Incidence of drug interactions in intensive care units in tertiary care settings: Classification, facts and measures

Hina Hasnain[1], Huma Ali[2], Farya Zafar[3], Ali Akbar Sial[1], Shazia Alam[1], Anwar Ejaz Beg[1], Rabia Bushra[4], Mehwish Rizvi[4], Maqsood Ahmed Khan[1], Huma Shareef[2], Ghazala R Naqvi[5] and Anum Tariq[1]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Ziauddin University, Karachi, Pakistan
[2]Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University, Karachi, Pakistan
[3]Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan
[4]Department of Pharmaceutics, Dow College of Pharmacy, Dow University of Health Sciences, Karachi, Pakistan
[5]Faculty of Pharmacy, Federal Urdu University of Arts, Science and Technology, Karachi, Pakistan

Abstract: Drug-drug interactions (DDIs) are extremely significant concern, particularly in sensitive population including pediatric and geriatric. Propensity for the development of DDIs is high in patients admitted at intensive care units (ICU). This study was conducted to evaluate the DDIs incidence, facts and measures in ICU. From a total of 150 cases studied for ICU patients, with the mean age of 56.37±12.45 years, 55.33% were male and the rest were female 44.66%. The demographic information like age, gender and main diagnosis details of study participants that were extracted from the patients' clinical record. A statistically significant association between the drug interaction and the number of drugs prescribed per prescription was observed ($p<0.0001$). Concerning the onset of outcome, 52% of DDIs distinguished as delayed onset of effect (past 24 hours) and 35% were categorized as rapid onset (within 24 hours). Despite the facts regarding patient safety and minimizing DIs error, polypharmacy is still frequent in critically ill patients admitted in ICU attributed high risk of adverse reactions due to use of multiple interventions to treat severity of disease condition. Such studies may be used to develop an effective tool for the diagnosis and management of DDIs.

Keywords: Drug interactions, ICU, geriatric, incidence, facts.

INTRODUCTION

Broadly the therapeutic response of medication therapies relies on the pharmacokinetic and pharmacodynamic of the drug substance which is affected by simultaneous administration of interacting drugs and can alter the response of other co-prescribed medication. Potentiating consequences on the pharmacodynamic and pharmacokinetic of drugs may vary from minute incidents to as deleterious which can lead to mortality and morbidity (Krahenbuhl-Melcher *et al*., 2007; Askari *et al*., 2013). Drug drug interactions (DDIs) are responsible for about 27.0% of complications in patient's medication therapy (Rivkin and Yin, 2011). One of the various clinically significant issues is DDI which is accountable for many adverse drug reactions as well as medication errors (Smithburger *et al*., 2012).

High number of medications, various co-morbid conditions, extended periods of hospitalization, physiological and age related factors end up in increased rate of incidence of DDIs (Johnell and Klarin, 2007; Kafeel *et al*., 2014). When more than a single drug that has potential to interact each other co-administered drug product are given to patient, it results in alteration in the effect of medication known as Pharmacodynamic drug interaction as well as it can lead to variations in absorption, distribution, metabolism excretion of the drug which is referred to as Pharmacokinetic drug interaction (Pronovost *et al*., 2005). According to various pharmacoepidemiological studies, significant drug interactions range from 5% to 80%. Globally these Drug interactions are now known to have centre of rumination for health care settings, regulators and public health authorities (Nasiripour *et al*., 2011).

In present study an investigation was carried out for significant potential DDIs in critically ill patients admitted in critical care units of the hospitals in order to analyze the clinical significance of these interactions to the patient's condition. Furthermore the frequency and nature of potential DDIs was also determined to develop recommendations to improve the management of DDIs contextual to our setting.

MATERIALS AND METHODS

This study was conducted in descriptive, cross sectional and qualitative way in University teaching hospitals in June 2015 - December 2016. Descriptive statistics such as frequency, mean, percentile and standard deviation were used to summarize the data set. This study included both male and female patients admitted in ICU, MICU, CCU and Surgical ICU. Data including age, gender, admission

**Corresponding author:* e-mail: humaali80@live.com

date and date of discharge along with medication records was recorded. The confidentiality of patients was highly maintained during research and ethical approval was obtained from Ethical Review Committee of Ziauddin University.

