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Original Article

Distribution of Adverse Drug Reactions at the Inpatients Department of Medicine in B.R.D. Medical College, Gorakhpur (Uttar Pradesh)

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ABSTRACT

Background: *An adverse drug reaction (ADRs) is injury observed during the patient's drug therapy, overdose, drug abuse, noncompliance, and medication errors. In this study we aim to evaluate the ADRs and its severity.*

Methods: *Total 150 patients were included in this study as per the study criteria. Adverse drug reactions were evaluated by causality assessment by Naranjo algorithm designed to determine whether the occurrence of ADRs is due to a drug or some other underlying cause. Their severity was evaluated by Hartwig scale in which ADRs were graded into mild, moderate and severe.*

Results: *The range of age was 18.0 to 90.0 years with mean 47.32±17.76 (years). The majority of the study subjects were males (61.33%). The severity of ADRs was significantly positive correlated with comorbidities and drug- drug interactions. The majority of the ADRs were mild. The most common organ system seen to be involved with the ADRs was gastrointestinal which comprised of 44.67% of the total ADRs*

Conclusion: *The incidence of ADRs increases with increasing the age of the patients. A male preponderance was seen in the occurrence of ADRs. The predominant organ system affected was the gastrointestinal system. A positive correlation between the severity of ADRs with comorbidities and drug-drug interactions was observed.*

Keywords: *Adverse drug reaction, Adverse drug event, Naranjo Scale, Hartwig scale*

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INTRODUCTION

Adverse drug reactions (ADRs) are a great cause of concern to all the stakeholders in the healthcare system including but not limited to the patients, healthcare givers and the authorities. According to World Health Organizations (WHO) adverse drug reactions (ADRs) are defined as "any response to a drug which is noxious, unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.[1] Adverse drug reactions can be classified into six types by the WHO's Adverse Reaction Terminology: dose-related (Augmented), non-dose-related

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(Bizarre), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of treatment), and failure of therapy.[2]

Adverse drug event (ADE) is defined as "any injury occurring during the patient's drug therapy as a result of appropriate care or from unsuitable or suboptimal care.[3] ADR contributes to the burden of drug related patient morbidity and mortality adding to the cost of patient health care. Detection and monitoring of ADRs is of vital importance for patient safety, as more than 50% of approved drugs are associated with some type of adverse effects that are not detected prior to their approval for clinical use.[4]

ADRs are one of the major causes of iatrogenic diseases.[5] ADE includes: the adverse drug reactions during normal use of the medicine and any harm secondary to an error of medication regimen, both omission or commission errors. ADE is any untoward occurrence that may present during treatment with a drug but which does not necessarily have a causal relationship to the drug. A serious adverse event means an adverse drug reaction leading to death or is life-threatening, requiring inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity or congenital anomaly. In an unexpected adverse drug reaction, the nature, severity or outcome is not consistent with the summary of existing information about ADRs. ADRs lead to hospital admission, prolonged hospital stay, disability and even death, being the 7th most common cause of death[6] 57% of ADRs are unrecognized by the treating physicians.[7] The incidence of ADR in the Indian population is 1.82%, with 2.8% resulting in hospitalization.[8]

In spontaneous reporting, healthcare professionals and patients (consumers of the drug/drugs) are relied on to identify and report any adverse drug event to their national pharmacovigilance centre, voluntarily. Active surveillance can be conducted by taking ward rounds to take history of patients, for the purpose of detecting ADRs and for looking into the drug or drugs which he has been prescribed or had taken in the past, so as to establish a connection between the drug exposure and the adverse event. Individuals with greater risk of adverse drug reactions can also be identified by ADR monitoring. ADR monitoring can be of 3 types: drug based by post marketing surveillance in phase 4 clinical trials; settings based: when ADRs are captured in health care facilities, hospital settings or even private setups; outcome based: to draw a correlation between drug exposure and toxicity.[9-11]

In both active surveillance and spontaneous reporting, a link between the drug exposure and occurrences of ADR is drawn by causality assessment. Causality assessment is the assessment of a causal relationship between a drug treatment and occurrence of an adverse event. It is mostly carried out by two methods: Naranjo scale and WHO –UMC (Uppsala Monitoring Centre) scale. The spontaneous reporting of data has led to underreporting of several adverse events as is prevalent in any other institution.[12] The patients, who are on long term treatment, afflicted with chronic diseases, comorbidities and have organ failure or deranged functions. In such cases, the patients are likely to have a larger number of ADRs than have been reported so far at our AMC.

