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Evaluation of potential drug-drug interactions in intensive care unit

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Abstract. – OBJECTIVE: Potential drug-drug interactions (pDDIs) and adverse drug reactions (ADRs) may be frequently observed in critically ill patients because of multiple drug use. It is important to identify pDDIs before their progression to ADRs. This study aimed to determine the prevalence and effect of pDDIs and possible ADRs in intensive care patients.

PATIENTS AND METHODS: In this retrospective cross-sectional study, the medical records of patients in the intensive care unit (ICU) of Bursa Uludag University Faculty of Medicine Hospital between January 1, 2018, and December 31, 2018, were examined. Medication orders were recorded on days 2, 5, and 10. pDDIs, defined using the lexi-interact (UpToDate, 2020), were classified based on the significance level.

RESULTS: A total of 144 patients were included in this study, and from the 395 medication orders, 1,776 had pDDIs. Of these interactions, 23.5% were major (n = 418), 71.4% were moderate (n = 1268), and 5.1% (n = 90) were minor. The majority of patients (96.9%) had at least one pDDI. There was a strong correlation between the number of drugs on days 2, 5, and 10 and the number of pDDIs ($p < 0.001$, $\rho = 0.7$; $p < 0.001$, $\rho = 0.72$; $p < 0.001$, $\rho = 0.73$, respectively). No significant correlation was found among the number of pDDIs, the APACHE II score, and the duration of ICU stay.

CONCLUSIONS: The prevalence of pDDIs was high and there was a strong correlation between the number of drugs and pDDIs. Detection of potential interactions through clinical decision support systems and checker tools should be used to increase patient safety.

Key Words:
Potential drug-drug interactions, Adverse drug reaction, Intensive care.

Introduction

Drug-drug interactions (DDIs) are defined by an increase in the anticipated or unexpected effects of a medication, caused by the concomitant use of multiple drugs[1,2]. These effects may result in therapeutic failure or life-threatening clinical adverse drug reactions (ADRs), which pose significant patient safety risks. A potential DDI (pDDI) is defined as database identified DDIs, which could potentially lead to ADR[3].

Pharmacokinetic and pharmacodynamic drug properties such as low therapeutic index, steep dose-response curve, high first-pass metabolism, and single mechanism of elimination are all factors that increase the risk of DDIs and ADRs. The most significant factors, however, are chronic diseases, especially renal failure, multidrug use, and advanced age[4-8].

Considering the coexistence of numerous factors in intensive care unit (ICU) patients that directly affect drug pharmacology, such as malabsorption, decreased metabolism, renal failure, and multidrug use, the prevalence of pDDI is expected to be high[9]. Furthermore, ADRs caused by pDDI are associated with increased morbidity and mortality, prolonged ICU stay, and increased costs in these patients[10,11].

In order to prevent ADRs, pDDIs should be determined and patients' medication orders should be reviewed. However, since there are considerable variations in the use of clinical decision support systems (CDSS) and interaction checker tools to identify pDDI in the literature, a significant difference in the methodology has been observed. Therefore, the prevalence of pDDIs and associated ADRs is expected to vary greatly[12,13].

The aim of this study was to determine the prevalence of pDDIs in our ICU patients and to examine their effect, as well as possible ADRs on the duration of ICU stay. Furthermore, we aimed to increase awareness by identifying the most frequently interacting drug pairs and discussing the clinical importance of pDDI and associated ADRs for intensive care.

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Patients and Methods

In this retrospective cross-sectional study, the medical records of patients in the ICU of the Anesthesiology and Reanimation Department of the Bursa Uludağ University, Faculty of Medicine between January 1, 2018, and December 31, 2018, were analyzed. Ethical approval was obtained from the Uludag University Institutional Ethic Committee Number: 2011-KAEK-26/134. A total of 254 files were initially examined and patients who were < 18 years of age, had an ICU stay of < 5 days, and had a medication order of < 5 drugs were excluded from this study (Figure 1).

