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Drug-Drug Interactions in the Red Zone of the Emergency Department: A Retrospective Study

Acil Servis Kırmızı Alanda İlaç-İlaç Etkileşimleri: Retrospektif Bir Çalışma

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ABSTRACT

Aim: This study aimed to assess the potential for drug-drug interactions in adult patients admitted to the emergency departments.
Material and Methods: This cross-sectional study included 410 patients who were admitted to the red zone of the emergency departments, examined, treated, and received multiple medications. Drug-drug interaction analysis was conducted using LexiInteract software.
Results: The median age of patients was 63 (range, 19-96) years, with 55.4% (n=227) being female and 44.6% (n=183) were male. A total of 1,230 medications were identified among the patients. In 181 (44.1%) patients, 330 possible drug-drug interactions were detected. While there was no significant difference in the rate of drug-drug interactions between male and female patients (p=0.658), this rate was higher in patients aged 65 years and over (p=0.048) and patients with polypharmacy (p<0.001). Also, the interaction rates were higher in patients admitted with cerebrovascular disease (p=0.038) and trauma (p=0.002). According to the Lexicomp© drug information system, potential drug-drug interactions were classified into risk category C (n=299, 72.9%), risk category D (n=22, 5.4%), and risk category X (n=9, 2.2%). The most frequently interacting drug pairs were Furosemide-Salbutamol in category C, Enoxaparin-Acetylsalicylic acid in category D, and Dexketoprofen-Acetylsalicylic acid in category X.
Conclusion: Nearly half of the patients treated in the red zone of the emergency department were at risk of drug interactions. Assessing the risk of drug-drug interactions is essential before initiating medical instructions in critical areas of emergency department patient care, and follow-up should be organized about potential adverse effects.
Keywords: Drug interaction; emergency service; red zone; clinical pharmacist.

ÖZ

Amaç: Bu çalışmanın amacı, acil servislere başvuran yetişkin hastalarda ilaç-ilaç etkileşimi potansiyelini değerlendirmektir.
Gereç ve Yöntemler: Bu kesitsel çalışmaya, acil servisin kırmızı bölgesine kabul edilen, muayene edilen, tedavi edilen ve birden fazla ilaç alan 410 hasta dahil edilmiştir. İlaç-ilaç etkileşimi analizi LexiInteract yazılımı kullanılarak gerçekleştirilmiştir.
Bulgular: Hastaların ortanca yaşı 63 (aralık, 19-96) yıl olup %55,4'ü (n=227) kadın ve %44,5'i (n=183) erkektir. Hastalar arasında toplam 1.230 ilaç tespit edilmiştir. 181 (%44,1) hastada 330 adet olası ilaç-ilaç etkileşimi tespit edilmiştir. Erkek ve kadın hastalar arasında ilaç-ilaç etkileşimi oranları bakımından anlamlı bir fark bulunmazken (p=0,658), 65 yaş ve üzeri hastalarda (p=0,048) ve çoklu ilaç kullanımı olan hastalarda (p<0,001) bu oran daha yüksekti. Ayrıca, serebrovasküler hastalık (p=0,038) ve travma (p=0,002) ile başvuran hastalarda da etkileşim oranları daha yüksek idi. Lexicomp© ilaç bilgi sistemine göre, olası ilaç-ilaç etkileşimleri risk kategorisi C (n=299, %72,9), risk kategorisi D (n=22, %5,4) ve risk kategorisi X (n=9, %2,2) olarak sınıflandırıldı. En sık etkileşime giren ilaç çiftleri, C kategorisinde Furosemid-Salbutamol, D kategorisinde Enoksaparin-Asetilsalisilik asit ve X kategorisinde Deksketoprofen-Asetilsalisilik asit idi.
Sonuç: Acil servisin kırmızı bölgesinde tedavi edilen hastaların neredeyse yarısı ilaç etkileşimi riski altındaydı. Acil servis hasta bakımının kritik alanlarında tıbbi talimatlara başlamadan önce ilaç-ilaç etkileşimi riskinin değerlendirilmesi esastır ve potansiyel yan etkilerle ilgili olarak takip düzenlenmelidir.
Anahtar kelimeler: İlaç etkileşimi; acil servis; kırmızı bölge; klinik eczacı.

