ORIGINAL ARTICLE

Comparing Important and Well-documented Potential Drug–Drug Interactions between Emergency, Medical, and Surgical ICUs of a Respiratory Referral Center

Zeinab Hosseinpoor[1], Behrooz Farzanegan[2], Shadi Baniasadi[3]

Abstract

Introduction: Drug–drug interaction (DDI) is one of the major healthcare challenges in intensive care units (ICUs). The prevalence of DDIs and interacting drug pairs may vary between different types of ICUs. This study aimed to compare the frequency and nature of important and well-documented potential DDIs (pDDIs) in three types of ICUs.

Materials and methods: A prospective study was conducted in medical (M), surgical (S), and emergency (E) ICUs of a tertiary referral center for respiratory diseases. A pharmacist checked the patients' files three days in a week for 6 months. The pDDIs were identified using the Lexi-Interact database. Interactions with a severity rating of D (modify regimen) and X (avoid combination) and with a reliability rating of good and excellent were considered important and well-documented. These pDDIs were evaluated in terms of drug combinations, mechanisms of interaction, and clinical management.

Results: One hundred eighty-nine patients admitted to MICU, SICU, and EICU were included in the study. The percentage of patients who experienced at least one important and well-documented pDDI was 18.8% in MICU, 11.1% in SICU, and 11.8% in EICU. The most common drug pairs causing important and well-documented interactions were atracurium + hydrocortisone in MICU, meropenem + valproic acid in MICU and EICU, and aspirin + warfarin in SICU.

Conclusion: The current study shows different frequency and nature of pDDIs between three types of ICUs. We recommend conducting similar studies in other settings to develop evidence-based guidance on clinically relevant pDDIs in different types of ICUs.

Keywords: Drug–drug interactions, Intensive care unit, Potential drug–drug interaction, Prevalence.

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Introduction

Drug–drug interactions (DDIs) are common health problems and sources of concern on an international level.[1] Consequences of DDIs may be significant, like increase in toxicity of interacting drugs or morbidity and mortality rate; however, they are predictable and preventable adverse drug events.[2,3] Screening patients' medications to detect DDIs can minimize the harmful consequences of the interactions.[4]

Critically ill patients are at an increased risk of DDIs due to the complexity of medications, the severity of the disease, and organ failure.[5] According to various studies, the prevalence of DDIs in intensive care units (ICUs) ranged from 44.3 to 86%.[6] This wide range may be related to variation in ICU settings, study populations, study designs, patient's diseases, interaction screening tools, medications' prescribing patterns, and availability of drug information and DDIs screening system in hospital.[4,7] The studies on DDIs in ICU settings clarify the clinical relevance of DDIs in the ICUs, provide a guide to develop or revise the clinical decision support system, and improve patient safety.[8,9]

Previous studies mainly reported the frequency and nature of DDIs in one type of ICU. Comparing DDIs data of patients admitted to various types of ICUs in a similar setting is rare.[10,11] In a systematic review and meta-analysis of potential DDIs (pDDIs) in the ICUs, Fitzmaurice et al. reported that sources of heterogeneity of the included studies were various types of ICUs and natures of DDIs.[8] Drug interacting pairs, severity, consequence, and management of pDDIs may vary between different types of ICUs. For example, a pDDI between two anticoagulants in a surgical ICU is more severe than a cardiac ICU. Therefore, DDIs data of one type of ICU cannot be generalized to another one.[12] The difference between the ICUs in terms of prescriptions and pDDIs.[9,12] is an important issue to be studied. We designed the current study to compare the frequency and nature of important and well-documented pDDIs between three types of ICUs [medical ICU (MICU), surgical ICU (SICU), and emergency ICU (EICU)] in a respiratory setting.

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

[2]Critical Care Quality Improvement Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3]Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author: Shadi Baniasadi, Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran, Phone: +98-21-26105387, e-mail: sbaniasadi@yahoo.com, baniasadi@sbmu.ac.ir

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Materials and Methods

Study Design

A cross-sectional study was conducted at MICU, SICU, and EICU of Masih Daneshvari hospital, a tertiary referral center for respiratory diseases from January 2018 to June 2018. Ethical approval was obtained from the Research Ethics Committee of the institute. A pharmacist checked the patients' files three days in a week. Both male and female patients aged 18 to 85 years old admitted to the MICU, SICU, and EICU were included in the study. Patients' data including age, sex, date of admission and discharge, prescribed medications, and main diagnosis were collected separately in each ICU. Primary diagnoses were classified according to International Classification of Diseases and Related Health Problems—Tenth Edition.[13] Lexi-Interact database was utilized to screen each patient's medication list in terms of pDDIs.

