11.02.2016 : müracaat tarihi / application date
20.04.2016 : kabul tarihi / acceptance date

Investigation of the presence of potential drug-drug interactions in the adult intensive care unit: a retrospective study

Yetişkin yoğun bakım ünitesinde potansiyel ilaç-ilaç etkileşimleri varlığının araştırılması: Retrospektif bir çalışma

* Halil Asci
** Yonca Sonmez
*** Mustafa Saygin
* Fatma Nihan Cankara
* Sukriye Yesilot
* Mustafa Kemal Yildirim

* Suleyman Demirel University, Medical Faculty, Department of Pharmacology, Isparta
** Suleyman Demirel University, Medical Faculty, Department of Public Health, Isparta
*** Suleyman Demirel University, Medical Faculty, Department of Physiology, Isparta

Corresponding Address:
Yrd. Doc. Dr. Mustafa Saygın
Suleyman Demirel University, Medical Faculty, Department of Pharmacology, Isparta
Phone: +90 246 2113605
e-mail: fizyolog@gmail.com

Özet

Amaç: Bu çalışmanın amacı, Üniversite Eğitim ve Araştırma Hastanesi Erişkin Yoğun Bakım Ünitesindeki hastalarda potansiyel ilaç-ilaç etkileşimleri türü ve sıklığı açıklamaktır. Gereç ve Yöntem: Bu çalışma Türkiye'de bulunan 18 yataklı erişkin Yoğun Bakım Ünitesine sahip Üniversite Eğitim ve Araştırma Hastanesinde yürütülmüştür. Çalışmaya Ocak 2013 ve Haziran 2013 tarihleri arasında yoğun bakım ünitesine yatırılan 111 hasta alınmıştır. İlaçlar anatomiksel kimyasal tedavi sınıflandırılmasına göre sıralanmıştır. Yoğun Bakım Ünitesine yatırılan 111 hasta çalışmaya dahil edildi. Potansiyel ilaç-ilaç etkileşimleri analizi için Lexi-Comp veritabanı kullanıldı. Bulgular: Altı aylık bir dönemde, 1681 potansiyel ilaç-ilaç etkileşimi toplam 102 (% 91.9) hastada belirlendi. 101 hastanın potansiyel ilaç-ilaç etkileşimlerinin en yaygın türü C tipidir (1232,% 73.2). Hastaların potansiyel ilaç-ilaç etkileşimleri ile polifarmasi varlığı, hastalık sayısı ve kalış süresi arasında anlamlı bir ilişki vardı. Potansiyel ilaç-ilaç etkileşimleri olan hastalarda meydana gelen ölümsayısı 68 (% 66.7) ve yoğun bakım ünitesinden taburcu edilen hasta sayısı 34 (% 33.3)' tür. D ve X-tipi potansiyel ilaç-ilaç etkileşimlerinin varlığı ile ilaçların sayısı ve yoğun bakımda kalış süresi arasında anlamlı bir ilişki vardı. Ayrıca ölüm oranı ile D-tipi ve X-tipi potansiyel ilaç-ilaç etkileşimleri arasında ilişki anlamlı derecede yüksekti. 49 (% 44.1) hastada adrenalin ve dopamin arasındaki etkileşim en sık görülen potansiyel ilaç-ilaç etkileşimleridir. Tartışma: Yoğun bakım hastalarında çoklu ilaç kullanımı ve hastalıkların sayısı; potansiyel ilaç-ilaç etkileşimleri ve polifarmasi görülme riskini, hastanede kalış süresini ve mortalite oranını artırmaktadır.

Anahtar Kelimeler: Potansiyel ilaç-ilaç etkileşimleri, yoğun bakım ünitesi, polimarfasi, mortalite

Abstract

Aim: The goal of this study is to describe the type and frequency of potential drug-drug nteractions in patients in the adult Intensive Care Unit of Research and Education University Hospital.Material and Method: This study was carried out in the research and education university hospital 18-bed adult Intensive Care Unit in Turkey. The study included 111 hospitalized patients in the Intensive Care Unit between January 2013 and June 2013. The drugs were classified according to the anatomical therapeutic chemical classification. Analysis of potential drug-drug interactions was performed using Lexi-Comp database.Results: In a six-month period, 1681 potential drug-drug interactions were detected in 102 (91.9 %) patients. In 101 patients the most common type of potential drug-drug interactions was C type (1232, 73.2%). The presence of potential drug-drug interactions and polypharmacy in patients had a significant relationship with the number of drugs, the number of diseases and the length of stay. In patients with potential drug-drug interactions, death occured in 68 (66.7%) patients and 34 (33.3%) patients were discharged from the intensive care unit. The presence of D and X-type potential drug-drug interactions had a significant relationship with the

between number of drugs used and the length of stay in the intensive care unit. Also death rate was significantly higher among D-type and X-type potential drug-drug interactions. Adrenaline and dopamine interactions were the most frequent potential drug-drug interactions in 49 (44.1%) patients. Discussions: In intensive care patients a multiple drug use and number of diseases increase potential drug-drug interactions, polypharmacy, the length of stay and the mortality rate. Additionally, the types of potential drug-drug interactions increased the same above mentioned parameter.

