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ORIGINAL ARTICLE

Potential Drug-Drug Interactions; A Study Among Patients of Intensive Care Unit (ICU) of a Tertiary Care Hospital of South Punjab, Pakistan

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ABSTRACT

Objective: To assess the prevalence of drug-drug interactions in medications prescribed to the admitted patients in Intensive Care Unit (ICU) of Bahawal Victoria Hospital (BVH), a tertiary care hospital of Bahawalpur, Pakistan.

Methodology: Present study was conducted by using retrospective cross-sectional study design. Medication data of 77 patients of any age group without gender discrimination admitted in ICU ward of BVH from January 2016 to March 2016 (three months) was collected and screened to identify drug-drug interactions. Drug interaction checker within www.drugs.com database and reference text book of "Drug Interaction Facts" were used as reference sources. Data was interpreted by using IBM SPSS version 20.0.

Results: During study period total 77 patients were admitted in the ICU ward comprised of, 53 females and 24 male patients. On averages 8.86 ± 2.42 drugs were prescribed in each prescription. About 92.2% prescriptions showed at least one drug-drug interaction. Moderate drug-drug interactions were more prevalent with score of 448 (75.04%) as compared to minor 114 (19.1%) and major 35 (5.86%) drug-drug interactions.

Conclusion: Detection of potential drug-drug interactions reveals the poor prescribing pattern and highlights the need of effective and regular screening for such interactions to improve the patient care.

Keywords: Intensive care unit, drug-drug interactions, Bahawalpur.

INTRODUCTION

Drug interaction is a well-known term to all healthcare professionals. A drug interaction is believed to occur when the effects of one drug on body are altered by the presence of any other drug, food or drink [1]. Commonly drug interaction means drug-drug interactions (DDIs), and it is considered as most important among all other types of drug interactions [2]. In reporting DDIs, one drug is called precipitant drug and the other is termed as objective drug. Precipitant drug is responsible for altering the pharmacologic response or the pharmacokinetic properties of the objective drug [3].

Various factors such as poly pharmacy, severe or multiple illnesses, advancing age, multiple prescribers, chronic therapeutic regimens, frequent modification in therapy and length of stay in hospital have association with development of DDIs [4-8]. Moreover, gender, genetics and co-morbidity also

affect the response to treatment that can contribute in DDIs [9]. It is reported that with 2-4 prescribed drugs, chances of DDIs are 6%, with 5 drugs the chance is increased to 50% and when 8 drugs are used, chance of DDIs is reached almost 100% [10]. Drug-drug interactions exhibit potential risk for medication safety and may cause adverse drug reactions [11]. It is evident from a reported data that 17% of all adverse drug reactions are attributed to DDIs [12].

Specifically DDIs are more prevalent in intensive care unit due to poly pharmacy, comorbidity and complexity of pharmacotherapy administered to patients [13]. ICU patients are predisposed to drug interactions that becomes complicated by disease severity and organ failure [13]. Patients in intensive care unit require various drugs to be administered and have 44.3% to 95% chance to have drug interactions [14]. One study concluded that 54% of all patients in ICU had drug-drug interactions that were two times greater than general wards [15]. A limited data is available in Pakistan regarding the evaluation of drug-drug interactions in ICU wards of hospitals and is same for DDIs in Pulmonology, Psychiatry, Pediatrics and internal medicine wards that showed high prevalence of DDIs in these wards [12, 16-18]. Therefore, the current study was aimed to evaluate the drug-drug interactions in ICU ward and current medication safety situation in the prescriptions for the patients admitted in public sector hospitals of Pakistan.

METHODOLOGY

A retrospective cross-sectional study design was adopted to assess the potential drug-drug interactions in medications given to the patients admitted in intensive care unit (ICU). Data was collected from ICU of Bahawal Victoria Hospital (BVH), Bahawalpur Pakistan that is the largest tertiary care hospital of the region.

Medication data of patients admitted in ICU of BVH during January 2016 to March 2016 (three months) was collected. All patients either male or female having all age ranges, who were admitted for more than 24 hours in intensive care unit were included in this study. A well-designed data collection tool was generated and validated which includes demographic characteristics, date of hospital admission, discharge date and medication data except electrolytes, nutritional supplements, serum and topical preparations.

