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Potential drug–drug interactions in a medical intensive care unit of a university hospital

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Background/aim: Drug–drug interactions (DDIs) can impact patient safety. Occurrence of clinically important DDIs is higher for intensive care unit (ICU) patients. This observational study aimed to evaluate the potential DDIs in medical ICU patients of a university hospital.

Materials and methods: The Medical Pharmacology Department organized consultation reports for ICU patients in order to detect the DDIs. To focus on clinically important DDIs, interactions in the C, D, or X risk rating categories of the Lexi-Interact online database were analyzed. Frequency and clinical risk rating categories of DDIs were detected. Relationship between number of prescriptions and DDIs were assessed. The most frequent drug/drug groups were identified.

Results: Of 101 ICU patients, 45.5% were found to have DDIs. We detected 125 C (72.2%), 37 D (21.4%), and 11 X (6.4%) risk category interactions. A statistically significant increase in the number of DDIs was shown with the number of prescriptions (P = 0.002). The most frequent DDIs were between agents acting on the cardiovascular system and corticosteroids (12.8%).

Conclusion: Results of this study show that pharmacological consultation plays a critical role in the recognition of DDIs for improvement of medication management and effective therapeutic endpoints without any adverse or toxic reactions.

Key words: Patient safety, adverse reaction, therapeutic failure, pharmacovigilance

1. Introduction

Alterations of pharmacological or clinical responses that occur during polytherapy are defined as drug–drug interactions (DDIs) (1). DDIs may lead to life-threatening adverse reactions or therapeutic failure by influencing the therapeutic efficacy of drugs. Five to twenty percent of serious adverse drug reactions due to DDIs have been reported to result in hospitalization or death (2). Many factors such as age, multiple diseases, and sex have been found to be risk factors for potential DDIs (3). Occurrence of DDIs is correlated with the number of prescriptions. Lima and De Bortoli Casiani demonstrated that incidence of DDIs increases by 10%–20% in patients using 10–20 drugs (4). In the elderly, DDIs may be diagnosed as adverse outcomes associated with drug therapy (5). The impact of DDIs on the mortality rate of elderly patients was determined in a retrospective research (6). Consideration of DDIs for patients in the intensive care unit (ICU) is critical for the quality of the patient's life. Clinically important DDIs are more likely for ICU patients with many medications, comorbid diseases, and altered organ functions (7). The rate of occurrence of potential DDIs in ICU patients (54%) was reported to be two times that of patients in other wards (8). The risk of DDIs can increase the length of hospital stay because new drugs are often added to an existing drug therapy (9).

Potential DDIs being reported early may prevent many complications, and this increases the medication safety of patients and promotes the quality of the patient's life. The present study was planned to detect the frequency and clinical severity of the potential DDIs of ICU patients.

2. Materials and methods

This is an observational and prospective study performed with the internal medicine patients of the ICU at the Marmara University Pendik Education and Research Hospital. This academic hospital has an eight-bed and closed-format ICU where pediatric and surgical patients are hospitalized in different ICUs and there is no data management system in the ICU to check on the occurrence of possible DDIs. The Medical Pharmacology Department organized reports on the first visit of the

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consultations for 4 months (April to August 2013) for ICU patients (n = 101) in order to determine possible DDIs in the medical ICU where 268 patients were consulted throughout 2013. The exclusion criteria were age below 18 years and duration of stay in the ICU of less than 24 h. Although the drug lists were checked every other day, the first data of all patients were included in this study. Demographic characteristics and medications on the charts were recorded and determination of DDIs was made on the first visit of ICU admission for each patient. Suggestions about dose adjustments were also given in the reports of patients with altered renal or hepatic functions based on the liver enzymes, blood urea nitrogen (BUN), creatinine, and albumin levels, recorded on the first visit of ICU admission for each patient. DDIs were evaluated using databases such as the Micromedex Health Care Series Volume 148, Rx Media 2013, Lexi Comp's Drug Information Handbook (19th Edition), the Lexi-Interact online "interactions checker", and PubMed by the same medical pharmacologist apart from the ICU and were presented to the intensivists. The DDIs were categorized in respect to their frequency among all detected DDIs. 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 C, D, or X risk rating categories in accordance with the Lexi-Interact online database system (10) (Table 1). Individual patient reports were uploaded to hospital database as consultation notes. Data were processed for statistical analysis and a test was performed using SPSS 15.0. Ethical approval for the study was provided by the Marmara University Ethics Committee (09.2013.0165).