Keywords: Potential drug-drug interactions, intensive care unit, polypharmacy, mortality

Introduction

A process, when the effect of one drug is changed by the presence of another drug(s) is called drug-drug interactions (DDIs) (1, 2). DDIs occur through basically two mechanisms pharmacodynamics (at level of receptors) and pharmacokinetic (absorption, distribution, metabolism and excretion) events (3). The investigation of potential drug-drug interactions (pDDIs) is quite important because of using several drugs in various treatment management and the presence of comorbid disease in patients in the intensive care units (ICU). There are some study examined the frequency of these pDDIs in the literature. For example Uijtendaal et al. studied ICU patients and found 54% drug-drug interactions which two times more than the rate seen in patients in general wards (4). On the other hand, some of researchers examined types of pDDIs according to their clinical significance level (5). Besides, some studies investigated the relationship between polypharmacy defined as usage of 5 or more drugs, and pDDIs. Combined treatments are commonly associated with an excessive use of drugs, and their simultaneous use constitutes a risk factor for adverse drug reactions, interactions, medication errors, hospitalization, and diminishing adherence to drug therapy (6).The interactions between these drugs show their effects as synergism (additive effect) or antagonism that lead to loss of drug efficacy, or increase the drug toxicity in clinical conditions (7, 8). The presence of these interactions especially with narrow therapeutic indexed drugs (phenytoin, warfarin, digoxin, etc.) which are used in cases of vital importance leads to an increase in the duration of hospital stay and economic costs (9, 10). Moura et al. reported that DDIs were associated with a longer length of stay and were an important indicator of the quality of health care delivered (9). In addition, the investigation and monitoring pDDIs in the adult ICU may improve the quality of the treatment and will increase the survival rate of patients. Moreover, the results of this study, taking into account cultural and characteristic differences in an ICU in Turkey, will make an important contribution to the literature. Such differences may relate to the provision of pharmaceutical care or the availability of intensive care physicians in the environment. For example, the high altitude of the average age, the low overall socio-economic level, limited diversity of drugs and comorbid secondary disease appear to occur more frequent in Turkey and act the way physicians treat.
Some databases and indexes have been developed to evaluate risk assessment of pDDIs and minimize its adverse effects (11). In several studies the database program Lexi-interact was used to determine pDDIs according to the interaction classification (12, 13).
The goal of this study is to describe the type and frequencies of pDDIs in patients in the adult ICU of the research and education university hospital and to give some recommendations to improve the management of the treatment.

Materials and Methods

Ethical approval

The study was approved by the Ethics Committee of Clinical Researches at Suleyman Demirel University (SDU), Isparta/Turkey (No: 02/04/2014-62).

Study design

This retrospective study was carried out in a Research and Education University Hospital of Suleyman Demirel University in the 18-bed adult ICU in Isparta/Turkey between the dates of 01 January 2013 to 30 June 2013.
The study included 111 of all hospitalized patients in the ICU who were hospitalized for more than 24 hours who stayed for more than 24 hours in ICU. So, 125 of

236 patients were excluded from the study because of staying less than 24 hours. The type of patients categorized as surgical, trauma, coronary and medical that includes neurology, chest disease, internal medicine and oncology. We analyzed these data; type of patients, age, disease, comorbid diseases, all prescribed drugs, the length of hospital stay, and mortality throughout the hospital stay of all eligible patients using the medical record system of hospital, the nursing record sheets and epicrisis. The patients' medication records were checked daily. All drugs were classified according to the anatomical therapeutic chemical (ATC) classification.

The mean number of drugs used daily was calculated as the sum of all drugs prescribed over all hospital days divided by the total number of hospital days for one patient. When a patient was prescribed a drug in different dosing regimens, the agent was counted only once. Combinations of drugs with a potential to interact which were prescribed for more than 1 day for the same patient were counted only once (14).

Medications given by any route included enteral, peripheral intravenous, central venous catheter, or rectal administrations. Lipid solutions, nutritional supplements and formulation excipients, topical forms of the drugs received by patients, were also excluded from the study, but other drugs were included in the study. In related network database program, there was not any information about these drugs: ornidazole, lornoxicam, cefoperazone, piribedil, propylthiouracil, and metamizole sodium. According to this reason interactions of these drugs were not analyzed in 23 patients.