INTRODUCTION

A healthcare system without adequate medical care can lead to illness, mortality, and economic hardship for communities (1). While the therapeutic effects of multiple medications can often be beneficial, some combinations pose serious risks, increasing the likelihood of drug-drug interactions (DDIs) (2). Challenges such as overcrowding, high-stress levels, understaffing, rapid patient turnover, and insufficient communication among multidisciplinary teams exacerbate these risks in emergency departments (EDs) (3).

In the Turkish healthcare system, EDs are classified into three triage levels, indicated by red, yellow, and green colors in descending order of priority. The red triage code denotes life-threatening situations that require urgent and simultaneous examination and treatment, necessitating immediate patient transfer to the red zone (4).

DDIs, adverse drug events (ADEs), allergic reactions, and medication errors are among the most critical issues associated with drug use in EDs, with ADEs being among the most frequently reported errors (5). DDIs, defined as altered toxicity or efficacy when medications are administered concurrently (6), significantly contribute to increases in ADEs, hospital admissions, ED visits, and rehospitalizations (7,8). They also drive up healthcare costs and hospitalization rates (2,9). Reports suggest that between 5% and 20% of severe drug reactions from DDIs lead to hospitalization or death (10). Therefore, managing DDIs is crucial to enhancing drug safety. Early identification and reporting of potential drug-drug interactions (pDDIs) can prevent numerous complications, ultimately improving patient safety and quality of life.

This study aimed to determine the frequency and clinical severity of pDDIs in patients admitted to EDs.

MATERIAL AND METHODS

Study Group

This cross-sectional study was conducted with red zone patients at the Emergency Medicine Clinic of the Mersin City Training and Research Hospital. Patients under 18 years old, those referred to departments outside the red zone of the ED, and those with inaccessible records were excluded from the study. Based on average monthly admissions to the ED, a minimum sample size of 355 patients was calculated to achieve a 95% confidence level and a 5% margin of error, with a final sample size of 410 patients chosen to account for a 15% attrition rate. A total of 410 adult patients admitted to the red zone of the ED were included. The inclusion criteria were patients over 18 years of age referred to the red zone of the ED between April 1, 2021, and April 1, 2022, with at least two drug administrations in their medical history and accessible medical records. Exclusion criteria included patients under 18 years old, patients referred to areas other than the red zone of the ED during the specified period, and patients with no recorded drug administration history. The study protocol received approval from the Mersin University Clinical Research Ethics Committee (06.04.2022, 232).

Data Collection

Drug evaluations included only medications administered within the first 24 hours of a patient's registration in the red zone, even if the patient was monitored for a longer period. Patient demographic and medication data were retrospectively obtained from the medical records. The concurrent use of five or more drugs was classified as polypharmacy. The LexiInteract software (Lexicomp Online®, Lexi-Comp, Inc., Hudson, Ohio) was utilized to assess co-prescriptions with known interactions. LexiInteract, typically not used in routine hospital practice, was employed here specifically for research purposes. In this system, pDDIs are graded: X for combinations with an unfavorable risk-benefit ratio and a recommendation to avoid, D for combinations where a treatment change should be considered, and C for cases requiring close monitoring. Clinically relevant exposures included grade X, D, or more than two grade C pDDIs in a patient's treatment regimen. Additionally, data reliability was categorized as excellent, acceptable, or moderate based on the quality of supporting information, and interaction significance was classified as major, moderate, or minor. Drugs were further categorized according to the Anatomic Therapeutic Chemical (ATC) Drug Classification system developed by the World Health Organization Collaborating Centre.

Statistical Analysis

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of the data, revealing that the data did not follow a normal distribution. Descriptive statistics were presented as counts with percentages and as medians with interquartile ranges. Chi-square or Fisher's exact test was used for group comparisons. The correlation between DDI risk categories and patient characteristics was assessed using Spearman's correlation coefficient. All statistical analyses were conducted using IBM SPSS v.25 for Windows, with statistical significance set at $p<0.05$.

