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Original Research Article

Identification of clinically significant drug-drug interactions in cardiac intensive care units of two tertiary care hospitals in Peshawar, Pakistan

Faisal Shakeel, Jamshaid Ali Khan*, Muhammad Aamir, Rabeea Shareef and Nazia Shah
Department of Pharmacy, University of Peshawar, Peshawar, Pakistan

For correspondence:* ***Email:* *jamshaidkhan@upesh.edu.pk;* ***Tel:*** *+923009592943*

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Abstract

Purpose: *To identify clinically significant potential drug-drug interactions in cardiac intensive care units of two tertiary care hospitals in Peshawar, Pakistan, and to compare the various potential drug-drug interactions related parameters between the government and private hospitals included in the study.*
Method: *A prospective study was conducted in the cardiac intensive care units of the two hospitals, viz, Lady Reading Hospital Peshawar (LRH) and Northwest General Hospital and Research Center Peshawar (NWGH &RC), which are government and private hospitals, respectively. Samples of 260 and 250 patients from LRH and NWGH & RC, respectively, were evaluated. Patient medication charts were evaluated for potential drug-drug interactions and clinically significant potential drug-drug interactions using Micromedex DrugReax. The data were statistically analyzed.*
Results: *A high prevalence of potential drug-drug interactions was reported in both hospitals: 92 and 96.9 % in Northwest General Hospital and Research Center, and Lady Reading Hospital, respectively, of which half were clinically significant. A total of 19 interacting drug pairs contributed to the clinically significant potential drug-drug interactions. Independent sample t-test showed a significant difference in the potential drug-drug interactions of both hospitals. Furthermore, a significant relationship was found between the number of potential drug-drug interactions, on the one hand, and the number of prescribed drugs and age, on the other.*
Conclusion: *A high prevalence of potential drug-drug interactions, particularly clinically significant potential drug-drug interactions, calls for proper identification of these interactions and monitoring of patients to minimize adverse outcomes and improve patient therapy.*

Keywords: *Pharmacy service, Drug interactions, Critical/intensive care, Adverse outcomes*

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INTRODUCTION

Cardiovascular diseases are a prime cause of high mortality rates throughout the world. In 2012, World Health Organization (WHO) estimated that 17.5 million people died worldwide due to cardiovascular diseases. Most of these deaths occurred in low or middle income countries [1]. Risk factors include diseases like hypertension, hyperlipidemia, diabetes or other diseases which require multiple drug therapy, while behavioral risk factors include unhealthy diet, tobacco use, lack of physical activity and stress [2,3]. Furthermore, treatment for these diseases require multiple drug administration which when combined with factors like advanced

age, co-morbidities and changes in hepatic and renal functions, increases the risk of potential drug-drug interactions (PDDIs) [4-6].

The presence of a potential drug-drug interaction (PDDIs) is highly probable in critical units like cardiac intensive care units (CCU), primarily due to the multiple drug therapy employed to combat the complex disease condition of the patient along with co-morbidities and age which further increases the risk of PDDIs [7,8]. However, not all the PDDIs are clinically significant and are not a predisposition of an adverse clinical event. Some PDDIs are employed to benefit the patient but these are very limited, for example the use of aspirin and clopidogrel in patients to prevent thromboembolism [9,10]. Apart for some rare instances, PDDIs are one of the leading causes of hospitalization [11,12].

METHODS

This prospective cross sectional study was carried out in CCUs of two tertiary care hospitals of Peshawar, Lady Reading Hospital (LRH) and Northwest General Hospital and Research Center Peshawar (NWGH & RC). LRH is a government tertiary care hospital while NWGH is a private hospital. The duration of the study was one year and was approved by the ethical committees of both hospitals vide letter number 010 and NWGH/Research/01, respectively. Patient demographics, duration of stay, diagnosis, drugs administered, dose, frequency and duration of drugs prescribed were recorded from the medication chart of the patient. Names of the patients, their identification numbers and medical records were kept confidential. Good clinical practice (GCP) guidelines were followed under the declaration of Helsinki (1964) by the International Conference on Harmonization and Nuremburg Code [26]. Patients admitted to the CCU for at least 24 h and prescribed at least 2 drugs were included in the study.

Micromedex database DrugReax [13] was used to analyze the potential drug-drug interactions among prescribed drugs to the patients. This database provides information on the clinical effect, severity, documentation, onset and mechanism of the PDDIs. Severity may be major, moderate or minor; documentation may be excellent, good or fair; onset may be rapid, delayed or unknown; nature of PDDIs may be pharmacokinetic, pharmacodynamic or unknown; while mechanisms of PDDIs include absorption, distribution, metabolism, elimination, synergism, antagonism or unknown.