The ADRs in such patients can be correlated with polypharmacy (5 or more medications) and comorbidities. Since the patients who are admitted to the ward are male or female adults, ADRs can be correlated with age and gender as well. Considering this, we have conducted an observational study for soliciting ADRs which otherwise probably go unnoticed. The causality and severity of the detected ADRs was assessed using the Naranjo and Hartwig scale respectively and their distribution was correlated with demographic characteristics, patient characteristics and polypharmacy (5 or more medications).

METHODS

This observational study was be conducted in the patients admitted to the Medicine ward, of BRD Medical College, Gorakhpur in which ADRs (if present) were captured by active surveillance. Total 150 patients were included in this study as per the study criteria. Patients with comatose/ unconscious, not able to communicate, <18 years of age and falling in the sampling frame were excluded from the study. A written informed consent was obtained from patients, as per the institute guidelines. Ethical approval was obtained Institutional Ethics Committee.

The classes of drugs of the causative agents were assigned a code as per the ATC (Anatomical Therapeutic Chemical Classification) system. Patients were interviewed for patient particulars, medical history and family history [13]. Drug history was also taken to rule out the causative drug or drugs because if a patient on a drug therapy had an adverse drug event; it could be due to the drug, the disease or some other causes. Adverse drug reactions were evaluated by causality assessment by Naranjo algorithm designed by Naranjo et al. (1981) to determine whether the occurrence of ADRs is due to a drug or some other underlying cause [14]. The ADR Probability Scale consisted of a questionnaire 10 questions that were answered as either Yes, No, or "Do not know" in Naranjo Scale different point values (-1, 0, +1 or +2) were assigned to each answer. Their severity was evaluated by Hartwig scale in which ADRs were graded into mild, moderate and severe [15]. The distribution of adverse reactions was to be correlated with demographic characteristics, patients' characteristics and polypharmacy.

Statistical Analysis: Data was presented as mean ± SD and frequencies and percentages. Data was statistically analyzed with graphpad instat software. Continuous variables were compared using independent sample t-test. Categorical variables were compared with chi-square statistics, or Fisher's exact test. Pearson's correlation was used to find out the correlation in between the severity of ADRs with comorbidities, drug interactions and polypharmacy. All P <0.05 was considered significant.

RESULTS

Table 1 shows the demographic profile of the patients with ADRs. The mean age of the patients were 47.32±17.76 with 18 to 90 years age range. The maximum patients (63.34%) were belonging to > 40 years age groups. Total 57 (38.0%) patients belong to Gorakhpur area and 93 (62.0%) patients were belonging to other than Gorakhpur area. The percentage of true and false polypharmacy was 48.67% and 51.33%, respectively.

Table 1: Demographic profile of the patients with ADRs.

Age (years)	Mean	47.32
	Median	50
	Std. Deviation	±17.76
	Minimum	18
	Maximum	90
Age Category (years)	18-25	30 (20.0%)
	26-40	25 (16.67%)
	41-60	60 (40.0%)
	61-80	34 (22.67%)
	>80	1 (0.67%)
Geographical Distribution	Gorakhpur	57 (38.0%)
	Other than Gorakhpur	93 (62.0%)
Gender	Male	92 (61.33%)
	Female	58 (38.67%)
Polypharmacy	True	73 (48.67%)
	False	77 (51.33%)

The distribution of patients according to J01(Antimicrobials), M01(Anti inflammotory), N02A(Opiod analgesics), R03DA(Xanthines), N03(Antiepileptics), C03(Diuretics), P01B (Antimalarials), A10(Drugs used in Diabetes), B03(Antianemics), R03BA01(Corticosteroids used in respiratory diseases), R03DB (Combinations of Xanthines and adrenergic drugs), D07(Corticosteroids in dermatological diseases), C10A (Lipid modifying agents), N07C (Antivertigo preparations), A04(Antiemetics), A07(Antidiarrheals), R06, A12 (Mineral supplements), A single ADR was caused by 2 causative agents A07+ A12, J01+N02A, R03DA+J01, A10 +R03DB and R03DB+C03 were, respectively as shown in Table 2.