Inclusion criteria

- All patients admitted to the critical care units (ICU, MICU, CCU, SICU) for 24hrs and who are given minimum two medications systemically were eligible for inclusion.

Exclusion criteria

- Patients stay in ICU is less than 24 hrs,
- No medication given during their ICU stay.
- Incomplete medical records.

Data collection method

A data collection form was used to collect the information including demographic characteristics of patients, the reasons for hospital admission, history of the present illness, main diagnosis, with all relevant details of medical data necessary to obtain essential information was extracted from the patients' clinical history records. Medications given during the initial 24 hours of admission, in the 50th length of hospital stay percentile and at the point of discharge were analyzed to recognize potential Interactions using DRUG-REAXH software. Review from clinical pharmacist and clinician were also taken related to patient medication records to develop a consensus on DDIs in certain cases. DDIs were categorized according to various pharmacokinetic or pharmacodynamic characteristics and severity of interactions. Lexi-interact software was used to classify interactions as rank A (Unknown interaction), B (No modification required), C (Therapeutic monitoring), D (Therapeutic modification needed) and X (Avoid incorporation) (Lexicomp, 2013). Free online drug interaction checker programs were also used to identify the clinical value (level of significance), documentation (level of evidence or records), onset of effect (rapid or delayed) and the severity of the interaction (minor, moderate or major).

STATISTICAL ANALYSIS

Drug-Drug Interactions were identified by the *Micromedex, Drug-Reax database*, Lexi-Interact. Results were statistically analyzed using SPSS 20.0.

RESULTS

Since there are high complexities associated with pharmacotherapy administered to patients in ICU, potential DDIs are more likely to occur which can further aggravate harm to patient condition. It is necessary to collect and classify such interactions contextual to local settings of Karachi, Pakistan. In this perspective, current study was designed to evaluate the DDIs in intensive care units of tertiary care setups. A total of 150 cases were studied, with the mean age of 56.37±12.45 years. 55.33% were male and the rest were female 44.66%. The demographic information like age, gender and main diagnosis details of study participants that were extracted from the patients' clinical history are summarized in table 1.

