ASSESSMENT OF POTENTIAL DRUG-DRUG INTERACTIONS AND ITS ASSOCIATED FACTORS IN MEDICAL INTENSIVE CARE UNIT OF A TERTIARY CARE HOSPITAL IN NEPAL

Upreti AR,[1] Shrestha D,[2] Thapa S,[3] Lingden BK[3]

[1]Clinical Pharmacist, [2]Department of Pharmacology, [3]Department of General Practice and Emergency Medicine, Nepal Medical College Teaching Hospital, Attarkhel, Gokarneshwor-8, Kathmandu, Nepal

ABSTRACT

Drug interaction may cause an increase in the toxicity of a drug, increases the likelihood of adverse drug reactions, or cause a reduction in the efficacy of particular drug therapy, which may worsen the patient's condition directly or indirectly. This study aims to assess the potential drug-drug interactions (pDDIs) and their associated factors in the Medical Intensive Care Unit (MICU). We carried out a descriptive retrospective study based on the hospital records of 100 MICU patients. Micromedex Interaction application, designed by Truven Health Analytics Inc., was used to screen prescribed medications. We found 219 drug interactions out of 856 drugs prescribed. The average number of drug interactions per patient was 2.19. The frequency of drugs prescribed, the number of days in MICU, and age had a positive correlation with the occurrence of pDDIs. There were 44.7% major pDDIs; pharmacodynamic being the commonest mechanism for it. Most patients in MICU were at the risk of developing pDDIs. A substantial number of interactions had a major severity. Therefore, there is a need for active surveillance for pDDIs to prevent patient harm during particular drug therapy.

KEYWORDS

Medical Intensive care unit, pharmacodynamics, pharmacokinetics, potential drug-drug interactions

CORRESPONDING AUTHOR

Dr. Anup Raj Upreti,
Clinical Pharmacist,
Nepal Medical College Teaching Hospital,
Attarkhel, Gokarneshwor-8, Kathmandu, Nepal
Email: upretianup1@gmail.com
Orcid No: https://orcid.org/0000-0002-6599-2739
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INTRODUCTION

Drug interaction is said to occur when the effect of one drug is altered by the presence of another drug, herbal medicine, or any chemical agent.[1] According to the author, drug interaction may cause an increase in the toxicity of the drug, increases the likelihood of adverse drug reactions, or cause a reduction in the efficacy of particular drug therapy.[1] These outcomes may worsen patients' condition directly or indirectly.

Drug interaction may be either pharmacodynamic or pharmacokinetic on the basis of the mechanism of action.[1] Pharmacokinetic interaction can affect the processes by which drugs are absorbed, distributed, metabolized, or excreted; while in pharmacodynamic interaction, the effects of one drug are changed by the presence of another drug at its site of action.

On the basis of severity; potential drug-drug interactions (pDDIs) are classified as 1) Major: the effects are potentially life-threatening or capable of causing permanent damage, (2) Moderate: the effects may cause deterioration in patients' clinical status, additional treatment, or extension of hospital stay, and (3) Minor: the effects are usually mild.[2]

Various studies, done in the past in the hospital especially in ICU, have concluded that the occurrence of potential DDIs are quite high and do require attention and follow-up for a better outcome in patients.[3-7] Therefore, this study aimed to assess pDDIs and thier associated factors in Medical Intensive Care Unit (MICU).

MATERIALS AND METHODS

It was a descriptive retrospective study based on hospital records of MICU patients of Nepal Medical College Teaching Hospital. Medical records of the randomly selected MICU patients; admitted between October 2018 and March 2019; were retrieved. The demographic data and the kadex of the patients were reviewed. The medicines, given at the mid-stay of the patient in MICU, were recorded. The medications were screened by Micromedex Interaction application designed by Truven Health Analytics Inc.

This application described all potential interactions. Collected data were entered in Microsoft Excel and analyzed in SPSS version 16.0. Pearson's correlation was used to associate risk factors with pDDIs. The level of significance was set at 0.05 and p value<0.05 was considered significant.

Ethical clearance was obtained from the Institutional Review Committee (IRC) of Nepal Medical College Teaching Hospital. (Ref. No: 048-075/076).