RESULTS

Basic Characteristics of Patients

Of the 410 patients included, 227 (55.4%) were female, and 183 (44.6%) were male. The median age of all patients was 63 (range, 19-96) years, and 195 (47.6%) of the patients were over the age of 65. The most common diagnoses among the 109 identified upon admission were respiratory disease (n=117, 28.5%), cardiovascular disease (n=63, 15.4%), and chest pain (n=54, 13.2%). The total number of drugs prescribed to patients in this study was 1,230. The median number of medications per patient was 3 (range, 0-8), and polypharmacy was observed in 12.9% (n=53) of the total patients. A total of 54 different types of medications were used across the study group. Detailed patient diagnoses were presented in Table 1 and the most used medications were detailed in Table 2.

Frequency and Qualities of pDDIs

A total of 330 pDDIs were identified in 181 (44.1%) patients. One pDDIs were observed in 105 (25.6%) patients, while eleven patients (2.7%) had five or more pDDIs (Table 3).

While the rate of patients with at least one interaction was 45.4% (n=83) in males, this rate was 43.2% (n=98) in females (p=0.658). While the number of patients aged 65 years and over who had at least one drug interaction was 96 (49.2%), this number was 85 (39.5%) in those under 65 years of age (p=0.048). While 45 (84.9%) of 53 patients with polypharmacy had at least one interaction, this rate was 38.1% (n=136) in those without polypharmacy (p<0.001).

When the presence of interaction was analyzed according to the other clinical characteristics of the patients, it was seen that diagnoses at the admission did not show a significant difference in having at least one interaction, except for the patients admitted due to cerebrovascular disease (p=0.038) and trauma (p=0.002), details were shown in Table 4.

A total of 330 pDDIs were identified and categorized using the Lexicomp© drug information system as risk category C (n=299, 72.9%), risk category D (n=22, 5.4%), and risk category X (n=9, 2.2%). In examining the relationships between the number of drugs used, age, and risk categories, a significant correlation was found between age and risk category C (r_s=0.163, p=0.001). Significant correlations were observed in both C (r_s=0.450, p<0.001) and D (r_s=0.180, p<0.001) risk categories with the number of drugs used (Table 5).

Regarding reliability, while 127 (31.0%) of the pDDIs were classified as good, 192 (46.8%) were classified as fair, and 11 (2.7%) of them were classified as excellent. The

Table 1. Characteristics of the study group

Characteristics	**(n=410)**
Age (year), median (IQR) [min-max]	63 (48-77) [19-96]
Gender, n (%)	
Male	183 (44.6)
Female	227 (55.4)
Diagnosis, n (%)	
Respiratory disturbances	117 (28.5)
Cardiovascular disorders	63 (15.4)
Chest pain	54 (13.2)
Pain	23 (5.6)
Trauma (Fracture, injury, etc.)	23 (5.6)
Gastrointestinal problems	22 (5.4)
Cerebrovascular diseases	12 (2.9)
Epilepsy - Neurological	12 (2.9)
Fever	7 (1.7)
Polypharmacy, n (%)	53 (12.9)
Number of drugs, median (IQR) [min-max]	3 (2-4) [0-8]

IQR: interquartile range (25^{th}-75^{th} percentile)

Table 2. Most used drugs in patients (active ingredients)

ATC Groups, and Active Ingredients	**n**
A - Digestive System and Metabolism	
Pantoprazole	130
Metoclopramide	48
C - Cardiovascular System	
Furosemide	111
H - Endocrine System (Except Gender Hormones and Insulin)	
Methylprednisolone	91
R - Respiratory System	
Salbutamol	85
Ipratropium bromide/Salbutamol	82
Budesonide	55
N - Nervous System	
Paracetamol	75
Acetylsalicylic acid	69

