Journal of Critical Care 43 (2018) 1–6

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Clinical Potpourri

Risk factors for potential drug-drug interactions in intensive care unit patients☆

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ARTICLE INFO

Keywords:
Drug-drug interactions
Intensive care unit
Risk factors

ABSTRACT

Purpose: To determine risk factors for each severity-based category of potential drug-drug interactions (DDIs) encountered at intensive care unit (ICU) patients.
Methods: This was a retrospective cohort analysis of patients treated at the ICU of the Clinical Center Kragujevac, a public tertiary care hospital in Kragujevac, Serbia. Three interaction checkers were used to reveal drug-drug interactions: Medscape, Epocrates and Micromedex.
Results: The study included 201 patients, 66.19 ± 16.11 years of age. Average number of DDIs per patient ranged from 10.49 ± 8.80 (Micromedex) to 29.43 ± 21.51 (Medscape). Antiarrhythmic or anticonvulsant drug prescription, Charlson Comorbidity Index, male sex, length of hospitalization, number of drugs or therapeutic groups prescribed and surgery increased the risk of DDIs in ICU patients, while presence of delirium or dementia and transfer from emergency department to ICU protected against.
Conclusions: The rate of the DDIs in ICU patients at a tertiary care hospital is high, and adversely influenced by number of drugs or drug groups prescribed per patient, antiarrhythmic or anticonvulsant drug prescription, comorbidities, length of hospitalization and surgery. On the other hand, presence of cognitive deficit and transfer from emergency department to ICU protect ICU patients from the DDIs.

1. Introduction

Drug-drug interactions (DDIs) implicate changes in a drug's intended or adverse effects due to recent or concurrent use of another drug or drugs. There are several classifications of drug-drug interactions and one of the most important is the one according to severity: drug-drug interactions could be contraindicated, major, moderate and minor [1]. In order to detect and analyze suspected drug-drug interactions clinicians and researchers nowadays frequently use different computer platforms - personal digital assistant software programs [2]. These computer platforms are in the form of databases which can be updated regularly [3]. There are several online databases for detection and analyzing drug-drug interactions, like Micromedex [4], Lexi-Interact [5], Epocrates [6] or Medscape [7]. However, it is important to note that all of these databases have some shortcomings and discrepancies, especially in regard to classification of interactions according to severity, so it is advisable to use more than one database for checking drug-drug interactions [2].

Patients in intensive care units (ICUs) usually have severe and life-threatening illnesses so they frequently receive complex pharmacotherapy with large number of different drugs [8]. On average patients in intensive care unit are receiving 15 different drugs [9], which puts them under high risk of drug-drug interactions [10]. Incidence of clinically significant drug-drug interactions in tertiary health institutions is as high as 54%, whereas average number of interactions per patient is 1.7 [11]. Consequences of drug-drug interactions could be serious, like potentiation of side effects or increase in the toxicity of interacting drugs [9-12]. Drug-drug interactions are responsible for 5%–9% of all adverse drug reactions in hospitalized patients [13]. It is also known that drug-drug interactions contribute to increased morbidity and mortality of patients in ICUs [8].

Drug-drug interactions are more frequent in patients who are elderly, hospitalized for longer period of time, receive more drugs per day [14], and have severe comorbidities [15]. In addition, higher risk for occurrence of drug-drug interactions is noted in patients who are on antithrombotic and/or anticoagulant therapy [16]. Among the identified risk factors for drug-drug interactions in patients of ICUs, large number

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification; DDI(s), drug-drug interaction(s); ED, emergency department; ICU, intensive care unit.

☆ Conflicts of interest: none.

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http://dx.doi.org/10.1016/j.jcrc.2017.08.021
0883-9441/

of prescribed drugs per day, prolonged stay in intensive care unit and pharmacokinetic/pharmacodynamics characteristics of the administered drugs are supported with the largest body of evidence [17-21]. However, previous studies which examined the risk factors for the occurrence of interactions did not pay particular attention to the severity of interactions, but concentrated mostly on risk factors for drug-drug interactions in general. This study was designed to determine risk factors for each severity-based category of drug-drug interactions encountered at ICU patients in a tertiary care hospital.

