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Original Article

Drug-drug interactions in intensive care units and potential clinical consequences of these interactions

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Abstract

Aim: Drug-drug interactions (DDIs) are an important factor that can lead to serious health problems by increasing or decreasing the effects of drugs. This study aimed to evaluate the frequency of DDIs in the intensive care unit (ICU).

Material and Methods: All patients who were hospitalized for more than 24 h in the ICU of our hospital between January and September 2018 and received 2 or more medications were included in this retrospective study. Frequency and severity of the DDIs were detected using the Rx Mediapharma and Lexi-Interact programs.

Results: Of the 972 patients enrolled in the study, 2742 incidences of DDIs were detected in 626 patients (64%). Of the different drug pairs administered, 422 had DDIs, and 64 of those had 10 or more DDIs, constituting 67% of all of the DDIs. The most common potential clinical consequences of DDIs were increased risk of bleeding (12.3%), hyperkalemia (8.2%), arrhythmia (7.9%), and CNS depression (6.6%).

Conclusion: The results indicated that DDIs in the ICU were very common in our hospital. Moreover, these results indicated that patients should be closely monitored for the prevention of adverse effects, such as electrolyte disturbance, bleeding risk, and arrhythmia of drugs.

Keywords: Drug-drug interaction; intensive care unit; adverse drug reaction.

INTRODUCTION

DDIs are significant medical issue that can change the effect of drugs, cause life-threatening adverse drug reactions (ADR), and prolong patient recovery time (1). DDIs are common in patients receiving a larger number of medications, but they can be preventable and easily detectable before administration. In addition to a larger number of medications, the frequency of DDIs changes according to age, gender, and the individual diseases of the patients (2). DDIs are responsible for 17% all of adverse drug reactions and approximately 1% in hospitalized patients (3). In many studies, DDIs have been revealed in very common prescriptions at different stages of health services, such as in a study that examined the prescriptions of patients who received primary health care services, where the rate of DDIs ranged from 9%–70%, and 1%–23% of them were shown to cause serious health problems (2). In another study, the rate of DDIs in prescriptions written to outpatients in hospitals was approximately 27/1000(4). In a different study, in which hospitalized patients were investigated, the DDI rate was 1/70 prescriptions (5).

Patients hospitalized in the intensive care unit (ICU) have more severe diseases, multiple organ failures, and more intensive drug treatments than other hospitalized patients. In addition, these patients have circulatory disorders and metabolism rate of drugs variety due to organ failure. Due to these factors, the incidence of DDIs in patients in the ICU is higher than in other outpatients and inpatients in hospitals (6). In a study conducted in

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the ICU, 10% of patients in the ICU were shown to develop ADRs due to DDIs (7). In another study, DDIs were found in 3892 of 9644 patients in the ICU (8). Reported that 54% of patients hospitalized in the ICU were found to have DDIs and the frequency of DDIs increased in direct proportion to the length of hospital stay and number of drugs used (9).

The aim of this study was to determine the frequency of DDIs in patients hospitalized in the ICU and the potential clinical consequences of these interactions.

MATERIAL and METHODS

Setting and study population

Ethical approval was provided by the Inonu University Scientific Research and Publication Ethics Committee (2018/21-7). This retrospective study was performed in the ICU of the Malatya Training and Research Hospital, in Turkey. This hospital has 36 beds in ICU unit and there is no a management system to detect possible DDIs. The data of 1257 patients who were hospitalized in the ICU between January and September 2018 were screened from the hospital's database. A total of 972 patients who received 2 or more systemic drugs were included in the study. The exclusion criteria were patients who were below 18 years of age, stayed for less than 24 h in the ICU, received less than 2 drugs or did not receive systemic drugs had a very long stay in the ICU and drug information could not be correctly detected. The demographic characteristics of the patients, diseases that cause hospitalization, duration of hospitalization, conditions of death and discharge, medications applied during the duration of hospitalization, and dates and numbers of the drug administration were recorded by the patient's epicrisis.

