Drug-Drug Interactions In The Risky Population: Elderly, Urological Patients Admitted To The Intensive Care Unit

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ABSTRACT

Drug-drug interactions are a common health problem. They cause more serious side effects and are more common in patients with multiple diseases, especially in the elderly. It was aimed herein to examine the frequency of drug-drug interactions in elderly patients treated in the intensive care unit due to urological diseases.

This retrospective study was performed on hospitalized patients over the age of 85 years who had urologic diseases and were treated in the intensive care unit. Drug-drug interactions were evaluated using the Rx mediapharma and Lexi interact programs.

A total of 91 different medications were administered to 100 patients. Of the patients, 87 had drug-drug interactions and the total number of drug-drug interactions was 550. When all of the interactions were examined, it was observed that drug-drug interactions were most often to cause side effects on the cardiovascular system, such as arrhythmia, hypotension, or hypertension (40%). The drugs that were most involved in drug-drug interactions were furosemide (n: 87), enoxaparin sodium (n: 74), and acetyl salicylic acid (n: 45).

The results of the study showed that drug-drug interactions were seen quite frequently in elderly patients hospitalized due to primary urological diseases in the intensive care unit. The most common adverse drug reactions in these patients were bleeding, changes in the therapeutic levels of drugs, and hyperkalemia.

Keywords: Drug-drug interactions, urology, elderly, intensive care units

Introduction

Drug-drug interactions (DDIs) are defined as clinical and pharmacological events that result from simultaneous administration of 2 or more drugs. DDIs are characterized by an increased or decreased effect of drugs, mainly as a result of the interaction between 2 drugs in the body at the pharmacokinetic and pharmacodynamic level. These interactions also cause life-threatening adverse drug reactions (ADRs) (1). In various studies, it was determined that DDIs were responsible for approximately 17% of ADRs. DDIs are common in all hospital services, including hospitalized, outpatient, and primary care.

There are many factors that change the frequency of DDI occurrence. The most important of these are age, comorbid diseases, hepatic and renal dysfunction, genetic polymorphisms, and the way that drugs are administered (2). In addition to all these factors, the most important risk factor in seeing DDIs and ADRs is polypharmacy. Multiple drugs are administered in many hospitalized patients. However, the most important group of patients that undergo polypharmacy is elderly and intensive care patients (3). In intensive care unit (ICUs), a higher number of patients with serious diseases and polypharmacy are treated when compared to other hospital services. In addition, in many of these patients, the rate of metabolism of medications changes due to circulatory disorders and organ failure, and this increases the incidence of both DDIs and ADRs when compared to those in other services of the hospitals (4). In a previous study, it was found

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that the incidence of DDIs in patients hospitalized in the ICU was quite common (64%) (5).

The proportion of the elderly population increases on a daily basis. For example, it has been estimated that approximately one-fourth of the entire population will be composed of people aged 65 and over in England by 2034. It is anticipated that the highest increase will be in individuals over the age of 85, which is called the older group. Therefore, future health systems will be more concerned with the health needs and problems of the elderly population (6). Elderly individuals often have more than one chronic disease. This situation leads to multiple drug use. At the same time, in many of these patients, hepatic and renal clearance decreases, leading to a change in the pharmacokinetics of drugs. For all of these reasons, elderly patients constitute the most important patient group in terms of DDI and ADR risk (7). In a study of outpatient prescriptions of elderly patients in Taiwan, the potential DDI rate in these patients was found to be 25.6% (8). In a study conducted on elderly patients with cardiovascular disease in Ethiopia, it was found that polypharmacy and DDIs were quite common (9).

In this study, it was aimed to examine the frequency of DDIs in elderly patients treated in the ICU due to urological diseases and determine the potential clinical reflections that may occur after these interactions.