The demographic characteristics, Acute Physiology and Chronic Health Evaluation (APACHE) II score, duration of ICU stay, and survival data on day 14 were collected through the electronic hospital registration system (MIA-MED, Hospital Information Management System, version 1.01.3760). Medication orders on days 2, 5, and 10 (if the patient had an ICU stay of > 10 days and the number of drugs was ≥ 5 on study day) were recorded. pDDIs, defined using the lexi-interact (a free online interaction checker, provided from UpToDate, 2020, https://www.uptodate.com/drug-interactions), were classified based on the significance of the interaction level (minor, moderate, major). According to risk rating of this interaction checker program the drug pairs whose combination is not usually recommended, or is contraindicated, were identified. Possible ADRs of the most commonly used drug pairs also given.

Statistical Analysis

The normal distribution of numerical variables was evaluated using the Shapiro-Wilk test. Since the number of drugs, pDDIs, APACHE II score, and the length of ICU stay were not normally distributed, they were presented as median and interquartile range (Q1-Q3). The demographic characteristics were shown as frequency (n) and percentage (%). The comparison between medication orders was made using the Friedman test, and if a significant difference was detected, pairwise comparisons were made using the Wilcoxon signed-rank test, with Bonferroni correction applied to the *p*-value. The correlation among the number of drugs, DDIs, APACHE II score, and the duration of ICU stay was evaluated using Spearman's correlation analysis. Statistical significance was set at a *p*-value of < 0.05. Data were analyzed using SPSS version 23.0 (IBM Corp., Armonk, New York, NY, USA).

Results

A total of 144 patients were included in this study. The median age of the patients was 58.5

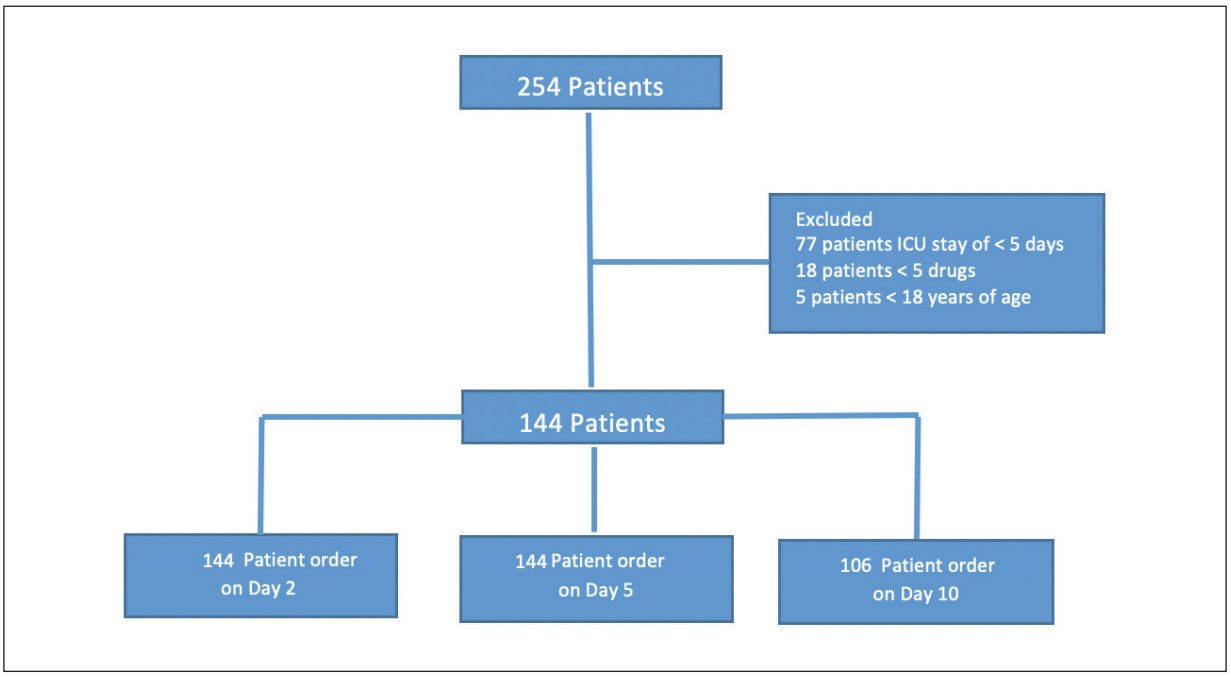

Figure 1. Flow diagram.