Screening for the potential DDIs was done by using drug interaction checker within www.drugs.com database [19] and a reference book of "Drug Interaction Facts" published in 2011 [20]. Detected drug-drug interactions were grouped as minor, moderate and major DDIs based on their clinical significance. If a drug interaction poses a serious threat to patient's life or cause permanent damage and need quick medical intervention to minimize adverse drug effect it was categorized as "major" [5]. "Moderate" drug interaction deteriorate the patient's clinical status and need alteration in drug therapy [17]. If the effect of drug interaction was observed little or mild, consequence may be bothersome or unnoticeable it was categorized as "minor" [21, 22]. The data was analyzed by using IBM SPSS 20.0.

Approval for this study was granted by the Research and Ethics Committee constituted under Department of Pharmacy, The Islamia University of Bahawalpur.

RESULTS

Out of total 77 patients included in the study 53 (68.8%) were female and 24 (31.2%) were male. Median age of the patient was 28 (Interquartile Range (IQR): 18.75). Total 682 drugs were prescribed with mean 8.86±2.42 drugs per prescription. About 92.2% prescriptions were noted with at least one drug interaction. Moderate drug interactions were maximum 75.04% followed by minor 19.1% and major drug interactions 5.86%. An overview is given in Table **1**.

Total 110 different drugs were prescribed in 77 prescriptions in which Metoclopramide, Metronidazole, Midazolam, Furosemide, Ceftriaxone, Nalbuphine, Ranitidine and Omeprazole were frequently prescribed. Most 20 frequently prescribed drugs are given in Table **2**.

Major Drug-Drug Interactions

In 35 major drug-drug interactions, 10 different interacting drug combinations were identified and are given in Table **3** with their outcomes.

Table 1. Demographic illustration of patients.

Variables		Frequency (N)	Percent (%)
Gender	Male	24	31.2
	Female	53	68.8
Total		77	100.0
Age of the respondents (median)		28 (IQR: 18.75)	
Patient's length of stay in the ICU (Median)		3 days (IQR: 3.5)	
Total Number of prescribed drugs		682 (Mean: 8.86±2.42)	
Prescriptions having at least one drug interaction		71	92.2
Number of major drug interactions		35	5.86
Number of moderate drug interactions		448	75.04
Number of minor drug interactions		114	19.1

Table 2. First 20 frequently prescribed drugs in intensive care unit.

S. No.	Drug	Frequency	S. No.	Drug	Frequency
1	Metoclopramide	66	11	Tranexamic acid	15
2	Metronidazole	50	12	Imipenem/Cilastatin	14
3	Midazolam	41	13	Calcium gluconate	14
4	Furosemide	40	14	Atracurium	13
5	Ceftriaxone	39	15	Magnesium sulphate	13
6	Nalbuphine	33	16	Lactulose	11
7	Ranitidine	32	17	Mannitol	10
8	Omeprazole	20	18	Captopril	9
9	Diclofenac sodium	18	19	Hydrocortisone	9
10	Amlodipine	17	20	Acetaminophen	9

Table 3. Top 10 major drug interaction combinations and their outcomes.

S. No.	Drugs Interaction Combination	Frequency	Outcome
1	Ceftriaxone + Calcium Gluconate	6	Precipitation of ceftriaxone-calcium salt
2	Furosemide + Amikacin	5	Potentiate the risk of oto- and nephrotoxicity
3	Atracurium + Amikacin	3	Severe and/or prolonged respiratory depression
4	Omeprazole + Clopidogril	2	Decreased effectiveness of Clopidogril
5	Aspirin + Clopidogril	2	Increased platelet inhibition effect
6	Nifedipine + Magnesium sulphate	2	Hypotension and neuromuscular blockade
7	Furosemide + Digoxin	2	Predispose patients to digitalis induced arrhythmias
8	Amikacin + Megnesium sulphate	2	Severe and/or prolonged respiratory depression
9	Hydrocartisone + Moxifloxacin	2	Potentiate the risk of tendinitis and tendon rupture
10	Carbamazepine + Nimodipine	1	Decreased plasma concentration of Nimodipine by enzyme induction

Moderate Drug-Drug Interactions

Moderate drug-drug interactions were more prevalent than major and minor. Among these top 10 moderate drug interaction combinations are given below in Table **4** with their outcomes.

Minor Drug-Drug Interactions

Out of 114 minor drug-drug interactions more prevalent drug interaction combinations with outcomes are given below in Table **5**.

Table 4. Top 10 moderate drug interaction combinations and their outcomes.