ATC: anatomic therapeutic chemical

Table 3. Frequency of pDDIs among patients

Number of pDDI per Patient	**n (%)**
Patients with 1 pDDI	105 (25.6)
Patients with 2 pDDIs	38 (9.3)
Patients with 3 pDDIs	23 (5.6)
Patients with 4 pDDIs	4 (1.0)
Patients with 5 or more pDDIs	11 (2.7)
Total Patients with pDDIs	181 (44.1)

pDDI: potential drug-drug interaction

Table 4. Comparison of the presence of interaction* according to the demographic and clinical characteristics

	Gender		**p**
	Female (n=227)	**Male (n=183)**	
Interaction, n (%)	98 (43.2%)	83 (45.4%)	0.658
	Age Group		**p**
	≥65 (n=195)	**<65 (215)**	
Interaction, n (%)	96 (49.2%)	85 (39.5%)	**0.048**
	Polypharmacy		**p**
	+ (n=53)	**- (n=357)**	
Interaction, n (%)	45 (84.9%)	136 (38.1%)	**<0.001**
	Respiratory Disturbances		**p**
	+ (n=117)	**- (n=293)**	
Interaction, n (%)	54 (46.2%)	127 (43.3%)	0.605
	Cardiovascular Disorders		**p**
	+ (n=63)	**- (n=347)**	
Interaction, n (%)	34 (54.0%)	147 (42.4%)	0.088
	Chest Pain		**p**
	+ (n=54)	**- (n=356)**	
Interaction, n (%)	23 (42.6%)	158 (44.4%)	0.805
	Pain		**p**
	+ (n=23)	**- (n=387)**	
Interaction, n (%)	7 (30.4%)	174 (45.0%)	0.173
	Trauma		**p**
	+ (n=23)	**- (n=387)**	
Interaction, n (%)	3 (13.0%)	178 (46.0%)	**0.002**
	Gastrointestinal Problems		**p**
	+ (n=22)	**- (n=388)**	
Interaction, n (%)	11 (50.0%)	170 (43.8%)	0.570
	Cerebrovascular Diseases		**p**
	+ (n=12)	**- (n=398)**	
Interaction, n (%)	9 (75.0%)	172 (43.2%)	**0.038**
	Epilepsy - Neurological		**p**
	+ (n=12)	**- (n=398)**	
Interaction, n (%)	7 (58.3%)	174 (43.7%)	0.382
	Fever		**p**
	+ (n=7)	**- (n=403)**	
Interaction, n (%)	1 (14.3%)	180 (44.7%)	0.140

*: number of patients with at least one interaction

Table 5. Correlation between the risk categories and number of drugs used and age of the patients

		Risk Category		
		C	**D**	**X**
Age	r_s	0.163	-0.027	0.003
	p	**0.001**	0.581	0.949
Number of Drugs	r_s	0.450	0.180	0.080
	p	**<0.001**	**<0.001**	0.106

LexiInteract categorization further classified the severity of interactions as 16 (3.9%) were major, 72 (17.6%) were classified as minor, and 242 (59.0%) were classified as moderate. Seventy-nine distinct interaction pairs were detected among patients admitted to the ED. The most frequently interacting drug pairs in category C were Furosemide-Salbutamol with 54 interactions, Glyceryl trinitrate-Furosemide with 27 interactions, and Furosemide-Methylprednisolone with 21 interactions. In category D, while Enoxaparin-Acetylsalicylic acid interaction was more common with 9 interactions, Phenytoin-Dexamethasone with 4 interactions, and Enoxaparin-Clopidogrel with 2 interactions were observed. For category X, the interactions included Dexketoprofen-Acetylsalicylic acid with 7 interactions, Atropine-Ipratropium and Salbutamol with one, and Pheniramine-Ipratropium and Salbutamol with one interaction (Table 6). Additionally, Furosemide, Diltiazem, and Metoprolol were each involved in multiple interaction pairs, forming 16, 11, and 7 distinct interactions, respectively (Table 7).

Overall, nine ATC drug groups were involved in the pDDIs, with the most common categories being drugs related to digestion and metabolism (21.6%, 266/1230), followed by the cardiovascular system (21.5%, 265/1230) and the respiratory system (20.5%, 252/1230).

