European Review for Medical and Pharmacological Sciences 2021; 25: 7108-7114

Potential drug-drug interactions in University Hospital Medical Intensive Care Unit patients in Turkey

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Abstract. – OBJECTIVE: Concomitant use of drugs not only enhances the therapeutic effect, but may also lead to undesirable interactions. Drug interactions are frequently seen in intensive care patients. In this study, we aimed to determine the frequency and clinical severity of drug interactions in Medical Intensive Care Unit (MICU) patients.

PATIENTS AND METHODS: The ordered drugs and blood analysis results of 314 patients aged ≥18 years who stayed in the MICU for at least 24 h between January and December 2020 were evaluated. Using the Lexi-Interact online database, clinically significant types of drug interactions, frequently interacting drug/drug groups, and potential adverse reactions were identified.

RESULTS: The average number of drugs in 314 patients was 8.98±5.19. It was determined that polypharmacy was associated with comorbidity and the amount of drug used increased as the number of diagnoses increased. Potential drug-drug interactions were observed in 69.7% of the MICU patients, and it was determined that the amount of interactions increased as the amount of drug used increased. The most common X, D, and C type potential drug-drug interactions, were found between furosemide and salbutamol, enoxaparin and acetylsalicylic acid, ipratropium and potassium chloride, respectively.

CONCLUSIONS: Use of frequently interacting drugs in the treatment of critically MICU patients may lead to potential drug-drug interactions and adverse reactions. Daily monitoring and updating of drug therapy can improve patient's quality of life by preventing or reducing potential drug-drug interactions.

Key Words:
Adverse reaction, Clinical pharmacology, Clinically significant drug-drug interactions, Patient safety, Pharmacovigilance.

Introduction

Co-administration of two or more drugs used in the same or different indications may cause interactions at the level of absorption, distribution, metabolism and excretion, as well as synergistic or antagonistic effects. Although this condition, which is defined as drug-drug interactions (DDI), is frequently used to increase the effectiveness of treatment, it can lead to undesirable and unintended consequences, such as decrease in efficacy, an increase in adverse reactions, and even death. In the event of serious and an unexpected adverse reaction due to DDI, new medications are added to the treatment, which leads to the formation of new DDI[1].

DDI is frequently seen in intensive care unit (ICU) patients, patients with significant or multiple comorbidities[1,2]. ICU patients are especially at high risk for DDI. This is thought to be due to the medicenes added to treatment and the complexity of the treatments in this setting[3]. Indeed, in a previous study[2], it was shown that the potential risk of DDI (54%) in ICU patients is twice that of patients hospitalized in other services. Checking treatment daily for DDI and timely detection of potential DDI (pDDI) and taking appropriate action can greatly prevent adverse reactions from DDI[4]. In previous study[5], it was reported that 7.5% of the patients admitted to MICU due to adverse reaction, 57% of the adverse reactions were caused by DDI and all were preventable. According to another study, approximately 10% of adverse reactions which was preventable are associated with a DDI, and approximately 5% of ICU patients experience a DDI-induced adverse reaction at admission[4]. Prevention of adverse reactions related to DDI

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increases the effectiveness of treatment and improves the quality of the patient's life[6].

In this study, we aimed to determine the frequency and clinical severity of pDDI in MICU patients.

Patients and Methods

Our study, which was designed as a retrospective cohort analysis, included consecutive patients (n=320) who were treated in Tekirdağ Namık Kemal University Hospital 10-bed MICU between January and December 2020. The data of 314 patients were used, excluding 6 patients who stayed in the MICU for less than 24 h. The patient's dermographic information, first day treatment in the MICU and the first blood analysis results (BUN, creatinine, ALT, AST and potassium levels) were obtained. pDDI were evaluated using databases such as Micromedex Health Care Series Volume 148, Lexi Comp's Drug Information Handbook (29th Edition), the Lexi-Interact online database system, and PubMed by the same medical pharmacologist. Clinically significant C, D, and X type pDDI were determined. In C type pDDI, only dose adjustment is sufficient as the benefits of concomitant use of drugs often outweigh the risks, whereas in D type pDDI, the benefit/risk ratio should be determined and measures such as aggressive monitoring, dose adjustment, or selection of alternative agents should be taken to realize benefits and/or reduce toxicity. In X type pDDI, it is recommended to avoid this combination, as the risks associated with concomitant use usually outweigh the benefits[7]. Comorbid diseases, blood analysis results and pharmacological groups were categorized. Ordered drugs and diagnoses groups were created. The relationship between comorbidity and polypharmacy, the relationship between polypharmacy and pDDI, frequently used drugs, clinically significant C, D and X type pDDI were examined. The SPSS 18.0 software was used for the analysis of the data. The study was approved by the Ethics Committee of Tekirdag Namık Kemal University (2021.57.02.20).

