Turk J Intensive Care
DOI: 10.4274/tybd.galenos.2022.32932

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Potential Drug-drug Interactions in Intensive Care Units in Turkey: A Point Prevalence Study

Türkiye'deki Yoğun Bakımlarda Potansiyel İlaç-ilaç Etkileşimlerinin Değerlendirilmesi: Nokta Prevalans Çalışması

Received/Geliş Tarihi : 12.05.2022
Accepted/Kabul Tarihi : 22.08.2022

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ABSTRACT *Objective:* Drug-drug interaction (DDI) is associated with complications and decreased effectiveness of drugs during treatment. Intensive care units (ICU) involve patients who are at high risk of potential drug-drug interactions (pDDI).
Materials and Methods: Here, we identified potential DDIs in similar patient groups in ICUs in Turkey. Invitations were sent to 20 hospitals in Turkey for a multicenter point prevalence study. Patient orders were determined for potential DDI using the Lexi Interact Online Interaction Checker software. Of 236 patients whose data were collected, patients <18 years of age, those <5 drugs in their drug order, and those with incomplete data were excluded. The remaining 194 patients were included in the study.
Results: A total 684 pDDIs were detected, of which 92 (13.4%) were major, 531 (77.6%) were moderate, and 61 (9%) were minor interactions. There was at least one drug interaction in 159 (81.9%) patients. There was a significant difference between the number of drugs in the 159 patients with drug interactions and those in the 36 patients without drug interactions (p<0.001). A significant correlation was found between the number of drugs and the number of interactions in patients with drug interactions (p<0.001. r=0.707).
Conclusion: No significant correlation was found between the length of stay in ICU and the number of drugs or the number of drug interactions (p=0.216, r=0.092; p=0.284, r=-0.080, respectively). The increased risk of pDDI due to the use of multiple drugs was observed in critically ill patients.
Keywords: Drug interactions, Intensive care unit, Adverse drug reactions

ÖZ*Amaç:* İlaç-ilaç etkileşimi (DDI), birden fazla ilacın birlikte kullanımıyla ortaya çıkan, advers ilaç reaksiyonlarından (ADR) olup, ilaçların tedavideki etkinliğinin azalması ve komplikasyonlarla ilişkilidir1,2. Yoğun bakım ünitesi (YBÜ) hastalarında çoklu ilaç kullanımı potansiyel DDI açısından bu hastaları risk grubu haline getirmektedir3-8. Çalışmamızda, ülkemizdeki farklı yoğun bakımlarında benzer hasta gruplarındaki pDDI'ları belirlemek istedik.
Gereç ve Yöntem: Bu çalışma Türkiye'deki yoğun bakımda yatan kritik hastalarda çok merkezli nokta prevalans çalışması olarak tasarlanmıştır. Hasta orderları 'Lexi interact online interaction checker program (https: //www.uptodate.com/drug-interactions) ile pDDI açısından analiz edildi.
Bulgular: 236 hasta verisi içinden Yaş <18 ve ilaç orderlarındaki ilaç sayı kriteri <5 veya verisi eksik doldurulan hastalar çalışma dışı bırakıldığında 194 hasta çalışmaya dahil edildi. 684 tane pDDI saptanmış olup bunların 92 (%13,4) tanesi major, 531 (%77,6) tanesi moderate, 61 (%9) tanesi minör etkileşim idi. 159 (%81.9) hastada en az bir tane ilaç etkileşimi mevcuttu. İlaç etkileşimi olan hastalar ile (159 hasta) olmayan 36 hastanın ilaç sayıları arasında anlamlı düzeyde fark mevcuttu (p<0,001). İlaç etkileşimi saptanan hasta grubunda ilaç sayıları ile etkileşim sayıları arasında yüksek düzeyde anlamlı korelasyon saptandı (p<0.001 r=0.707). İlaç sayısı ve ilaç etkileşim sayıları ile yoğun bakım yatış süresi arasında anlamlı düzeyde bir korelasyon saptanmamıştır (p=0.216 r=0,092; p=0,284 r=-0.080, sırasıyla).
Sonuç: Bu çalışma ile benzer YBÜ'lerdeki kritik hastalarda çoklu ilaç kullanımına bağlı pDDI görülme riskinin arttığı görülmüştür. Saptanan pDDI'ların çoğunluğunu orta düzeyde etkileşimler oluşturmakla beraber bu etkileşimlerin önceden saptanması hasta güvenliğini artırıcı nitelikte olabilir.
Anahtar Kelimeler: İlaç etkileşimleri, yoğun bakım, advers ilaç reaksiyonları

Introduction

Drug-drug interactions are adverse drug reactions (ADR) that occur due to the combined use of more than one drug. They result in effects other than the expected drug effects. This situation is associated with complications and a decreased effectiveness of drugs in treatment (1,2). Conditions that occur due to drug interactions other than ADRs are called potential drug-drug interactions (pDDI).