Analysis of pDDIs was performed using Lexi-Comp database (Lexi-Comp, Inc, Hudson, Ohio) and the software identified and classified the interactions into five categories according to risk rating as A, B, C, D, and X. The database was an electronic platform with sensitivity of 87–100 % and specificity of 80–90 % (15, 16). This database provides the classification of the interactions importance that was shown in Table 1. The progression of interactions from A to X is accompanied by an increased urgency for responding to the data. In general, type A (not demonstrated either pharmacodynamics or pharmacokinetic interactions) and type B (no evidence of clinical concern) show low clinical significance degrees.

Table 1 . Classification of importance of interactions.*

Risk Rating	Action	Description
A	No Known Interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions
B	No Action Needed	May interact with each other, but there is no evidence of clinical concern
C	Monitor Therapy	The benefits of concomitant use of these two medications usually outweigh the risks
D	Therapy Modification	Assess whether the benefits of concomitant therapy outweigh the risks or not
X	Avoid Combination	The risks associated with concomitant use outweigh the benefits
* Classification of importance of interactions were carried out using the software Lexi-Interact™ 2014		

Polypharmacy defined as patient received five or more drugs (17). Polypharmacy is the most common reason for pDDIs, and was calculated per patient receiving more than 5 drugs according to the nursing record sheets. The hospitalized patients' entire demographic information (age, sex), the number and frequency of diseases, administered drugs according to ATC classification, the presence of polypharmacy and pDDIs, the number and type of pDDIs, the length of stay, the relationship with the presence of polypharmacy, the most frequent pDDI pairs, the presence of D and X type pDDIs relationship among the number of drugs, number of diseases, length of stay were observed.

Data Analysis

Variables were presented as frequencies, percentages, mean±standard deviations, median or min-max. The Kolmogorov–Smirnov test was used to test the distribution of continuous variables and Levene test was used for homogeneity of variance. Data characterized by a normal distribution were expressed as mean and standard deviation. Parameters without such a distribution were expressed as median with minimum, maximum and interquartile range. The groups were compared using Pearson chi-square, Fischer's exact test, and Mann-Whitney U test. The relationship among the number of pDDIs and the number of drug used, the number of diseases, and the length of stay in hospital was evaluated using Spearman Correlation Analysis. $p<0.05$ was set as the value for significance.

Results

There were 111 patients enrolled in the study within 236 patients between the specified dates. In total of 111 patients, 67 (60.4%) patients were male and 44 (39.6%) patients were female. The number of the patients types are 63 (57%) medical, 33 (30%) surgical, 11 (10%) coronary and 4 (3%) trauma briefly. The mean age of the patients was 65.8±18.4. The median value of the length of stay was 7 (2-100) days. The mean value of diseases was 3.8±1.6, and respiratory diseases were found to be the most common diseases in the ICU patients. The number of drugs per patient was 17.0±8.2 and drugs for peptic ulcer disease were the most commonly used drugs according to the ATC classification. The presence of polypharmacy was found in 104 (93.6%) patients. Medications prescribed for patients in a six-month period were 1880 difference drugs, and 1681 pDDIs were detected in 102 (91.9 %) patients. In 101 patients the most common type of pDDIs was C type (1232, 73.2%). D type (241, 14.3%) and X type (44, 2.6%) pDDIs were also detected in 75 and 35 patients respectively (Table 2).

Table 2. Patient characteristics and incidence of clinically significant drug interactions (n=111)

Characteristic	Value
Sex	
Male, n (%)	67 (60.4)
Female, n (%)	44 (39.6)
Age, median (min-max), interquartile range	71 (21-100), 28
Length of stay, median (min-max), interquartile range	7 (2-100), 11
The number of diseases, median (min-max), interquartile range	3 (1-8),2
The most frequent diseases, n (%)	
- Respiratory Disease	100 (90.0)
- Cardiovascular Disease	47 (42.3)
- Neurologic Disease	17 (15.3)
- Malignancy	15 (13.5)
- Renal Disease	14 (12.6)
- Diabetes Mellitus	13 (11.7)
Number of medications, mean±SD*	17.0±8.2
The most frequently administered drug classes and individual drugs according to ATC classification, n (%)	
A02 - Drugs for acid related disorders	110 (99.1)
R05 - Cough and cold preparations	104 (93.7)
J01 - Antibacterials for systemic use	97 (87.4)
C01 - Cardiac therapy	85 (76.6)
B01 - Antithrombotic agents	85 (76.6)
N05 - Psycholeptics	82 (73.9)
Presence of polypharmacy, n (%)	104 (93.6)
Presence of drug drug interactions, n (%)†	102 (91.9)
Number of drug interactions, median (min-max), interquartile range	13.5 (1-73), 19
Presence of type of interaction, n (%)†	
A	17 (15.3)
B	62 (55.9)
C	101 (91.0)
D	75 (67.6)
X	35 (31.5)

The relationship between the presence of pDDIs and the type of disease were not significant (The presence of pDDIs; for surgery 93.9%, for medical 91.4%, or coronary 90.0%, for trauma 90.0%, p = 0.960)
There was no significant relationship between sex and pDDIs (Table 3). The number of pDDIs in women (18.1 ± 14.6) was more frequent than in men (13.5 ± 11.4) (p>0.05).
The presence of pDDIs in patients had a significant relationship with the presence of polypharmacy (p<0.001) and mortality (p<0.001) (Table 3).