DDI evaluated

All the drugs administered to the patient during the DDIs scan were determined according to the application days and the two potential drugs were given to the patient at the same time were included in the study however drugs that were not administered at the same time were excluded from the study. The DDIs were evaluated using databases such as Rx Mediapharma 2018, which is a patented and widely used drug information system for the detection of DDIs in Turkey, the Lexi-Interact online interactions checker, drug prospectuses, pharmacology books, and other similar studies in the ICU. Between which drugs did the interactions occur, and the clinical consequences, severity, and frequency of the DDIs were recorded. Frequency of each risk rating category of DDIs was calculated by percentage of total number of DDIs [number of each risk rating category DDI / total number of DDIs × 100]. The clinical severity of DDIs was classified as 1, 2, 3 with the Rx and C, D, X risk rating categories in accordance with the Lexi- Interact online database system. The severity of the DDIs was categorized as 1, 2, and 3, with minor, moderate, and severe in Rx mediapharma. However, the severity of DDIs was categorized as C, D, and X with moderate, major, and severe in Lexi-Interact. Nevertheless, the recommended opinion for 1, 2, and 3, and C, D, and X are similar in both databases. For example, 1/C: monitor therapy, 2/D: consider therapy modification, 3/X: avoid combination. Therefore, the severity of the DDIs was classified in accordance with both database systems.

Statistical analysis

The statistical package program SPSS 23.0 for Windows (IBM Corp., Armonk, N.Y., USA) was used to perform the descriptive statistics analysis of the data. The categorical variables in the study were indicated by numbers and percentages and the Z-ratio test was used for comparisons between the two ratios. Statistical significance level (α) was taken as 5% in the calculations and Minitab (Statistical Software for Windows, Ver.17) statistical package program was used for the calculations.

RESULTS

The demographic characteristics of the 972 patients included in the study are shown in Table 1. The number of

Table 1. Characteristics of the study population

Total patients (n: 972)	n	%
Male	505	52
Female	467	48
Discharge from hospital/transfer to general wards	719	74
Mortality	253	26
Age		
>80	278	29
≥50–80	538	55
<50	156	16
Diseases		
Respiratory diseases	305	31
CNS diseases	162	17
Trauma	152	16
Cardiovascular diseases	75	8
Post-op observation	74	8
Other diseases	56	6
Intoxication	53	5
Renal diseases	50	5
Malignity	45	4
Number of drugs used		
1–10	438	45
11–20	408	42
20>	126	13

CNS, central nervous system

females and males included in the study was similar (48%–52%). The patient ages ranged between 18 and 102, and most were between 50 and 80 years old (55%). The total number of days in the ICU for these patients was 6722 and the median length of stay in the ICU was 6.9 days.

DDI frequency

Drugs were administered 53,379 times to 972 patients and the number of DDIs were 2742 (5.1%). The mean DDIs range per patient was 2.8%. DDIs were detected in 626 patients and the DDIs range in these patients was 4.4%. The number of patients with only 1 instance of DDIs was 163 (17%), with 2–10 instances was 409 (65%), and with >10 instances was 54 (6%). DDIs were seen on a total of 5348 days in the ICU (80%). Although there was no statistically significant difference between the frequency of DDIs in male and female patients, DDIs was significantly higher in female patients compared to hospitalization period ($p<0.05$). The frequency of DDIs were significantly higher in died patients than patients who were transferred to other wards ($p<0.05$). The frequency of DDIs were significantly higher in patients who were older than 50 years and administered more than 10 drugs and hospitalized for more than 5 days than others patients ($p<0.05$). Diseases with the most DDIs were respiratory diseases, such as chronic obstructive pulmonary disease, pneumonia, and cardiovascular disease (CVD) (77% and 75%, respectively) and DDIs frequency were significantly higher in these diseases compared to others ($p<0.05$) (Table 2).

Table 2. Main parameters of patients with DDIs

	Patient with DDIs Total patients n: 972	No. of ICU days with DDIs Total n: 6722
Total	64% (626)	80% (5348/6722)
Gender		
Male	63% (318/505)[a]	78% (2838/3658)[b]
Female	66% (308/467)[a]	82% (2510/3064)[a]
Age		
>80	67% (187/278)[a]	83% (1918/2308)[a]
>50–80	69% (372/538)[a]	81% (2995/3675)[a]
≤50	43% (67/156)[b]	59% (435/739)[b]
Discharge from hospital	60% (433/719)[b]	75% (2988/3978)[b]
Mortality	76% (193/253)[a]	86% (2360/2744)[a]
Length of stay in the ICU, days		
1	50% (113/226)[b]	50% (113/224)[b]
2–5	57% (229/404)[b]	59% (724/1233)b
>5–10	81% (134/166)[a]	80% (1019/1268)[a]
>10	85% (150/176)[a]	87% (3492/3997)[a]
Diseases		
Respiratory diseases	77% (236/305)[a]	87% (2345/2690)[a]
Cardiovascular diseases	75% (56/75)[a]	87% (609/704)a
CNS diseases	67% (109/162)[a]	78% (1115/1432)[ab]
Trauma	58% (88/152)[b]	85% (661/779)[a]
Renal diseases	56% (28/50)[b]	63% (170/272)[b]
Malignity	56% (25/45)[b]	67% (76/113)[b]
Post-op observation	55% (41/74)[b]	44% (119/272)[c]
Other diseases	54% (30/56)[b]	70% (222/319)[ab]
Intoxication	25% (13/53)[c]	22% (31/141)[d]
Number of different drugs used		
1–10	40% (176/438)[b]	36% (414/1142)[b]
11–20	82% (333/408)[a]	81% (2187/2712)[a]
20>	93% (117/126)[a]	96% (2747/2868)[a]