Materials and Method

Setting and Study Population: Approval was obtained from the scientific research board of the Malatya Training and Research Hospital for the study (decision number: 2018/21-7). This retrospective study was performed in patients over the age of 85 who were hospitalized due to urologic diseases in the ICU of the Training and Research Hospital located in Malatya, Turkey. No system was used to detect DDIs in the ICU. The information of 100 patients, who were hospitalized between 2017 and 2020, was scanned from the database used by the hospital. A total of 100 patients who received 2 or more systemic drugs were included in the study, while patients who were under the age of 85, hospitalized for less than 1 day, used less than 1 drug, were not given systemic medication, were hospitalized for a long period of time (3 or 4 mounts), and whose drug information was not determined properly were excluded. The demographic characteristics of the patients, diseases that caused their

hospitalization, comorbid diseases, duration of hospitalization, death-discharge status, medications administered during the hospitalization period, and the number of drugs and the dates were administered were recorded from the patient epicrises.

DDI Detection: When the DDIs were detected, attention was paid to the fact that 2 potentially interacting drugs were given to the patient at the same time. DDIs were evaluated using the findings of the Rx mediapharma drug information system, which was patented in Turkey and has been widely used for DDI detection throughout the country, in addition to the International Lexi-Interact program, drug prospectuses, pharmacology books, and findings from other similar studies in the ICU. The drug interactions, clinical results that may have occurred as a result of the interaction, and degree and frequency of the drug affected were recorded. The DDI level was classified according to the Rx mediapharma system as 1 = mild, 2 = moderate, and 3 = severe. DDI severity was classified as C = moderate, D = major, and X = severe according to the Lexi-Interact program. Hence, 1, 2, and 3, and C, D, and X were recommended for drug combinations in both programs. Thus, the following were used herein: 1, C = monitor therapy, 2, D = consider therapy modification, and 3, X = avoid combination.

Statistical Analysis: Data were performed descriptive statistics using IBM SPSS Statistics 23.0 (Armonk, NY, USA).

Results

The demographic characteristics of the patients are given in Table 1. There were more male patients than females (62%). Most of patients had undergone surgery due to benign prostatic hyperplasia and other urological problems and were followed-up in the postop ICU (30%), followed by patients who had been treated for infection (20%).

DDI Frequency: A total of 91 different medications were administered to 100 patients, a total of 1423 times. Of the patients, 87 had DDIs and the total number of DDIs was determined as 550. The average DDI rate per patient was 6.3.

Type of DDI: The number of DDIs with 5 or more interactions, classified according to clinical results, was 226 (41%) (Table 2). The number of level 1 DDIs was 399 (72.5%), level 2 was 117 (21.3%), and level 3 was 34 (6.2%). When all of the interactions were examined, DDIs were determined to most often

Table 1. Characteristics of the study population

Total patients (n: 100)	n	%
Male	41	41
Female	59	59
Discharge from hospital/transfer to general wards	67	67
Mortality	33	33
Age		
>95	6	6
≥85–95	94	94
Disease		
Cardiovascular diseases	31	31
Respiratory diseases	25	25
CNS diseases	16	16
Renal diseases	12	12
Trauma	7	7
Other diseases	8	8
Intoxication	1	1
Number of drugs used		
1–10	41	41
11–20	44	44
20>	15	15
CNS: central nervous system		

to cause side effects on the cardiovascular system (CVS), such as arrhythmia, hypotension, or hypertension (43%). This was followed by DDIs that may cause changes in the therapeutic effect of drugs, such as increased adverse or toxic effects or decreased therapeutic effects (22%) (Table 3). The drugs that were most involved in DDIs were furosemide (n: 87), enoxaparin sodium (n: 74), and acetyl salicylic acid (n: 45) (Table 4).

Discussion

In a meta-analysis, it was found that approximately 95.1% of patients over 65 years of age had comorbid diseases. In a study conducted in Scotland, this rate was found to be 81.5% in people over 85 years of age (9). The most important of these diseases are hypertension, ischemic heart disease, pain, chronic kidney failure, and diabetes. For this reason, elderly patients use many different drugs due to these comorbid diseases, and this can also lead to deadly levels of ADRs and increase the risk of DDIs. Another risk factor for DDIs in older people is physiological changes in the body. This situation concentrates on the distribution, excretion, and metabolism of drugs, causing ADRs that will not be seen in other people under normal conditions.