Table 3. Presence of pDDIs relationship between sex, presence of polypharmacy and mortality#

	Presence of pDDIs				
	Present (n=102)		Absent (n=9)		P value**
	n	%*	n	%*	
Sex					
Female (n=44)	41	93.2	3	6.8	1.000
Male (n=67)	61	91.0	6	9.0	
Presence of polypharmacy					
Present (n=104)	101	97.1	3	2.9	<0.001
Absent (n=7)	1	14.3	6	85.7	
Mortality					
Present (n=68)	68	100.0	0	0.0	<0.001
Absent (n=43)	34	79.1	9	20.9	

#Verification of potential drug interactions was carried out using the software Lexi-Interact™ 2014.
*Row percentage, ** Fisher's exact test

The presence of polypharmacy and pDDIs relationships among the age, the number of drugs, the number of diseases and the length of stay were identified in Table 4. The median age of the patients with pDDIs was 71 (21-100) and the median age of patients without pDDIs was 52 (21-78). The median age of the patients with polypharmacy was 71 (21-100) and the median age of patients without polypharmacy was 53 (21-78). The presence of pDDIs (p=0.061) and the presence of polypharmacy (p=0.098) had not significant relationship with age. The presence of pDDIs in patients had a significant relationship with the number of drugs (r=0.80, p ≤0.001), the number of diseases (r=0.26, p=0.001) and the length of stay (r=0.60, p=0.001). The presence of polypharmacy in patients also had a significant relationship with the number of drugs (r=0.80, p <0.001), the number of diseases (r=0.26, p<0.001) and the length of stay (r=0.60, p=0.001).
In this study, the presence of D and X-type pDDIs had a significant relationship between the number of drugs (p<0.001 for both types) used and the length of stay (p<0.001 for both types) in the ICU. There was no significant relationship between the number of diseases and the presence of D (p=0.121), and X (p=0.137) types pDDIs (Table 5).
In patients with pDDIs, death occurred in 68 (66.7%) patients and 34 (33.3%) patients were discharged from the ICU. The relationship between the death and presence of pDDIs was found significant (p<0.001).
In patients with the presence of D-type pDDIs, death occurred in 54 (72.0%) patients and

Table 4. Presence of polypharmacy and pDDIs relationship between age, the number of drugs, the number of diseases and the length of stay#

	Presence of pDDIs Median (min-max)			Presence of polypharmacy Median (min-max)		
	Present (n=102)	Absent (n=9)	p value*	Present (n=104)	Absent (n=7)	p value*
Age	71 (21-100)	52 (21-78)	0.061	71 (21-100)	53 (21-78)	0.098
Number of drugs	18 (4-46)	5 (2-10)	<0.001	18 (6-46)	4 (2-5)	<0.001
Number of diseases	4 (2-8)	2 (1-5)	0.001	4 (2-8)	2 (1-2)	<0.001
Length of stay (day)	7.5 (2-100)	3 (2-9)	0.001	7.5 (2-100)	2 (2-4)	<0.001

#Verification of potential drug interactions was carried out using the software Lexi-Interact™ 2014.
* Mann-Whitney U test.

Table 5. Relationship between the presence of D-X type of pDDIs and number of drugs, number of diseases and length of stay#

	Presence of D type interaction median (min-max)			Presence of X type interaction median (min-max)		
	Present (n=75)	Absent (n=36)	p value*	Present (n=35)	Absent (n=75)	p value*
Number of drugs	21 (11-46)	14 (2-29)	p<0.001	21 (11-46)	14 (2-29)	p<0.001
Number of diseases	4 (2-8)	3 (1-8)	p=0.121	4 (2-8)	3 (1-8)	p=0.137
Length of stay	10 (2-100)	4 (2-95)	p<0.001	13 (2-100)	5 (2-34)	p<0.001

Verification of potential drug interactions was carried out using the software Lexi-Interact™ 2014
* Mann-Whitney U Testi

21(28.0%) patients were discharged from the ICU. In the presence of X-type, the death was occurred in 27 patients (77.1%) and 8 (22.9%) patients were discharged from ICU. The relationship between death and the presence of D type (p = 0.001) or X type (p = 0.020) was significant.