Patients in intensive care units (ICUs) have been believed to comprise the risk group for pDDI due to multiple drug use and alterations in drug metabolism (3-8). There is evidence that this situation increases morbidity and increases treatment costs by prolonging stay in the ICU (9-11). Therefore, it is important to detect pDDIs and take precautions in patients under intensive care.

Due to variation in the databases used to detect the pDDIs, several reports on the prevalence of different pDDIs are available. In addition, apart from the differences in the intensive care population studied here (such as surgical/medical intensive care or transplant patients), drug use habits and intensive care levels are other factors that cause variable pDDIs (10,12-14).

In the present study, we aimed to determine pDDIs in similar patient groups from different intensive care units in Turkey. We also aimed to identify the most frequently interacting drug pairs and further discuss the importance of these interactions.

Materials and Methods

This study was carried out between January and February 2021 after receiving the approval of the ethics committee of Bursa High Specialization Training and Research Hospital numbered 2011-KAEK-25 1029/04-10 and the approval of the ethics committees of the participating hospitals responding to the invitation. This study was designed as a multicenter point prevalence study in critically ill patients under intensive care in Turkey. Twenty hospitals with multidisciplinary intensive care units and intensive care sub-branch specialists were invited for the study. Due to the observational nature of the study, patient informed consent form was not obtained. A study chart was created, and it included the following information: patients' age, sex, comorbidities, diagnosis at intensive care hospitalization, acute physiology and chronic health evaluation II (APACHE II), study day sequential organ failure assessment (SOFA) scores, ordered drugs and their numbers, drug doses and drug administration routes, and length of stay in the intensive care unit. This chart was sent to the physicians responsible for patient treatment in the general intensive care unit of the relevant hospital by e-mail. On the day after the e-mail was sent, the charts containing the single day information were requested for each patient and were subsequently collected by e-mail every day and the data were computerized. The orders of patients in the chart were analyzed for pDDI using the Lexi Interact Online Interaction Checker software program (https://www.uptodate.com/drug-interactions). Nutritional support, electrolyte replacements, and vitamins were excluded from the analysis. Detected interactions were classified on the basis of severity and risk rating. Severity was defined as major/moderate/minor interaction, and Risk Rating as X: avoid the combination, D: consider treatment change, C: monitor the treatment, and B: no change needed.

Statistical Analysis

Statistical analyses in this study were performed using the IBM SPSS statistics 20.0 (IBM Corp., Armonk, New York, USA) software package. For the evaluation of the data, in addition to descriptive statistical methods (median, interquartile range), the distribution of variables was checked using the Shapiro-Wilk test. Intergroup comparisons of non-normally distributed variables were made using the Mann-Whitney U test. Spearman correlation test was further used to determine the relations of variables with each other. The results were evaluated according to a significance level of $p<0.05$.

Results

Requests for participation were sent to 20 hospitals and 10 positive responses were received. Data of a total of 236 patients were collected from these 10 hospitals. The patients who were <18 years of age, those with <5 drugs in their drug orders, or those whose data were filled incompletely were excluded from the study. The remaining 194 were included in the study. While 103 (53.1%) of the patients were male, their median age was determined to be 69.5 years (59-78) (Table 1).

The number of pDDIs detected in the patient orders were 684; of which 92 (13.4%) were major, 531 (77.6%) were moderate, and 61 (9%) were minor interactions (Figure 1). There was at least one drug interaction present in 159 (81.9%) patients. According to risk the rating, the number of

Table 1. Demographical data	
	Median (Q1-Q3) n=194
Age (year)	69.5 (59-78.25)
Gender (male) n (%)	103 (%53.1)
APACHE II	22 (14-28)
SOFA	5 (3-8)
Length of stay (days)	11 (5-22)
Number of drugs (n)	8 (7-10)
Number of intereaction (n)	2 (1-5)