3. Results

Prescriptions on the charts of ICU patients were recorded and analyzed using databases. The demographic variables of patients are presented in Table 2. Patients had elevated liver enzymes (28%) and creatinine levels (58%). Of the 101 patients, 29 (28%) were receiving vasoactive drugs such as norepinephrine or dopamine whereas 59 (58%) were on salbutamol, ipratropium bromide, or budesonide therapy. Only 43% of patients had one diagnosis and the rest had other concurrent diseases (Table 2).

Drugs were analyzed for DDIs and details are listed in Table 2. Of 101 ICU patients, 45.5% were found to have DDIs and 173 DDIs were established from the medication profiles of patients. We detected 125 category C (72.2%), 37 category D (21.4%), and 11 category X (6.4%) risk category interactions. Table 3 shows the drugs found to have X risk category interactions. As the number of drugs and the number of drug interactions were cross-tabulated, no interaction was detected in the prescriptions of 45 patients (44.5%; Table 4). A significant difference between the number of prescriptions and the number of interactions was found (P = 0.002). As the number of prescriptions rose above 7, it was found that 24.2% (n = 8) had one interaction and the remaining 75.8% (n = 25)

Table 1. Lexi-Interact Online DDI risk rating categories (10).

Risk rating	Action	Description
A	No known interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents.
B	No action needed	Data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use.
C	Monitor therapy	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects. Dosage adjustments of one or both agents may be needed in a minority of patients.
D	Consider therapy modification	Data demonstrate that the two medications may interact with each other in a clinically significant manner. A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken in order to realize the benefits and/or minimize the toxicity resulting from concomitant use of the agents. These actions may include aggressive monitoring, empiric dosage changes, or choosing alternative agents.
X	Avoid combination	Data demonstrate that the specified agents may interact with each other in a clinically significant manner. The risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

Table 2. Demographic characteristics and pharmacological data of the medical ICU patients (n = 101).

Demographic characteristics	Groups	Patients n	Patients %
Age	60.9 (female) 61 (male)	42 59	42 58
Number of diagnoses	1 2 3 4	43 38 15 5	42.6 37.6 14.9 5
Diagnoses	Pulmonary infectious disease (chronic obstructive pulmonary disease, pulmonary embolism, asthma) Malignant diseases (multiple myeloma, lung cancer, esophageal cancer, lymphoma, breast cancer, or colon cancer) Infectious diseases Renal failure Liver failure Rare: Cardiac disorders (congestive heart failure or coronary arterial disease), central nervous system diseases, trauma (traffic accident), familial Mediterranean fever, systemic lupus erythematosus, drug intoxication, diabetes mellitus, or hypertension	21 20 19 15 3	21 20 19 15 3
Biochemical variables	ALT (unit/L) <40 >40	73 28	72 28
	AST (unit/L) <40 >40	67 34	66 34
	BUN (mg/dL) 5–25 >25	35 66	35 65
	Creatinine (mg/dL) 0.5–1.1 >1.1	43 58	43 57
Pharmacological data	Categories	n	%
Number of ordered drugs	1–4 5–8 9–15 >15	8 59 30 4	8 58 30 4
Number of detected interactions	None 1 2 >2	45 23 7 26	45 23 7 25
Risk category of the interactions	C D X	125 37 11	72.2 21.4 6.4

Table 3. X risk rating category DDIs in the medical ICU patients.

Patient characteristics: sex (age), diagnosis	Interacting drugs	Predicted clinical outcomes by databases	Reference
Female (24), cystic fibrosis, pneumonia	Antibiotics - antidepressants (linezolid-mirtazapine)	Serotonin syndrome	(27)
Female (23), cystic fibrosis	Antibiotics - antidepressants (linezolid-escitalopram)	Serotonin syndrome	(27)
Male (53), prostate cancer, pneumonia	Antipsychotics - antidepressants (haloperidol-escitalopram)	Arrhythmia	(28)
Male (53), prostate cancer, pneumonia	Antipsychotics - antidepressants (ciprofloxacin-escitalopram)	Arrhythmia	(28)
Female (75), chronic myeloid leukemia, pericardial effusion	Antiarrhythmics - prokinetics (amiodarone-domperidone)	Arrhythmia	(29)
Male (73), pulmonary embolism	Antipsychotics - antiarrhythmics (haloperidol-amiodarone)	Arrhythmia	(29)
Male (66), chronic obstructive lung disease	Antipsychotics - antipsychotics (haloperidol-quetiapine)	Arrhythmia	(29)
Male (26), trauma	Antibiotics - antidepressants (ciprofloxacin-escitalopram)	Arrhythmia	(30)
Male (26), trauma	Antibiotics - antibiotics (ciprofloxacin-fluconazole)	Arrhythmia	(30)
Female (65), multiple myeloma	Antibiotics - antidepressants (ciprofloxacin-trazadone)	Arrhythmia	(30)
Male (26), trauma	$5HT_3$ antagonist - antidepressants (granisetron-escitalopram)	Arrhythmia	(31)
Female (24), acute lymphoblastic leukemia	Antipsychotics - $5HT_3$ antagonist (quetiapine-granisetron)	Arrhythmia	(32)
Male (42), hepatic cirrhosis	Anticholinergics (ipratropium) - potassium chloride	Ulcerogenic effect	(33)
Male (42), hepatic cirrhosis	Beta adrenergic receptor agonist - beta adrenergic receptor antagonist (salbutamol-propranolol)	Diminished bronchodilatory effect	(34)