Various studies have found that DDI rates in the elderly ranged from 13% to 92% (10). It was also found that the rate of multiple drug use in patients between the ages of 73 and 78 was between 5% and 9.1% (10). Similar findings have been obtained in various studies conducted in different countries. For example, in Ireland, 78% of patients over the age of 70 developed at least 1 ADR within a 6-month period. It was found that the incidence of DDIs in elderly patients who stayed in nursing homes ranged between 1.5% and 46%, while it was between 3.3% and 55% in patients who stayed at home, and 11.5% and 80% for those who stayed in hospitals (6). In a study conducted in Taiwan, the DDI rate was found to be approximately 25.6% in elderly patients who applied as outpatients (7). It was determined that the rate of DDIs in elderly patients with cardiovascular disease in Ethiopia was 84.3% and 17.3% were serious DDIs. Also in this study, the most common DDIs were found to be those that could cause bleeding between acetylsalicylic acid and enoxaparin (8). In a meta-analysis, it was found that the drugs that interacted the most and at the highest frequency in DDIs in hospitalized elderly patients were ACE inhibitors, potassium-sparing diets, ACE inhibitors or ARBs, sulfamethoxazole or diazem, calcium channel

Table 2. DDIs in patients

Drug A	Drug B	Clinical consequences	n/%	Severity-Rx/lexi
Enoxaparin	NSAIDs, piracetam, clopidogrel, ASA, SSRI	Bleeding risk	48	1/C
Furosemide	ASA, NSAIDs	Effects of furosemide may decrease	30	1,C
Enoxaparin	Potassium chloride, ACE, ARB, spironolactone	Hyperkalemia	26	1/C
ASA	Clopidogrel, diltiazem piracetam, NSAIDs	Bleeding risk/adverse/toxic effect of ASA may increase	18	2/C(1)
Digoxin	Furosemide, spironolactone	Adverse/toxic effect of digoxin may increase	14	1/C
Midazolam	Magnesium sulfate, opioid analgesics, propofol, levetiracetam	Increased risk of central nervous system depression	9	2/C, only opiod D
Furosemide	Opioid analgesics	Adverse/toxic effect of furosemide may increase	6	1/C
Furosemide	Propofol, thiopental, amiodarone	Hypotension	9	1/C
Methylprednisolone	ASA, diltiazem	Adverse/toxic effect of methylprednisolone may increase	5	1/C
Methylprednisolone	Fluoroquinolones	Adverse/toxic effect of fluoroquinolones may increase	5	1/C
Fluoroquinolones	Domperidone, amiodarone	Arrhythmia	5	1/D,X
Furosemide	Insulin	Effects of insulin may decrease	8	1/C
Furosemide	ACE inhibitors	Hyperkalemia/effect of hypertensive may increase	6	1/C
ASA	ACE inhibitors	Nephrotoxicity/effect of antihypertensive may decrease	5	1/C
Furosemide	Phenytoin, antipsychotics	Effects of furosemide may decrease	6	1/C
Furosemide	Quetiapine	Increased risk of hypotension	5	1
Midazolam	Quetiapine, Magnesium sulfate, Tramadol	Increased risk of central nervous system depression	6	1/C
Total			226/41%	

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

blocker and macrolides, and digoxin and macrolide antibiotics (11). As far as is known, the current study is very important in terms of being the first to investigate the frequency of DDIs in elderly patients in Turkey. The findings of this study were similar to those mentioned above. The frequency of DDIs in elderly urological patients was quite high (87%). All of the patients had at least 1 concomitant disease. The most common comorbid disease was CVD (31%), and the second most common was lung diseases (25%). The drugs that interacted most frequently differed from some studies, but were generally similar. Most commonly, DDIs were the cause of ADRs, which could increase bleeding between enoxaparin, aspirin, non-steroidal anti-inflammatory drugs