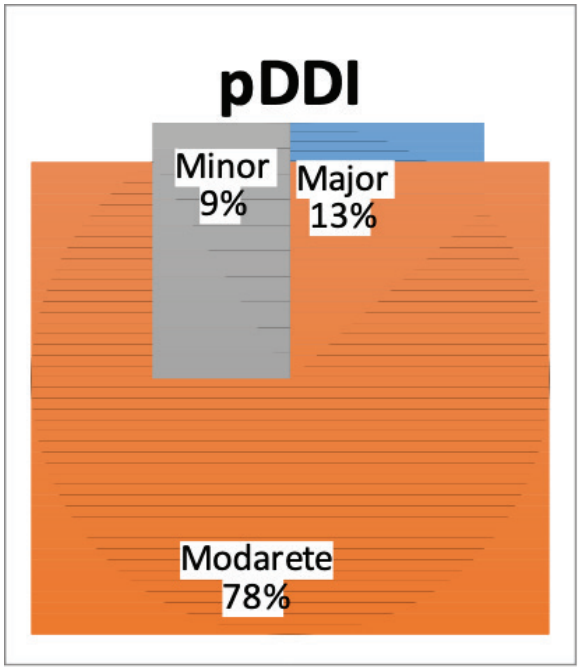

Figure 1. Distribution of detected pDDIs by severity category

patients under category X was determined to be 10 (1.5%); category D had 166 (24.3%), category C had 444 (64.9%), and category B had 64 (9.3%) patients.

There was a significant difference between the number of drugs in the 159 patients with drug interactions and those in the 36 patients without drug interactions (p<0.001). There was no difference between the age, APACHE II, and SOFA scores of these two patient groups and their ICU hospitalization days (p=0.831, p=0.918, p=0.087, p=0.253, respectively) (Table 2).

A significant positive correlation was found between the number of drugs and the number of interactions in the patient group with drug interactions (p<0.001, r=0.707).

In the patient group with drug interaction, there was no significant correlation between the number of drug interactions and the APACHE II or SOFA scores (p=0.937, r=0.006; p=0.910, r=0.008, respectively); however, there was a weak significant correlation between the SOFA score and major drug interactions (p=0.024 r=0.167). A moderate level significant correlation was found between the number of interactions and the number of major drug interactions (p<0.001, r=0.574).

Table 2. Comparison of age, APACHE II, SOFA score, intensive care hospitalization day and number of drugs in the order of patients with and without pDDI			
	Patients without pDDI n=35	Patients with pDDI n=158	p-value
Age (year)	68 (55-78)	70 (59-79)	0.831
APACHE II	22 (14-28)	21.5 (14-28)	0.918
SOFA	6.5 (4-9.5)	5 (3-8)	0.087
Hospitalization day	17 (5-24)	11 (5-21)	0.253
Number of drugs	6 (5-7)	9 (7-10.2)	<0.001
Mann-Whitney U test was used. A value of p<0.05 was considered significant			

No significant correlation was observed between the length of stay in the intensive care unit and the number of drugs or the number of drug interactions (p=0.216, r=0.092; p=0.284, r=-0.080, respectively). A weak correlation was found between the APACHE II score and the length of stay in the intensive care unit (p=0.036, r=0.256).

Among drug interactions, acetylsalicylic acid-enoxaparin (44 times), enoxaparin-clopidogrel (20 times), furosemide-methylprednisolone (19 times), and furosemide-acetylsalicylic acid (19 times) pairs were observed most frequently (Table 3 and Table 4).

Discussion

Our study showed that most of the critically ill patients (81.9%) were exposed to pDDI when their drug orders were reviewed on any day during their ICU hospitalization. As the number of drugs were increased, the number of drug interactions also increased. However, statistically significant relationship was not observed between the length of stay in the intensive care unit and the number of drugs or the number of drug interactions.

Based on literature reports, the prevalence of pDDI in intensive care patients varies considerably. In their studies, Abarca et al. (16) and Vanham et al. (13) have reported that the compatibility of databases used for pDDI detection was

very low. Acharya et al. (10) had also used the same Lexicomp Interaction Checker software program and reported similar pDDI prevalence. In the same study, similar rates of severity category and risk rating have been reported. The prevalence differences observed in the literature may be due to the data bank used or may arise from the different drug use habits of patient groups or their physicians. In order to mitigate this effect, similar ICUs were invited to our study and attempts were made to reduce such differences.

Many studies have demonstrated that pDDIs increase with the increase in the number of drugs used (7,8,10,17). Likewise, we found a high level of correlation (r=0.707) between the two conditions in our study. This high correlation reveals the necessity of checking the prescribed drug orders with respect to pDDIs.

When we consider the recommended risk rating for interacting drug pairs, we observe that the 'category C: monitor therapy' is the most common. In this category, a follow-up is recommended to monitor potential effects without making a change in the treatment. Such follow-up for effects was included in the daily routine follow-up of most critically ill patients (18). As an example, the effect furosemide-methylprednisolone interaction was evident from the hypokalemia-inducing effect of furosemide. In routine biochemistry or arterial blood gas analyses of intensive care patients, routine follow-up of the interaction with electrolyte monitoring and treatment can protect patients from the effects of pDDIs of such electrolytes.

