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Pattern of medication related problems in patients admitted to intensive care units at a Teaching Hospital in Western Nepal: a Pharmacovigilance Study

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Abstract

Background: Adverse drug reaction (ADR), medication error (ME) and drug-drug interaction (DDI) are the major medication related problems that affect the pharmacotherapy success.
Aim: To know the pattern of ADR, ME and DDI and to assess their causality, severity and preventability among the hospitalized patients in different Intensive Care Units (ICU).
Methods: Cross-sectional and Prospective Cohort study was carried out in ICU, coronary care unit (CCU) and Neuro Intensive Care Unit (NICU) at Manipal Teaching Hospital in Western Nepal. Data were collected during physician's ward round, nursing round using the patients profile form, ADR form, ME form and DDI form. Naranjo Algorithm, modified Hartwig & Siegel and modified Shumock & Thornton Scales were used for assessment of causality, severity and preventability of ADR respectively. The medications were analyzed for possible DDI using standard drug interaction database micromidex 2.0 (Thomson Reuters). Descriptive statistics were used to analyze the data using SPSS version 22.0.
Results: Among 316 patients, 27 patients have experienced ADRs; rashes (22.22%), edema (11.11%) and fever (7.40%) were the commonest ADR. Patients of age group 41-50 (25.92%) were commonly exposed to ADR. Dermatological system (22.22%) was commonly affected by ADR. Most of the ADRs (55.56%) were probable and 77.78% ADR were preventable. Forty two ME were identified. Most of the ME (61.90%) were of Category B. Incidence of DDI was found to be 21.2%. Total of 92 DDI were identified; 56.7% DDI were pharmacokinetic reactions. The interacting combination of moderate severity (59.78%) constituted majority of DDIs. Aspirin (23.91%) and Clopidogrel (14.13%) were most common drugs on the DDI encountered.
Conclusions: Careful monitoring, providing education and awareness regarding the health impact of drugs related problems are very much essentials for its minimization.

Keywords: Adverse drug reactions; Drug-drug interactions; Medication error; Medication-related problems

INTRODUCTION

Pharmacovigilance is the science and activity relating to the detection, assessment, understanding and prevention of medications related problems (MRP) including adverse drug reactions (ADR), medication errors (ME) and drug-drug interactions (DDI) [1,2]. ADRs occur at therapeutic doses and are responsible for 6.5 % of all the hospital admissions [3,4]. ME is any preventable event that may cause or lead to inappropriate use or patient harm [5]. It can occur during prescribing & diagnosis by doctors, during dispensing by pharmacists, during administration and monitoring by nurses [6,7]. DDI are altered responses due to drugs administered simultaneously or concurrently and the outcome may be harmful [8]. About 6-30% of all ADRs are due to DDI and accounts about 2.8% of hospital admission every year [9,10].

Nepal is a developing country with poor healthcare status with large number of MRP like ADR, ME and DDI. According to Bista et al,53% of the patient admitted to internal medicine department experiences one or more DDIs in Nepal [11]. Another study also had reported that 47.5% of medication potentially interacts with cardiovascular drugs [12].Practice of Pharmacovigilance is still in preliminary stage in Nepal [13].

Detection, assessment, monitoring and reporting of ADR and other MRP is necessary to prevent its occurrence in future. Pharmacovigilance program was started recently to monitor drug related problems in Nepal [14]. Currently, twelve regional Pharmacovigilance centers exist in our country. Manipal Teaching Hospital is one of regional Pharmacovigilance centers situated in Western Nepal. The hospital has Drug and Therapeutic committee (DTC) that takes many steps to ensure the safe use of medicines [15]. There are very few reports on pattern of ADR, ME and DDI in the critical care units in Nepal. The objectives of the study were to know the pattern of ADR, ME and DDI and to assess their causality, severity and preventability among the hospitalized patients in different ICU.

MATERIALS AND METHODS

A cross-sectional prospective cohort study was carried out in at ICU, Cardiac Care Unit (CCU) and Neuro Intensive Care Unit (NICU) at Manipal Teaching Hospital (MTH) between Augusts to December 2015. MTH is an 825 bedded tertiary care hospital situated in Pokhara, Nepal. The hospital has altogether 32 intensive care beds (ICU=16 beds, CCU=8 beds and N-ICU= 8 beds).