2. Methods

Our study was designed as retrospective cohort analysis of patients treated at the Intensive Care Unit of the Clinical Center Kragujevac (CCK), a public tertiary care hospital in Kragujevac, Serbia. The cohort consisted of all consecutive patients who were admitted to the 14-beds central ICU between July the 1st 2016 and December the 31st 2016. The Ethics Committee of Clinical Center Kragujevac had approved the study prior to its initiation.

The data that are used for the study were collected from the patient's files. Pharmacotherapy data regarding every day of the patients' treatment were collected, as well as the sociodemographic and details about the patients' current conditions which could be potential risk factors for the occurrence of drug-drug interactions. The drugs were classified according to the Anatomical Therapeutic Chemical Classification codes (ATC) [22]. The following variables were taken into account for this study: socio-demographic data of the patients (age, gender), clinical history data (main diagnosis, length of hospitalization, transfer from other departments to the ICU, mechanical ventilation, previous surgeries, state of consciousness), comorbidities (especially presence of dementia or delirium, renal failure, liver cirrhosis, diabetes mellitus, chronic obstructive pulmonary disease, bronchial asthma, hypertension, heart failure), Charlson Comorbidity Index [23], in-hospital medication details (total number of prescribed drugs, number of different pharmacological/therapeutic subgroups [2nd level of ATC classification] prescribed, prescribing antiaggregation drugs, prescribing anticoagulants, prescribing anticonvulsants, prescribing antidepressants, prescribing antiarrhythmic drugs (other drug groups could not be considered as variables, because either such drugs were prescribed to almost every patient, e.g. analgesics or antibiotics, or just a few patients or none received particular drug group, e.g. there were several patients with antifungal drugs and none with HIV medication), drug-related skin rash, number of physicians who prescribed therapy to a particular patient), and interaction checker data (number and description of the DDI). Prescribed drugs were administered in doses and intervals according to recommendations from Summaries of product characteristics (SPCs) issued by Serbian Drug Agency, starting with the first doses for each day at 8 a.m.

For the purpose of this study a potential DDI was defined as possible interaction between two drugs, which might cause an alteration of the therapeutic effect and/or the toxicity of one or both of the drugs involved. The presence and classification of drug-drug interactions was determined by parallel use of three relevant interaction checker databases which operate on the principle of Internet applications: Medscape [7], Epocrates [6] and Micromedex [4]. Medscape categorized the severity of DDIs as Contraindicated, Serious – Use alternative, Monitor closely and Minor, Epocrates as Contraindicated, Avoid/use alternative, Monitor/modify therapy, Caution advised, and Micromedex as Contraindicated, Major, Moderate and Minor. The Micromedex also offered the documentation status of the interactions found (excellent, good, fair and unknown). Drug-enteral nutrition interactions were intended to be included in the study, but none was encountered.

2.1. Statistics

The study data were analyzed by descriptive statistics and presented in tables. Mean was used as a measure of central tendency and standard deviation as a measure of dispersion for continuous variables. Values of categorical variables were presented as rates or percentages. Influence of potential risk factors on number of drug-drug interactions per patient was evaluated by multiple linear regression analysis. Statistical validity of the regression was checked by analysis of variance (F value) and percentage of outcome (number of DDIs per patient) variability explained (R^2). Influence of potential risk factors on number of DDIs per patient was assessed by their B coefficients within the regression equation, including confidence intervals (CIs). All calculations were performed by the Statistical Program for Social Sciences (SPSS version 18).

3. Results

The study included 201 patients who were hospitalized in the ICU. Characteristics of the patients are shown in the Table 1. Only two patients (1%) didn't have a single drug-drug interaction detected by any of the used interaction checkers. Average number of potential drug-drug interactions detected by each of the interaction checkers is shown in the Table 2. The largest number of potential drug-drug interactions was detected by Medscape, followed by Epocrates and Micromedex.

Results of the last step of the backward multiple linear regression analysis are presented in the Tables 3–5. Variables entered at the beginning of the analysis for all types of drug-drug interactions were: number of prescribed drugs, number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, number of physicians who prescribed drugs to single patient, presence of delirium or dementia, Charlson Comorbidity Index, length of hospitalization, gender of the patient, age of the patient, transfer from another ward, transfer from emergency department, renal failure, surgery, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, anticoagulant therapy, drug-related skin rash, antiepileptic therapy, antiarrhythmic drugs, mechanic ventilation and state of consciousness.