DISCUSSION

The use of multiple medications poses a substantial risk of DDIs, with potential adverse outcomes ranging from toxicity to treatment failure and even death (11,12). Most studies on this topic have focused on patients presenting to EDs with high medication counts and/or older adults. However, the severity of cases in the ED varies, and more medications may be required as patient acuity increases.

Our study findings revealed that nearly half (44.1%) of critically ill patients in the ED were at risk of a DDI. Of the 181 pDDIs identified among the 410 patients, 72.9% were moderate interactions, while 2.2% were classified as contraindicated. Another study on neuroleptic malignant syndrome (NMS) in ED patients highlighted that DDIs could significantly alter plasma drug concentrations. In that study, interactions between ciprofloxacin and quetiapine were implicated in causing NMS in a patient. Therefore, it is essential for clinicians to evaluate DDIs carefully when managing patients on psychiatric medications (13).

Critically ill patients treated in the ED are at risk for DDIs, regardless of age. As the number of medications administered increases, so does the likelihood of DDIs. The present study found that both the number of DDIs and the risk of interactions increased with patient age. Similarly,

Table 6. Most frequently interacting drug pairs

Interaction Pair	Risk Category	n	Mechanisms	Severity	Reliability Rating
Furosemide - Salbutamol	C	54	Beta2-agonists may enhance the hypokalemic effect of loop diuretics.	Minor	Good
Glyceryl trinitrate - Furosemide	C	27	Blood pressure-lowering agents may enhance the hypotensive effect of hypotension-associated agents.	Moderate	Fair
Furosemide - Methylprednisolone	C	21	Corticosteroids (systemic) may enhance the hypokalemic effect of loop diuretics.	Moderate	Fair
Enoxaparin - Acetylsalicylic acid	D	9	Agents with antiplatelet properties may enhance the anticoagulant effect of enoxaparin.	Moderate	Fair: Reported in the prescribing information
Phenytoin - Dexamethasone	D	4	Phenytoin may decrease the serum concentration of dexamethasone (systemic). Dexamethasone (systemic) may decrease/increase the serum concentration of phenytoin.	Major	Fair
Dexamethasone - Rocuronium	D	2	Neuromuscular-blocking agents (nondepolarizing) may enhance the adverse neuromuscular effect of corticosteroids (systemic). Increased muscle weakness, possibly progressing to polyneuropathies and myopathies, may occur.	Major	Excellent
Enoxaparin - Clopidogrel	D	2	Agents with antiplatelet properties may enhance the anticoagulant effect of enoxaparin.	Moderate	Fair: Reported in the prescribing information
Tramadol - Iohexol	D	2	Agents with seizure threshold-lowering potential may enhance the adverse/toxic effect of iohexol. Specifically, the risk for seizures may be increased.	Major	Fair
Dexketoprofen - Acetylsalicylic acid	X	7	Salicylates may enhance the adverse/toxic effect of dexketoprofen. Dexketoprofen may diminish the therapeutic effect of salicylates. Salicylates may decrease the serum concentration of dexketoprofen.	Major	Fair
Atropine - Ipratropium and Salbutamol	X	1	Ipratropium (oral inhalation) may enhance the anticholinergic effect of anticholinergic agents.	Moderate	Fair
Pheniramine - Ipratropium and Salbutamol	X	1	Ipratropium (oral inhalation) may enhance the anticholinergic effect of anticholinergic agents.	Moderate	Fair

Table 7. Top 10 drugs with the most different drug interaction pairs

Drugs	Number of Interaction Pairs	The ATC Group That Forms the Most Interaction Pairs
Furosemide	16	C - Cardiovascular System
Diltiazem	11	C - Cardiovascular System
Metoprolol	7	C - Cardiovascular System
Metoclopramide	7	A - Digestive System and Metabolism
Acetylsalicylic acid	7	N - Nervous System
Glyceryl trinitrate	7	C - Cardiovascular System
Captopril	6	C - Cardiovascular System
Salbutamol	5	R - Respiratory System
Hyoscine-N-butylbromide	5	A - Digestive System and Metabolism
Dexketoprofen	5	M - Musculoskeletal System
Methylprednisolone	5	H - Endocrine System (Except Gender Hormones and Insulin)

ATC: anatomic therapeutic chemical

Hovstadius et al. (14) reported a significant positive correlation between polypharmacy and older age, adding to previous findings that highlighted a high prevalence of polypharmacy among older ED patients in the UK. Additionally, prior research has associated factors such as female sex, polypharmacy, and chronic conditions with advancing age, all of which contribute to an elevated DDI risk (15).