The patients aged 15 years and above and admitted to the ICU, CCU and NICU units and treated with at least one medicine were included in the study. Patients not treated with any medicine or attended the out-patient department or admitted in the emergency department during the study period were excluded from the study.

The data were collected using 4 types of semi-structured proforma. Socio-demographic form was used to collect variables like age, gender, marital status, personal history, medical history, diagnosis, clinical laboratory data, medicines prescribed; ADR form for the suspected ADR and drugs (dose, frequency and route of administration, duration); ME form for medication errors, its types and its outcome and DDI form for types and severity of drug-drug interactions. Naranjo Algorithm scale was used to categorize ADR as Definite (score more than or equal to 9), Probable (score 5-8), Possible (score 1-4), Doubtful (score less than or equal to 0) [16].Modified Hartwig and Siegel Scale was used to find the severity of ADRs as mild (level 1 or level 2); moderate [level 3 or level 4(a) or 4(b)]; and severe (level 5 or level 6 or level 7) [17]. Modified Shumock and Thornton Scale was used for preventability assessment as definitely preventable, probably preventable and not preventable [18]. Micromedex 2.0 software was used to identify and analyze the pattern of DDIs as major (Potentially life-threatening, requires medical intervention to minimize or prevent the serious adverse effects), moderate (potential deterioration of patient clinical condition and may require an alteration in therapy) and minor (The effects are usually mild and may not require change in therapy). On the basis of documentation status, DDI was also classified as excellent (the existence of the drug interaction has been clearly established by the controlled studies), good (the existence of drug interaction has been clearly established by the controlled studies), fair (available documentation is poor), poor (documentation is scant; However, the possibility of clinical conflicts exists.) or unlikely (documentation as well as a sound pharmacological basis is lacking). A pilot study was carried out in ICU, CCU and NICU in MTH for one week for validating the different data collecting forms. Necessary modification and correction on the data collection method and other assessment parts was done based on the results of the pilot study. The patients used in the pilot study were not included in the study. The study was approved form the Ethical Review Board of MTH. Data were collected during physician's ward round, at the time of medicine administration by nurses and by interviewing the patient or patient parties in the ward. No incentive was given to the patients. Confidentiality of the patients was maintained.

Statistical Analysis

The data were rechecked and entered into Microsoft Office Excel 2010. Descriptive statistics mean, frequency, percentage and standard deviation were calculated using SPSS version 11.5.

RESULTS

Pattern of Adverse drug reaction

A total of 316 patients were studied during the study period and among them 27 (8.54%) patients had ADRs. Female patients (15, 55.55%) were found to have more ADRs than male patients (12, 44.45%). The ADRs were more common in the patients age group of 41-50 years (7, 25.92%) followed by the age group of 31-40 (6, 22.22%) (**Table 1**).

Table 1: Age of patients with ADRs (n=27)

Age	Number	Percentage
15-20	3	11.1
21-30	3	11.1
31-40	6	22.2
41-50	7	25.9
51-60	4	14.8
61-70	3	11.1
71-80	0	0.0
81-90	1	3.7

Antibiotics (14, 51.85%) and cardiovascular drugs (7, 25.92%) were the major class of drugs causing ADRs (**Table 2**).

Table 2: List of category of drugs responsible for ADRs (n=27)

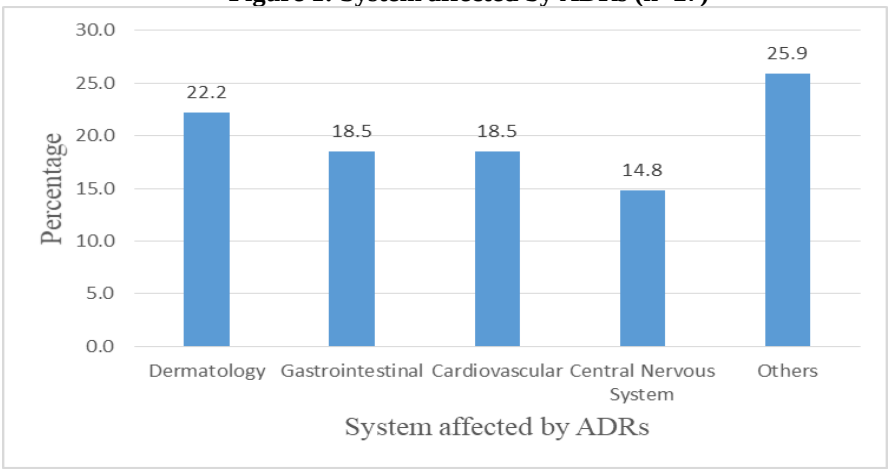
Drug category	Number	Percentage
Antibiotics	14	51.9
Cardiovascular	7	25.9
Benzodiazepines	3	11.1
Antihelmintics	1	3.7
Anticholinergics	1	3.7
Antiemetics	1	3.7