Table I. The severity category (major and moderate) and the number of drugs in patients' medication orders on Days 2, 5 and 10 in intensive care unit.

Order	Day 2 n = 144	Day 5 n = 144	Day 10 n = 106	*p*-value
Median number of drugs, median (IQR)	8 (3)[a]	9 (4)[a,b]	9 (4)[b]	< 0.0167*
Number of pDDI, median (IQR)	3 (5)	3 (5)	4 (6)	0.546
Number of major pDDI, median (IQR)	1 (2)	2 (3)	2 (4)	0.564
Number of moderate pDDI, median (IQR)	2 (4)	2 (4)	2 (4)	0.052

*p-value was corrected by Bonferroni correction. $p < 0.0167$ was considered statistically significant.

years (36-70), and 40.3% (n = 58) were female. The median APACHE II score and duration of ICU stay were 18 (14-27) and 18 days (10-33), respectively. ICU mortality on day 14 was 14.4%. Out of the 395 medication orders, 1,776 were shown to have pDDIs. Of these interactions, 418 (23.5%) were major, 1268 (71.4%) were moderate and 90 (5.1%) were minor. Furthermore, 96.9% of the patients had at least one pDDI.

There was a strong correlation between the number of drugs on days 2, 5, and 10 and the number of pDDIs ($p < 0.001$, $p = 0.7$; $p < 0.001$, $p = 0.72$; $p < 0.001$, $p = 0.73$, respectively). The number of drugs on days 5 and 10 was significantly higher than that of day 2 ($p = 0.009$ and $p = 0.011$, respectively). No statistically significant difference was found between the number of drugs on days 5 and 10 ($p = 0.942$). Moreover, no statistically significant difference was found between pDDI subcategories (major and moderate) and medication orders given during that time (Table I).

A total of 538 different drug pairs were identified, the most common of which involved those acting on the central nervous system (CNS) [fentanyl (Topkapı, İstanbul, Turkey) and midazolam (Pendik, İstanbul, Turkey)], vasoactive agents [(adrenaline (Pendik, İstanbul, Turkey) and noradrenaline (Brussels, Belgium)], antibiotics [(clarithromycin (Gebze, Kocaeli, Turkey)], antifungals [(fluconazole (Ortaköy, İstanbul, Turkey)], anti-thrombotics [(acethylsalicylic acid (Zeytinburnu, İstanbul, Turkey)] and anticoagulants [enoxaparin (Le Trait, France)]. Table II lists the unique drug pairs and their prescription frequency.

Although there was a significant correlation between the number of drugs on days 2, 5, and the APACHE II score, the correlation coefficients were considerably low ($p = 0.011$, r = 0.19; $p = 0.018$, r = 0.21, respectively). There was no significant correlation between the number of pDDIs, the APACHE II score, and the duration of ICU stay (Table III).

Overall, among drug pairs identified with pDDI, eight were known to have contraindicated interactions (CI) and were prescribed 16 times to 10 different patients. Five (50.0%) of these patients were discharged from the ICU and the remaining five died. Interacting drug pairs are mostly ones that act on the CNS and the cardiovascular system (CVS) and are used by patients for prolonged

Table II. The most frequently prescribed drug pairs with pDDI and their mechanism of interaction.