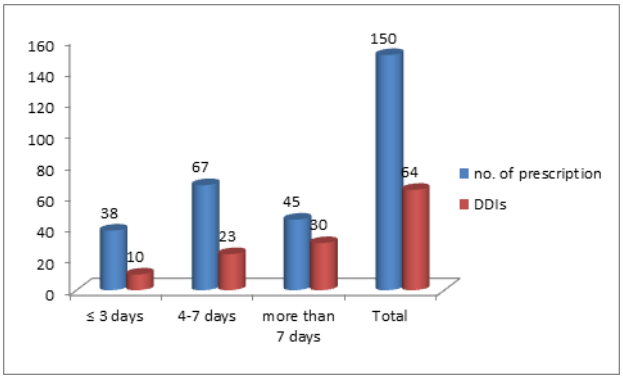

Fig. 1: Length of hospitalization in ICU and DDIs

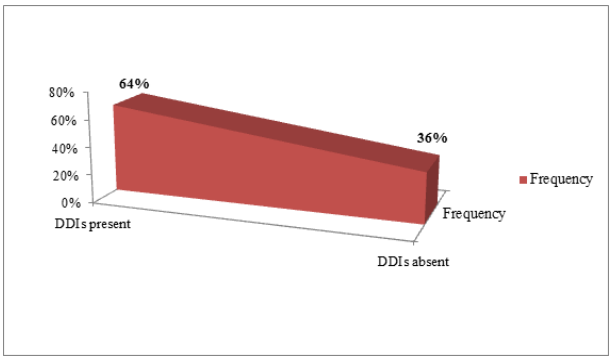

Fig. 2: Incidence of DDIs in studied population

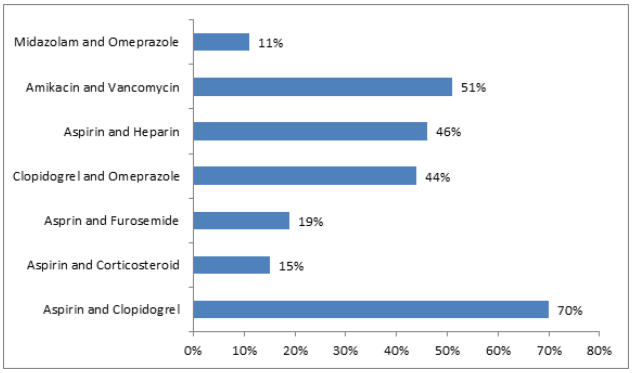

Fig. 3: Frequency of various drug - drug interactions

Cardiovascular disorders were most found most common than neurological and other diseases. Patients with hepatic and renal dysfunctions were found to be 59.33% (n=89) and 52%with various co-morbid status were identified (table 1). Majority of patients stayed in ICU for 4 to 7 days with high rate of prescriptions (n=67) but DDI was

significant among them who hospitalized for more than a week (fig. 1). A significant association between length of hospitalization and DDIs was found with χ^2 = 15.913, P 0.04 at 5% level of significance. table 2 described the drugs prescribing details and DDIs during ICU stay of patients with respect to number of drugs prescribed including 1-4, 5-8, 9-12 or more than 12 in ICU patients. Highest DDIs were observed with 5-8 and 9-12 drugs per prescription. Overall, high proportion of drug interactions was observed in first 24 hours of prescription especially with 9-12 drugs, while in 50th length of percentile stay and at discharge majority of interactions was observed within 5-8 drug cohorts. An approximate of 64% prescriptions was found with various types of DDIs (fig. 2). Out of all DDIs, 36.8% were minor, 32.8% and 23.4% were found to be moderate and major DDIs respectively (table 3). Various DIs and their co-administrations are given in fig. 3 and most common were aspirin and clopidogrel 70%, amikacin and vancomycin 51%, aspirin with heparin 46% and clopidogrel in combination of omeprazole 44%. In terms of mechanism underlying drug interactions, the total numbers of pharmacodynamic DDIs were 45.33% while pharmacokinetic drug interactions were found to be 49.32% (table 4).

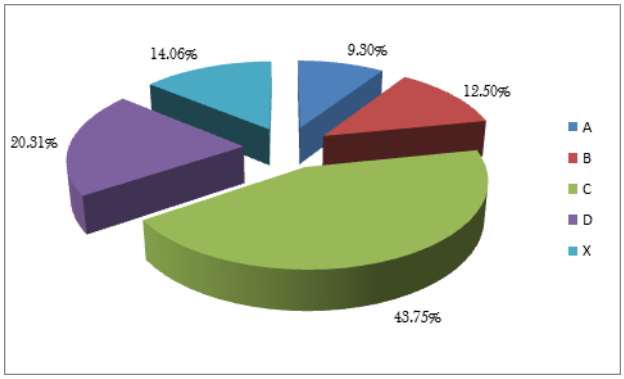

Fig. 4: Risk score distribution of DDIs

Furthermore, there was a statistically significant association between the drug-drug interaction and the number of drugs prescribed per prescription (p<0.0001). In terms of the level of clinical consequence, the preponderance of DDIs were categorized as type C 43.75% followed by D (20.71%) (fig. 4). The distribution pattern of potential DDIs were presented in fig. 5 according to their severity (5A), onset (5B) clinical value (5C) and documentation (5D). With respect to clinical consideration (fig. 5A), the uppermost percentage of interactions (32.43%) had a significance number 4.0, followed by significant numbers 3.0 and 6.0 (22.29% and 17.21%, respectively). Concerning the onset of outcome (fig. 5B), 52% of DDIs distinguished as delayed onset of effect (past 24 hours) and 35% were categorized as rapid onset (within 24 hours). In view of severity, 38.60% interactions were elucidated as moderate effects (aggravation of the clinical situation) and 22.40% were identified as major effects (latent risk for life or irreparable harm). Whereas 36.80% interactions were found in minor class (indiscernible) (fig. 5C). While documented evidences were portrayed in fig. 5D. Table 5 describes the subsequent effects of concomitant drugs observed during study.