Table 1
Characteristics of the study sample. Number of prescribed drugs included "as needed" drugs and ophthalmic or topical medication.

Variable	Mean ± standard deviation (range) or number (%)
Age (years)	66.19 ± 16.11 (2–93)
Gender	Male: 124 (61.7%) Female: 77 (38.3%)
Length of hospitalization (days)	6.67 ± 6.69 (1–32)
Transfer from another ward	122 (60.7%)
Transfer from emergency department	85 (42.3%)
Number of prescribed drugs	23.32 ± 9.72 (3–53)
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	11.93 ± 3.96 (2–25)
Number of physicians who prescribed drugs to single patient	4.49 ± 3.10 (1–14)
Drug-related skin rash	25 (12.4%)
Surgery	108 (53.7%)
Charlson Comorbidity Index	1.70 ± 1.85 (0–9)
Delirium or dementia	4 (2.0%)
Renal failure	19 (9.5%)
Liver cirrhosis	1 (0.5%)
Diabetes	40 (19.9%)
Chronic obstructive pulmonary disease	12 (6.0%)
Asthma	1 (0.5%)
Hypertension	92 (45.8%)
Heart failure	11 (5.5%)
Anticoagulant therapy	107 (53.2%)
Anticonvulsants	75 (37.3%)
Antidepressants	3 (1.5%)
Antiarrhythmic drugs	85 (42.3%)
Mechanical ventilation	183 (91.0%)
Coma	77 (38.3%)

Table 2
Average number of potential drug-drug interactions per patient.

Type of interaction	Mean ± standard deviation (range)
Medscape	
Contraindicated	0.00 ± 0.00 (0)
Serious – Use alternative	3.34 ± 3.45 (0–17)
Monitor closely	20.35 ± 15.21 (0–80)
Minor	5.74 ± 5.18 (0–30)
Total	29.43 ± 21.51 (0–105)
Epocrates	
Contraindicated	0.01 ± 0.10 (0–1)
Avoid/use alternative	3.28 ± 3.21 (0–14)
Monitor/modify therapy	8.22 ± 7.43 (0–35)
Caution advised	5.14 ± 5.19 (0–30)
Total	16.66 ± 14.27 (0–70)
Micromedex	
Contraindicated	0.10 ± 0.35 (0–2)
Major	5.84 ± 5.24 (0–28)
Moderate	3.71 ± 3.56 (0–19)
Minor	0.84 ± 1.07 (0–6)
Total	10.49 ± 8.80 (0–44)

When we compare all independent factors which entered final regression models we can see that 11 different factors were included. These factors in descending order of frequency are: number of prescribed drugs, antiarrhythmic drugs, number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, surgery, transfer from emergency department, anticonvulsants prescribed, delirium or dementia, length of hospitalization, number of physicians who prescribed drugs to single patient, Charlson Comorbidity Index and male sex (Fig. 1). Eight factors were positively correlated with number of drug-drug interactions, i.e. we can say that they contribute to their occurrence: antiarrhythmic drugs, anticonvulsants, Charlson Comorbidity Index, male sex, length of hospitalization, number of different therapeutic groups prescribed, number of prescribed drugs and surgery. Two factors were negatively correlated with number of drug-drug interactions (protective factors): delirium or dementia and transfer from emergency department. Number of physicians who prescribed drugs to single patient was negatively correlated with number of Serious – Use alternative interactions by Medscape (Table 3), but was positively correlated with the number of Caution advised interactions by Epocrates (Table 4).

The Table 6 shows the most frequent contraindicated/serious/major interactions detected by the interaction checkers. The most frequently occurring interaction was between midazolam and tramadol which was detected in 83 (41.3%) patients. More detailed description of the most frequent interactions discovered by the interaction checkers are shown in the tables included in the Supplementary file.

Table 3
Significant risk factors for potential drug-drug interactions detected by Medscape.