Interacting drugs	Prescription frequency	Severity category	Mechanism of action
Fentanyl-Midazolam	31	Major	Increases CNS depression
Dopamine-Noradrenaline	24	Moderate	Increases blood pressure and heart rate
Adrenaline-Noradrenaline	14	Moderate	Increases blood pressure and heart rate
Fentanyl-Fluconazole	15	Moderate	Increases serum concentration of fentanyl
Acetylsalicylic acid-Enoxaparin	15	Moderate	Increases anti-coagulant effect
Midazolam-Morphine	14	Major	Increases CNS depression
Adrenaline-Dopamine	14	Moderate	Increases blood pressure and heart rate
Fluconazole-Midazolam	11	Moderate	Increases serum concentration of midazolam
N-acetyl cysteine- NTG	11	Minor	Increases the vasodilator effect of NTG
Furosemide-Morphine	10	Moderate	Reduces therapeutic effect of furosemide
Clarithromycin–Midazolam	10	Major	Increases serum concentration of midazolam

CSN: central nervous system; NTG: nitroglycerine; pDDI: potential drug-drug interactions.

Table III. Correlation of pDDIs and the number of drugs in patients' medication orders on Days 2, 5 and 10 with APACHE II score and the duration of ICU stay.

	Day 2 (n = 144)				Day 5 (n = 144)				Day 10 (n = 106)			
	N. of drugs		N. of interaction		N. of drugs		N. of interaction		N. of drugs		N. of interaction	
	r	p	r	p	r	p	r	p	r	p	r	p
APACHE II score	0.2	0.018	0.070	0.402	0.210	0.011	0.064	0.448	0.133	0.176	0.027	0.780
Day of ICU stay	0.142	0.091	0.163	0.051	0.106	0.208	0.142	009	0.067	0.491	0.013	0.091

pDDI: potential drug–drug interactions; APACHE: acute physiology and chronic health evaluation; ICU: intensive care unit.

periods of time due to their comorbidities. These drugs and their mechanisms of action have been shown in Table IV.

Discussion

The results of this study found that the overwhelming majority of patients had at least one pDDI. There was a strong correlation between the number of drugs on days 2, 5, and 10 and the number of pDDIs. No significant correlation was found among the number of pDDIs, the APACHE II score, and the duration of ICU stay.

In our study, the prevalence of pDDIs in ICU patients was found to be 96.9%, which is the highest reported rate in the literature[2]. This may be due to the inclusion criteria of our study (patients prescribed ≥ 5 drugs and an ICU stay of ≥ 5 days) that was chosen to establish the relationship between pDDIs, polypharmacy, and evaluate duplicate medication orders in the same patient. We observed that other studies[14,15] reporting high pDDI prevalence rates included patients with a large number of prescribed drugs or with an ICU duration of stay of > 3 days. However, the study by Rodrigues et al[3] reported a high prevalence of pDDIs (89%) despite the fewer number of drugs (≥ 2) and the absence of criteria for prolonged hospitalization. Nevertheless, that study was conducted in an ICU where the FAST HUG protocol which is a mnemonic used to facilitate the continuous monitoring of patients in relation to: feeding; analgesia; sedation; thromboembolic prophylaxis; head-of-bed elevation; stress ulcer prophylaxis; and glycaemic control was routinely used. So, this has caused the continuous repetition of similar drug pairs with each order, illustrated by the 132-time prescription of dipyrone-enoxaparin drug pair. In our study, with the prediction that at least five drugs would be administered in accordance with the FAST HUG protocol, we attempted to prevent certain repetitions by including patients with a higher number of drugs on their medication order. In our study, we observed that the most frequently prescribed drug pair was 31 times in 144 patients. Therefore, we consider that our study was conducted with an approach that better reflects the general condition and more accurately examines the correlation between polypharmacy and pDDIs.

Our study reported a strong correlation between the number of drugs and pDDIs, which was consistent with the literature[2]. This demon-

Table IV. Contraindicated drug pairs in the patients' medication orders and their mechanism of interaction.