DISCUSSION

Drug interactions (DIs) are still main issue for health care decision makers on international level because of significant and persistent rise in the morbidity and death of patients (Aljadhey *et al*., 2013). DIs are associated with either limitizing the effectiveness of other medicinal agents or provoke toxicity (Moura *et al*., 2009). A variety of research conclusions described the occurrence of DIs among ICU patients ranges between 44.3% and 87.9% (Seynaeve *et al*., 2011; Abideen *et al*., 2015). Moreover, the responsible risk factors of DIs involved extended hospitalization, increased number of prescribed drugs, drugs having narrow therapeutic index and more than 70% events of undesirable responses are reported due to inadequate dose of administered drugs, which could be potentially controllable with early detection (Gallagher *et al*., 2007; Vonbach *et al*., 2008). Despite the facts to consider patient safety and minimizing DIs error, polypharmacy is still frequent in critically ill patients admitted in ICU attributed high risk of adverse reactions due to use of multiple interventions to treat severity of disease condition. Similarly, co-morbid conditions and altered pathophysiology may also change the pharmacokinetics and pharmacodynamics effects of drugs so it is essential to optimize the adequacy of dose to achieve pharmacodynamic targets (Seynaeve *et al*., 2011; Cascorbi, 2012). Results of a clinical investigation regarding pharmacokinetics (20.57%) and pharmacodynamics (77.01%) DIs (Jain *et al*., 2017) fluctuates with the results of present study. However, a non-significant difference reported for both pharmacokinetics (49.32%) and pharmacodynamics (45.33%) (table 4). Results of our study showed maximum number of admissions (%) during stayed period of 4-7 days in ICU but DIs was increased on prolong stay described in fig. 1. A wide range of medications and prolong hospitalization may also influence the incidence rate of DIs (Gagne and Rabinowitz, 2008). The results of a research showed prevalence and ranges of DIs from 13% for 2 drugs and 82% for 7 or more drugs (Goldberg *et al.,* 1996). In general, the most common combinations of medications in which potential DDIs occurred during hospitalization were a combination of potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), combination of aspirin and non-selective β-blockers in patients concomitantly treated with a β_2 agonist (Moura *et al*., 2009; Egger *et al*., 2003; Murtaza *et al*., 2016). The rate of the DDIs in ICU patients at a tertiary care hospital