Micromedex® categorizes drug-drug interactions according to onset, severity, and documentation.[8] The onset of drug interactions may be either rapid, appearing within 24 hours of administration, or delayed, which occurs after 24 hours of administration. According to the severity, Micromedex classifies drug-drug interactions into major (which is life threatening and requires medical intervention), moderate (may require medical intervention), or minor (has a mild effect and often does not require medical intervention). Concerning documentation, Micromedex classifies interactions into excellent, good, fair, poor, or unlikely. Based on the documentation of evidence of pDDI, excellent documentation refers to interactions evidenced by controlled clinical trials. Likewise, when interactions are documented by studies other than well-controlled trials, it is good documentation. Fair and poor documentation is associated with the interactions that lack good evidence to support. Unlikely documentation lacks a pharmacological basis.

The sample size was calculated using following formula:

$N = z^2pq/d^2$

$= (1.96)^2*50*50/5^2$

$= 384$

N (Population size) = 134

$n` = N/1+N/n$

$= 384/ 1+384/134$

$= 384/1+2.86$

$= 99.4$

$= 100$

RESULTS

The mean age of the study population was 61.5±19.3 years; the majority of them were above 50 years of age (77.0%). The male to female ratio was 1.04:1. The mean stay of patients in MICU was 4.5 days. The average number of drugs prescribed per patient was 8.56±2.71. Two hundred and nineteen drug interactions were found in 856 drugs prescribed. The average number of drug interactions per patient was 2.19 (219 drug interactions in 100 patients).

Table 1:Most Common drug interactions

	Frequency (%)
Enalapril and furosemide	11 (5.0)
Albuterol(salbutamol) and furosemide	9 (4.1)
Hydrocortisone and levofloxacin	6 (2.7)
Azithromycin and atorvastatin	6 (2.7)
Atorvastatin and clopidogrel	5 (2.3)
Doxycycline and antacid	4 (1.8)
Aspirin and furosemide	4 (1.8)
Levothyroxine and pantoprazole	4 (1.8)
Piperacilin and doxycycline	3 (1.3)
Enalapril and spironolactone	3 (1.3)

Table 2: Most Common major drug interactions

	Frequency
Hydrocortisone and levofloxacin	6
Aspirin and furosemide	4
Aspirin and clopidogrel	2
Enalapril and spironolactone	2
Enoxaparin and clopidogrel	2

There was a moderately positive correlation between the frequency of drug prescribed and drug interaction (r = 0.573, p= 0.00). However, there was a very weak positive correlation between the number of days in MICU and drug interactions (r = 0.136, p= 0.177). Very weak positive correlation was found between age and drug interactions (r = 0.213, p= 0.034). Based on severity, 44.7 % were major (n=98), 46.1% moderate (n=101), 7.7% were minor (n=17), and 1.3% contraindicated (n=3) pDDIs. The drug interaction (Table 1) between enalapril and furosemide was most frequent (n=11).

Based on the severity; the most frequently encountered major drug interaction was the interaction between hydrocortisone and levofloxacin (Table 2). Three contraindicated drug interactions were found (Table 3). Based on the onset, 12.7% rapid (n=28), 29.6% delayed (n=65), and 57.5% (n=126) were not specified. Enalapril and furosemide (5.02%) was the most common drug interaction that had rapid onset

Table 3: Contraindicated drug interactions

	Frequency
KCL and hyoscamine	1
Tranxemicacid and levonorgesterol	1
Amantadine and Potassium Chloride	1

Table 4: Most common drug interactions based on the onset of action

	Frequency
Enalapril and furosemide	11
Doxycycline and antacid	4
Enalapril and aspirin	2
Metoprolol and prazosin	1
Amlodipine and digoxin	1

Table 5: Most common drug interactions based on documentation

	Frequency
Hydrocortisone and levofloxacin	6
Atorvastatin and clopidogrel	2
Enalapril and aspirin	2
Paracetamol and isoniazid	1
Aspirin and ranitidine	1

Table 6: Most common drug interactions on the basis of mechanisms

Mechanism	Frequency (%)
Unknown	48 (21.9)
Pharmacokinetics	73 (33.3)
Pharmacodynamics	98 (44.7)
Total	219 (100.0)

Table 7: Pharmacokinetic drug interactions

	Frequency (%)
Absorption	28 (38.3)
Metabolism	35 (47.9)
Distribution	4 (5.4)
Excretion	6 (8.2)
Total	73 (100.0)

(Table 4). Hydrocortisone and levofloxacin was the most common drug interaction that had excellent documentation (Table 5). Regarding the mechanism of drug interactions, 44.7% were

pharmacodynamics, 33.3% pharmacokinetics, and 21.9% had unknown mechanisms (Table 6). Metabolism (Table 7) and QT-prolongation (Table 8) were the most common pharmacokinetic and pharmacodynamic drug interactions, respectively. Levofloxacin and ondansetron was the most common QT-prolonging drug interaction (Table 9).