The severity and documentation of the PDDIs reported in Micromedex DrugReax was used to create a list of clinically significant PDDIs, on the basis of which the following PDDIs were considered as clinically significant:

- PDDIs having severity of major and of excellent or good documentation
- PDDIs having severity of moderate and of excellent or good documentation

Frequencies were used to summarize gender, number of prescribed drugs, diagnosis, duration of stay, frequency of PDDIs, interacting drug pairs and their severity, documentation, onset and clinical significance. Multiple linear regression was used to determine the relationship between number of prescribed drugs, duration of stay and the number of PDDIs. *P* values of < 0.05 was considered statistically significant. Independent samples t test was performed to the compare the means of clinically significant PDDIs in both hospitals. All the analysis was performed using IBM SPSS Statistics for Windows, Version 20 (Armonk, NY: IBM Corp) [14].

RESULTS

General characteristics

A total of 510 patient prescriptions were evaluated, of which 250 were from NWGH & RC, while 260 were from LRH, representing private and government sector respectively. The proportion of male patients as compared to female patients was higher in both the hospitals, 59.2 % in NWGH & RC while 66.2 % in LRH. The mean age of the patients was 58.06 ± 12.75 (range 19 - 88) and 55.24 ± 13.58 (range 12 - 95) in NWGH & RC and LRH, respectively. The median duration of stay was 3 days for both hospitals while the median number of drugs prescribed was higher in NWGH & RC (6 drugs per prescription) as compared to LRH (5 drugs per prescription). The general characteristics of the patients are displayed in Table 1.

Diagnosis

The most frequent diagnosis of patients admitted in both NWGH &RC and LRH was myocardial infarction (MI), while acute coronary syndrome (ACS) and heart failure were the other most frequent diagnosis of the patients. The comparison of the percentage of diagnosis in both hospitals is displayed in Figure 1.

Table 1: General patient characteristics in CCU of NWGH and LRH

Variables	Frequency (%) NWGH	Frequency (%) LRH
Gender		
Male	148 (59.2)	172 (66.2)
Female	102 (40.8)	88 (33.8)
Age (years)		
Mean ± SD	58.06 (± 12.75)	55.24 (± 13.58)
≤ 18	0	2 (0.8)
19-59	127 (50.8)	144 (55.4)
≥ 60	123 (49.2)	114 (43.8)
Drugs prescribed per patient		
Mean ± SD	5.81 ± (1.94)	5.70 ± (1.328)
≤ 4	56 (22.4)	44 (16.9)
5-6	113 (45.2)	158 (60.8)
≥ 7	81 (32.4)	58 (22.3)
Stay in ICU		
Mean ± SD	3.62 ± (1.78)	3.73 ± (2.265)
≤ 2	74 (29.6)	54 (20.7)
3-5	118 (47.2)	151 (58.1)
≥ 6	58 (23.2)	55 (21.2)