Lexi-Interact categorizes the interactions into five categories based on the risk rating. The categories include A (no known interaction), B (no action needed), C (monitor therapy), D (modify regimen), and X (avoid combination).[14] The reliability rating of the interactions, which indicates the quantity and nature of documentation for interaction, is scaled as excellent (E), good (G), or fair (F).[15]

Data Analysis

Data were analyzed using SPSS version 22.0 for Windows (SPSS, Chicago, Illinois, USA). The frequency of interactions with all risk ratings (A, B, C, D, and X) was calculated. However, D and X categories with reliability ratings of E and G (as important and well-documented pDDIs) were evaluated in terms of drug combinations, mechanisms of interaction, and clinical management. Descriptive statistical analysis was performed on demographic and clinical data to measure mean, median, standard deviation, interquartile range, and percentage where appropriate.

Table 1: Demographic and clinical characteristics of the ICU patients

Characteristic	*MICU*	*SICU*	*EICU*
Number of patients (*N*)	48	90	51
Age, years (mean ± SD)	62 ± 16	52 ± 15	64 ± 15
Gender (male/female)	25/23	58/32	31/20
Length of hospital stay, days (median, (IQR))	12 (7–20)	5 (4 –10)	13 (7–25)
Number of prescriptions (mean ± SD)	10 ± 4.1	9 ± 4.1	10 ± 3
Number of A-pDDIs (*N*)	7	8	6
Number of B-pDDIs (*N*)	82	99	91
Number of C-pDDIs (*N*)	360	477	280
Number of D-pDDIs (*N*)	52	78	29
Number of X-pDDIs (*N*)	3	9	4
Diagnoses classification (*N*)			
Diseases of circulatory system	5	26	7
Injury, poisoning, and certain other consequences of external causes	0	19	1
Diseases of the respiratory system	26	14	27
Neoplasms	13	13	6
Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified	1	7	1
Certain infectious and parasitic diseases	0	5	2
Factors influencing health status and contact with health services	0	3	0
Diseases of the nervous system	1	1	3

Results

During the study period, 189 patients admitted to the ICUs were included. The number of patients in the MICU, SICU, and EICU was 48, 90, and 51, respectively. Table 1 shows the demographics and clinical characteristics of the patients and the number of interactions with different risk ratings in three types of ICUs. The most common diagnosis in MICU and EICU was diseases of the respiratory system and in SICU was diseases of the circulatory system. The percentage of patients who experienced at least one important and well-documented pDDI was 18.8, 11.1, and 11.8% in MICU, SICU, and EICU, respectively. The important (D and X) pDDIs with excellent or good reliability ratings in three ICUs are shown in Tables 2 to 4. The most common drug pairs causing the interactions were atracurium + hydrocortisone in MICU, aspirin + warfarin in SICU, and meropenem + valproic acid in MICU and EICU.

Discussion

Published studies on DDIs in the ICUs are generally limited to one type of ICU. The current study evaluates the frequency and nature of pDDIs in three types of ICUs in a respiratory setting. The setting and intensivists who prescribe medications are the same for included ICUs. The main differences are diagnoses and prescriptions for admitted patients, which cause different natures of drug interactions. Several studies emphasized that their data from a specific patient population cannot be compared to other settings.[16,17] Our study mainly focuses on comparing the interaction profiles of the drugs used in the MICU, SICU, and EICU of a respiratory setting.

Previous studies reported that the risk of pDDIs increases with the number of prescribed medications.[18–21] In the current study, the percentages of important and well-documented pDDIs are different between three types of ICUs but there is no considerable difference between the ICUs in terms of the number of prescribed medications. A higher percentage of evaluated interactions in MICU may be related to the prescription of medications with a more potential risk of interactions such as antimicrobials (meropenem, fluconazole), neuromuscular blocking agents (atracurium), and anticonvulsants (valproic acid).

