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Original article

Predictors of Potential Drug-Drug Interactions in Patients at Intensive Care Unit

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SUMMARY

Drug-drug interactions (DDIs) with serious adverse consequences for patients at intensive care unit (ICU) occur with the prevalence of 5.3%. The aim of our study was to reveal the risk factors for potential DDIs among the ICU patients.

This retrospective cohort analysis took place in the ICU of the Clinical Center Podgorica, Montenegro, between June 1, 2017 and September 30, 2018. The study was conducted as a chart review of the ICU patients (n = 99) who spent ≥ 2 days in the ICU. The main outcome measure was the number of DDIs per patient.

Ninety-four percent of patients had at least one potential DDI, while 20% of patients had at least one potential DDI which required a change of therapy. The number of potential DDIs per patient according to the Medscape was 6.6 ± 9.1 and 3.8 ± 4.9 according to the Epocrates. A higher number of drugs (or therapeutic groups) prescribed per patient increased the number of potential DDIs, including those which required a change of therapy.

The patients who were prescribed antiarrhythmics, anticoagulants or two antiplatelet drugs experienced more DDIs than patients without these therapeutic groups, while delirium, dementia and drug allergy were protective factors. The main limitation of our study was its uni-centerdness, which allowed for certain degree of bias.

Routine screening of the ICU patients with high number of prescribed drugs who receive antiarrhythmics, anticoagulants or double antiplatelet therapy for potential DDIs may prevent a great deal of DDIs with potentially deleterious effects.

Key words: **drug-drug interactions, risk factors, intensive care unit**

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INTRODUCTION

Drug-drug interactions (DDIs) with serious adverse consequences for patients at intensive care unit (ICU) occur with high prevalence of 5.3% and are responsible for almost 15.5% of all adverse drug reactions in that patient population (1). In principle, DDIs are all preventable if potential for their occurrence is noticed on time (2). There are numerous softwares providing for rapid, bed-side discovery of clinically relevant potential DDIs, which were already validated in practice, and demonstrated significant sensitivity and specificity. However, such tools differ among themselves in severity classification of DDIs and recommendations, and their use should be considered as a screening procedure only (3).

As with any screening tool, effectiveness of DDI checkers is much higher if used in subpopulations with high risk of the target problem. Risk factors for DDIs in patients at ICU were studied in several settings, and the following were repeatedly reported: the length of stay and number of drugs or therapeutic groups prescribed (3-6). However, a few other risk factors may be of importance, especially prescription of certain drug groups which are prone to DDIs, like anticonvulsants or anticoagulans (3), but their true significance remain to be elucidated. The aim of our study was to test the significance of previously identified risk factors for potential DDIs, as well as to search for other not yet investigated risk factors which could help with more precise definition of subpopulation of the ICU patients with high risk for DDIs.

METHODS

We conducted retrospective cohort analysis of patients treated at the Intensive Care Unit of the Clinical Center (CC), a public tertiary care hospital in Podgorica, Montenegro. The cohort consisted of all consecutive patients who were admitted to the 34-beds ICU between June 1, 2017 and September 30, 2018. The Ethics Committee of Clinical Center Podgorica had approved the study prior to its onset (No 03/01-1055/1 on 13.03.2017.).

The data used for the study were collected from the patient's files. The data about the patients' drug treatment, sociodemographic characteristics, and current conditions which could be potential risk factors for the occurrence of drug-drug interactions were entered in the study database. The drugs were classified according to the Anatomical Therapeutic Chemical Classification codes (ATC) (7). The following variables were followed in this study: socio-demographic data of the patients (age, gender), clinical history data (main diagnosis, length of stay in the hospital, mechanical ventilation, transfer from other departments to the ICU, state of consciousness, previous surgery), comorbidities (especially the presence of dementia or delirium, renal failure, liver failure, diabetes mellitus, chronic obstructive pulmonary disease, bronchial asthma, heart failure, hypertension), Charlson Comorbidity Index (8), and hospital medication details (total number of prescribed drugs, number of different pharmacological/therapeutic subgroups [2nd level of ATC classification] prescribed, prescription of antiplatelet drugs, anticoagulants, antiepileptic drugs, antidepressants, antiarrhythmic drugs (other drug groups could not be used as variables, because either such drugs were prescribed to almost every patient, e.g. analgesics or antibiotics, or just a few patients (or nobody) received particular drug group), drug-related allergy, number of physicians who prescribed therapy to a particular patient, and interaction checker data (number and description of the DDI). Prescribed drugs were administered according to the recommendations of Summaries of product characteristics (SPCs) issued by Montenegrin Drug Agency, starting with first doses for each day at 8 a.m.