Table 3. Potential clinical consequences of DDIs

	n/%
CVS side effects (such as arthmi, hypotension, hypertension)	236/43
Increased risk of side effects/toxicity	120/22
Changes in therapeutic effect of drugs	70/13
CNS side effects	48/9
Hyperkalemia	39/7
Nephrotoxicity	16/3
Nephrotoxicity + rhabdomyolysis	7/1.3
Hepatotoxicity	4/0.7
Ulcerogenic effect	4/0.7
Hypokalemia	2/0.4
Nephrotoxicity + ototoxicity	2/0.4
Rhabdomyolysis	2/0.4
Total	550/100

CVS, cardiovascular system; CNS, central nervous system

Table 4: Drugs most involved in DDIs

	n
Furosemide	87
Enoxaparin	74
Acetylsalicylic acid	45
Midazolam	23
Amiodarone	13
Fluoroquinolones	14
Diltiazem	13
Methylprednisolone	10

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

(NSAIDs), and clopidogrel. This was followed by furosemide between ASA and NSAIDs. The reason for the difference in the frequency of both the DDIs and other interacting drugs from other studies may have been due to the characteristics of the patients. In addition, the current study revealed that, since the rate of DDIs in the elderly and ICU inpatients was quite high, it was necessary to reduce the ADRs and possible mortality rate of these patients, and closely monitor them for DDIs.

Patients with urological problems were those who used relatively fewer drugs than individuals with CVS, lung disease, and internal diseases. Except for urological cancers, beta-lactam or quinolone group antibiotics are commonly used for urinary tract infections, while alpha-blockers, such as NSAIDs and alfuzosin, are used for benign prostatic hypertrophy. For this reason, people with general urological disease receive less polypharmacy treatment and thus, have a relatively lower risk of DDIs. Nevertheless, there is a risk of DDIs in urological patients due to comorbid diseases, and this condition is often overlooked in the clinic. At the same time, the lack of resources in the literature on this issue does not raise sufficient awareness in terms of DDIs for the clinician. Few studies have shown that DDIs also develop in urological patients. For example, in a study conducted in Germany, the rate of DDIs in patients in the urology clinic was found to be 25.5%. In the same study, the rate of drug-related problems was found to be 29.5% (12). Another disease that poses a risk for DDIs in urological patients is prostate cancer. For example, antiandrogens, such as bicalutamide, are widely used for prostate cancer. This drug is highly bound to plasma proteins. When used with drugs, such as warfarin, phenytoin, theophylline, and aspirin, which are highly bound, free drug concentration increases and toxic effects of the drug may occur (10). It has also been determined that DDIs can occur in many chemotherapeutic agents, such as Gnrh anologists, and in new generation antiandrogens, such as bitreaon acetate and doxtaxel. In the current study, the primary

disease of patients hospitalized in the ICU was of urological origin. The most common disease was in patients admitted for postop observation. The rate of inpatients due to urological malignancy was 12%. There were no patients who were receiving chemotherapy due to these diseases. Almost all of these patients had polypharmacy, and the emerging DDIs were generally those caused by drugs used for secondary disease. However, it was observed that antibiotics, which are widely used in urology, such as fluoroquinolone, were highly involved in the interactions (10%). This study was very important in terms of being the first study to investigate DDIs in urological patients in Turkey. However, there is still a need for new and comprehensive and studies on urological diseases in which drugs in this patient group are more specifically investigated.

The results of this study showed that DDIs were seen quite frequently in elderly patients hospitalized due to primary urological diseases in the ICU, and all of these patients had at least one comorbid disease and received multiple drug therapy. Again, the most common ADRs in these patients were bleeding, changes in the therapeutic levels of the drugs, and hyperkalemia.

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