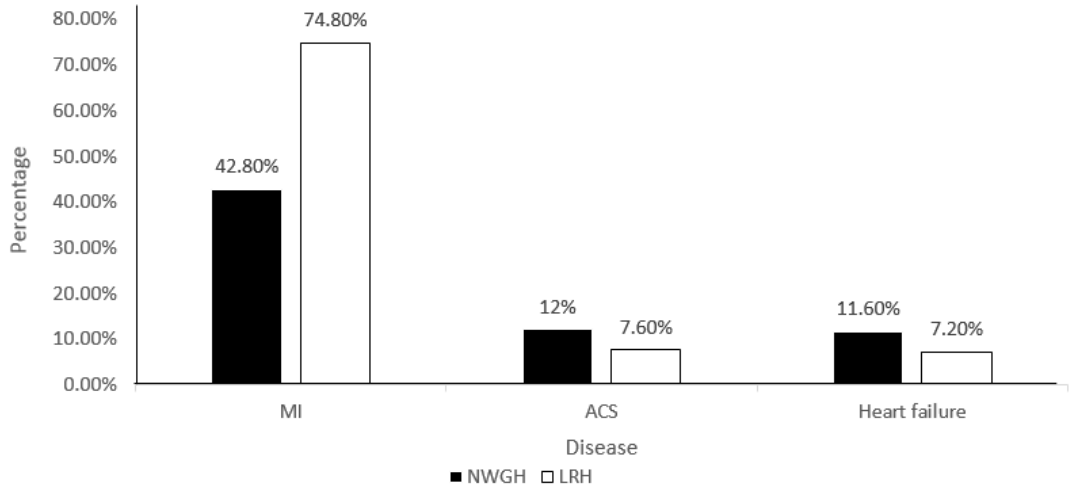

Figure 1: Comparison of diagnosis between NWGH & RC and LRH

Prevalence of PDDIs and categories

At least one potential drug-drug interaction (PDDI) was encountered in 92 and 96.9 % of the patients in NWGH &RC and LRH, respectively. A total of 105 interacting drug pairs contributed to the 909 PDDIs encountered in NWGH &RC while 76 interacting drug pairs contributed to the 1204 PDDIs encountered in LRH. The severity, documentation, onset, nature and mechanism of the PDDIs encountered in both hospitals are displayed in Table 2.

Clinically significant PDDIs

Clinically significant PDDIs were identified using the predetermined criteria. Using this criteria along with the frequency of PDDIs, a list of 19 interacting drug pairs was prepared from both the hospitals which were considered to be significant clinically, because of the associated high risk and occurrence in the cardiac critical care unit. The list of clinically significant PDDIs from both hospitals along with their frequencies and potential outcome is displayed as Table 3. These PDDIs contributed to 44.6 and 51 % of the total PDDIs encountered in NWGH & RC and LRH respectively. Furthermore, it was observed that 3.63 and 4.63 PDDIs were present per patient in NWGH & RC and LRH respectively while 2.07 and 2.54 clinically significant PDDIs were present per patient in the hospitals respectively.

Independent sample *t-test*

An independent sample t-test was performed to compare the means of clinically significant PDDIs between NWGH and LRH. The t-test showed a significant difference ($t = 3.435$, $p = 0.001$) in the number of clinically significant PDDIs between NWGH and LRH.

Table 2: Categories of Potential drug-drug interactions in NWGH and LRH

Variable	Frequency (%) NWGH	Frequency (%) LRH
Severity of PDDIs		
Major	377 (41.4)	639 (53.1)
Moderate	496 (54.6)	563 (46.8)
Minor	36 (4.0)	2 (0.1)
Documentation of PDDIs		
Excellent	79 (8.7)	72 (6.0)
Good	479 (52.7)	614 (51.0)
Fair	351 (38.6)	518 (43.0)
Onset of PDDIs		
Rapid	135 (14.8)	194 (16.1)
Delayed	267 (29.4)	255 (21.2)
Unkonwn	507 (55.8)	755 (62.7)
Type of interaction		
Pharmacodynamic	675 (74.3)	946 (78.6)
Pharmacokinetic	211 (23.2)	252 (20.9)
Unknown	23 (2.5)	6 (0.5)
Mechanism of interaction		
Synergism	383 (42.1)	645 (53.6)
Antagonism	292 (32.2)	301 (25.0)
Absorpiton	29 (3.2)	4 (0.3)
Metabolism	69 (7.6)	48 (4.0)
Elimination	111 (12.2)	200 (16.6)
Absorption/metabolism	2 (0.2)	0
Unknown	23 (2.5)	6 (0.5)

Table 3: Clinically significant PDDIs in NWGH and LRH

Interacting drug pair	Frequency NWGH	Frequency LRH	Potential outcome
Aspirin-enoxaparin	64	161	Increased risk of bleeding.
Clopidogrel-omeprazole	7	10	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis.
Ramipril-spironolactone	10	11	May result in hyperkalemia.
Digoxin-spironolactone	2	15	May result in increased digoxin exposure.
Aspirin-metoprolol	31	32	May result in decreased antihypertensive effect.
Aspirin-nitroglycerin	14	68	May result in an increase in nitroglycerin concentrations and additive platelet function depression.
Furosemide-ramipril	22	18	May result in postural hypotension (first dose).
Aspirin-furosemide	57	51	May result in decreased diuretic and antihypertensive efficacy.
Aspirin-spironolactone	23	35	May result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.
Aspirin-carvedilol	20	7	May result in decreased antihypertensive effect.
Aspirin-bisoprolol	58	87	May result in decreased antihypertensive effect.
Aspirin-losartan	11	5	May result in decreased antihypertensive effects and an increased risk of renal impairment.
Aspirin-valsartan	16	6	May result in decreased antihypertensive effects and an increased risk of renal impairment.
Aspirin-candesartan	1	16	May result in decreased antihypertensive effects and an increased risk of renal impairment.
Aspirin-hydrochlorothiazide	11	3	Decreased diuretic and antihypertensive efficacy.
Digoxin-furosemide	11	20	May result in digoxin toxicity (nausea, vomiting, cardiac arrhythmias).
Aspirin-lisinopril	4	47	May result in decreased lisinopril effectiveness.
Aspirin-glimepiride	18	4	Increased risk of hypoglycemia.
Atorvastatin-clopidogrel	25	18	Decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.