a, b, c: Show the difference between categories in the same column for each attribute according to z test.

Table 3. The most common DDIs (n ≥ 10)

Drug A	Drug B	Clinical consequences	n/%	Severity-Rx/lexi
Enoxaparin	NSAID, piracetam, clopidogrel, ASA, SSRI	Bleeding risk	263/9.2	1/C
Enoxaparin	Potassium chloride, ACE, ATII, spironolactone	Hyperkalemia	215/7.5	1/C
Furosemide	ASA, NSAIDs	Effects of furosemide may decrease	168/5.9	1,C
Midazolam	Magnesium sulfate, opioid analgesics, propofol, levetiracetam	Increased risk of central nervous system depression	100/3.5	2/C, only opiod D
Furosemide	Opioid analgesics	Adverse/toxic effect of furosemide may increase	87/3	1/C
Furosemide	Propofol, thiopental, amiodarone	Hypotension	83/2.9	1/C
Furosemide	Aminoglycosides	Nephrotoxicity and ototoxicity	69/2.4	2/C
ASA	Clopidogrel, diltiazem piracetam, NSAIDs	Bleeding risk/adverse/toxic effect of ASA may increase	64/2.2	2/C
Methylprednisolone	ASA, diltiazem	Adverse/toxic effect of methylprednisolone may increase	62/2.2	1/C
Digoxin	Furosemide, diltiazem	Adverse/toxic effect of digoxin may increase (AV bloc)	57/2	1/C
Methylprednisolone	Fluoroquinolones	Adverse/toxic effect of fluoroquinolones may increase	56/2	1/C
Fluoroquinolones	Domperidone, amiodarone	Arrhythmia	53/1.9	1/D,X
Furosemide	Insulin	Effects of insulin may decrease	45/1.6	1/C
Midazolam	Diltiazem, fluconazole	Adverse/toxic effect of midazolam may increase	40/1.5	1/C
Pantoprazole	Fluconazole, modafinil	Adverse/toxic effect of pantoprazole may increase	41/1.4	1/C
Atorvastatin	Pantoprazole	Adverse/toxic effect of Atorvastatin may increase	34/1.2	3/n.i
Methylprednisolone	Phenytoin	Effects of Methylprednisolone may decrease	33/1.2	1/D
Noradrenaline	β-adrenergic blockers	Hypertension	32/1.1	3/n.i
Fluoroquinolones	Propofol, metronidazole	Arrhythmia	27/0.9	2/B,C
Phenytoin	Pantoprazole	Effects of phenytoin may decrease	27/0.9	1/n.i
Metoclopramide	Opioid analgesics	Adverse/toxic effect of metoclopramide may increase	27/0.9	2/C
Midazolam	Theophylline	Effects of Midazolam may decrease	21/0.7	1/D
Ceftriaxone	Calcium gluconate	Adverse/toxic effect of ceftriaxone may increase	19/0.6	2/D
Noradrenaline	Linezolid	Hypertension	17/0.6	1/D
Furosemide	ACE inhibitors	Hyperkalemia/effect of hypertensive may increase	15/0.5	1/C
ASA	ACE inhibitors	Nephrotoxicity/effect of antihypertensive may decrease	14/0.5	1/C
Gentamicin	Cephalosporins	Nephrotoxicity	14/0.5	2/C
ASA	Insülin	Hypoglycemia	13/0.4	1/C
Domperidone	Linezolid	Adverse/toxic effect of domperidone may increase	13/0.4	1/C
Furosemide	Phenytoin, antipsychotics	Effects of furosemide may decrease	12/0.4	1/C
Tramadol	Ondansetron	Effects of tramadol may decrease	12/0.4	1/C
Midazolam	Atorvastatin	Adverse/toxic effect of midazolam may increase	11/0.4	2/C
Paracetamol	Phenytoin	Hepatotoxicity	11/0.4	1/C
Noradrenaline	Theophylline	Effects of sympathicomimetic effect may increase	11/0.4	2/C
Domperidone	Metoclopramide	Arrhythmia	11/0.4	1/ni
Digoxin	β-adrenergic blockers	Bradycardia	10/0.3	1/C
Diltiazem	Magnesium sulfate	Adverse/toxic effect of magnesium sulfate may increase	10/0.3	1/C
Amiodarone	β -adrenergic blockers	Bradycardia/ventricular arrhythmia	10/0.3	1/C
Phenytoin	Midazolam	Effects of midazolam may decrease	10/0.3	1/D
Insulin	Fluoroquinolones	Hypoglycemia/hyperglycemia	10/0.3	1/C
Total			1827/67	