The most common interactions observed in patients, possible clinical significance levels and their possible effects were shown in Table 6.

Table 6. Top ten medication therapeutic classes that caused pDDIs, number of pDDIs, clinical significance level and possible effects of pDDIs.*

Interacting drug pair	Patients with potential DDIs n (%)	Clinical significance level (A-X)	Possible effects*
1- Adrenaline-Dopamine	49 (44.1)	C	Sympathomimetics may enhance the adverse/toxic effect of other sympathomimetics (eg, increased blood pressure, tachycardia).
2- Furosemide-Vecuronium + Rocuronium	40 (36.0)	C	Loop diuretics may enhance the neuromuscular blocking effect of neuromuscular-blocking agents.
3- Enoxaparin sodium-Potassium chloride	27 (24.3)	C	Heparin (Low Molecular Weight) may enhance the hyperkalemic effect of potassium salts.
4- Acetylsalicylic acid-Enoxaparin sodium	21 (18.9)	C	Each of these agents possess the potential to cause bleeding. Their combined use would seem to increase that potential.
5- Midazolam-Tramadol	21 (18.9)	C	CNS depressants may enhance the adverse/toxic effect of other CNS Depressants.
6- Adrenaline- Sodium Bicarbonate	19 (17.1)	C	Sodyum bicarbonate may decrease the excretion of alpha/beta-agonists.
7- Furosemide-Insulin NPH	17 (15.3)	C	Loop diuretics may diminish the hypoglycemic effect of hypoglycemic agent.
8- Dopamine-Linezolid	17 (15.3)	D	Linezolid may enhance the hypertensive effect of sympathomimetics.
9- Furosemide-Tramadol	17 (15.3)	C	Analgesics (Opioid) may enhance the adverse/toxic effect of diuretics.
10- Adrenaline-Linezolid	16 (14.4)	C	MAO Inhibitors may enhance the hypertensive effect of epınephrine.

Verification of potential drug interactions was carried out using the software Lexi-Interact™ 2014

Adrenaline and dopamine interactions were the most frequent pDDIs in 49 (44.1%) patients. The interactions between furosemide and neuromuscular agents (Vecuronium, Rocuronium) were observed in 40 (36.0%) patients. C-type pDDIs (moderate) was the most common type among the top 10 pDDIs. Aminophylline-midazolam, esomeprazole-carbamazepine, haloperidol-metoprolol are some examples of D-type pDDIs. On the other hand there are serious X-type pDDIs that physicians should avoid. For example, the interactions between atropine-ipratropium bromide, esomeprazole-clopidogrel, haloperidol- ipratropium bromide, carvedilol-salbutamol, amiodaron- ciprofloxacin and atropine-potassium chloride were seen.

Discussion

The goal of this study was to describe the types and frequency of pDDIs in patients in the adult ICU of the Research and Education University Hospital, and give some recommendations to improve the management of the treatment.

This study was performed on 111 patients in the ICU. In 104 patients, many significant findings were observed, such as the relationship between the presence and type of pDDIs and the number of drugs, the number of diseases and the length of stay. Additionally, the relationship between the type of pDDIs and the death rate was significant.

pDDIs and the presence of comorbid diseases lead to serious complications in elderly patients. In our study participants were elderly and had more comorbid diseases. Respiratory diseases especially respiratory insufficiencies were the most frequent diseases in patients in the ICU. Because, the respiratory insufficiency is among the most common reason for admission to the ICU (18).

The ICU patients often have multiple comorbid diseases that require multidrug therapy. An increase in the number of administered drugs also causes an increase in severity and incidence of pDDIs. The occurrence of interactions also results in the increase of the length of stay (19). Parallel to this, there was a statistically significant relationship between the presence of pDDIs with the number of diseases and the length of stay in the ICU, as observed in this study.

In a multicentered prospective study, comprising 398 patients from Brazil in 2006, physicians found that ranitidine was the most commonly used drug in the pediatric ICU for stress ulcer prophylaxis (20). Similarly, ranitidine, H2 receptor blocker, was found as the most commonly used drug, in our study.

Polypharmacy increased the risk of pDDIs encountering according to the multidrug treatment. In this study polypharmacy was detected in high rate that contributed to the increasing of severity and incidence of pDDIs.

C type (moderate) pDDIs was the most frequent type among pDDIs types. In a prospective study in a teaching hospital in Iran, C type pDDIs was the most frequent type identified and the results were concordant with our study (21). In C type, the benefits often outweigh the risks in combination and physicians must monitor the patients with C type pDDIs to minimize the side or toxic effects.

