Turk J Intensive Care 2023;21:93-9
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 related with complications and diminished efficacy of medications throughout the treatment process. Intensive care units (ICU) involve patients who are at elevated 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. A notable disparity was observed in the quantity of drugs in the 159 patients with drug interactions and those in the 36 patients without drug interactions (p<0.001). A substantial correlation was detected between the quantity of medications and the incidence of interactions among patients experiencing 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 ICU patients.
**Keywords:** Drug interactions, intensive care unit, adverse drug reactions

**ÖZ** *Amaç:* İlaç-ilaç etkileşimi (İİE), birden fazla ilacın birlikte kullanımıyla ortaya çıkan, advers ilaç reaksiyonlarından (AİR) olup, ilaçların tedavideki etkinliğinin azalması ve komplikasyonlarla ilişkilidir. Yoğun bakım ünitesi (YBÜ) hastalarında çoklu ilaç kullanımı potansiyel İİE açısından bu hastaları risk grubu haline getirmektedir. Çalışmamızda, ülkemizdeki farklı yoğun bakımlarında benzer hasta gruplarındaki potansiyel ilaç-ilaç etkileşimlerini (pİİE) belirlemek istedik.
*Gereç ve Yöntem:* Bu çalışma Türkiye'deki YBÜ'de 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 pİİE açısından analiz edildi.
*Bulgular:* İki yüz otuz altı 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. Altı yüz seksen dört tane pİİE saptanmış olup bunların 92 (%13,4) tanesi majör, 531 (%77,6) tanesi moderate, 61 (%9) tanesi minör etkileşim idi. Yüz elli dokuz (%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 pİİE görülme riskinin arttığı görülmüştür. Saptanan pİİE'lerin çoğunluğunu orta düzeyde etkileşimler oluşturmakla beraber bu etkileşimlerin önceden saptanması hasta güvenliğini artırıcı nitelikte olabilir.
**Anahtar Kelimeler:** İlaç etkileşimleri, yoğun bakım ünitesi, advers ilaç reaksiyonları

## Introduction

Drug-drug interactions (DDI) are adverse drug reactions (ADR) that occur due to the combined use of more than one drug. This circumstance is associated with the occurrence of complications and a decline in the effectiveness of medications during treatment (1,2). The conditions that arise as a consequence of drug interactions, as opposed to ADRs, are referred to as potential drug-drug interactions (pDDI).

Intensive care unit (ICU) patients are commonly considered to belong to the high-risk category for pDDI due to the utilization of multiple medications and changes in drug metabolism (3-8). Evidence suggests that this circumstance elevates illness severity and amplifies healthcare expenses through the extension of ICU duration (9-11). Therefore, the identification of pDDIs and implementation of precautionary measures in intensive care patients hold significant importance.

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 ICUs in Turkey. Furthermore, our objective was to identify the drug pairs that exhibited the highest frequency of interactions and subsequently elaborate on the significance 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 Yüksek İhtisas Training and Research Hospital numbered 2011-KAEK-25 2019/04-10 (date: 10.04.2019) 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 ICUs 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 (LOS) in the ICU. This chart was sent to the physicians responsible for patient treatment in the general ICU 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. The identified interactions were categorized based on their 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 identify the relations of variables with each other. The outcomes were examined utilizing a significance threshold 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 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).

Significantly 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 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).

There was no statistically significant correlation identified between the duration of ICU stay and either the quantity of medications or the occurrence 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 LOS in the ICU (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, 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.

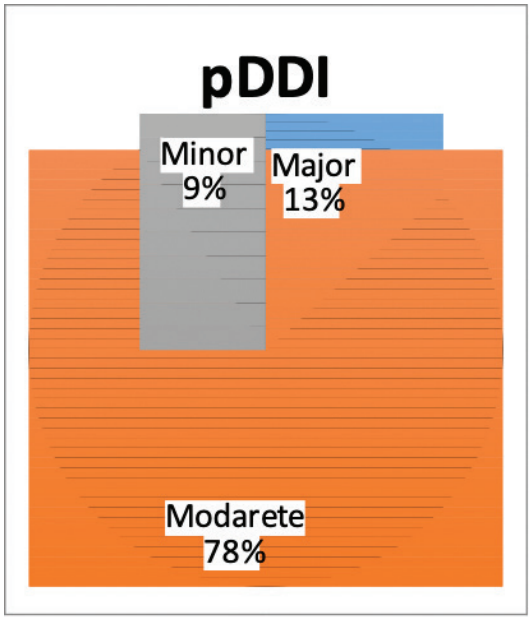


**Figure 1.** Distribution of detected pDDIs by severity category
pDDI: Potential drug-drug interactions

**Table 1. Demographical data**

| | Median (Q1-Q3)<br>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) |

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment

**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 |

APACHE-II: Acute Physiology and Chronic Health Evaluation-II, SOFA: Sequential Organ Failure Assessment, pDDI: potential drug-drug interactions. Mann-Whitney U test was used. A value of p<0.05 was considered significant

**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% |

pDDI: Potential drug-drug interactions

Although there was an increase in the number of drug interactions as the quantity of medications escalated, no statistically significant correlation was observed between the LOS in ICU and either the number of drugs or the number of drug interactions.

According to literature reports, the occurrence of pDDIs in intensive care patients exhibits significant variations. In their studies, Abarca et al. (15) and Vanham et al. (13) have indicated that the concordance among databases utilized for the detection of pDDIs was remarkably 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.

Numerous studies have provided evidence that the incidence of pDDIs escalates in correlation with the augmentation in the quantity of administered medications. (7,8,10,16). Similarly, in our study, we discovered a substantial level of correlation (r=0.707) between the two conditions. 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 (17). 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.

| Table 4. The interaction mechanisms of the most frequently interacting drug pairs | | |
|---|---|---|
| **Most frequent drug pairs** | **Risk category** | **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 |

Within our study, we established that the acetylsalicylic acid-enoxaparin drug pair exhibited the highest frequency of interactions. We believe that prolonged intensive care hospitalization after coronavirus disease-2019 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 (4,12,15,18). For example, in their study with renal transplantation patients, Amkreutz et al. (12) have reported the most frequently interacting drug pair to be tacrolimus-prednisolone, which causes an immunosuppressive effect. Also, Rodrigues et al. (19) have reported the most frequently interacting drug pair is enoxaparin-dipyrone. However, dipyrone is not available in every country.

In contrast to the findings reported in the existing literature (9,10,20), our study did not reveal a positive association between the LOS in ICU and either the number of medications or the number of drug interactions. We anticipated such results due to the limitation of using working days as a measure for hospital stay, which may not accurately reflect the total length of ICU stay. Notably, no significant differences were observed in the APACHE-II score, SOFA score, and number of medications between the groups with and without drug interactions, and there were no disparities in the duration of hospitalization among these groups. These findings suggest that an increased number of pDDIs may not necessarily lead to a prolonged ICU stay, which contradicts previous literature findings (9,10,20). However, it is worth noting that a moderate correlation was found between the SOFA score and major drug interactions, indicating that the severity of the disease might contribute to a higher likelihood of prescribing multiple medications. This, in turn, increases the potential occurrence of pDDIs and the subsequent prolongation of 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 LOS in the ICU constitutes another limitation of this study, as this duration did not reflect the actual total LOS 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 (date: 10.04.2019) 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

Surgical and Medical Practices: D.G., M.Ş.D., İ.C., N.K.G., Concept: D.G., N.K.G., Design: D.G., M.Ş.D., İ.C., 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., M.Ş.D., Writing: D.G., M.Ş.D., İ.C.

**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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