We found the most common pDDIs in MICU occur between atracurium and hydrocortisone, and between meropenem and valproic acid. Atracurium is a neuromuscular blocking agent, which facilitates tracheal intubation and is frequently used in the management of critically ill patients.[22] It has been suggested that the combination of muscle relaxants and corticosteroids may be a cause of difficulty in reversing residual neuromuscular block in ICU patients.[23] This interaction leads to prolonging the effects of neuromuscular blocking agents. Critical care guidelines recommend using a neuromuscular blocking drug only when necessary and administrating the lowest dose possible.[24] Lexi-Interact recommendation for management of

Table 2: Important potential drug–drug interactions with excellent or good reliability in medical ICU patients

Drug combination (frequency)	*Risk rating*	*Mechanism/effect*	*Recommendations*
Atracurium + hydrocortisone (5)	D	Metabolism/atracurium enhances the adverse neuromuscular effect of hydrocortisone	Use a neuromuscular blocking drug only when necessary. Employ the lowest doses to limit the risk of developing myopathy.
Meropenem + valproic acid (2)	D	Metabolism/meropenem may decrease the serum concentration of valproic acid	Consider alternative antibiotic agents or antiseizure. Monitor closely if combined.
Allopurinol + warfarin (1)	D	Additive/allopurinol may enhance the anticoagulant effect of warfarin	Monitor for increased prothrombin time.
Methadone + fluconazole (1)	D	Additive/methadone may enhance the QTc-prolonging effect of fluconazole	Consider an alternative to this combination. If combined use, monitor closely for evidence of QT prolongation and cardiac rhythm.

Table 3: Important potential drug–drug interactions with excellent or good reliability in surgical ICU patients

Drug combination (frequency)	*Risk rating*	*Mechanism/effect*	*Recommendations*
Aspirin + warfarin (2)	D	Additive/aspirin may enhance the anticoagulant effect of warfarin.	Avoid combining. Monitor for increased signs and symptoms of bleeding.
Indomethacin + aspirin (1)	D	Additive/indomethacin may enhance the adverse effect of aspirin.	Monitor for increased risk of bleeding.
Diclofenac + furosemide (1)	D	Antagonistic/diclofenac may diminish the diuretic effect of furosemide.	Monitor for decreased therapeutic effect of furosemide.
Famotidine + itraconazole (1)	D	Absorption/famotidine may decrease the serum concentration of itraconazole.	Administer famotidine at least 2 hours before or 2 hours after itraconazole. Monitor patients closely for reduced itraconazole efficacy if combined.
Cyclosporine + mycophenolate (1)	D	Metabolism/cyclosporine may decrease the serum concentration of mycophenolate.	Monitor mycophenolate dosing and response to therapy closely, particularly when start, stop, or change cyclosporine dose.
Ibuprofen + furosemide (1)	D	Antagonistic/ibuprofen may diminish the diuretic effect of furosemide.	Monitor patients for decreased therapeutic effect of furosemide.
Pantoprazole + itraconazole (1)	D	Absorption/pantoprazole may decrease the serum concentration of itraconazole.	Administer itraconazole at least 2 hours before or 2 hours after itraconazole. Monitor patients closely for reduced itraconazole efficacy if combined.
Amlodipine + phenytoin (1)	D	Metabolism/amlodipine may increase the serum concentration of phenytoin. Phenytoin may decrease the serum concentration of amlodipine.	Monitor for phenytoin toxicity. Monitor for reduced therapeutic effects of amlodipine.
Cyclosporine + atorvastatin (1)	X	Metabolism/cyclosporine may increase the serum concentration of atorvastatin.	Avoid concomitant use of cyclosporine and atorvastatin. Consider changing to a statin that is less sensitive to this interaction. Limit atorvastatin dose to no more than 10 mg daily.