A few studies addressed the relationship between pDDIs and the other important factors, such as the length of stay, and the hospital mortality (22). In our study, increase in the number of diseases caused an increase in the number of drugs. The multiple medication use often resulted in polypharmacy and DDIs. Finally, all these parameters caused a prolonged length of stay. In addition, all of these factors may lead to a severe increase in the worsening of the patient's condition worsen and hospital cost severely.

Type of pDDIs has high importance which can change the course of treatment. Clinical significance levels of type C, type D, or type X always require the physicians' attention. Potential DDIs, especially D and X types were considered to be the major DDIs. In D type pDDIs; benefits of this interaction were greater than risks of these interacted drug pairs. Conversely, in X -type the risks were greater than benefits (23).

D and X types were defined as requiring therapy modification and avoiding combination respectively. For example, in several retrospective studies, an increased risk of negative cardiovascular-related outcomes associated with concurrent esomeprazole and clopidogrel was reported, because esomeprazole exhibited a statistically significant decrease in clopidogrel antiplatelet activity (24, 25). In this study; there were critical D and X type of pDDIs found in many patients. For instance, the concomitant use

of highest risk QTc-prolonging agent amiodarone with the other QTc-prolonging agent ciprofloxacin illustrates X type interaction because of increasing risk for serious toxicities, including the development of torsades de pointes or other significant ventricular tachyarrhythmias (26). Thus, physicians should avoid using of these drugs in combination.

In our study, the prevalence of D and X types of interaction increased with the number of drugs used. Prolongation was observed in the length of stay due to the severity of this type of pDDIs. There was no significant relationship between the presence of D and X-type pDDIs and the number of diseases. This situation showed that the increase in the number of diseases did not affect the type of pDDIs.

The presence of pDDIs and D-X type's affects mortality rate of patients (27). There was a relationship between the presence of D and X type pDDIs and the increase of deaths. These findings indicated that a severity of pDDIs may influence the condition of patients in the ICU. In a study performed on elderly patients in China, pDDIs were associated with an increased mortality (28).

As shown in Table 5, the most frequently pDDI was observed between dopamine-adrenaline in this study. These drugs have wide range usage in emergency situations in the intensive care. Both of these two drugs have sympathomimetic effects and the interaction is generally positive for the patient, increasing the heart rate (29).

Low doses of the commonly used loop diuretics appear to enhance blockade, whereas higher doses may diminish blockade. The mechanism of this interaction is unknown (30). Low molecular weight heparins (enoxaparin) suppress adrenal aldosterone secretion that has been widely reported as potential causes of hyperkalemia (31). So potassium levels must be monitored for preventing cardiac complications.

Both acetylsalicylic acid and enoxaparin sodium increase the potential of bleeding (32). That is why the diligence in monitoring diligence should be increased for signs and symptoms of bleeding if these agents are used concomitantly.

The usage of two central nervous system depressants midazolam and tramadol in combination will have more additive analgesic effects, ataxia, confusion, drowsiness, respiratory depression, and weakness (33, 34).

Sodium bicarbonate increases pH of urine which causes existing in a more absorbable non-ionized form of alpha/beta-agonist (35, 36). The loop diuretic furosemide diminishes the effect of insulin and might influence the glucose control, but it is unclear (37).

There are several mechanisms to avoid combinations of binary drugs which has D and X type interactions. For instance, if a concurrent use of ipratropium with any other drugs (atropine) cannot be avoided, it is necessary to monitor patients closely for evidence of anticholinergic-related toxicities (e.g., urinary retention, constipation, tachycardia, dry mouth, etc.).

The only one D type pDDIs in top ten interactions was dopamine and linezolid combination. In this combination, benefits of these two drugs are greater than risks. Linezolid primarily is an antibacterial drug that also has monoamine oxidase (MAO) inhibitory side effects (38). Administration of MAO inhibitors with dopamine or adrenaline can cause an accumulation of norepinephrine within adrenergic neurons at arterial blood vessels. So release of the stored norepinephrine by dopamine or adrenaline can increase blood pressure (39). To avoid or reduce the potential interaction between these drugs, it is necessary to reduce initial doses of sympathomimetic agents, and closely monitor for enhanced blood pressure elevations, in patients receiving linezolid. Specific dose adjustment recommendations are not presently available (15).

For furosemide and tramadol interaction; opioids may decrease the efficacy of diuretics causing the release of antidiuretic hormone (40). Although some opioids are also warned to cause the spasm of the sphincter of the bladder, which may lead to an acute urinary retention, especially in men with prostatic hypertrophy (41). Patients should be monitored for reduced efficacy of diuretics, and urinary retention when treated with both a diuretic and an opioid analgesic. So the best way to reduce the potential effects of pDDIs are monitorization of patients biochemically and clinically especially for D and X type of interactions. Although physicians must be aware of side effects and avoid from the use of these drug combinations.