had 2 or more interactions (Pearson χ^2 test, $\chi^2 = 9.40$, df = 1; P = 0.002). Analysis of the number of diagnoses and the number of interactions revealed no significant difference (Pearson χ^2 test, $\chi^2 = 6.347$, df = 1; P = 0.376).

The most frequent interactions were between agents acting on the cardiovascular system and corticosteroids (n = 13). Other frequent interactions were observed between 2 agents acting on the cardiovascular system (n = 12), an antibacterial agent and an antidepressant agent (n = 8), or an antidepressant and an antipsychotic agent (n = 6) (Table 5). Additionally, critical DDIs occurred between immunosuppressive agents and antidepressants or between opioids and antibacterial agents. An interaction between levothyroxine and carbamazepine that may cause a decrease in serum carbamazepine level was also detected.

4. Discussion

The results of this study show a high frequency of clinically important DDIs (C, D, and X risk categories) in medical ICU patients. Almost half of the patients (45.5%) were found to have DDIs. Both female and male patients were found to be on polytherapy with drugs that may possibly lead to serious DDIs. The most frequent interactions were detected between agents acting on the cardiovascular system and corticosteroids. As the number of prescriptions increases, the number of DDIs increases.

Table 4. Cross-tabulation of the number of drugs and DDIs.

Number of drugs	Number of detected interactions			
	None	1	>2	Total
1–3	8	0	0	8
4–7	29	15	8	52
>7	8	8	25	41
Total	45	23	33	101

The importance of DDIs in ICU patients has been defined in many studies (2,11). The frequency of DDIs may change for different ICU types, particularly for medical ICU and cardiac ICU patients (7). It has been reported that there were more DDIs in the cardiac ICUs than the medical ICUs (11,12). The most frequent drug groups involved in DDIs can show variability in different ICUs due to the comorbid diseases of patients. In ICU patients of Brazil, the most common DDIs were associated with nervous system drugs, midazolam and fentanyl (4). Aspirin and heparin or antithrombotic agents and antibacterial agents were the most common DDIs in other different medical ICU patients (7,13). A diltiazem and methylprednisolone interaction was the most frequent in our study. Because ICU patients have more than one diagnosis with comorbid diseases, medication regimens with polytherapy can be critical in producing unwanted DDIs. Patients in the present study had a variety of diagnoses involved in pulmonary and central nervous system disorders or malignancies. Some of the patients had renal or hepatic failure, which can influence pharmacokinetic properties of drugs and cause clinically serious DDIs. The number of prescriptions is also directly involved in the incidence of DDIs. Clinically vital adverse reactions can develop or therapeutic efficacy can be diminished with the increase in DDIs with use of multiple drugs. The risk of therapeutic failure in the emergency department of a university hospital was found to increase with the number of drugs, being greater due to the advanced age of the patients (14). A strong relationship between the number of prescribed drugs and the potential

Table 5. The most common DDIs detected between pharmacological groups in the ICU patients (n = 101).