Variables	B	p	95%CI
Serious – Use alternative interaction			
Constant	−2.618	0.000*	−3.633 to −1.604
Number of prescribed drugs	0.246	0.000*	0.195 to 0.298
Number of physicians who prescribed drugs to single patient	−0.230	0.003*	−0.379 to −0.082
Surgery	1.888	0.000*	1.165 to 2.610
R^2; F (p)	0.514; 33.979 (0.000*)		
Monitor closely interaction			
Constant	−8.714	0.000*	−12.360 to −5.067
Number of prescribed drugs	1.180	0.000*	1.026 to 1.334
Delirium or dementia	−12.694	0.010*	−22.316 to −3.071
Antiarrhythmic drugs	4.255	0.004*	1.378 to 7.131
R^2; F (p)	0.604; 99.494 (0.000*)		
Minor interaction			
Constant	−5.054	0.000*	−6.540 to −3.658
Number of prescribed drugs	0.165	0.009*	0.042 to 0.288
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.384	0.005*	0.120 to 0.648
Length of hospitalization	0.137	0.002*	0.053 to 0.222
Antiarrhythmic drugs	1.448	0.003*	0.493 to 2.402
R^2; F (p)	0.637; 48.068 (0.000*)		

Variables included in the last step of the model: Serious – Use alternative interaction: number of prescribed drugs, number of physicians who prescribed drugs to single patient, Charlson Comorbidity Index, surgery, hypertension, antiarrhythmic drugs; Monitor closely interaction: number of prescribed drugs, delirium or dementia, antiarrhythmic drugs; Minor interaction: number of prescribed drugs, number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, delirium or dementia, length of hospitalization, anticoagulant therapy, antiepileptic drugs, antiarrhythmic drugs.
B – unstandardized coefficient.
CI – confidence interval.
p – statistical significance.
* Statistically significant.

Table 4
Significant risk factors for potential drug-drug interactions detected by Epocrates.

Variables	B	p	95%CI
Avoid/use alternative interaction			
Constant	−3.399	0.000*	−4.370 to −2.428
Number of prescribed drugs	0.133	0.001*	0.054 to 0.211
Length of hospitalization	0.075	0.006*	0.022 to 0.128
Surgery	1.234	0.000*	0.633 to 1.835
Anticonvulsants	0.808	0.012*	0.181 to 1.436
R^2; F (p)	0.610; 50.327 (0.000*)		
Monitor/modify therapy interaction			
Constant	−7.711	0.000*	−9.927 to −5.495
Number of prescribed drugs	0.224	0.020*	0.035 to 0.412
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.600	0.003*	0.211 to 0.989
Delirium or dementia	−4.969	0.048*	−9.901 to −0.038
Charlson Comorbidity Index	0.412	0.028*	0.045 to 0.779
Surgery	1.798	0.014*	0.363 to 3.233
Antiarrhythmic drugs	3.036	0.000*	1.597 to 4.475
R^2; F (p)	0.601; 41.346 (0.000*)		
Caution advised interaction			
Constant	−4.437	0.000*	−6.238 to −2.636
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.551	0.000*	0.392 to 0.709
Number of physicians who prescribed drugs to single patient	0.449	0.000*	0.243 to 0.656
Male sex	1.245	0.027*	0.146 to 2.345
Transfer from emergency department	−1.286	0.020*	−2.366 to −0.206
Antiarrhythmic drugs	1.821	0.001*	0.715 to 2.298
R^2; F (p)	0.478; 35.481 (0.000*)		

Variables included in the last step of the model: Avoid/use alternative interaction: number of prescribed drugs, number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, length of hospitalization, gender of the patient, surgery, anticonvulsants; Monitor/modify therapy interaction: number of prescribed drugs, number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, delirium or dementia, Charlson Comorbidity Index, length of hospitalization, surgery, antiarrhythmic drugs; Caution advised interaction: number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, number of physicians who prescribed drugs to single patient, gender of the patient, transfer from emergency department, antiarrhythmic drugs.
B – unstandardized coefficient.
CI – confidence interval.
p – statistical significance.
* Statistically significant.

4. Discussion

Our study showed that antiarrhythmic drugs, anticonvulsants, Charlson Comorbidity Index, male sex, length of hospitalization, number of different therapeutic groups prescribed, number of prescribed drugs and surgery increase the risk of DDIs in ICU patients, while presence of delirium or dementia and transfer from emergency department to ICU protect against them. There is also one factor whose influence is

Table 5
Significant risk factors for potential drug-drug interactions detected by Micromedex.