Table 4: Important potential drug–drug interactions with excellent or good reliability in emergency ICU patients

Drug combination (frequency)	*Risk rating*	*Mechanism/effect*	*Recommendations*
Meropenem + valproic acid (2)	D	Metabolism/meropenem may decrease the serum concentration of valproic acid.	Consider alternative antibiotic agents or antiseizure. Monitor closely if combined.
Ciprofloxacin + theophylline (1)	D	Metabolism/ciprofloxacin may increase the serum concentration of theophylline.	Avoid combination. Monitor for toxic effects of theophylline. Theophylline dose reductions will likely be required.
Naproxen + aspirin (1)	D	Additive/naproxen may enhance the adverse effect of aspirin.	Monitor for increased risk of bleeding.
Naproxen + furosemide (1)	D	Antagonistic/naproxen may diminish the diuretic effect of furosemide.	Monitor for decreased therapeutic effect of furosemide.
Multivitamins and minerals + levothyroxine (1)	D	Absorption/multivitamins and minerals may decrease the serum concentration of levothyroxine.	Separate the oral administration of iron-containing multivitamins and levothyroxine by at least 4 hours.

this DDI is monitoring for new onset of muscle weakness or loss of deep tendon reflexes. This DDI is supported by excellent scientific evidence.[14] The interaction between atracurium and hydrocortisone reported as the most common interaction in MICU by Abideen et al. who assessed the prevalence of pDDIs in India.[25]

Meropenem is used for a variety of respiratory infections in critically ill patients. This medication is also prescribed for the treatment of hospital-acquired infections. It is a suitable choice for critically ill patients with sepsis or septic shock because of its very broad spectrum of activity.[26] Some studies reported that concomitant use of meropenem can decrease the serum concentration of valproic acid.[27,28] Respiratory diseases are the main diagnoses in patients admitted to the MICU and EICU in the current study. Therefore, this interaction is more common in these ICUs. The reliability rating of this DDI is excellent. According to the recommendation of the Lexi-Interact, concomitant use of valproic acid with meropenem should be avoided. The recommendation to reduce the probability of this interaction is the replacement of meropenem with other antibiotics showing a similar antimicrobial spectrum. If meropenem is indispensable, the selection of other antiepileptic drugs is recommended.[29]

Patients admitted to critical care are predisposed to venous thromboembolism due to prolonged immobility, vascular injury, and invasive intervention treatments.[30] Aspirin and warfarin are widely used for the prevention of thromboembolic diseases in hospitalized patients. Many patients who take warfarin for any indication may also receive aspirin because of other comorbidities.[31] Both the European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) atrial fibrillation guidelines do not recommend a combination of aspirin and warfarin except in patients with an acute ischemic event or a coronary intervention.[32,33] The combination of these medications may enhance bleeding rates in hospitalized patients.[32] Lexi-Interact recommends monitoring for increased signs and symptoms of bleeding whenever a coumarin derivative and a salicylate are used concomitantly.[34] In the current study, patients in SICU are more prone to this interaction than patients in MICU or EICU since surgical interventions and circulatory diseases are more prevalent in SICU than in other ICUs.

We did not find any adverse drug reactions resulting from the DDIs. This may be related to warning clinicians about the pDDIs and preventing the occurrence of real DDIs. In a systematic review by Kane-Gill et al., considering the severity and clinical relevance of pDDIs is recommended to reduce alert fatigue related to clinical decision support systems in the ICUs.[35] The results of the studies that evaluate important and well-documented pDDIs in the ICUs can be used for developing practical clinical decision support systems.

Evaluation of pDDIs in one setting, a large respiratory referral center, is a limitation for the current study and some of the results may not be extrapolated to other settings. We recommend designing similar studies in other settings to highlight common drug combinations, which may lead to important and well-documented pDDIs in the ICUs.

Conclusion

The current study shows the prevalence and nature of pDDIs that vary between different types of ICUs. The interactions between anticoagulants and antiplatelet agents (in SICU), neuromuscular blocking agents and corticosteroids (in MICU), and carbapenems and anticonvulsants (in MICU and EICU) are the most prevalent, important, and well-documented pDDIs in the ICU settings. These results increase clinician's awareness about the interactions of commonly used drug combinations for critically ill patients.

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Orcid

Zeinab Hosseinpoor https://orcid.org/0000-0001-9682-4271
Behrooz Farzanegan https://orcid.org/0000-0002-6353-5761
Shadi Baniasadi https://orcid.org/0000-0002-3918-0104

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