The potential DDI in our study was defined as a 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 two relevant interaction checker databases which operate on the principle of Internet and Smartphone applications: Medscape (9) and Epocrates (10). Medscape had categories of the severity of DDIs as Contraindicated, Serious – Use alternative, Monitor closely and Minor, and Epocrates as Contraindicated, Avoid/ use alternative, Monitor/modify therapy and Caution advised. We clustered Contraindicated and Serious - use alternative DDIs according to Medscape as "potential DDIs that require change of drug therapy", as well as Contraindicated and Avoid/ use alternative according to Epocrates. The drug-enteral nutrition interactions were not observed in the study.

Statistics

The study data were in the first place tabulated and analyzed by descriptive statistics. Mean and median were used as a measure of central tendency and standard deviation and range as measures of dispersion for continuous variables. Values of categorical variables were presented as numbers or percentages. Multiple li-

near regression analysis was used to investigate the influence of potential risk factors on number of drug-drug interactions per patient. Statistical validity of the regression model was tested by analysis of variance (F value) and percentage of explained variability of the outcome (R^2). The influence of potential risk factors on the 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).

RESULTS

The study sample included 99 patients (32 females and 67 males) hospitalized at Intensive Care Unit (ICU) of Clinical Center in Podgorica, Montenegro. An average age of the patients was 56.0 ± 18.2 years. Ninety-four percent of patients had at least one potential DDI, while 20% of patients had at least one potential DDI which required a change of therapy. Detailed characteristics of the study patients are shown in Table 1.

Table 1. **Characteristics of the study sample**

PARAMETER	VALUE (mean ± SD or number)	VALUE (median and range or percent)
Age (years)	56,0 ± 18.2	61 (5-88)
Sex (M/F)	6. / 32	68% / 32%
Total number of potential DDIs per patient according to Medscape	6.6 ± 9.1	4 (0-43)
Total number of potential DDIs per patient according to Epocrates	3.8 ± 4.9	2 (0-28)
The number of potential DDIs per patient that require a change of drug therapy according to Medscape	0.9 ± 1.2	1 (0-7)
The number of potential DDIs per patient that require a change of drug therapy according to Epocrates	0.9 ± 1.2	1 (0-5)
An average number of drugs per patient	7.8 ± 3.5	8 (2-17)
An average number of prescribers per patient	1.9 ± 0.7	2 (1-4)
An average number of therapeutic groups (according to the ATC classification) prescribed per patient	6.0 ± 2.5	6 (0-13)
Charlson Comorbidity Index	3.1 ± 2.7	3 (0-9)
The length of stay in the hospital (days)	7.7 ± 5.3	6 (1-28)
Diagnosis of deliruim or dementia (yes/no)	4. / 95	4% / 96%
Transferred to the ICU from other ward (yes/no)	42. / 57	42% / 58%
Physically restrained for at least one day during hospitalization (yes/no)	42. / 57	42% / 58%
Confined to the bed (yes/no)	91. / 8	92% / 8%
Any degree of renal failure (yes/no)	26. / 73	26% / 74%
Having surgery (yes/no)	64. / 35	65% / 35%
Receiving anticoagulants (yes/no)	64. / 35	65% / 35%
Receiving double antiplatelet therapy (yes/no)	10. / 89	10% / 90%
Smoker (yes/no)	20. / 79	20% / 80%
Alcoholic (yes/no)	9. / 90	9% / 91%
Receiving anticonvulsants (yes/no)	33. / 66	33% / 67%
Receiving antiarrhythmics (yes/no)	13. / 86	13% / 87%
Drug allergy (yes/no)	2 / 97	2% / 98%