Interacting drugs	Predicted clinical outcomes by databases	n	Frequency %
Drugs interacting with corticosteroids		13	12.8
Diltiazem-methylprednisolone	Increase in efficacy	8	7.9
Furosemide-methylprednisolone	Electrolyte disorder	5	4.9
Drugs interacting with cardiovascular system agents		12	11.8
Diltiazem-furosemide, isosorbide mononitrate-metoprolol, nifedipine-furosemide, pentoxifylline-diltiazem, pentoxifylline-propranolol	Increase in antihypertensive effect	7	6.9
Diltiazem-digoxin, furosemide-digoxin	Arrhythmia	3	2,9
Metoprolol-noradrenalin	Increase in efficacy	2	1.9
Antibacterial agents and antidepressant agents		8	7.9
Ciprofloxacin-trazadone, ciprofloxacin-escitalopram	Arrhythmia	4	3.9
Clarithromycin-mirtazapine, lopinavir-mirtazapine, ritonavir-mirtazapine	Increase in efficacy	3	2.9
Linezolid-mirtazapine	Serotonin syndrome	1	1
Antidepressant and antipsychotic agents	Increased risk of central nervous system depression		
Clonazepam-haloperidol, escitalopram-risperidone, clonazepam-haloperidol		3	2.9
Escitalopram-risperidone, escitalopram-haloperidol		2	1.9
Escitalopram-haloperidol	Serotonin syndrome Arrhythmia	1	1
Antibiotics and chemotherapeutics			
Clarithromycin-trimethoprim/sulfamethoxazole, moxifloxacin-trimethoprim/ sulfamethoxazole, ciprofloxacin-fluconazole, clarithromycin-fluconazole	Arrhythmia	4	3.9
Clarithromycin-fluconazole	Increase in efficacy	1	1
Sympathomimetic agents			
Noradrenalin-dopamine, noradrenalin-dobutamine, dopamine-dobutamine	Increase in efficacy	5	4.9

type C or type D DDI was reported in elderly Swedish patients (15). In our study 61% of patients on polytherapy with more than 7 drugs were found to have more than 2 DDIs, whereas this was 15% for patients using 4–7 drugs concurrently. The incidence of DDIs also increased with age. As seen in Table 4, 5 out of 8 patients, who were on polytherapy with the X risk category for drug interactions were over the age of 65. Geriatric pharmacology is one of the most challenging tasks in clinical medicine. Physicians should be aware of the fact that older patients, those over 65, are particularly susceptible to adverse drug reactions.

In earlier case reports concurrent use of antipsychotics and antidepressants such as linezolid and mirtazapine or sertraline was reported to lead to a life-threatening state, the serotonin syndrome (16,17). Because linezolid can block the intracellular metabolism of amines, it can interact with agents acting on amines such as serotonin or noradrenalin in neuronal synapses and can induce a lethal serotonin syndrome. This DDI is defined as X type in the Lexi-Interact database, indicating that there is enough evidence for clinical concern resulting from the concomitant use of drugs. Similar to Lexi- Interact, another database, Micromedex 2.0, defines this combination also in the contraindicated class. A female ICU patient with cystic fibrosis and pneumonia in this present study was detected to be using linezolid and mirtazapine. Physicians of the ICU were informed about this possible X risk category DDI and warned for possible symptoms such as hyperthermia, tachycardia, hyperreflexia, agitation, or confusion. Combination of antipsychotics and antidepressants can cause QT prolongation and result in a life-threatening ventricular arrhythmia, torsades de pointes, a well-known cause of ventricular fibrillation and sudden cardiac death (18). Although it has been suggested that antipsychotics and antidepressants, particularly serotonin reuptake inhibitors or tricyclic antidepressants, prolong QT interval independently, combination therapy has been reported to influence QT interval significantly compared to monotherapy with antipsychotics in female patients. In the present study a male ICU patient with pneumonia and prostate cancer was detected to be using haloperidol and escitalopram. The physicians were informed about this possible interaction, categorized as X in Lexi- Interact. However, the clinical importance of DDIs may vary according to database system. This interaction was in the 'moderate' class in Micromedex 2.0, which may result in an exacerbation of the patient's condition and require an alteration in therapy. These contradictory versions of DDI classifications can easily result in new DDIs and cause new health problems. Therefore, more than one reference or literature source should be investigated for evaluation of a DDI before deciding and writing reports that alert the physicians.