Results

Of the 314 patients with a mean age of 64.50±15.42 years who participated in the study, more than half (58.3%) were male. Comorbid diseases were cardiovascular diseases (CVD, 54.1%), malignant diseases (48.1%), infectious diseases (37.6%), endocrine disorders (30.9%), central nervous system (CNS) diseases (17.8%), gastrointestinal bleeding (13.7%) and pulmonary disease (13.7%). Top ten commonly used drugs were pantoprazole (64.3%), enoxaparin (35.4%), paracetamol (34.7%), furosemide (30.9%), salbutamol (30.9%), ceftriaxone (26.8%), ipratropium (23.6%), lactulose (23.2%), potassium chloride (22.9%), and budesonide (19.4%).

In the blood analysis results, BUN (>23 mg/dL, 61.1%) and creatinine (>0.9 mg/dL, 61.8%) were predominantly high, ALT (<33 unit/L, 70.7%) and AST (<33 unit/L, 54.1%) were predominantly low. While potassium levels were higher than 3.5 mmol/L in 80.9% of patients, it was found to be low in 19.1%.

It was determined that 314 patients used 2820 drugs and the average number of drugs per patient was 8.98±5.19. While the average number of drugs per patient was 4.68±3.49 in patients with a one diagnosis; it was 8.31±4.22, 11.11±4.47, 14.21±4.73 in patients with two, three, four or more diagnoses, respectively. Statistically significant relationship was found between the number of diagnoses and the number of ordered drugs (Pearson-χ^2, χ^2=134.891, p=0.000, Table I).

Table I. Real time PCR primers.

Number of ordered drugs	Number of diagnoses 1 n (%)	2 n (%)	3 n (%)	≥ 4 n (%)	Total n (%)	Statistical analysis* Possibility
1-4	49 (65.3)	24 (21.2)	3 (3.6)	–	76 (24.2)	χ^2 = 134.891
5-8	15 (20.0)	41 (36.3)	23 (27.4)	6 (14.3)	85 (27.1)	p = 0.000
9-15	11 (14.7)	40 (35.4)	46 (54.8)	22 (52.4)	119 (37.9)	
≥ 16	–	8 (7.1)	12 (14.2)	14 (33.3)	34 (10.8)	
Total n (%)	75 (100)	113 (100)	84 (100)	42 (100)	314 (100)	

*Pearson - χ^2 crosstabs were used to analyze the relationships of two qualitative variables.

Interaction was observed in 69.7% of 314 patients. Statistically significant relationship was found between the number of ordered drugs and pDDI (Pearson-χ^2, χ^2=270.672; p=0.000, Table II). C, D and X type pDDI were detected in 65.3%, 37.3% and 14.6% of patients, respectively. A total of 1501 (mean 6.85±7.33) pDDI were detected, with 1147 (mean 5.59±5.53) in C type, 295 (mean 2.52±2.63) in D type, and 59 (mean 1.28±0.50) in X type. The most common C type pDDI (22.4%) were found between furosemide and salbutamol, with a risk of hypokalemia. The most common D type pDDI (17.9%) were found between enoxaparin and acetylsalicylic acid (ASA), with an increase in anticoagulant effect. The most common X type pDDI (37.0%) were found between ipratropium and potassium chloride, with a risk of ulcerogenic effect.

Types of pDDI and Clinical Outcomes Predicted by Databases Due to Frequently Interacting Drugs

Interactions with CNS agents: An increase in CNS depressant effect may be observed due to the interaction of midazolam with fentanyl, remifentanil or tramadol, morphine with fentanyl, pheniramine, propofol or metoclopramide (MCP), and tramadol with hyoscine, pheniramine or MCP. The frequency of this clinical outcome predicted by databases in our study were 32.2% in C type and 57.2% in D type pDDI. C type pDDI due to concomitant use of ipratropium with morphine or tramadol were found in 15.1%, according to databases, this interaction may lead to constipation and/or urinary retention. Type D pDDI due to the use of clarithromycin (CTM) with midazolam or fentanyl was found to be 12.8% with an increase in efficacy (Table III and IV).

Interactions with cardiovascular system agents: Electrolyte disorder due to interaction of furosemide with salbutamol or methylprednisolone (mPRED), decrease in diuretic effect due to interaction with ASA can be seen. In our study, the frequency of this clinical outcomes predicted by databases linked to type C pDDI were 31.7% and 6.8%, respectively. Type C pDDI of salbumol with metoprolol and norepinephrine can cause a decrease in bronchodilator effect and an increase in sympathomimetic effect, respectively, the frequency of each of these predicted clinical outcomes was 6.8% (Table III).