Table 2. **Predictor variables with significant influence on the number of potential DDIs according to the drug checker used and degree of severity**

DDI CHECKER USED AND SEVERITY OF DDIs	PREDICTOR VARIABLE	UNSTANDARDIZED „B" COEFFICENT	CONFIDENCE INTERVAL (95%)	P - VALUE
Medscape – all degrees of severity	*The number of drugs prescribed per patient*	1.023	0.526 – 1.521	0.000
	The number of therapeutic groups (ATC classification) prescribed per patient	1.277	0.621 – 1.933	0.000
	Prescription of double antiplatelet therapy	6.034	1.990 – 10.079	0.004
	Drug allergy	-12.205	-20.008 - -4.402	0.003
	Prescription of antiarrhytmics	9.924	5.336 – 14.512	0.000
Epocrates – all degrees of severity	*The number of drugs prescribed per patient*	1.187	0.940 – 1.434	0.000
	Diagnosis of deliruim or dementia	-6.393	-10.562 - -2.224	0.003
Potential DDIs that require a change of drug therapy according to the Medscape	Prescription of anitarrhytmics	1.085	0.320 – 1.849	0.006
	Prescription of anticoagulant therapy	0.860	0.307 – 1.414	0.003
Potential DDIs that require a change of drug therapy according to the Epocrates	Sex of a patient	0.462	0.039 – 0.885	0.033
	The number of drugs prescribed per patient	0.153	0.088 – 0.218	0.000
	The number of therapeutic groups (ATC classification) prescribed per patient	0.101	0.005 – 0.196	0.039
	Prescription of double antiplatelet therapy	1.278	0.721 – 1.836	0.000
	Drug allergy	-1.612	-2.734 - -0.490	0.006

When the number of potential DDIs per patient according to the Medscape interaction checker was taken as the outcome variable, multiple linear regression model ($R^2 = 0.773$, $F = 33.012$, $p = 0.000$) included the following independent and confounding variables: the number of drugs prescribed per patient, number of therapeutic groups (according to the ATC classification) prescribed per patient, prescription of double antiplatelet therapy, drug allergy, smoking and prescription of antiarrhythmics. Unstandardized B coefficients, their 95% confidence intervals and p-values are shown in Table 2 only for variables with significant influence on the outcome variable, for the purpose of clarity.

Multiple linear regression model with the total number of potential DDIs per patient according to the Epocrates interaction checker was slightly less explanatory ($R^2 = 0.645$, $F = 36.872$, $p = 0.000$), and included the following predictors: the number of drugs prescribed

per patient, prescription of double antiplatelet therapy and diagnosis of delirium or dementia. However, only the number of drugs prescribed per patient and diagnosis of delirium or dementia were significant predictors, as shown in Table 2.

When the number of potential DDIs per patient that require a change of drug therapy according to the Medscape was taken as the outcome variable, a multiple linear regression model ($R^2 = 0.402$, $F = 7.918$, $p = 0.000$) included the following independent and confounding variables: the number of therapeutic groups (according to the ATC classification) prescribed per patient, prescription of double antiplatelet therapy, prescription of antiarrhythmics, prescription of anticoagulant therapy and Charlson Comorbidity Index. Unstandardized B coefficients, their 95% confidence intervals and p-values are shown in Table 2 only for variables with significant influence on the outcome variable, again for the purpose of clarity.