In our study, we determined that the most frequently interacting drug pair was acetylsalicylic acid-enoxaparin. We believe that prolonged intensive care hospitalization after Covid-19 has caused this situation. The most common drug pairs reported in the literature are also quite variable, probably due to difference in drug availability among countries, drug use habits, and different patient groups (4,12,15,19). For example, in their study with renal transplantation patients, Amkreuts et al. (12) have reported the most frequently interacting drug pair to be tacrolimus-prednisolone, which causes an immunosuppressive effect. Also, Rodrigues et al. (15) have reported the most frequently interacting drug pair

Table 3. The most common pDDI and risk rating categories

pDDI	Frequency	
	n	%
Contraindicated		
Quetiapine-ipratropium	5	50%
D		
Consider therapy modification		
Acetylsalicylic acid -enoxaparin	44	26.5%
Enoxaparin-clopidogrel	20	12%
Enoxaparin-piracetam	9	5.4%
Clopidogrel-omeprazole	8	4.8%
Fentanyl-midazolam	7	4.2%
C		
Monitor therapy		
Acetylsalicylic acid-furosemide	19	4.3%
Fentanyl-furosemide	15	3.4%
Acetylsalicylic acid-clopidogrel	13	2.9%
Clopidogrel-pantoprazole	13	2.9%
Furosemide-methylprednisolone	11	2.5%
Amlodipine-doxazosine	11	2.5%
B		
No action needed		
Pantoprazole-levothyroxine	10	15.6%
Atorvastatin-amlodipine	5	7.8%
Atorvastatin-clopidogrel	5	7.8%

Table 4. The interaction mechanisms of the most frequently interacting drug pairs

Most frequent drug pairs	Risk cathegory	Mechanism of action
Acetylsalicyclic acid/enoxaparin	Moderate (D)	Enhance the anticoagulant effect
Enoxaparin/clopidogrel	Moderate (D)	Enhance the anticoagulant effect
Acetylsalicyclic acid/Furosemide	Moderate (C)	Enhance the anticoagulant effect
Fentanyl/furosemide	Moderate (C)	Opioids may diminish the effects of diüretics
Acetylsalicyclic acid/clopidogrel	Moderate (C)	Enhance the anticoagulant effect
Clopidogrel/pantaprozole	Major (C)	Pantoprazole may decrease serum concentrations of the active metabolite(s) of Clopidogrel
Furodemide/ methylprednisolone	Moderate (C)	Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics
Amlodipine/doxazosin	Moderate (C)	Alpha1-Blockers may enhance the hypotensive effect of Calcium Channel Blockers
Enoxaparin/piracetam	Moderate (D)	Enhance the anticoagulant effect

is enoxaparin-dipyrone. However, dipyrone is not available in every country.

Unlike literature reports, we were not able to determine a positive relationship between the length of stay in the intensive care unit and the number of drugs or the number of interactions (9,10,20). As the duration of hospital stay corresponding to working days would not reflect the total length of stay in the ICU, such results were already expected. However, the fact that there the results of APACHE II, SOFA, and the number of drugs of were not different between the groups with and without drug interactions and that no differences were found in the numbers of days of hospitalization among the two groups suggests that the length of stay in ICU is likely not be prolonged with increased numbers of pDDIs, which is inconsistent with the literature (9,10,20). Nevertheless, the moderate correlation found between the SOFA score and major drug interactions indicates that increases in the severity of the disease result in the possibility of more drugs being prescribed. This increases the possibility of pDDI occurrence and prolongation of the hospital stay.

The most important limitation of our study is that pDDI-related ADR could not be examined. Moreover, considering hospitalization duration based on working days to derive the total length of stay in the ICU constitutes another limitation of this study, as this duration did not reflect the actual total length of stay in the ICU.

Conclusion

In this study, the risk of pDDI due to disease severity and simultaneous use of multiple drugs was observed to increase in patients in similar ICUs. Although the majority of pDDIs detected consist of moderate-level interactions, the early detection of these interactions may reduce pDDI risk in patients.

Ethics

Ethics Committee Approval: This study was carried out between January and February 2021 after receiving the approval of the Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital numbered 2011-KAEK-25 1029/04-10 and the approval of the ethics committees of the participating hospitals responding to the invitation.

Informed Consent: Due to the observational nature of the study, patient informed consent form was not obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.G., M.Ş.D., İ.C., N.K.G., Design: M.Ş.D., İ.C., N.K.G., Data Collection and Process: D.G., M.Ş.D., Analysis or Interpretation: D.G., M.Ş.D., İ.C., N.K.G., Literature Search: D.G., Writing: D.G., M.Ş.D., İ.C., N.K.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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