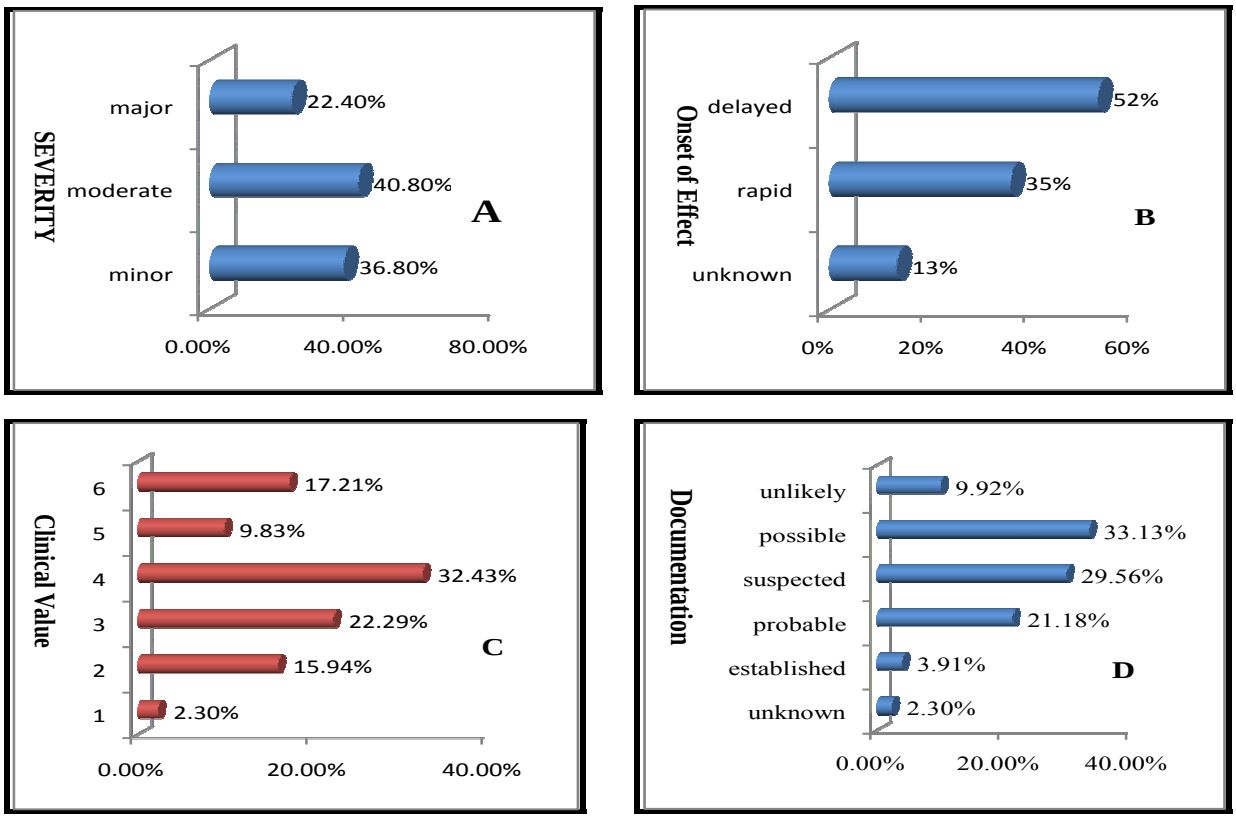

Fig. 5: Division of DDIs for prescribed medications in ICUs with respect to A) severity of the interactions B) onset C) clinical importance D) documentation (El Samia *et al*., 2013).

Table 1: Age, gender distribution and diagnostic details of study participants admitted in ICU

Age Distribution		
Age range (years)	Frequency	Valid Percentage
18-30	18	12.00 %
31-45	35	23.33 %
46-60	54	36.00 %
Above 60	43	28.66 %
Mean Age	56.37 ± 12.45	
Gender Distribution		
Male	83	55.33%
Female	67	44.66%
Total	150	100.0%
Diagnosis		
Digestive system disease	35	23.33%
Cardiovascular system disease	59	39.33%
Respiratory system diseases	30	20.00%
Neurological disorders	14	9.33%
Others	12	8.00%
Hepatic or renal impairment		
Yes	89	59.33%
No	61	40.66%
Presence of co-morbidities		
Yes	78	52%
No	72	48%

Table 2: Prescribing detail of drugs during ICU stay of patients

Number of drugs prescribed	In first 24 hours		In 50th length of ICU stay		At the time of discharge	
	Frequency (N)	DDIs (N)	Frequency (N)	DDIs (N)	Frequency (N)	DDIs (N)
1-4	15	4	46	13	67	23
5-8	57	20	59	30	42	32
9-12	60	31	28	19	13	8
>=12	18	9	3	2	2	1
$P < 0.001$						

Table 3: Categorization of DDIs (Minor, Moderate and Major)

No. of DDIs	Minor		Moderate		Major	
	Frequency (N)	Percentage (%)	Frequency (N)	Percentage (%)	Frequency (N)	Percentage (%)
1-3	56	27.9	29	14.4	45	22.4
4-6	12	6.0	12	6.0	1	0.5
> 6	6	3.0	25	12.4	1	0.5
Total	74	36.8	66	32.8	47	23.4
Total DDIs	187					