Variables	B	p	95%CI
Major interaction			
Constant	−3.981	0.000*	−5.322 to −2.639
Number of prescribed drugs	0.381	0.000*	0.323 to 0.439
Antiarrhythmic drugs	1.173	0.028*	0.127 to 2.220
R^2; F (p)	0.562; 62.529 (0.000*)		
Moderate interaction			
Constant	−3.033	0.000*	−4.193 to −1.874
Number of prescribed drugs	0.126	0.005*	0.039 to 0.213
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.256	0.012*	0.057 to 0.455
Transfer from emergency department	−0.828	0.026*	−1.554 to −0.102
Anticonvulsants	1.168	0.003*	0.396 to 1.941
Antiarrhythmic drugs	1.373	0.000*	0.624 to 2.121
R^2; F (p)	0.528; 30.637 (0.000*)		
Minor interaction			
Number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed	0.090	0.000*	0.052 to 0.128
Transfer from emergency department	−0.535	0.000*	−0.790 to −0.280
R^2; F (p)	0.275; 18.510 (0.000*)		

Variables included in the last step of the model: Major interaction: number of prescribed drugs, delirium or dementia, surgery, antiarrhythmic drugs; Moderate interaction: number of prescribed drugs, number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, delirium or dementia, transfer from emergency department, drug-related skin rash, anticonvulsants, antiarrhythmic drugs; Minor interaction: number of pharmacological/therapeutic subgroups (2nd level of ATC classification) prescribed, number of physicians who prescribed drugs to single patient, transfer from emergency department, antiarrhythmic drugs.
B – unstandardized coefficient.
CI – confidence interval.
p – statistical significance.
* Statistically significant.

equivocal, i.e. it depends on the interaction checker used: number of physicians who prescribed drugs to single patient.

When compared for their performance, drug-drug interaction checkers significantly vary between themselves. Although Micromedex is rated as the most competent, comprehensive, and user-friendly, Epocrates is the most accurate of the three, and it shares the second place with Medscape in regards to comprehensiveness [2]. However, if they are used in combination, sensitivity of revealing DDIs is increased, as demonstrated in our study: each of the three checkers revealed at least one interaction that would have been missed by the other two (see Supplementary file). Factors which in our study increase chances of DDIs according to all three checkers are number of prescribed drugs

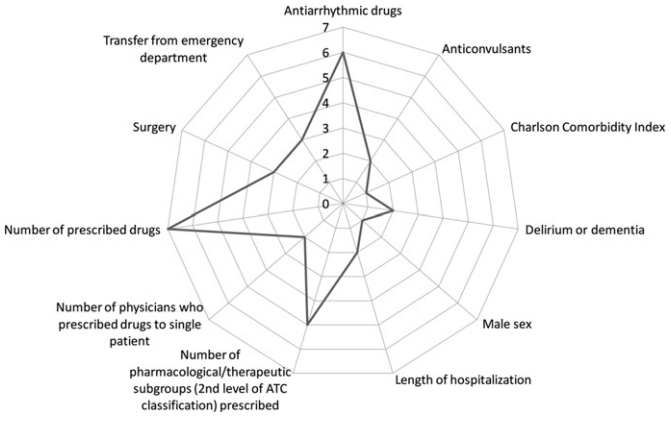

Fig. 1. Relative impact of factors associated with drug-drug interactions in ICU patients. Number in the graph designates how many times each factor was found to be significantly related to DDIs regardless of the severity.

or drug groups and prescription of antiarrhythmic drug(s), which gives to these factors special significance. A lot of previous studies came to the same conclusion that chances for DDIs increase with number of prescribed drugs, especially if they belong to different pharmacological groups. This was expected in a way, since many drugs share relatively limited number of elimination pathways and are not that selective in their action mechanisms [17-19]. Antiarrhythmic drugs are specific risk factor for DDIs in ICU patients due to their prolonging effect on QT-interval [24], which is shared with many drugs from other therapeutic groups, like antipsychotics, antidepressants, etc. However, while large number of prescribed drugs/drug groups increased risk of all severity categories of the DDIs, prescribing of an antiarrhythmic in our study facilitated emergence of mostly minor and moderate DDIs. This could be explained by common behavior of ICU physicians who pay little attention to DDIs which due to their low severity have little influence on drug selection [25].

