Another recent study reported that antibiotics (20.8%) are the second most common medication class associated with ADRs.[24]

The results of our study also agree with other studies that documented that this class is prescribed for unindicated conditions providing an opportunity to develop antimicrobial resistance.[25–27] Antimicrobials and non-steroidal anti-inflammatory (NSAIDS) ADRs were reported to have a high case incidence which is similar to a study by Basavarajetal.[28] (NSAIDS= 22.5%).

Based on the affected system it was found that most of the ADRs were related to skin and appendages disorders (33.9%), gastrointestinal (28.1%) followed by ADRs related to kidney and electrolyte disorders, liver and biliary system disorders, neurological, hematological and metabolic abnormalities (Fig. 2). These results were also similar with other reported studies.[29–31]

Table 1. WHO-UMC Causality Assessment Scale[15]

Causality Term	Assessment Criteria	Number	Percentage
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary	0	0
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required	40	38.8
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear	63	61.1
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations	0	0
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed • Additional data under examination	0	0
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified	0	0

Table 2. Modified Hartwig and Siegel Severity Assessment Scale

Level	Description	Number	Percentage (%)
Level 1	An ADR occurred but required no change in treatment with the suspected drug.	20	19.4
Level 2	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay (LOS)	13	12.6
Level 3	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in length of stay (LOS)	45	43.6
Level 4	Any level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission	25	24.2
Level 5	Any level 4 ADR which requires intensive medical care	0	0
Level 6	The adverse reaction caused permanent harm to the patient	0	0
Level 7	The adverse reaction either directly or indirectly led to the death of the patient	0	0

Causality analysis of ADRs was done per the WHO-UMC scale which classifies ADRs as certain, probable, possible, unlikely, conditional and un-assessable. All the reported ADRs were probable and possible as per WHO-UMC classification (Table 1) with possible being more common i.e. 63 (61.1%), the reason for which could be polypharmacy and comorbidity which makes temporal association difficult and is similar to findings in other studies.[10,32]

The severity of ADRs was assessed by Modified Hartwig and Siegel scale.[16] According to this scale there are seven levels of severity ranging from "No change in treatment" in level 1 to "Death" in level 7. Overall, the severity assessment of ADRs using the Modified Hartwig and Seigel scale found that most of the ADRs belonged to moderate. i.e. 70 (67.9%) followed by mild i.e. 33 (32.0%). This could be attributed to the timely intervention of treating health care professionals who used a precautionary antidote or made other remedial measures to prevent progression. (Table 2)

Preventability was assessed using Modified Schumock and Thornton scale.[17] Any " yes " answer to any question on this scale suggests that ADR might have been preventable. This scale categorizes ADRs as definitely preventable, probably preventable and not preventable. Our study's most common culprit group was antiepileptics, followed by analgesics, antibiotics and others. Emma and Colleagues[33] and Remesh et al.[29] reported similar findings from the United Kingdom among 3695 hospitalized inpatients.

Table 2. Modified Hartwig and Siegel Severity Assessment Scale

Preventability Term	Description	Number	Percentage (%)
Definitely Preventable	Was there a history of allergy or previous reaction to the drug?	3	2.91
	Was the drug involved inappropriate for the patient's clinical condition?	7	6.79
	Was the dose, route, or frequency of administration inappropriate for patient's age, weight or disease state?	5	4.85
	Was toxic serum drug concentration or lab monitoring test documented?	4	3.88
	Was there a known treatment for ADRs?	3	2.91
Probably Preventable	Was therapeutic drug monitoring or other necessary lab test not performed?	8	7.76
	Was the drug interaction involved in ADRs?	17	16.50
	Was poor compliance involved in ADRs?	10	9.70
	Were preventative measures not prescribed or administered to the patient?	15	14.56
Not Preventable	If all the above criteria not fulfilled.	31	30.09

The preventability of ADRs was assessed by the Modified Suchumock and Thornton scale which revealed that 72 (69.9%) were definitely or probably preventable and 31 (30.0%) were not preventable which may be contributedto the lack of drug therapeutic monitoring facilities and drug-drug interaction and conform with a study by Rautet al.[2] (Table 3) However Remesh et al. opined that majority of the ADRs encountered in their study were not preventable the reason for which could be selection bias[29].

The main limitations of our study were that the study was of shorter duration and the target group was undergraduates only, excluding the ADR reporting by residents, postgraduates and other health care professionals thereby limiting the ADRs to 103 in number.

Conclusion

This study was based on a spontaneous reporting system by undergraduate students to sensitize and develop a culture of ADR reporting. The study suggests that there is a greater need for streamlining hospital-based ADR reporting and promoting the reporting of ADRs among undergraduate students. As most ADRs in this study are preventable, management of such ADRs through therapeutic interventions for better patient outcomes and multidisciplinary strategies involving physicians, pharmacists and other healthcare workers along with education, awareness of patients and incentives is required. Lastly prudent use of antimicrobials is once again proven as a need of the hour for which an antimicrobial stewardship program (ASP) should be implemented in every hospital.

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Conflict of Interest
None declared.

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