Table 4: Pharmacodynamic and pharmacokinetic drug interaction in selected cohort

No. of prescriptions	No. of drugs	No. of Pharmacodynamic DDIs		No. of Pharmacokinetic DDIs	
		Frequency (N)	Percentage (%)	Frequency (N)	Percentage (%)
55	1-3	31	20.66%	43	28.66%
34	4-6	24	16.00%	17	11.33%
22	7-9	7	4.66%	3	2.00%
18	10-12	4	2.66%	6	4.00%
21	>12	2	1.33%	5	3.33%
Total 150	-	68	45.33%	74	49.32%

Table 5: Common drug-drug interaction pairs in studied cohort

Potentially interacting combinations/pairs	Effects
Aspirin and Clopidogrel	Enhance Anti-platelet effect
Aspirin and Corticosteroid	Aspirin enhances corticosteroid toxicity and corticosteroid decreases serum concentration of aspirin
Aspirin and Furosemide	Aspirin declines diuretic effect of the drug
Clopidogrel and Omeprazole	PPIs decreases serum concentration of clopidogrel
Aspirin and Heparin	Enhanced anti-coagulation effects
Amikacin and Vancomycin	Amikacin and vancomycin both increase nephrotoxicity and/or ototoxicity.
Midazolam and Omeprazole	Omeprazole increases levels of midazolam by decreasing metabolism

found high, which is badly influenced by number of drugs or therapeutic groups prescribed per patient. Inappropriate drug combinations were identified and classified with a standard drug interaction source. The purpose of study is to identify, quantify and recognize the severity of drug interactions. Based on severity, most of the drug interactions were significant in nature followed by minor and serious drug interaction which is consistent with other study (Patel *et al*., 2014). The study findings of a trial demonstrated 10 drugs/prescription/patient and the incidence of potential DIs found mild (34.5%), moderate (62.7%) and major (2.8%) (Olumuyiwa *et al*., 2017). Another study revealed minor DIs (26%), moderate (61.2%) and major (12.8%) with 3 or more medications (Bhagavathula *et al*., 2014). Similar results found in the present study population in case of minor DIs (36.8%), although moderate DIs were lesser (32.8%) but in comparison to previous trial major DIs reported extensively (23.4%). Highest DDIs were observed with 5-8 and 9-12 drugs per prescription. Severity of DIs refers to minor (no need of medical intervention), moderate (require medical intervention) and major (consequences

could be mortality, prolong admission or therapeutic failure). fig. 5 illustrated the allocation outline of potential DDIs in term of severity, onset, clinical value and documentations were found in good agreement with previously reported studies (Rafiei *et al*., 2013). In current investigation according to risk score distribution Rank C were 43.75% followed by D (20.71%) (fig. 4) In another investigation DIs noted as D or X were determined by Lexi-Interact software. 70% patients were identified with Category D while 11% had shown Category X interaction (Greene *et al*., 2014). With respect to documented evidence (fig. 5D) possible, suspected and probable interactions were in order of 33.13%, 29.56% and 21.18%. Interactions with unknown documentations were the least common (2.30%). The interaction involving aspirin and clopidogrel was the most repeated event in present investigation. Both aspirin and clopidogrel are anti-platelet agents, and collectively, influence synergistic anti-platelet activity in other investigation such interaction has been reported as well (Shagufta *et al*., 2018).

A substantial number of potential DDI were identified during evaluation of various prescriptions. Results of this study indicate association of DDI with number of prescribed drugs, increased duration of stay in the hospital that pointed out significant clinical issues. The frequent occurrence of DIs among seriously ill patients directs the need of further investigations in health care system to improve awareness regarding hazard and benefits in clinical management.

CONCLUSION

Successful and safe combination therapy can be achieved by promoting the knowledge of potential changes in therapeutic efficacy and unwanted drug reactions, rationale prescribing and performing pharmaco-therapeutic monitoring. Such studies may be used to develop an effective tool for the diagnosis and management of DDIs by monitoring, sophisticated clinical judgment support systems and by linking laboratory data to prescriptions.

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