Table 2: Distribution of patients with ADRs, according to gender

	Total	
	n	%
Antimicrobials for systemic use (J01) [17 Drugs used in this class]	83	55.33%
Antinflammotory and antirheumatic (M01) [Diclofenac]	13	8.67%
Opiod analgesics (N02A) [Tramadol]	8	5.33%
Xanthines (R03DA) [Theophylline]	6	4.00%
Antiepileptics (N03) [Phenytoin and Gabapentin]	6	4.00%
Diuretics (C03) [Furosemide]	5	3.33%
Antimalarials (P01B) [Artensuate]	5	3.33%
Drugs used in Diabetes (A10) [Metformin+ Glibencia, Metformin, and Insulin]	3	2.00%
Antianemic agents (B03) [Iron]	3	2.00%
Corticosteroids in respiratory diseases (R03BA01) (Beclomethasone used) +Corticosteroids in dermatological diseases(D07) [Betamethsone]	5	3.33%
Combinations of Xanthines and adrenergic drugs(R03DB) [Terbutaline and Salbutamol]	2	1.33%
Lipid modifying agents (C10A) [Atorvastatin with Fenofibrate]	2	1.33%
Antivertigo preparations(N07C) [Betahistidine]	2	1.33%
Antiemetics (A04) [Ondansetron]	1	0.67%
Antihistaminic agents(R06) [Fexofenadine]	1	0.67%
A07+ A12 (Normal Saline)	1	0.67%
J01+N02A	1	0.67%
R03DA+J01	1	0.67%
A10 +R03DB	1	0.67%
R03DB+C03	1	0.67%

The distributions of causative drugs belonging to ATC Code J01 are shown in Figure 1. The frequencies of antimicrobial causative drugs (J01) such as Ceftriaxone, Doxycycline, Linezolid, Azithromycin, Cefixime, Levofloxacin, Metronidazole, Piperacillin, Clindamycin, Ciprofloxacin, Gentamicin, Neomycin, Meropenem, Rifaximin, Amoxycillin, Amoxycillin and Clauvinic Acid and Imipenem were 27.38%, 17.86%, 10.71%, 8.33%, 7.14%, 5.95%, 4.76%, 3.57%, 2.38%, 2.38%, 2.38%, 1.19%, 1.19%, 1.19%, 1.19%, 1.19%, and 1.19%, respectively.

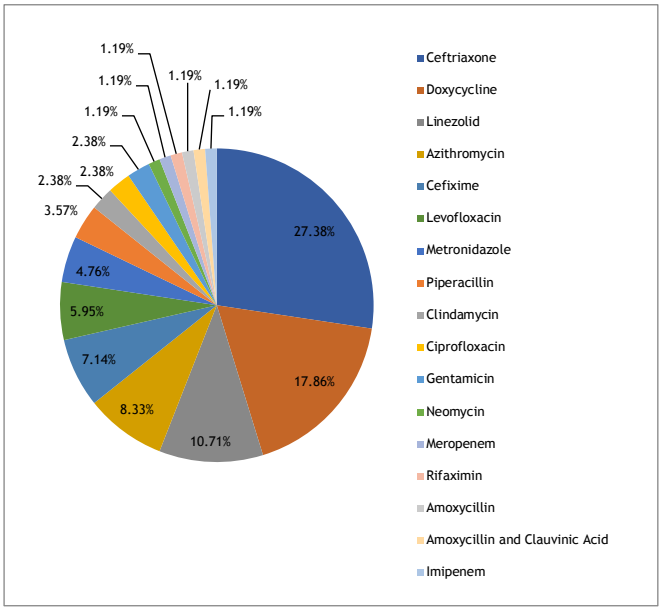

Figure 1: Causative Drugs belonging to antimicrobial group (ATC Code J01)

The frequencies of mild, moderate and severe adverse reaction severity were 103 (68.67%), 46 (30.67%) and 1 (0.67%) respectively. Out of 150, total 96 (64%) patients were probable (5-8 Naranjo score) and 54 (36%) patients were Possible (1-4 Naranjo score). The Naranjo score were not significantly different in between mild, moderate and severe adverse reaction as shown in Table 3.