Among patients aged 65 and older, 96 (49.2%) experienced at least one DDI, while 99 (50.8%) had none. The absence of a significant difference in DDIs in this study may be attributed to the inclusion of only patients in the red zone, despite the median age being comparable to other studies. Another significant finding was the evaluation of diagnoses; aside from trauma, and cerebrovascular disease. Further research is warranted to investigate preventable DDIs in patients with these specific medical conditions.

With advancements in health information and computerized decision-support systems, various online databases —some available free of charge— now provide critical medical information on medications and assess potential DDIs. Commonly used databases include Clinical Pharmacology, Micromedex, Medscape, Lexi-Comp Online, Facts & Comparisons 4.0, Epocrates Online Premium, RxList.com, and Drugs.com. Differences in evaluation criteria and DDI results can occur across these platforms. A study evaluating the clinical decision-support capabilities of these databases found that paid databases generally answered a greater number of DDI-related queries compared to free databases (16).

Another comparison of five DDI databases identified Lexi-Interact and Micromedex as the most authoritative, comprehensive, and user-friendly options. Despite the utility of these databases, using multiple databases alongside expert intervention is recommended to enhance accuracy (17). Lexi-Interact, in particular, is widely used across various professions and conditions due to its ease of use (18-20). It offers quick, accessible information on the risk, severity, and safety of pDDIs, and this study provides additional recommendations for the prevention and management of pDDIs (21).

In this study, the Lexicomp© drug information system was used as the primary tool to identify pDDIs, with 330 identified interactions, 72.9% of which were classified under risk category C. The primary factors contributing to DDI risk include the high patient volume in the ED, the presence of multiple comorbidities requiring numerous medications, and the need to administer drugs without comprehensive knowledge of patient's medical histories to expedite emergency procedures. Given their high-pressure environments, EDs are inherently high-risk areas for DDIs. The implementation of clinical decision-support systems, managed by clinical pharmacists, could help mitigate drug-related problems in these settings.

To ensure patient safety in clinical environments, alerting systems are essential, particularly as the use of databases grows. DDI decision support is crucial for healthcare professionals, including prescribers, pharmacologists, pharmacists, and nurses. Therefore, hospital administrators and technology providers should develop electronic alert systems and preventive measures accessible to all healthcare professionals to improve prescribing practices and enhance patient safety. Additionally, longitudinal studies are needed to observe patients over extended periods, as this would provide a deeper understanding of DDIs' real-world consequences in clinical practice. The results of such research will be invaluable in shaping future DDI management strategies.

This study had several limitations. Although the hospital confirmed that the patients in the ED generally represented the population’s ethnic and demographic composition, the single-center design introduced a risk of selection bias. Another limitation was that only data from patients in the ED's red zone were analyzed, excluding those receiving care in other sections. Consequently, the findings may not reflect the entire ED population, as data from all emergency areas would likely result in lower DDI rates. Additionally, we examined only DDIs occurring within the first 24 hours of admission, without accounting for the timing of drug administration, which may have affected DDI identification. Lastly, critical patient care is a dynamic process, with the potential for DDIs to arise from medications administered to address complications or new conditions during patient follow-up.

CONCLUSION

This study highlights the prevalence of pDDIs in the red zone of the ED. These findings may help raise clinician awareness of the interactions associated with commonly used drug combinations in critically ill patients. Future directions include evaluating the prevalence and impact of these pDDIs across multiple centers and investigating their relevance in outpatient settings.

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