Interactions with antithrombotics: Interaction of enoxaparin with ASA or clopidogrel may cause increase in anticoagulant effect, interaction with potassium chloride may cause electrolyte disorder, clopidogrel-pantoprazole interaction may cause decrease in efficacy. The frequency of these clinical outcomes predicted by databases were 23% in D type pDDI, 11.2% and 7.8% in C type pDDI, respectively (Table III and IV).

Various interactions: The interaction of CTM with budesonide or mPRED, posaconazole-pantoprazole can cause an increase in activity, ipratropium- MCP interaction may decrease in prokinetic effect and mPRED-rocuronium interaction can cause myopathy or neuropathy. The frequency of this clinical outcomes predicted by databases in our study were 9.3% in C type and 12% in D type, 11.2% in C type and 4.3% in D type pDDI, respectively (Table III and IV).

X-type pDDI was associated with the use of drugs that interact with potassium chloride (69.8%), antibacterials and/or antimycotics (32.6%), salbutamol (10.9%), MCP (8.7%), and antithrombotics (6.5%). Drugs such as ipratropium, pheniramine, hyoscine, olanzapine, atropine, hydroxyzine, haloperidol, and quetiapine that interact with potassium chloride can lead

Table II. Relationship between number of ordered drugs and number of detected interactions in MICU patients.

Number of pDDI	Number of ordered drugs					Statistical analysis* Possibility
	1-4 n (%)	5-8 n (%)	9-15 n (%)	≥ 16 n (%)	Total n (%)	
None	62 (81.6)	26 (30.6)	7 (5.9)	–	95 (30.3)	χ^2 = 270.672
1	13 (17.1)	32 (37.6)	9 (7.6)	–	54 (17.2)	p = 0.000
2	1 (1.3)	13 (15.3)	12 (10.1)	–	26 (8.3)	
3	–	9 (10.6)	9 (7.6)	–	18 (5.7)	
≥ 4	–	5 (5.9)	82 (68.8)	34 (100)	121 (38.5)	
Total n (%)	76 (100)	85 (100)	119 (100)	34 (100)	314 (100)	

*Pearson - χ^2 crosstabs were used to analyze the relationships of two qualitative variables.

Table III. The most common C type pDDI in MICU patients (n = 205).

Interacting drugs	N (%)	Predicted clinical outcomes by databases
Drugs interacting with CNS agents: morphine – MCP, morphine – ipratropium, tramadol – ipratropium, tramadol – MCP	66 (32.2)	Increase in CNS depressant effect, constipation and/o r urinary retention
Drugs interacting with cardiovascular system agents: furosemide – salbutamol, furosemide – mPRED, metoprolol – salbutamol, norepinephrine – salbutamol, ASA - furosemide, furosemide – morphine, furosemide – insulin human	132 (64.3)	Electrolyte disorder, decrease in bronchodilatory effect, increase in sympathomimetic effect, decrease in diuretic effect, increase in antihypertensive effect, decrease in antidiabetic effect
Drugs interacting with antithrombotic agents: enoxaparin – potassium chloride, clopidogrel – pantoprazole	39 (19)	Electrolyte disorder, decrease in efficacy
Various drug interactions: budesonide – CTM, mPRED – CTM, ipratropium – MCP	42 (20.5)	Increase in efficacy, decrease in prokinetic effect

MCP: metoclopramide, mPRED: methylprednisolone, ASA: acetylsalicylic acid, CTM: clarithromycin.

to the ulcerogenic effect according to databases. QTc prolonging effect with a frequency of 21.7% in our study, can be seen due to interaction of amiodarone with CTM, levofloxacin or moxifloxacin, interaction of posaconazole with CTM or quetiapine. An increase in efficacy can be seen due to CTM-ibrutinib, tamsulosin–CTM, tamsulosin-posaconazole interaction, disulfiram like reaction can be seen due to diazepam-metronidazole interaction. The frequency of this clinical outcomes in our study were 8.7% and 2.2%, respectively. Interaction of salbutamol with carvedilol or propranolol may decrease the bronchodilator effect. Interaction of MCP with haloperidol, quetiapine, or trimetazidine may cause extrapyramidal symptoms. Interaction of ASA-dexketoprofen and enoxaparin-apixaban can cause decrease in cardioprotective effect and increase in anticoagulant effect, respectively. The frequency of this clinical outcomes predicted by databases in our study were 10.9%, 8.7% and 6.5%, respectively (Table V).