It was not surprising that prescribing of anticonvulsants increased the number of serious (by Epocrates) and moderate (by Micromedex) potential DDIs, since phenobarbital, which is well known cytochrome inducer [26], was primarily prescribed, in order to prevent convulsions in immediate postoperative period after neurosurgery. Other anticonvulsants that were commonly used for prophylaxis after craniotomy are also drug-metabolism inducers, like phenytoin and carbamazepine. It remains open whether anticonvulsant use for prophylaxis is bringing more benefit than harm, since significant decrease in seizures rate was not demonstrated, and at least one study pointed to increased mortality, whose relation with pharmacokinetic drug-drug interactions could not be excluded [27].

Surgery during hospitalization in the ICU in our study was related to increased number of serious potential DDIs revealed by Epocrates and Medscape. It was already shown for potassium-increasing DDIs in patients after pulmonary allograft procedure [28], and is probably associated with increased drug prescribing in the immediate postoperative period, especially antibiotics and analgesics [29]. From the Table 6 one may see that the most frequent potential DDIs in our study, where 53.7% of patients underwent surgery, involved postoperative analgesics tramadol and ketorolac.

Prolonged hospitalization in our study was associated with increased rate of both moderate and serious potential DDIs (each additional day of stay in ICU increase number of DDIs for about 0.1), and this effect was already demonstrated in ICU patients from general (secondary care) hospital [19]. The effect of prolonged hospitalization on number of DDIs is probably indirect one, through increased number of prescribed drugs, as relation between hyper polypharmacy and hospitalizations was found previously [30]. Indeed, in our study very high number of drugs was on average prescribed to a patient (23.3), which at least partly could be explained by organizational issues at the study site. Intensive care physicians at CCK are working in 8-hourly shifts, sharing responsibility for patients in the ICU, so they make frequent changes of therapeutic regimens (adding or changing already prescribed drugs) according to their own understanding of patients' conditions, as recommendations from the clinical guidelines are usually not that specific. The treatment plans are not reviewed jointly, and high number of prescribed drugs reflects actual diversity of the physicians' knowledge, attitudes and behaviors.

It is interesting that cognitive impairment of the patients (delirium or dementia) and previous transfer of a patient from Emergency Department (ED) acted protectively in our study. While it is well known that multiple medication and DDIs may contribute to cognitive impairment, especially in elderly [31], protective effect of cognitive impairment against occurrence of DDIs was not demonstrated up to date. One of the explanations could be related to the fact that physicians take over complete responsibility for prescribing to cognitively impaired patients [32], who are in the same time deprived of the right to take on their own medication they were using at home before current hospitalization. However, true causes of this phenomenon remain to be elucidated by

Table 6
The most frequent contraindicated/serious/major potential interactions detected by the interaction checkers.

Drug combinations		Description	Number (%) of patients
Medscape			
Serious – Use alternative			
1.	Fentanyl + tramadol	Either increases effects of the other by pharmacodynamic synergism	49 (24.4%)
2.	Fentanyl + sevoflurane	Either increases effects of the other by pharmacodynamic synergism	48 (23.9%)
3.	Fentanyl + rocuronium	Either increases effects of the other by pharmacodynamic synergism	46 (22.9%)
4.	Metoclopramide + dopamine	Metoclopramide decreases levels of dopamine by pharmacodynamic antagonism	38 (18.9%)
5.	Epinephrine + amiodarone	Epinephrine and amiodarone both increase QTc interval	33 (16.4%)
Epocrates			
Contraindicated			
1.	Aspirin + ketorolac	Combo may increase risk of GI bleeding	2 (1.0%)
Avoid/use alternative			
1.	Midazolam + tramadol	Combo may increase risk of profound CNS and resp. depression, psychomotor impairment	83 (41.3%)
2.	Fentanyl + tramadol	Combo may increase risk of profound CNS and resp. depression, psychomotor impairment	49 (24.4%)
3.	Fentanyl + midazolam	Combo may increase risk of profound CNS and resp. depression, psychomotor impairment	48 (23.9%)
4.	Acetaminophen + phenobarbital	Combo may increase risk of acetaminophen toxicity, and decrease efficacy	28 (13.9%)
5.	Amikacin + furosemide	Combo may increase risk of ototoxicity, nephrotoxicity, hypocalcemia	25 (12.4%)
Micromedex			
Contraindicated			
1.	Diclofenac + ketorolac	Enhanced gastrointestinal adverse effects	4 (2.0%)
2.	Ketoconazole + midazolam	Increased midazolam concentrations, and potentially increased midazolam toxicity	3 (1.5%)
3.	Metoclopramide + risperidone	Increased risk of extrapyramidal reactions or neuroleptic malignant syndrome	3 (1.5%)
4.	Amiodarone + fluconazole	Increased amiodarone exposure and an increased risk of cardiotoxicity	2 (1.0%)
5.	Aspirin + ketorolac	Gastrointestinal adverse effects	2 (1.0%)
Major			
1.	Midazolam + tramadol	Increased risk of CNS depression	83 (41.3%)
2.	Amiodarone + ranitidine	Increased amiodarone exposure	55 (27.4%)
3.	Fentanyl + tramadol	Increased risk of respiratory and CNS depression; increased risk of serotonin syndrome	49 (24.4%)
4.	Fentanyl + midazolam	Increased risk of CNS depression	48 (23.9%)
5.	Metoclopramide + tramadol	Increased risk of seizures	45 (22.4%)