Parenteral route (19, 70.4%) was more responsible for causing ADRs than oral route (8, 29.6%).The top 10 drugs responsible for causing 70.37 % (19 out of 27) ADRs are given in **Table 3**.

Table 3: Top 10 drugs causing ADRs (n=27)

Drug	Number	Percentage
Ceftriaxone	5	18.5
Amlodipine	3	11.1
Lorazepam	2	7.4
Amoxicillin + Clavulanic acid	2	7.4
Aspirin	2	7.4
Levofloxacin	1	3.7
Cefotaxime	1	3.7
Metoprolol	1	3.7
Metronidazole	1	3.7
Midazolam	1	3.7

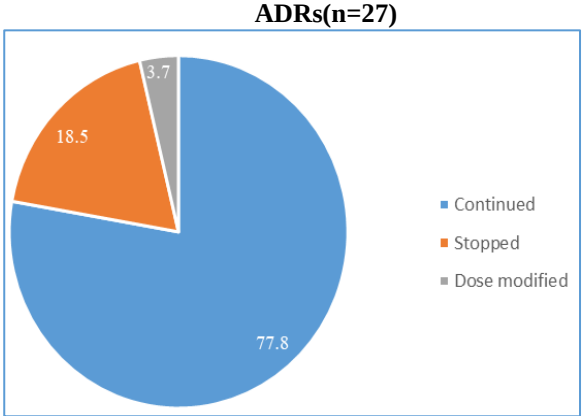
Figure 1: System affected by ADRs (n=27)



*Other include nausea, vomiting, itching, pin and needle sensation, headache, drowsiness.

Rashes (6, 22.22%), edema (3, 11.11%), fever (2, 7.40%) and constipation (1, 3.7%) were the four commonest ADRs respectively. The other ADR were nausea, vomiting, itching, pin and needle sensation, headache, drowsiness. Dermatological system (6, 22.22%) was the most commonly affected by ADRs followed by gastrointestinal (5, 18.52%) cardiovascular (5, 18.52%) and central nervous system (4, 14.81%) (**Figure 1**).
In majority of the cases, the suspected drug was continued (21, 77.8%) (**Figure 2**).

Figure 2: Action on drugs suspected for ADRs(n=27)



Most of the ADRs were probable (15, 55.6%)on causality assessment, mild level 1 (11, 40.7%) on severity assessment and probably preventable (14, 51.9%) on preventability assessment respectively. A total of 80% of ADRs were preventable (**Table 4**).

Pattern of Medication Error

Altogether 42 ME (13.3%) were occurred during the study period. Nineteen (45.2%) prescription errors occurred followed by 14 (33.3%) transcription errors, 7 (16.7%) administration error and 2 (4.8%) documentation error. Most of the ME (26, 61.9%) was of 'Category B' followed by 7 (16.7%) 'Category D' and 6 (14. 9%) 'Category A' on medication error index. Most of the ME (81%) were of Category B on severity index followed by Category A (14.3%) and Category C (4.7%).

Table 4: Causality, severity and preventability assessment of ADRs (n=27)

Category of Assessment		Number	Percentage
Causality	Definite	Nil	Nil
	Probable	15	55.6
	Possible	12	44.4
	Doubtful	Nil	Nil
Severity	Mild Level -1	11	40.7
	Mild Level -2	4	14.8
	Moderate Level -3	9	33.3
	Moderate Level -4(a)	2	7.4
	Mild Level 4	1	3.7
	Severe Level -5	Nil	Nil
	Severe Level -6	Nil	Nil
	Severe Level -7	Nil	Nil
Prevent-ability	Definitely Preventable	7	25.9
	Probably Preventable	14	51.9
	Not Preventable	6	22.2

Pattern of Drug-drug Interaction

Potential DDI were found in 67 patients (21.2%) out of 316 patients. A total of 92 DDIs were identified. Pharmacokinetic types of reactions [53, 57.61%] were found to be more common than pharmacodynamics type [35, 38.04%]. Among the total DDIs identified, the interacting combination of moderate severity (59.78%) constituted majority followed by major severity (35.86%). The most common interacting pairs identified were Aspirin and Clopidogrel (11 encounters). DDIs involving Aspirin (22, 23.9%) was the most common. Interacting pairs of major severity with the potentially hazardous effect and documentation status are shown in the **Table 5**.