S. No.	Drug Interaction Combination	Frequency	Outcome
1	Metoclopramide + Midazolam	31	Increased CNS and respiratory depressant effect
2	Metoclopramide + Nalbuphine	31	Antagonize gastro-prokinetic effect of Metoclopramide, increased CNS sedation, dizziness, confusion, and mental depression
3	Midazolam + Nalbuphine	20	Increased CNS and respiratory depressant effect
4	Ceftriaxone + Furosemide	20	Increased nephrotoxicity
5	Furosemide + Midazolam	20	Additive hypotensive effect
6	Furosemide + Nalbuphine	19	Additive hypotensive effect
7	Furosemide + Omeprazole	16	Hypomagnesaemia
8	Atracurium + Metoclopramide	10	Enhanced Atracurium effects
9	Furosemide + Magnesium sulphate	10	Increased loss of fluid and electrolytes
10	Furosemide + Diclofenac	10	Adversely affect renal function

Table 5. Top 10 minor drug interaction combinations and their outcomes.

S. No.	Drug Interaction Combination	Frequency	Outcome
1	Midazolam + Omeprazole	18	Increased serum level of Midazolam
2	Ranitidine + Midazolam	11	Increased plasma concentration of Midazolam
3	Ceftriaxone + Diclofenac	9	Increase biliary and decreased renal excretion of Ceftriaxone
4	Captopril + Furosemide	8	Increased hypotension and hypovolemia
5	Captopril + Amlodipine	4	Additive hypotensive effect
6	Ranitidine + Acetaminophen	4	Increased hepatotoxicity of Acetaminophen
7	Ranitidine + Diazepam	4	Increased plasma concentration of Diazepam
8	Diazepam + Omeprazole	4	Omeprazole may increase the serum level of certain Benzodiazepines
9	Isosorbide dinitrate + Omeprazole	4	Omeprazole may inhibit the drug delivery of oral nitrates
10	Dexamethasone + Midazolam	3	Decreased concentration of Midazolam

DISCUSSION

Identification of drug interactions is a very critical issue in drug therapy and needs immediate attention. Present study concluded that the prevalence of potential DDIs in intensive care unit is very high that can be compared to other studies conducted in intensive care units of various healthcare facilities in different regions [13, 15, 23, 24]. Current study exposed total 597 cases of drug-drug interactions in 77 prescriptions. This high prevalence may be due to clinical situation of patients requiring more drugs to manage, characteristic of prescribed drugs or due to wrong administration of drugs. Difference in the prevalence of DDIs in current study and other above mentioned studies can be attributed to use of other classification scheme and inclusion/exclusion criteria [25].

Furthermore, it was noted that about 110 different drugs were prescribed in a total of 682 prescribed drugs with an average of 8.86 drugs per prescription that can be taken as a justification of high number of DDIs as the number of prescribed drug is increased the chance of interactions is also increased [26, 27]. Moderate DDIs were more prevalent in the present study followed by minor and major interactions respectively. In one study conducted by Almeida *et al*., moderate DDIs were much higher in prevalence as compared to major DDIs [7].

Most of DDIs observed in the study were of pharmacodynamic in nature. In major DDIs, six were related to Ceftriaxone and calcium gluconate which leads to precipitation of ceftriaxone-calcium salt in lungs and kidney. Drug-drug interaction between furosemide and amikacin encountered five times. This was a major interaction that leads to ototoxicity and nephrotoxicity. Interaction between Atracurium and Amikacin causes severe respiratory depression and encountered three times.

Most prevalent outcome observed was excessive or prolonged CNS and respiratory depression due to pharmacodynamic interaction between (Metoclopramide – Midazolam and Midazolam – Nalbuphine), increased CNS sedation caused by interaction between (Metoclopramide – Nalbuphine), additive hypotensive effect due to interaction between (Furosemide – Nalbuphine and Furosemide – Midazolam). Drug interaction between Ceftriaxone and Furosemide leads to increased nephrotoxicity and interaction between Furosemide and Omeprazole causes hypomagnesaemia. These all interactions were moderate and pharmacodynamic in nature.

Metoclopramide, Midazolam, Nalbuphine, Furosemide, Ceftriaxone and Omeprazole were key drugs which are associated with majority of DDIs in current study setting.

CONCLUSION

Study results presented an alarming picture of prescribing practices in Intensive Care Units as a high incidence of drug interactions was observed. Although a large number of potential DDIs are predictable and can be prevented easily to stop further medical threats. A joint effort of physician and pharmacist is the need of hour to avoid such drug interactions. Additionally, government should make policies and initiate such programs which give an insight to healthcare professionals regarding prevention of drug interactions.

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