Conclusions

In conclusion, physicians can avoid DDIs by monitoring, reducing or increasing the doses of interacted drugs and changing them. All these findings show that the awareness of pDDIs is very important for ICU patients. In the intensive care, patients' multiple drug use and the number of diseases increase pDDIs, polypharmacy, the length of stay and the mortality rate. Also the types of pDDIs increase the same parameters mentioned above. Physicians who work in these units should know the pDDIs and be careful for planning the treatment for patients.

Conflict of Interest

No conflict of interest was declared by the authors.

Acknowledgements

The authors declared that this study has received no financial support.

References

1. Bista D, Palaian S, Shankar PR, Prabhu MM, Paudel R, Mishra P. Understanding the essentials of drug interactions: a potential need for safe and effective use of drugs. Kathmandu Univ Med J. 2007;5(3):421-430.
2. Bjerrum L, Andersen M, Petersen G, Kragstrup J. Exposure to potential drug interactions in primary health care. Scand J Prim Health Care. 2003;21(3):153-158.
3. Beers MH, Storrie M, Lee G. Potential adverse drug interactions in the emergency room. An issue in the quality of care. Ann Intern Med. 1990;112: 61-64.
4. Uijtendaal EV, van Harssel LL, Hugenholtz GW, Kuck EM, Zwart-van Rijkom JE, Cremer OL et al. Analysis of potential drug-drug interactions in medical intensive care unit patients. Pharmacotherapy 2014;34(3):213-219.
5. Roblek T, Trobec K, Mrhar A, Lainscak M. Potential drug-drug interactions in hospitalized patients with chronic heart failure and chronic obstructive pulmonary disease. Arch Med Sci. 2014; 10(3): 920-932.
6. Rollason V, Vogt N. Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. Drugs Aging. 2003;20(11):817-832.
7. Lee A, Stockley IH. Drug interactions In: Walker R, Edwards C. Clinical Pharmacy and Therapeutics. 3rd edition. Churchill Livingstone, Philadelphia; 2003. p. 21-31.
8. Flepisi BT, Bouic P, Sissolak G, Rosenkranz B.Drug-drug interactions in HIV positive cancer patients. Biomed Pharmacother. 2014;68(5):665-677.
9. Moura C, Prado N, Acurcio F. Potential drug-drug interactions associated with prolonged stays in the intensive care unit: a retrospective cohort study. Clin Drug Investig. 2011;31(5): 309-316.
10. Kane SL, Weber RJ, Dasta JF. The impact of critical care pharmacists on enhancing patient outcomes. Intensive Care Med. 2003;29(5): 691-98.
11. Van Leeuwen RWF, Brundel DHS, Neef C, van Gelder T, Mathijssen RH, Burger DM, et al. Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer. 2013;108(5): 1071-1078.
12. Farhoudi M, Khalili H, Karimzadeh I, Abbasian L.Associated factors of drug-drug interactions of highly active antiretroviral therapy: report from a referral center. Expert Opin Drug Metab Toxicol. 2015;11(4):471-479.
13. Roblek T, Vaupotic T, Mrhar A, Lainscak M. Drug-drug interaction software in clinical practice: a systematic review. Eur J Clin Pharmacol. 2015;71(2):131-142.
14. Obreli-Neto PR, Nobili A, de Oliveira Baldoni A, Guidoni CM, de Lyra Júnior DP, Pilger D,et al. Adverse drug reactions caused by drug-drug interactions in elderly outpatients: aprospective cohort study. Eur J Clin Pharmacol. 2012;68(12):1667-1676.
15. Lexi-Interact™ Online. 2014, http://www.uptodate.com/crlsql/interact/frameset.jsp, Accessed: December 05, 2015.
16. Stoll P, Kopittke L. Potential drug-drug interactions in hospitalized patients undergoing systemic chemotherapy: a prospectivecohort study. Int J Clin Pharm. 2015;37(3):475-484.
17. Bjerrum L, Rosholm JU, Hallas J, Kragstrup J.Methods for estimating the occurrence of polypharmacy by means of a prescription database. Eur J Clin Pharmacol. 1997;53(1):7-11.
18. Rossi A, Ganassini A, Tantucci C, Grassi V. Aging and the respiratory system. Aging (Milano). 1996;8(3):143-61.
19. Tavakoli-Ardakani M, Kazemian K, Salamzadeh J, Mehdizadeh M. Potential of drug interactions among