future, targeted research. On the other hand, emergency admission is associated with increase in rate of DDIs from the moment of admission to discharge, due to participation of many clinical specialties in the treatment of the same patient, who primarily (if not only) pay attention to their therapeutic area [33]. Indeed, rate of minor DDIs in our study increased with number of physicians involved in prescribing to single patient at ICU (see Table 4), while the opposite was true with serious interactions according to Medscape checker. At the study site all emergency patients were admitted to special Emergency Department, from which they were transferred later to either ICU or normal care wards, depending on their general condition. When transferred, the physicians from the ED have to review current therapy and explain prescribing rationale to the physicians from ICU, which is perfect occasion to discover at least some potential DDIs and avoid further administration of involved drugs if not absolutely necessary [34]. However, this plausible assumption needs confirmation by further research, probably using grounded theory or similar qualitative methodology.

Significant comorbidities increased rate of potential DDIs in our study, as it was previously observed by others [35]. Each comorbidity requires its specific drug therapy, and some hamper drug elimination capacity, leading to polypharmacy and a condition where otherwise minor interactions could have serious consequences. Even complete adherence to current therapeutic guidelines will result with significant number of DDIs in such circumstances, as recently demonstrated, because guideline developers do not pay enough attention to a variety of comorbid combinations [36].

Although we found that male patients had higher rate of DDIs than females, the opposite was reported from general hospitals in Iran [37] and Brazil [38], and no gender differences were observed in a study from Thailand [39]. Whether male or female patients will experience more DDIs probably depends on the settings where a study was done, because the settings are related to differences among genders in drug utilization rates. While it is known that females use more drugs as outpatients [40], these differences blend in general hospitals and the opposite could be true in tertiary care hospitals (like the one where this study was conducted) where number of prescribed drugs per patient is not further related to the patient's attitudes and preferences, but to severity of the patient's condition.

The limitations of our study are its unicentredness, which introduces bias of local and national quality of medical education in the results, and relatively modest sample size, which could have led to omission of some important factors with influence on the DDIs rate. Clinical outcomes of the patients related to the DDIs could not be followed in our study, which is another limitation. Many of the DDIs are only theoretically defined, and their clinical relevance remains unclear. It is clinician's judgment what is ultimately important to distinguish relevant from irrelevant interactions.

In conclusion, the rate of the DDIs in ICU patients at a tertiary care hospital is high, and adversely influenced by number of drugs or drug groups prescribed per patient, antiarrhythmic or anticonvulsant drug prescription, value of the Charlson Comorbidity Index, length of hospitalization and surgery. On the other hand, presence of cognitive deficit and transfer from emergency department to ICU protect ICU patients from the DDIs. Practicing physicians at ICUs should pay more attention (be “ultra-vigilant”) to the possibility of drug-drug interactions in patients harboring factors which increase their rate. If available in a hospital, clinical pharmacist or clinical pharmacologist could be of great help to ICU clinicians, as they may routinely make every-day check of possible interactions among drugs prescribed to high-risk ICU patients, and therefore prevent their actual occurrence.

Acknowledgments

This study was partially supported by bilateral scientific project between Serbia and Montenegro entitled “Risk factors for DDIs in tertiary care hospitals.”

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2017.08.021.

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