Discussion

The present study showed that the clinically significant pDDI (C, D, and X type), is high in MICU patients. In our study, we found clinically significant pDDI in 17.2% of patients with at least one interaction, in a total of 69.7% patients. The pDDI frequency we obtained in our study was found to be consistent with Reis et al[8]. In some studies, this frequency was found to be lower and much higher in others[9,10]. The reason for this contradictory may be geographical variation in the study population, the number of patients, studies designed with different ICUs (medical, cardiol-

Table IV. The most common D type pDDI in MICU patients (n = 117).

Interacting drugs	N (%)	Predicted clinical outcomes by databases
Drugs interacting with CNS agents: fentanyl – morphine, midazolam – remifentanil, hyoscine - tramadol, fentanyl – midazolam, midazolam – tramadol, tramadol – pheniramine, morphine – pheniramine, morphine – propofol, midazolam – CTM, fentanyl – CTM	67 (57.2)	Increase in CNS depressant effect, increase in efficacy
Drugs interacting with antithrombotic agents: enoxaparin – ASA, clopidogrel – enoxaparin	27 (23)	Increase in anticoagulant effect
Various drug interactions: posaconazole – pantoprazole, mPRED – rocuronium	19 (16.3)	Increase in efficacy, myopathy or neuropathy

CTM: clarithromycin, ASA: acetylsalicylic acid, mPRED: methylprednisolone.

Table V. Frequency of X type pDDI in MICU patients (n = 46).

Interacting drugs	N (%)	Predicted clinical outcomes by databases
Drugs interacting with potassium chloride: ipratropium, pheniramine, hyoscine, olanzapine, atropine, hydroxyzine, haloperidol, quetiapine	23 (69.8)	Ulcerogenic effect
Drugs interacting with antibacterials and/or antimycotics: CTM – posaconazole, CTM – amiodarone, quetiapine – posaconazole, levofloxacin – amiodarone, gemifloxacin – amiodarone, moxifloxacin – amiodarone, CTM – ibrutinib, tamsulosin – CTM, tamsulosin – posaconazole, diazepam – metronidazole	15 (32.6)	QTc prolonging effect, increase in efficacy, disulfiram like reaction
Drugs interacting with salbutamol: carvedilol, propranolol	5 (10.9)	Decrease in bronchodilatory effect
Drugs interacting with MCP: haloperidol, quetiapine, trimetazidine	4 (8.7)	Extrapyramidal symptoms
Drugs interacting with antithrombotic agents: ASA – dexketoprofen, enoxaparin - apixaban	3 (6.5)	Decrease in cardioprotective effect, increase in anticoagulant effect

CTM: clarithromycin, MCP: metoclopramide, ASA: acetylsalicylic acid.

ogy, neurology, etc.), drug interaction screening tools, administration of drugs that frequently cause pDDI, significant comorbidity, and polypharmacy.

In our study, the frequency of C, D and X type pDDI was found to be 65.3% with an average 5.59±5.53, 37.3% with an average 2.52±2.63, and 14.6% with an average 6.85±7.33, respectively. This finding was consistent with previous studies[4,10]. The high frequency of pDDI in ICU patients may be due to several reasons. The most important of these is polypharmacy. Since patients admitted to the ICU often have multiple and complex problems, polypharmacy can be applied[3,4]. In one of the previous studies, it was shown that the number of drugs used simultaneously and the risk of pDDI-related adverse reactions were linearly proportional[1]. In our study, we observed that 314 patients used 2820 drugs in total, and the average number of drugs per patient was 8.98±5.19. In previous studies, the average number of drugs per patient was found to be low or high[10,11]. The wide variation in the average number of prescribed drugs may be due to different ICUs and different comorbidities. In our study, statistically significant relationship was found between the number of ordered drugs and pDDI. We observed that there is no interaction mainly due to the use of less than 5 drugs, pDDI are observed in the use of 5 or more drugs, and pDDI increases as the number of drugs increases. In other words, polypharmacy can lead to drug interactions.

Significant comorbidity is another reason of high pDDI frequency[11]. In our study, statistical significance was found between the number of diagnoses and the number of ordered drugs. We observed that while patients with a single diagnosis were using less than 5 drugs, the number of drugs ordered increased as the number of diagnoses increased, that is, polypharmacy was applied. This supports the association of comorbidity with multidrug use and high pDDI potential, even without age factor. Based on this information, we can say that comorbidity leads to polypharmacy and polypharmacy leads to pDDI.