Table 5: Interacting pairs of major severity with the potentially hazardous effect and documentation status (n=27)

Interacting pairs	No. of encounter	Severity	Potentially hazardous effect	Documentation status
Aspirin/Clopidogrel	11	Major	Increase risk of bleeding	Good
Pantoprazole/Digoxin	2	Major	Hypomagnesia	Good
Levofloxacin/ Ondansetron	2	Major	Bradyarrhythmia	Good
Octreotide/Ondansetron	2	Major	Bradyarrhythmia	Good
Enalapril/Aspirin	2	Major	Renal function deterioration	Good
Ketorolac/Dexamethasone	2	Major	Increase risk of gastrointestinal ulceration	Good
Aspirin/Metoprolol	1	Major	Decrease prostaglandin synthesis	Good
Amiodarone/Metoprolol	1	Major	Bradycardia	Good
Losartan/Ketorolac	1	Major	Renal function deterioration	Good
Promethazine/ Haloperidol	1	Major	Increase anti-dopaminergic activity	Good
Digoxin/ Metoprolol	1	Major	Bradycardia	Good
Spironolactone/ Digoxin	1	Major	Decrease renal clearance & Increase serum potassium	Good
Metoprolol/ Aspirin	1	Major	Decrease prostaglandin synthesis	Good
Aspirin/ Ketorolac	1	Major	Increase risk of bleeding	Good
Enoxaparin/Clopidogrel	1	Major	Enhance risk of bleeding	Good
Hydrocortisone/ Levofloxacin	1	Major	Increase risk of tendon rapture	Good
Enoxaparin/Aspirin	1	Major	Enhance risk of bleeding	Good
Enoxaparin/Losartan	1	Major	Hyperkalemia	Good

DISCUSSION

Prevalence of ADRs was 8.5% during the study period of three months in the ICUs. Similar results had been documented in a systematic review [19]. A higher rate of prevalence (13.7% and 72.3%) of ADR were observed in hospitalized patients in other studies [20,21]. ADRs were more common in females and in aged 41-50 year. Similar to our findings, an analysis of 48 cohort studies showed that a higher percentage of female (20.6%) had ADRs and 61-70 year age group was commonly affected by ADRs in a study by Martin et al and Davis et al [22,23]. This variation can be due to difference in the pattern of drug use, associated disease, local factors and individual variations.

Generally oral route of drug administration is considered safer and has less potential than parenteral route to cause ADRs which is supported by our study. Antibiotics and cardiovascular drugs were the major class of drugs that cause most of the ADRs in the study. Davis et al had also reported that antibiotics, diuretics, cardiac glycosides and antidiabetics as the drugs most frequently linked to ADRs [23]. Subish et al had also reported that antimicrobials were the most common cause of ADRs [13,24].

Ceftriaxone was the most common drugs for causing ADR. In contrast to this, Cotrimoxazole was the most common drug causing ADRs in an Indian study [25].This difference may be due to the reason that Cotrimoxazole and Choloroquineare used frequently used in Indian Setting but not in the setting where this study is carried out. Rashes were the most common ADRs in our study and dermatological system was the most commonly affected by ADRs which was similar to other reports [8,25,26].Majority of suspected drugs (77.78%) were continued by judging the benefit and risk ratio. In the same way 81.48% of ADRs were recovered. This indicates that condition of patient can be improved. Monitoring, reporting and close observation of ADRs are important steps.

In this study, Naranjo's causality assessment showed that most of the ADRs (55.6%) were probable. A higher percentage of probable ADRs had been reported in other studies [23,24]. Modified Hartwig and Siegel severity assessment scale showed that most of the ADRs (40.74%) were mild 1, followed by 14.81% mild level 2, 33.33% moderate level 3 and 7.41%of moderate level 4(a) that was slightly different to the prospective analysis of 3695 patient who reported that 20.6% of cases were mild level 2 and 56.3% were moderate level 3 [23].