Table 3: Comparisons of Causality assessment (Naranjo score) and severity assessment (Hartwig Scale) in patients with ADRs

Naranjo score	Total (%)	Mild (n=103)	Moderate (n=46)	Severe (n=1)	p-value
Definite (≥9)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.500
Probable (5-8)	96 (64.00%)	68 (52.31%)	27 (58.70%)	1 (100%)	
Possible (1-4)	54 (36.00%)	35 (47.69%)	19 (41.30%)	0 (0.0%)	
Doubtful (0)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Table 4 shows the organ systems affected and their comparisons according to the severity of ADRs. The frequencies of distribution of patients in Cardiovascular, Central Nervous System (CNS), Gastrointestinal System, Haematological, Immune System, Integumentary System, Musculoskeletal System, Respiratory System, Vestibular System, Endocrine, Hepatobiliary, Orofacial, Electrolyte Homeostasis and Gastro+ CNS Organ system were 11 (7.33%), 13 (8.67%), 67 (44.67%), 6 (4.0%), 5 (3.33%), 24 (16.0%), 6 (4.0%), 2 (1.33%), 3 (2.0%), 3 (2.0%), 2 (1.33%), 2 (1.33%), 4 (2.67%) and 3 (2.0%), respectively.

Table 4: Comparisons of ADR severity with organ system involvements

Organ systems with total number of ADRs	Mild		Moderate		Severe	
	n	%	n	%	n	%
Cardiovascular 11 (7.33%)	3	2.91	8	17.39	0	0
Central Nervous System (CNS) 13 (8.67%)	9	8.74	4	8.7	0	0
Gastrointestinal System 67 (44. 67 %)	64	62.14	3	6.52	0	0
Haematological 6 (4.0%)	5	4.85	0	0	0	0
Immune System 5(3.33%)	4	3.88	1	2.17	0	0
Integumentary System 24 (16.0%),	9	8.74	15	32.61	0	0
Musculoskeletal System 6 -4.00%	4	3.88	1	2.17	1	100
Respiratory System 2(1.33%)	0	0	2	4.35	0	0
Vestibular System 3 (2.0%)	1	0.97	2	4.35	0	0
Endocrine 3(2.0%)	1	0.97	2	4.35	0	0
Hepatobiliary 2(1.33%)	0	0	2	4.35	0	0
Orofacial 2 (1.33%)	2	1.94	0	0	0	0
Electrolyte Homeostasis 4(2.67%)	1	0.97	3	6.52	0	0
Gastro+ CNS 3(2.0%)	0	0	3	6.52	0	0

The severity of ADRs was significantly positive correlated with comorbidities. The severity of ADRs was highly significantly positive correlated with drug- drug interactions. Whereas, the severity of ADRs was not significantly associated with polypharmacy as shown in Table 5.

Table 5: Correlation between the severity of ADRs and comorbidities, drug interactions, sex and polypharmacy in all the study participants

	Karl-Pearson's correlation coefficient	p-Value
Severity with comorbidities	0.175*	0.032
Severity with drug- drug interactions	0.274**	0.001
Severity with Polypharmacy	0.018	0.829

DISCUSSION

In this study the range of age was 18.0 to 90.0 years with mean 47.32±17.76 (years). Moreover, majority of the patients (63.34%) were more than 40 years age which is in consonance with previous studies due to an increased incidence of diseases like hypertension, diabetes in the aforementioned age group, resulting in an increased usage of medicines, increased visit to the hospital for regular check- up associated with an increase in complaints of drug related adverse events.[8,16] The incidence of ADRs increases with age, due to ADR-related problems, hospitalized was double in 65 years or older patients as compared to younger.[17]

In our study, majority of the study subjects were males (61.33%) indicating a higher occurrence of ADRs in males which is in consonance with earlier documented reports.[8]

In present study the patients with ADRs; subjected to Polypharmacy (patients with > 5 medications) in which73 (48.67%) patients were True (the ones with polypharmacy) and 77 (51.33%) patients were False (the ones without polypharmacy). Polypharmacy is usually explained as the use of five or more prescribed medications.[18] Polypharmacy has been associated with an increased risk of ADRs, drug–drug interactions, hospitalizations, and mortality.[19-21]

In our study majority of the patients belonged to J01(Antimicrobials) class of drugs causing the ADR followed by NSAIDs (anti-inflammatory drugs) causing ADRs in 8.67% of study subjects, opioid analgesic caused ADRs in 5.33% of study subjects, followed by methyl xanthines induced ADRs in 4% of study subjects. Anti-epileptics caused ADRs in 4% of the study participants. Antimalarials and Diuretics each caused ADRs in 3.33% of study subjects. Which is consistent with previous study probably because they are most prescribed drugs in hospital settings.[6]