ni, no interaction; NSAIDs, nonsteroidal antiinflamatuary drugs; ASA, acetylsalicylic acid; SSRI, selective serotonin reuptake inhibitor; ACE, angiotensin converting enzyme inhibitor; ATII, angiotensin receptor blocker

DDIs type

DDIs with 10 or more interactions, classified according to the clinical results, are shown in Table 3. DDIs were observed in 422 different drug pairs, and of those, 64 different drug pairs had 10 or more DDIs, which constituted 67% of all DDIs. The number of drug pairs showing interaction only once was 152. The number of level 1 DDIs was 2047 (75%), level 2 was 591 (21%), and level 3 was 104 (4%) in accordance with Rx and C 2195 (83%), D 312 (12%), and X 94 (3.6%) in accordance with lexi interact (Table 3). DDIs caused a change in the therapeutic effect of drugs, such as increased adverse or toxic effects, or decreased therapeutic effects (45.4%). Side effects in the cardiovascular system (CVS) were second (31.5%). This classification was performed according to the presence of a specific clinical result (arrhythmia, hypotension, etc.) after the DDIs (Table 4). Furosemide was the most common drug to cause DDIs (n: 545), followed by enoxaparin sodium (n: 508) and acetyl salicylic acid (ASA) (n: 464, respectively) (Table 5).

Table 4. Potential clinical consequences of DDIs

	n	%
Changes in therapeutic effect of drugs	1246	45.4
Increased risk of side effects/toxicity	717	26.1
Decreased risk of efficacy	529	19.3
CVS side effects	863	31.5
Bleeding risk	350	12.8
Arrhythmia (AV bloc-ventricular arrhythmia torsade de points, prolong QT)	225	8.2
Hypotension	155	5.6
Hypertension	68	2.5
Bradycardia	39	1.4
Increased risk of sympathomimetic effect	26	0.9
Electrolyte disorder	236	8.6
Hyperkalemia	231	8.4
Hypokalemia	5	0.2
CNS side effects	221	8
Increased risk of	189	6.9
CNS depression		
Serotonin syndrome	20	0.7
Increased risk of epileptic seizures	8	0.3
Increased risk of anticholinergic effect	4	0.1
Other systems	176	6.4
Nephrotoxicity + rhabdomyolysis	42	1.5
Hypoglycemia	41	1.5
Nephrotoxicity + ototoxicity	36	1.3
Nephrotoxicity	34	1.2
Hepatotoxicity	8	0.3
Ulcerogenic effect	7	0.3
Increased risk of NMB	5	0.2
Rhabdomyolysis	3	0.1
Total	2742	100

NMB, neuromuscular blockade; CVS, cardiovascular system; CNS, central nervous system

Table 5. Most involved drugs to DDIs	
	n
Furosemide	545
Enoxaparin	508
Acetylsalicylic acid	464
Fluoroquinolones	238
Midazolam	228
Diltiazem	141
Methylprednisolone	140
Amiodarone	120
Phenytoin	117
Metoclopramide	99
Domperidone	92
Noradrenaline, adrenaline	75
Atorvastatin	74

The number of interactions between drugs was calculated by including the number of interactions with each other.

DISCUSSION

The results of our study indicated that the number of patients with DDIs in our hospital was very high (64%). Once the length of patient hospitalization was evaluated, the frequency of DDIs was even higher (80%), where 25% of these DDIs were interactions at the moderate-severe level. The most common interactions were with the CVS, antibiotics, and central nervous system (CNS). The most common clinical results of the DDIs were increased risk of bleeding (12.3%), hyperkalemia (8.2%), arrhythmia (7.9%), and CNS depression (6.6%).