Pharmacokinetic DDIs can result in an increase or decrease in the therapeutic efficiency of the affected drug or can produce adverse or toxic reactions by changing the serum concentration of a drug. Diltiazem is a well-known calcium channel antagonist that inhibits the hepatic cytochrome P450 (CYP) 3A4 enzyme. Combination of diltiazem with prednisolone or methylprednisolone has been reported to increase the area under the curve of both drugs by reducing their clearance (19,20). As a result of this pharmacokinetic interaction, systemic exposure to corticosteroids increases. Therefore, dosages of steroids should be adjusted to prevent enhanced pharmacological responses or adverse/toxic reactions in concurrent use with diltiazem. The most frequent DDI group of the present study was found between corticosteroids and diltiazem or furosemide (12.8%). Corticosteroids can induce the hypokalemic effect of loop diuretics (21). Monitoring of serum electrolytes, especially potassium levels of patients, is recommended or an alternative diuretic can be substituted in order to avoid hypokalemia and subsequent arrhythmias. Although interactions between loop diuretics and corticosteroids can be considered to be a risk factor for enhanced hypokalemia, synergistic effects of these drugs have also been reported. Concurrent use of furosemide and methylprogesterone, particularly in patients with an acute myocardial infarction, was found to reduce the mortality rate (22). Monitoring of blood pressure and heart rate due to increases in the response to alpha or beta agonists can be suggested for patients who are using beta receptor blockers. Concurrent use of propranolol and norepinephrine was shown to increase blood pressure and decrease heart rate (23). Norepinephrine-dependent vasodilatation by beta-2 receptors can be blocked by nonselective beta blockers such as propranolol, whereas this effect has been reported to be less with metoprolol, a beta-1 selective antagonist agent (24). Therefore, it is critical for patients on norepinephrine therapy to use an alternative cardiovascular agent or a selective beta blocker rather than a nonselective one, or to optimize the dosage of norepinephrine. Patients (11.8%) of the present study were detected to be on combination therapy with cardiovascular agents. Antihypertensive agents such as calcium channel antagonists, beta receptor blockers, or diuretics may induce hypotensive effects in combination therapies. Although a combination therapy of antihypertensive agents is generally preferred for a more effective decrease in blood pressure, the hemodynamic status of patients should be followed closely in respect to additive or synergistic effects of these agents. Adverse or toxic reactions, particularly cardiovascular effects, may be increased with a combination of sympathomimetic agents such as norepinephrine, dopamine, or dobutamine. Therefore, blood pressure and heart rate monitoring of patients with concomitant use of sympathomimetic

agents is recommended to prevent the increased effects. According to Lexi- Interact, DDIs of sympathomimetics are in the C category and the therapy should be monitored. However, a combined use of sympathomimetic agents is frequently employed in ICU patients in order to improve the systemic hemodynamic effects. Norepinephrine and dobutamine have been shown to be a safer strategy than monotherapy with epinephrine in patients with cardiogenic shock in terms of lactic acidosis, heart rate, and arrhythmia (25). Also, no difference was found between the efficacy and safety of epinephrine and polytherapy with norepinephrine and dobutamine in patients with septic shock (26). Therefore, DDIs should be checked with a database system and reports for DDIs should be reviewed after evaluation of clinical trials.

To our knowledge, this is the first study evaluating the clinically relevant DDIs in Turkish intensive care patients. Interacting drug groups should be checked before administration to ICU patients. Our results showed the necessity of pharmacological consultation reports for detecting the potential drug interactions and informing physicians in order to prevent therapeutic failure or adverse/toxic reactions related to the use of combination therapies. Lack of clinical outcomes of the patients related to DDIs could be a limitation of this study. Although there are many theoretically defined DDIs, the clinical relevance of these interactions should be checked for evidence-based therapy. In this study, arrhythmia was the most frequently predicted clinical outcome as a result of DDIs; however, electrocardiographic data of the patients were not analyzed. As we lacked feedback from the intensivists about the outcome of the consultation reports, it would be valuable to see the extent of intensivists using the comments in the treatment of patients on the consecutive days. Future studies evaluating DDIs should be planned with multiple visits and larger populations of patients, not only to compare and follow up DDIs but also to track the clinical consequences of the potential interactions. Other medication or diminished hepatic or renal functions of the patient can lead to unwanted reactions. Therefore, follow-up of the patients is essential for determining the cause of clinical responses. In our study, patients with altered hepatic or renal functions were 28% and 58%, respectively. Suggestions on dose adjustments were made in the reports; however, the relationships between DDIs and altered organ functions were not assessed.

In conclusion, the results of this study showed that clinically important DDIs that may require therapeutic modification are fairly common in medical ICU patients under complex medication regimens. Since one of the aims of pharmacovigilance is to investigate the characteristics of adverse drug reactions, the role of pharmacological consultation is critical for not only the recognition of possible DDIs and making physicians aware of them but also for providing suggestions and alternative drugs in order to improve medication safety for the patients with many medications and comorbid diseases.

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