High numbers of comorbidities, such as CVD, endocrine disorders, CNS diseases and kidney diseases were significantly affected the frequency of pDDI in previous studies[12-15]. In present study, we observed that more than half of the patients (54.1%) had CVD. Patients had also a variety of diagnoses involved endocrine disorders, malignant, infection, and CNS diseases. Renal failure and liver failure were also detected in our study, which are important comorbidities that predispose to pharmacokinetic drug interactions. Each comorbidity requires its specific drug therapy, which leads to polypharmacy. Since concomitant used drugs affect each other at pharmacokinetic and pharmacodynamic levels, they cause serious adverse events, especially due to clinically important interactions. Unfortunately, even adhering to current guidelines while administering treatment does not prevent pDDI. Indeed, in a study conducted in the UK in 2015, the National

Institute of Health and Care Excellence (NICE) clinical guidelines for type 2 diabetes, heart failure, and depression were examined and serious pDDI were identified in these guidelines[16]. In the light of this information, we can say that if the clinical guideline for a single disease is insufficient on pDDI, serious and high number of pDDI are inevitable in patients with various comorbidities. Even patients with a single comorbidity should be followed up for clinically significant pDDI (C, D and X type), especially type X pDDI can have serious adverse life-threatening consequences.

According to the effects on the systems, the interaction was often with the CNS, cardiovascular system, and antithrombotic agents. This finding was consistent with previous studies[4]. In previous studies, it was determined that the most frequently interacting drugs were phenytoin, midazolam, dexamethasone, and enoxaparin[8,10,11,17]. In our study, the most frequently interacting drug was furosemide. Loop diuretic furosemide, which ranks 4th in terms of frequency of use, creates C type pDDI with the 5th most frequently used beta-adrenoceptor agonist salbutamol, causing an increase in the hypokalemic effect, which is the clinical outcome predicted by databases[18]. X type pDDI, whose concomitant use is contraindicated, was most frequently seen between ipratropium and potassium chloride, used in the 7th and 9th frequencies, respectively. The clinical outcome predicted by databases due to this drug combination is ulcerogenic effect[19]. Ipratropium, an anticholinergic agent and quaternary ammonium derivative of atropine, is used in respiratory diseases accompanied by bronchospasm due to its bronchodilator effect[20]. The drug it interacts with is potassium chloride, which is used in the treatment of hypokalemia. In blood analysis results, hypokalemia was seen in only 19.1% of patients. Hypokalemia is likely due to the interaction of furosemide with salbutamol or mPRED (C type pDDI) according to clinical outcomes predicted by databases. Due to the critical condition of ICU patients, respiratory distress and electrolyte dysbalance are frequently seen, and these drugs are frequently used. Other drugs that were contraindicated to use together with potassium chloride were pheniramine, hyoscine, olanzapine, atropine, hydroxyzine, haloperidol, and quetiapine, since they have the potential to have an ulcerogenic effect according to clinical outcomes predicted by databases.

In our study, X type pDDI was seen with the second frequency in drugs interacting with antibacterials and/or antimycotics. The clinical outcome predicted by databases due to CTM-posaconazole, CTM-amiodarone, quetiapine-posaconazole, levofloxacin-amiodarone, moxifloxacin-amiodarone combinations is QTc prolonging effect[21]. The clinical outcome predicted by databases due to CTM-ibrutinib, tamsulosin- CTM and tamsulosin-posaconazole combinations is increase in efficacy[22]. CTM and posaconazole strongly inhibit CYP3A4, an enzyme responsible for the metabolism of ibrutinib and tamsulosin, increasing the serum concentration of these drugs. Concomitant use of metronidazole with diazepam, containing propylene glycol may lead to a disulfiram like reaction according to clinical outcomes predicted by databases. In addition to diazepam, drugs such as digoxin, etomidate, lorazepam, pentobarbital, phenobarbital, phenytoin, and sulfamethoxazole have also been associated with similar pDDI since they contain propylene glycol[23]. According to the clinical results predicted by the databases, concomitant use of drugs that affect beta adrenoreceptors was associated with a decrease in bronchodilator effect, use of drugs that interact with prokinetics was associated with extrapyramidal symptoms, and use of drugs that interact with antithrombotic agents were associated with decreased cardioprotective effect and increased anticoagulant effect[24-26]. These combinations should be avoided as the interactions of these drugs are type X and the harm to the patient outweighs the potential benefit.

Conclusions

While current treatment guidelines of diseases are insufficient in terms of pDDI, it may be difficult to avoid concomitant use of drugs that cause clinically significant pDDI, as ICU patients with at least one comorbidity are critically ill. Monitoring daily treatments for pDDI and updating treatment in line with reports will prevent and/or reduce pDDI-related adverse reactions and their clinical consequences.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Financial support and Sponsorhip
This article was funded by researchers.

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