Modified Shumock and Thornton preventability scale showed that most of the ADR (51.85%) were probable preventable and 22.22% were not preventable. A study from one of the teaching hospital from Kathmandu reported that 22.2% ADRs were definitely preventable while 77.7% were not preventable [24]. The variations in results of different studies may be due to various factors affecting the drug usage, difference in coordination, time and knowledge among health professionals, complex pharmacokinetic and pharmacodynamics nature of drugs, lack of patient education, physician's drug preferences and different scales used. In our study the short duration of study may be an important factor for variation in results.

Prevalence of ME was 13.3% during the specified study period of three months and most of them were prescription error. The majority of ME were potentially avoidable category. It should also be emphasized that pharmacists and nurses may paid attention to minimize the events. Administration error minimization depends on doctors, nurses and pharmacists working together as a role in improving the quality of drug administration. Doctors must use the drugs generic name for error minimization. ME occurs due to the communication gap between personnel, unreadable handwriting, distractions during drug preparation or administration of medications, similar names drugs availability, dosage assessment and lack of knowledge [27]. Majority of our findings holds the above said parameters. Due to the limited size of sample population and the facts that the scope was limited to one hospital, this study indicates little difference between the number or medication errors and work experience.

In this study most of the ME(61.9%) were found to be of 'Category B' that means error occurred but did not reach to the patients followed by 'Category D' (16.66%) that suggests the need for increased patient monitoring but no harm and 'Category A' (14.28%) suggesting circumstances or events that have capacity to cause error. Our findings supported other study in which more than 75% of potential ME were preventable.[7]Similarly in the study conducted in Thailand, 76.71% of ME were preventable [28]. According to our study more than two third the ME were found to be clinically significant error which can increase need for patients monitoring. Similarly a study conducted in Israel found that 11%, 16%, 34% and 80% of clinically significant error occurs per day in Internal medicine, Intensive care Units, Surgery and Haemato-Oncology department respectively [29].

Total of 92 DDI were identified in 67 patients (21.2%). Similar finding was also reported by Sharma et al in which prevalence of DDI was 21.3%.[30]In contrast to this finding, a higher prevalence of DDI was reported in Palestine among hypertensive patients.[31]Most of the DDI were pharmacokinetic types (57.61%) and similar finding was also reported by Vonbach et al. and Aparasu et al in which pharmacokinetic type DDI consisted of 76%.[32,33] In the same way, our study showed that interacting drug combination of moderate severity (59.78%) constituted majority of interactions than major severity (35.86%) and these findings were similar to the other reports [30,31,34,35].

The most common interacting drug pairs identified were Aspirin/Clopidogrel, Pantoprazole/Digoxin, Levofloxacin/Ondansetron, Enalapril/Aspirin, Octreotide/Ondansetron, Ketorolac/Dexamethasone. Aspirin (22, 23.91%) was the most frequently encountered drug inDDIs followed by Clopidogrel(14, 14.13%), Pantoprazole (10, 10.86%), Phenytoin (9, 9.78%), Losartan (9, 9.78%) and Metoprolol (6, 6.52%)and these findingswere quite different than the other study conducted in India where Aspirin (44.85%), Heparin (42.78%), Clopidogrel (22.16%), warfarin (11.59%), atorvastatin (7.22%) and Ramipril (6.95%) were the commonly encountered drug pairs in DDI [34].This can be due to the difference in wards and types of diseases. The most common drug Aspirin and clopidogrel in the DDI encountered in this study. This might be because Aspirin and Clopidogrel was one of the most commonly prescribed medicines in the present study.

Limitations

Due to small sample size, the results of this study may not be generalized to whole country.

CONCLUSIONS

Prevalence of ADRs was low and that of medication errors and drug interactions was high. Careful monitoring, providing education and awareness regarding the health impact of drug related problems are very much essentials for its minimization. Pharmacovigilance is the major concern that will help the doctors, nurses, pharmacists and other healthcare professionals to point out the suitable medication for the concerned patients and at correct timing with fewer adverse effects so that unnecessary suffering as well as cost of the patients reduces. Similar study in larger sample and at multiple centers are required to sustain our findings and for improving patient care and safety.

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