Table 4: Prediction of clinically significant PDDIs

No. of clinically significant PDDIs	Coefficient	Standard error	t	*P*-value
Constant	-0.091	0.379	-0.241	0.810
No. of prescribed drugs	0.580	0.041	13.795	0.000
Duration of stay	0.001	0.034	0.020	0.984
Age	-0.16	0.005	-3.196	0.001

Prediction of clinically significant PDDIs

Multiple linear regression model was fitted to predict the number of clinically significant PDDIs based on number of prescribed drugs, duration of stay and age. The effect of number of prescribed drugs on number of clinically significant PDDIs, controlling for the effect of duration of stay and age, was found to be significant. ($t = 13.795$, $p < 0.0001$). The effect of age on number of clinically significant PDDIs, controlling for the effect of duration of stay and number of prescribed drugs, was also found to be significant. ($t = -3.196$, $p = 0.001$). The effect of duration of stay on number of clinically significant PDDIs, controlling for the effect of number of prescribed drugs and age, was found to be insignificant ($t = 0.020$, $p = 0.984$) (Table 4).

DISCUSSION

This study reported a high prevalence of PDDIs which corresponds to other studies reporting a similar higher prevalence in cardiology. University of Pittsburg conducted a study in cardiac and cardiothoracic ICU patients, found 87.7 % patients having at least a single PDDI [15]. Cross sectional studies conducted in Pakistan also reported a prevalence of 91.1 and 77.5 % cardiology patients having a PDDI [4,16]. It was also reported that 72.5 % of ICU patients had PDDIs in the ICU of a Brazilian hospital [17]. While another Brazilian study reported 87.2 % patients in cardiology encountered a PDDI [18].

A Brazilian study evaluated 1785 prescriptions and recorded similar trends as seen in this study with the severity of most PDDIs being moderate (78.6 %), documentation of most PDDIs was good (29.5 %) and most (42.5 %) were pharmacodynamics in nature [19] Another study reported PDDIs of moderate severity to be the most common (62.5 %) [20]. In 203 patients, 75.03 % of PDDIs were in Category C which corresponds to moderate severity [21]. A record of 1124 patients were evaluated for PDDIs at 24 h and 120 h after admission to the hospital. The severity of most interactions was moderate in both the time frames (50.1 and 51.4 %), most of the interactions were good documentation (63.9 and 59.1 %) and most of were of pharmacodynamic in nature at 120 h (45.2 %) [22]. To our knowledge no previous study has focused on the clinically significant interaction in cardiac intensive care units. Our study shows that 3.63 and 4.63 PDDIs were present per patient in NWGH & RC and LRH respectively while 2.07 and 2.54 clinically significant PDDIs were present per patient in the hospitals respectively. This is of great concern because more than half of the PDDIs encountered were clinically significant and can have a significant impact on the advanced disease condition of the patient.

A significant association was found between clinically significant PDDIs and number of prescribed drugs and age of the patient. This association was similar to that of reported in other studies [4,18,23-25]. A Nepalese study reported a significant linear association between length of stay and occurrence of PDDIs [20]. Another study conducted in cardiology department of Pakistan also reported a significant association between PDDIs and prescribed drugs and age [4].

Proper PDDIs identification and management system are lacking in these hospitals which contribute to this high prevalence of PDDIs. Pharmacists should update themselves regarding the knowledge of clinically significant PDDIs and timely interventions implemented.

Limitations of the study

Monitoring of the adverse outcomes due to the PDDIs and lack of interventions were some of the limitations of this study. This study identified clinically significant PDDIs on the basis of literature and drug interaction database, while clinical studies can be conducted in the future to monitor the actual clinically notable adverse outcomes of these PDDIs and their effect on the patient disease.

CONCLUSION

This study identified not only a high prevalence of PDDIs but also clinically significant PDDIs which have greater potential for significant

changes in patients' condition. Also notable was the significant difference in PDDIs between the private and government hospital, which demands for the implementation of proper drug interaction monitoring systems across all hospitals to minimize this health care hazard.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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