In this study we found that the antimicrobials, ceftriaxone was responsible for majority (27.38%) of adverse effects which is similar to earlier studies, as it is the most commonly prescribed antibiotic in our hospital setting.[22] Doxycycline caused ADRs in 17.86% of the study subjects. Linezolid was responsible for pain abdomen, diarrhea, skin rashes and pruritus in 10.71% of study subjects. Azithromycin caused ADRs in 8.33% of the study subjects. Cefixime was implicated in 7.14% of the cases. Levofloxacin caused ADRs in 5.95% of the cases. Metronidazole was the causative agent in 4.76% of the cases. Piperacillin caused ADRs in 3.57% of the study subjects. Clindamycin, Amoxicillin and clavulanic acid fixed drug combination, Ciprofloxacin and Gentamicin caused ADRs in 2.38% of the patients each. Neomycin, Meropenem, Rifaximin and Imipenem caused ADRs in 1.19% of the study subjects each.

In our study the majority of ADRs were probable (5-8 Naranjo score) that is, out of 150, total 96 (64%) were probable and 54 (36%) patients were possible (1-4 Naranjo score) while none lay in the definite and doubtful categories. Moreover, the severity assessment was conducted according to the Hartwig's scale in which 68 (52.31%) were mild, 27 (58.70%) were moderate and 1(1%) were severe in the probable category of causality assessment while 35 (47.69%) with mild, 19 (41.30%) with moderate levels of severity and with no severe level ADRs in the possible category of causality assessment. The difference in the levels of severity of ADRs (according to the Hartwig's scale) was not significantly different between the probable and possible Naranjo scores as a result of which the causality of the ADRs was not associated with their severity. Palaniappan et al. (2015) reported that most of the reports were possible (68.8%) followed by probable (29.7%) as per Naranjo's scale.

In this study the assessment of severity of ADR was based on Hartwig scale. Majority of the ADRs were mild, 103 (68.67%) followed by moderate, 46 (30.67%) and severe ADRs, 1 (0.67%). Similarly, Palaniappan et al. (2015) observed that majority of the reports were mild (95%) followed by moderate (4.5%) according to Hartwig severity scale.[23] A study reported that the ADRs are mild (12.4%), moderate (66.12%) and severe (12.4%). Hartwig and Siegel scale. Moreover, the ADRs were commonly moderate.[24]

In our study the most common organ system seen to be involved with the ADRs was gastrointestinal which comprised of 44.67% of the total ADRs followed by dermatological manifestation of ADRs which was seen in 16% of the subjects. This was followed by involvement of central nervous system in 9.33%. The cardiovascular system was implicated in 7.33% of the subjects. Haematological and musculoskeletal ADRs were individually found in 4% of the subjects. Total 3.33% ADRs were related to the immune system. ADRs leading to electrolyte imbalance were found in 2.67% of the study subjects. Similarly, Khan et al. (2015) reported that the gastrointestinal system was the most common (38.75%) organ system affected due to ADRs.[25]

In our study, the commonest comorbidity diabetes (26.42%) of the ADRs followed by hypertension (13.21%), diabetes along with hypertension (11.32%), hypothyroidism and Bronchial asthma (7.55% each). Bassi et al. (2017) reported that the comorbidity was common in hypertensive patients (36%) followed peptic ulcer disease (16.4%), HIV/AIDS (10.4%), diabetes (4.4%), asthmatic (4.3%) and hypertensive-diabetes (2.2%).[26]

In this study, the severity of ADRs was, had a positive correlation with comorbidities and drug- drug interactions. Schmid et al. (2022) reported that the comorbidities were significantly associated with increased risk of ADR related admission.[27]

CONCLUSION

The incidence of ADRs increases with increasing the age of the patients. A male preponderance was seen in the occurrence of ADRs. The predominant causative drugs were antimicrobials, NSAIDs and opioid analgesics agents. The predominant organ system affected was the gastrointestinal system followed by the dermatological, central nervous and cardiovascular system. Majority of ADRs were probable in causality assessment, mild in severity assessment. The factors like age, gender, polypharmacy and class of causative drugs were not statistically significant for either the occurrence or severity of ADRs. A positive correlation between the severity of ADRs with comorbidities an drug – drug interactions.

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