Finally, the multiple linear regression model with the number of potential DDIs per patient that require a change of drug therapy according to the Epocrates was more explanatory than that with Medscape and therapy-changing DDIs ($R^2 = 0.662$, $F = 18.892$, $p = 0.000$), and included the following predictors: sex of a patient, number of drugs prescribed per patient, number of therapeutic groups (according to the ATC classification) prescribed per patient, prescription of double antiplatelet therapy, drug allergy and prescription of an anticonvulsant. However, only the sex of a patient, number of drugs prescribed per patient, number of therapeutic groups (according to the ATC classification) prescribed per patient, prescription of double antiplatelet therapy and drug allergy were significant predictors, as shown in Table 2.

The most frequent potential DDIs found in our study that require a change of drug therapy according to Medscape and Epocrates interaction checkers are shown in Table 3.

Table 3. **Top five potential DDIs that require a change of drug therapy according to Medscape and Epocrates interaction checkers, found in our study**

MEDSCAPE	EPOCRATES
ceftriaxone or cefuroxime + enoxaparine (ceftriaxone and cefuroxime increase the effects of enoxaparin)	**clopidogrel + enoxaparine** (increased the risk of bleeding)
phenobarbital + enoxaparine (phenobarbital decreases effects of enoxaparin by increasing metabolism)	**clopidogrel + fluconazole** (decreased clopidogrel efficacy by inhibition of metabolism)
propofol + norepinephrine (propofol increases plasma levels of norepinephrine by decreasing metabolism)	**benzodiazepines + tramadol** (increased sedation and risk of respiratory depression)
ceftriaxone + calcium gluconate (chemical incompatibility and precipitation of drug complexes in tissues)	**ceftriaxone + calcium gluconate** (chemical incompatibility and precipitation of drug complexes in tissues)
furosemide + gentamycin (increased ototoxicity and nephrotoxicity)	**beta blockers + insulin** (prolonged hypoglycemia and masked hypoglycemia)

DISCUSSION

Our study confirmed the findings of others that the larger number of drugs (or therapeutic groups) prescribed per patient increases the number of potential DDIs in ICU patients, including those which require a change of therapy. However, we also found that the patients who were prescribed antiarrhythmics, anticoagulants or two antiplatelet drugs experienced more DDIs than patients without these therapeutic groups. On the other hand, delirium or dementia and drug allergy were

protective factors, which largely decreased the chances of and the number of DDIs. Finally, the male sex increased the chances of DDIs in ICU patients.

While the number of prescribed drugs or drug groups is linked to chances of DDIs for purely mathematical (statistical) reasons (11), an increased number of DDIs after prescription of antiarrhythmics, anticoagulants or antiplatelet drugs could be explained by high potential of these drugs to interact both pharmacokinetically and pharmacodynamically with numerous drugs from other groups. Indeed, studies of ICU patients showed that agents acting on the cardiovascular system, aggregation and coagulation are the most frequently engaged in DDIs (12, 13) because coagulation and platelet aggregation are complex processes with multiple regulatory points (where many drugs may interfere) and heart rhythm is based on coordinated functioning of ion channels, which are target of action not only of antiarrhythmics, but of anticonvulsants, anesthetics, psychotropic drugs, and others (14). Although only 10% of our patients received double antiplatelet therapy and only 13% antiarrhythmic drugs, DDIs from these groups were among the top five (Table 3).

Delirium and dementia are drug-induced in about 10% of cases (15), but, paradoxically, when observed in a patient, they may have protective effect against DDIs, as observed in our study. Deleterious effects of delirium in ICU patients were recognized, and current guidelines for treatment of such patients require among other careful analysis adjustment of drug therapy as well, which decreases the chances of DDIs (16). Routine checking of prescribed drug therapy for DDIs in ICU patients with the signs of delirium or dementia is increasingly performed in various healthcare settings (17).

Protective effect of drug allergy status of an ICU patient against DDIs could be explained by increased attention of prescribers to all aspects of drug therapy when prescribing to such patients. Prescribers not only avoid all drugs and drug groups which may cross-react with the drug a patient is allergic to, but also check for potential DDIs, which is not a routine procedure otherwise (18).