hospitalized cancer patients in a developing country. Iran J Pharm Res. 2013; 2 (Suppl.):175-82.
20. Araujo TE, Vieira SM, Carvalho PR. Stress ulcer prophylaxis in pediatric intensive care units. J Pediatr (Rio J). 2010;86(6):525-530.
21. Haji Aghajani M, Sistanizad M, Abbasinazari M, Abiar Ghamsari M, Ayazkhoo L, Safi O, et al. Potential Drug-drug interactions in Post-CCU of a Teaching Hospital. Iran J Pharm Res. 2013;12(1):243-248.
22. Moura CS, Acurcio FA, Belo NO. Drug-drug interactions associated with length of stay and cost of hospitalization. J Pharm Pharm Sci. 2009;12(3):266-272.
23. Bacic-Vrca V, Marusic S, Erdeljic V, Falamic S, Gojo-Tomic N, Rahelic D. The incidence of potential drug-drug interactions in elderly patients with arterial hypertension. Pharm World Sci. 2010;32(6):815-21.
24. Ray WA, Murray KT, Griffin MR, Chung CP, Smalley WE, Hall K, et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. Ann Intern Med. 2010;152(6):337-345.
25. Evanchan J, Donnally MR, Binkley P, Mazzaferri E. Recurrence of acute myocardial infarction in patients discharged on clopidogrel and a proton pump inhibitor after stent placement for acute myocardial infarction. Clin Cardiol. 2010;33(3):168-71.
26. Ponte ML, Keller GA, Di Girolamo G. Mechanisms of Drug Induced QT Interval Prolongation. Curr Drug Saf. 2010;5(1): 44-53.
27. Rivkin A, Yin H. Evaluation of the role of the critical care pharmacist in identifying and avoiding or minimizing significant drug-drug interactions in medical intensive care patients. J Crit Care. 2011;26(1):104.e1-6.
28. Chiang-Hanisko L, Tan JY, Chiang LC. Polypharmacy issues in older adults. Hu Li Za Zhi. 2014;61(3):97-104.
29. Buijs EA, Reiss IK, Kraemer U, Andrinopoulou ER, Zwiers AJ, Ince C, et al. Increasing mean arterial blood pressure and heart rate with catecholaminergic drugs does not improve the microcirculation in children with congenital diaphragmatic hernia: a prospective cohort study. Pediatr Crit Care Med. 2014;15(4):343-54.
30. Scappaticci KA, Ham JA, Sohn YJ, Miller RD, Dretchen KL. Effects of furosemide on the neuromuscular junction. Anesthesiology. 1982;57(5):381-388.
31. Siebels M, Andrassy K, Vecsei P, Seelig HP, Back T, Nawroth P, et al. Dose dependent suppression of mineralocorticoid metabolism by different heparin fractions. Thromb Res. 1992;66(5): 467-73.
32. Kosar A, Cipil HS, Kaya A, Uz B, Haznedaroglu IC, Goker H, et al. The efficacy of Ankaferd Blood Stopper in antithrombotic drug-induced primary and secondary hemostatic abnormalities of a rat-bleeding model. Blood Coagul Fibrinolysis. 2009;20(3):185-190.
33. Okulicz-Kozaryn I, Leppert W, Mikolajczak P, Kaminska E. Analgesic effects of tramadol in combination with adjuvant drugs: an experimental study in rats. Pharmacology. 2013;91(1-2):7-11.
34. Worthley LI. Clinical toxicology: part I. Diagnosis and management of common drug overdosage. Crit Care Resusc. 2002;4(3):192-215.
35. Chang KY, Lee IH, Kim GJ, Cho K, Park HS, Kim HW. Plasma exchange successfully treats central pontine myelinolysis after acute hypernatremia from intravenous sodium bicarbonate therapy. BMC Nephrol. 2014;15:56.
36. Brater DC, Kaojarern S, Benet LZ, Lin ET, Lockwood T, Morris RC, et al. Renal excretion of pseudoephedrine. Clin Pharmacol Ther. 1980;28(5):690-69.
37. Weinberger MH. Mechanisms of diuretic effects on carbohydrate tolerance, insulin sensitivity and lipid levels. Eur Heart J. 1992;Suppl.G:5-9.
38. Flanagan S, Bartizal K, Minassian SL, Fang E, Prokocimer P. In vitro, in vivo, and clinical studies of tedizolid to assess the potential for peripheral or central monoamine oxidase interactions. Antimicrob Agents Chemother. 2013;57(7):3060-3066.
39. Rasmussen LE, Nedergaard OA. Effects of reboxetine on sympathetic neuroeffector transmission in rabbit carotid artery. J Pharmacol Exp Ther. 2003;306(3):995-1002.
40. Craft RM, Ulibarri CM, Raub DJ. Kappa opioid-induced diuresis in female vs. male rats. Pharmacol Biochem Behav. 2000;65(1):53-59.
41. Edwards RT, McCormick-Deaton C, Hosanagar A. Acute urinary retention secondary to buprenorphine administration. Am J Emerg Med. 2014;32(1):109.e1-2.