DDIs are quite common in hospitalized patients and they cause a significant proportion of ADRs. However, they are more common in patients in various ICU units, such as coronary, cardiovascular, and reanimation, which should be followed closely and may lead to more adverse events. However, the frequency of DDIs varies in many studies conducted in different countries in the ICU. For example, a study conducted in Brazil indicated that 72.5% of patients in the ICU had DDIs (10). In a study conducted in the Netherlands, this rate was 40% (8). In a US study, similarly, the rate of DDIs was 46.3% (11). In another study by the same authors, the cardiac and cardio-thoracic ICU results indicated that 56% of the patients had DDIs (12). As far as we have investigated, there have been 2 studies on DDIs in Turkey. The first was the study of the interaction between antibiotics and other drugs in the 1-day patient stay of 5 different hospitals. This study included 427 patients (number of patients in the ICU: 108) and the DDI rate was 26.4% (13). The second study was a single-center perspective study in which 101 patients were included in the ICU and the DDI rate for all of the drugs administered to patients was investigated. In that study, DDIs were detected in 45.5% of patients (1). Our study, which included most patients with this ICU issue in Turkey (n = 972) and the DDI proportion, was determined to be higher than the majority (64%) of studies, both performed in different countries and those in Turkey. It was evaluated that the DDIs were higher in our study than in the other studies, because of the different types of drugs used and the ICU patient conditions, such as age, gender, type of disease, and the presence of a concomitant disease.

The incidence of DDIs was found to increase with an increase in the number of drugs administered and the length of hospital stay (1, 10). Our results corresponded to these studies, where the rate of DDIs was 40% in patients treated with 1–10 drugs, but the rate in patients who were administered over 20 drugs was 93% ($p<0.05$). Again, once the number of hospitalization days was evaluated, the rate of DDIs in patients hospitalized for a day was 50%, while in patients hospitalized for more than 10 days, this rate was 85% ($p<0.05$). In addition to the number of medications and the duration of hospitalization, the prevalence of DDIs in patients increases depending on their age and type of disease (3). For example, in a study investigating the frequency of DDIs in hospitalized patients, the prevalence of DDIs in patients over 75 years of age was higher than patients within a low age group (14). In a study conducted on outpatient geriatric patients, 50% of patients had DDIs and approximately 1/4 had ADRs due to DDIs. In our study, the frequency of DDIs was higher in patients over 50 years of age similar to these studies ($p<0.05$). However, there was no significant difference in the frequency of DDIs in patients over 80 years of age who were expecting greater frequency of DDIs and between 50 and 80 years of age. This condition may be caused by existing and comorbid diseases of individuals over 80 years of age. Many studies have indicated that DDIs are more common in individuals with CVS and CNS diseases (14, 15). In our study, although DDIs were quite high in these 2 disease groups (CVD 75%, CNS 69%), they were most commonly found in individuals with lung disease (77%, $p<0.05$). However, it should be considered that the frequency of DDIs among the disease groups, the severity of the disease, the age, and the presence of an accompanying disease can change. In our study, the DDIs difference seen among the disease groups may have been caused by these reasons. However, there is a distinct coronary ICU in our hospital, where cases of cardiac origin are located; therefore, it is thought that this ICU may have caused by low number of results with cardiac origin. Another important finding in our study was that the frequency of DDIs in patients who died was much higher than in patients who were discharged (76%, 60%, respectively $p<0.05$). The intense use of medications may have contributed to the excess of DDIs in these patients, due to factors such as the severity of the disease in individuals, presence of co-morbid disease, and desire to rapidly correct the age and general condition. In this case, it is important to make a more careful evaluation in terms

of the DDIs risk in these patients, before the administration of ADRs, because the occurrence of ADRs due to DDIs will worsen the course of the current disease or the general condition of the patients.