Table 8: Pharmacodynamic drug interactions

	Frequency (%)
QT prolongation	18 (18.3)
Additive cardiovascular effect	4 (4.1)
Additive effect of hypokalemia	12 (12.2)
Decreased renal prostaglandin synthesis	15 (15.3)
Additive effect of bleeding	10 (10.2)
Additive potassium retention	8 (8.1)
Synergistic effect	6 (6.1)
Anatgonist effect	3 (3.0)
Addicitve effect on AV node conduction	2 (2.0)
Diuretic induced hypokalemia and hypomagnesaemia may result in digoxin toxicity	2 (2.0)
Additive nephrotoxic and Ototoxic	3 (3.0)
Additive serotogenic effect	4 (4.0)
GI ulcer or bleeding	8 (8.1)
Additive CNS depressant	3 (3.0)
Total	98 (100)

Table 9: Most common QT prolonging drug Interaction

	Frequency
Levofloxacin and ondansetron	6
Domperidone and ondansetrone	3
Domperidone and amlodipine	2
Azithromycin and levofloxacin	3
Amiodarone and azithromycin	2

DISCUSSION

An application-based approach to detect potential drug-drug interactions (pDDIs) does not necessarily mean that the possible adverse effect can manifest clinically in all patients. However, the application is an essential tool to verify pDDIs because it generates a signal, which may be an important finding to consider in clinical practice.

The average number of medicines prescribed per patient in our study was 8.56. In the study done by Jankovic *et al* on ICU patients, the average number of pDDIs per patient ranged from 10.4±8.8 to 29.4±21.5.[9] A total of 100 patients were prescribed 856 number of medicines. We considered injectable dosage forms, oral dosage forms (tablets, capsules, syrup, and solution), and inhalers for the analysis. We excluded intravenous fluids (normal saline, dextrose, Ringer Lactate, etc.), multivitamin tablets/syrups, ophthalmic drug preparations, protein supplement powders, and ointments in the analysis.

There was a positive correlation between the number of medicines prescribed and the occurrence of pDDIs; which was statistically significant (r = 0.573, p= 0.00). This finding was similar to the studies done by various authors suggesting that polypharmacy is a predisposition factor for pDDIs.[10-12] There was a very weak positive correlation between pDDIs and number of days in MICU (r = 0.136, p= 0.177), age of the patient (r = 0.213, p= 0.034). In a study done by Jain *et al*[11] on patients of ICCU, positive correlations were observed between patient's age and number of drugs prescribed (r=0.178, p<0.001), number of drugs prescribed and pDDIs (r= 0.788, p<0.001), and patient's age and pDDIs (r=0.338, p<0.001).

The most interacting pair was enalapril and furosemide. In a study done in ICU, the most commonly involved interacting medications were between antihypertensive medications.[6]

Based on the severity, the most prevalent were moderate (46.1%) followed by major (44.7%); this was similar to the studies done in adult ICUs of Brazil[4], Pakistan[14], and Nepal.[10]

Hydrocortisone and levofloxacin topped the list of major drug interaction in our study. According to a study done; on the Dutch national drug database to identify pDDI occurrence in ICU admissions; antibacterials were one of the most frequently encountered interacting drug class.[13]

We found pharmacodynamic DDI, followed by pharmacokinetic, was common mechanism of pDDI; similar to the study done in India.[11] However, in the study done among HIV patients, pharmacokinetic DDI was the most common mechanism.[15] Metabolism was the most common in pharmacokinetics DDI while QT prolongation was the most common in

pharmacodynamics DDI, similar to the study done in an academic medical center of the US.[3] Levofloxacin and ondansetron combination was the most common QT-prolonging drug combination; followed by combination of domperidone and ondansetron. In a study done in medical wards of two major tertiary care hospitals of Pakistan, it was concluded that the most frequent QT-prolonging risk factors included the use of ≥1 QT-prolonging drug and there was a significant association of antimicrobial agents and antiemetics with QT-DDIs.[16] Regarding the onset, the majority of drug interactions in our study were not specified followed by delayed onset.

This study concludes that most patients in MICU are at the risk of pDDIS. Most of the pDDIs had moderate severity and a substantial number of interactions had major severity. Therefore, pharmacological consultation with the clinical pharmacist can play a crucial role in recognizing DDIs for improvement of medication management and effective therapeutic endpoints with fewer adverse effects. The limitation of this study is the use of an application-based approach to detect potential drug-drug interactions (pDDIs) which cannot be generalized as it does not necessarily mean that the possible adverse effects can manifest clinically in all patients.

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