Although in our study male sex turned to be a weak risk factor for potential DDIs in ICU patients, other studies gave conflicting results, either showing no influence of gender, or favoring either female or male sex interchangeably (19) (3) (20). Further studies are necessary to clarify the influence of gender to DDIs in ICU patients.

The main limitations of our study were its unicenterdness, which allows for certain degree of bias introduced by local policies and practices, and a relatively small study sample, dictated by admission rate to the ICU in Podgorica. A larger sample of ICU patients would in-crease statistical power and allow for inclusion of more potential risk factors in the regression analysis.

CONCLUSION

In conclusion, our study showed that ICU patients with a high number of prescribed drugs who receive antiarrhythmics, anticoagulants or double antiplatelet therapy are at higher risk of experiencing DDIs. Routine screening of such patients for potential DDIs by means of drug-drug interaction checking software may prevent a number of DDIs with potentially deleterious effects and increase their chances for survival and recovery.

Human rights

The study was approved by the ethical review board.

A name and date approval granted by the ethical board is included in the manuscript.

A written or verbal informed consent was not obtained from each patient included in the study, because the study was retrospective and based on documentation only. The written informed consent was not necessary because no patient data has been included in the manuscript.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

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Authorship

All of the authors did the following:

(i) contributed to the concept or design of the work, acquisition, analysis and interpretation of data;

(ii) Drafted the article and revised it critically for important intellectual content;

(iii) Approved the version to be published;

(iv) Each author participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Availability of data and materials

The table with original data is available from the corresponding author on request.

Informed consent

The study was conducted in accordance with the principles of Helsinki Declaration for research on human subjects. Written or verbal informed consent was not obtained from each patient included in the study, because the study was retrospective and based on documentation only. Written informed consent was not necessary because no patient data has been included in the manuscript.

Ethical approval

The study was endorsed by the Ethics Committee of Clinical Center in Podgorica, No 03/01-1055/1 on 13.03.2017.

Conflict of interest

The authors declare that there is no conflict of interest.

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Prediktori mogućih interakcija između lekova kod pacijenata u intenzivnoj nezi

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SAŽETAK

Interakcije između lekova (IIL) sa ozbiljnim posledicama po pacijente u intenzivnoj nezi (IN) događaju se sa prevalencijom od 5,3%. Cilj naše studije bio je da otkrije faktore rizika za nastanak mogućih IIL kod pacijenata u IN.

Ova retrospektivna kohortna studija sprovedena je u IN Kliničkog centra Podgorica, Crna Gora, između 1. juna 2017. i 30. septembra 2018. godine. Studija je sprovedena u vidu analize terapijskih lista pacijenata (n = 99), koji su proveli ≥ 2 dana u IN. Glavni ishod studije bio je broj mogućih IIL po pacijentu.

Devedeset četiri procenta pacijenata imalo je bar jednu moguću IIL, dok je 20% pacijenata imalo bar jednu moguću IIL koja je zahtevala promenu terapije. Broj mogućih IIL po pacijentu prema Medscape softveru bio je 6,6 ± 9,1, a 3,8 ± 4,9 prema softveru Epocrates. Veći broj propisanih lekova (ili terapijskih grupa) po pacijentu bio je povezan sa većim brojem potencijalnih IIL, uključujući i one koje su zahtevale promenu terapije.

Pacijenti kojima su propisani antiaritmici, antikoagulansi ili dva antiagregaciona leka imali su više potencijalnih IIL nego pacijenti bez tih terapijskih grupa, dok su delirijum, demencija i alergija na lekove delovali protektivno. Glavno ograničenje naše studije je činjenica da je sprovedena samo u jednom centru, što je moglo uneti neproporcionalno veliki uticaj lokalne kliničke prakse.

Rutinska kontrola mogućih IIL kod pacijenata u IN sa velikim brojem propisanih lekova, među kojima su antiaritmici, antikoagulansi i dvostruka antiagregaciona terapija, mogla bi sprečiti nastanak velikog broja IIL sa mogućim teškim posledicama.

Ključne reči: **interakcije između lekova, faktori rizika, intenzivna nega**