Due to the differences in diseases in individuals, there was a change in the drugs that caused DDIs among the general services of hospitals and the ICU or outpatients. For example, in a study investigating the frequency of DDIs in hospitalized patients, it was reported that there was an interaction between angiotensin converting enzyme (ACE) inhibitors and diuretics and renin-angiotensin system (RAS) inhibitors and potassium (16). In another study performed in inpatients, the interaction between aspirin and warfarin, digoxin and furosemide was the most common (14). In a study of outpatients, it was found that DDIs were the most common with antiparkinsonian drugs and dopamine receptor antagonists (4). In another study, in which ambulatory patients were examined, diuretics, nonsteroidal antiinflammatory drugs (NSAIDs), and ACE inhibitors were found to be drugs with DDIs (17). In this sense, drugs seen with DDIs in ICU patients differ slightly. For instance, coronary ICU inpatients were most commonly found to have DDIs with anticoagulants or antiplatelet agents, aspirin, and heparin (12). The same researchers, in a study of ICU patients with DDIs, found insulin and beta-blockade and phenytoin and dexamethasone to be the second most common interactions, while in the coronary ICU, anticoagulant or antiplatelet drugs were found to be among the most common (11,18). In another study conducted on ICU patients, similar to the above study, it was found that the interactions between insulin and beta blockers were the highest DDIs and the second most frequent interaction was between midazolam and CYP3A4 inhibitors (9). A study performed in Turkey indicated that the most common DDIs in ICU patients was between methylprednisolone and other drugs, while the second was among the CVS drug groups, such as digoxin, diltiazem, and furosemide (1). In our study, the most common drugs in DDIs were anticoagulants, antiplatelets, and CVS drugs, such as enoxaparin, ASA, and furosemide. DDIs involving furosemide were found 545 times with 18 different drugs, those involving enoxaparin were found 508 times with 13 different drugs, and those involving ASA were found 464 times with 18 different drugs. Again, DDIs involving diltiazem, methylprednisolone, and midazolam were quite high. Fluoroquinolone group antibiotics, such as ciprofloxacin, moxifloxacin, and levofloxacin were the most common antibiotics to cause DDIs. Once the DDI results were classified according to the clinical events, the interaction between enoxaparin and ASA, clopidogrel, NSAIDs, etc., was the most common cause of bleeding (9.2%). Moreover, second frequently there were DDIs (7.5%) that can cause hyperkalemia between enoxaparin and ACE inhibitors, potassium drugs vs. these results indicated that although there were some differences, the drugs that caused DDIs in our hospital ICU were similar to the drugs studied in other countries. Our study, as well as being the most patient study of the involvement of hospitals in Turkey, it is important to determine that the majority of the drugs used in ICU patients are similar drugs such as furosemide, enoxaparin and ASA. The results of our study also indicated that anticoagulant agents, such as enoxaparin, are routinely used to prevent deep vein thrombosis in patients in the ICU, and that such patients should be closely monitored for ADR prevention, especially for the risk of bleeding and potassium elevation. Again, because of the widespread use of drugs such as midazolam, it is important to closely monitor patients in the ICU in terms of the prevention of ADR, for such things as arrhythmia with pulmonary disease, CNS depression and pneumonia, and especially cardiac diseases such as arrhythmia.

There were differences between the Rx Mediapharma and lexi programs in terms of the presence of DDIs in both programs. For example, in level 1, the number of DDIs in Rx mediapharma was 2047 (75%), in level 2 it was 591 (21%), and in level 3 it was 104 (4%), whereas in the lexi program, it corresponded to C 2195 (83%), D 312 (12%), and X 94 (3.6%). Of the DDIs, 36 were minor (B) and no was action needed (1.4%). With some drugs, such as atorvastatin/pantoprazole and domperidone/methochlorpramide, the lexi program did not show DDIs. However, other studies on this issue and drug prospectuses were found to have a potential interaction between these drugs (12). Another important aspect of our study was the evaluation of both programs and the detection of significant differences in the severity of DDIs and the comparison of DDIs in both programs. Therefore, the use of different programs when investigating DDIs and knowledge of the drug's properties may be more useful for preventing possible DDIs. In addition to the programs in which DDIs are identified, the participation of medical pharmacist physicians in patient visits, especially in units such as ICU and evaluation of drugs by these experts and giving information to other physicians in this sense is another important aspect for preventing DDIs.

CONCLUSION

The results of our study indicated that DDIs in the ICU were very common in our hospital and the frequency of DDIs increased directly proportionally to the duration of hospitalization, age, and number of drugs used. Moreover, these results indicated that patients should be closely monitored for the prevention of adverse effects, such as electrolyte disturbance, bleeding risk, arrhythmia, because the effects of the drugs diminished, and to monitor the drug orders or to use a variety of software. In our study, the possible clinical consequences of DDIs were evaluated. However, determining the frequency of clinical consequences that may result from potential DDIs is a more important finding for the evaluation of DDIs. In this sense, new prospective studies are needed to determine DDIs and frequency of ADRs which resulting from DDIs.

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