Contraindicated drugs	Mechanism of interaction
Desmopressin-Methylprednisolone	Induces hyponatraemia
Doxazosinmesylate-Tamsulosin	Increases anti-hypertensive effect
Salbutamol-Carvedilol	Reduces bronchodilator effect
Silodosin-Voricanozol	Increases the serum concentration of silodosin
Rasagiline-Fentanyl	Serotonergic syndrome may develop
Linezolid-Levodopa	Increases the toxic effect of MAO inhibitors
Rasagiline-Linezolid	Increases serotonergic effect
Amiodarone-Levofloxacin	Causes prolonged QT

MAO: monoamine oxidase inhibitor.

strates that polypharmacy is directly associated with pDDIs and is one of the important risk factors for patients in ICUs. However, we did not detect a significant difference between the number of detected pDDIs on days 2 and 5 despite the increased number of drugs on prolonged hospitalization days. Similarly, we did not find any significant correlation among the number of pDDIs, the duration of ICU stay, and the APACHE II score (a predictor of mortality in the ICU), which contradicts the literature[10-16]. Although Moura et al[11] found a significant correlation among these parameters in their study, this may have been due to the confounding effect of the high Charlson comorbidity index, as they have stated. In addition, a scoring scale indicating the severity of disease was not used by Hasnain et al[10], and the clinical picture of an acute illness was not accounted for, despite it being a confounding factor that is expected to prolong the duration of ICU stay. Moreover, the authors examined the medication order for pDDIs on the first day, the last day, and the median day of ICU hospitalization, and then evaluated the relationship with the duration of ICU stay. However, in reality, each medication order was evaluated on a different day, as the median hospitalization duration and the last day of hospitalization vary from one patient to another. These differences raise concerns about whether the duration of ICU stay constitutes a risk for pDDIs and supports the possibility that more drugs are prescribed to patients because of the severity of acute diseases. Thus, pDDIs may be observed simply due to polypharmacy. pDDIs appear to be a consequence rather than a cause in ICU patients, however, accurate conclusions cannot be made on the cause-and-effect relation due to the limited number of studies[10,11,16].

Although studies[3,13] have reported on the major pDDIs more frequently, the most common subgroup was the moderate one in our study, which is consistent with the majority of the literature[3,11,12,14,17,18]. This difference is caused by CDSS and interaction checker tools based on different databases used to detect pDDIs. Therefore, we consider that more consistent and reliable results can be obtained from future studies using similar methodologies.

In the ICUs, physicians often combine drugs to benefit from pDDIs. When we examine the drug pairs identified as pDDI in our study, it is evident that the primary purpose of using fentanyl-midazolam is to increase the depressant effect on the CNS. Because critically ill patients are constantly followed up, physicians can monitor and treat the adverse effects of overdosage. Although physicians are aware that drug-specific ADRs can happen, it is quite difficult to determine both theoretically and practically whether this is caused by the interaction of drug pairs in critically ill patients. Therefore, we consider that the development and utilization of specific scoring protocols that allow the determination of whether ADRs are caused by pDDIs are needed, and the conduction of studies using these protocols will likely yield more reliable results[19].

In our study, we found that CI drug pairs were prescribed to 10 patients. We are unable to comment on the severity and the impact on pDDIs, ICU length of stay, and mortality because of the low prevalence. Severity was similar among patients with prolonged hospitalizations. The CI drug pairs with major interactions were CNS, CVS, and antibiotic medications. Therefore, we believe that medications administered by primary physicians in the ICU and those used for chronic disease management should be checked for CIs using a CDSS or an interaction checker tool to increase patient safety.

The most significant limitation of our study is due to its retrospective nature. The prevalence of ADRs in clinical setting showing the clinical importance of pDDIs was not identified. A prospective study by Bertsche et al[15] has reported that the prevalence of ADRs is 44%. However, the authors did not provide details on the approach used to distinguish ADRs caused by pDDIs and ADRs caused by the drugs alone. This is particularly important because the metabolic changes of acute illnesses in critically ill patients can lead to either overdosage or insufficiency.

Conclusions

This study found that the prevalence of pDDIs in ICU patients was high. Since the drugs used in the acute and chronic setting can vary considerably, clinicians should be aware of their effects and pDDIs. Moreover, the manifestation of ADRs should be differentiated from the clinical course of acute diseases, and CDSS or an interaction checker tool should be used when necessary. Future studies should focus on examining the cause-and-effect relationship between the duration of ICU stay and pDDIs.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Declaration of Funding Interests

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