Drug-drug interactions and potential adverse outcomes among hospitalized patients in Gjilan region, Kosovo

Driton Shabani[1,2], Petrit Bara[2], Klejda Hudhra[2], Ledian Malaj[2], Besnik Jucja[2], Adnan Bozalia[1]

[1]Department of Pharmacy, Faculty of Medicine, University of Pristine, Kosovo;
[2]University of Medicine, Tirana, Albania.

Corresponding author: Driton Shabani, Faculty of Medicine, Pristine;
Address: Rr. "Bulevardi i Dëshmorëve", p.n. 10000, Pristine, Kosovo;
Telephone: +37744 178150; E-mail: farmacisti_gl@hotmail.com

Abstract

Aim: Drug-drug interactions are increasingly acknowledged as an area of major concern in medical care due to their serious health consequences and clinical damage. Our aim was to assess the potential adverse outcomes of drug-drug interactions among hospitalized patients in Gjilan region, Kosovo.

Methods: This was a cross-sectional study which included a representative sample of 1921 patients aged 18 years and over (50.3% women) from the regional hospital of Gjilan, Kosovo, during 2011-2013. Drug-drug-interactions were assessed employing the Drug Interactions Checker within www.drugs.com database. In addition, potential adverse outcomes of drug-drug interactions, other relevant clinical data, as well as demographic and socioeconomic information were collected.

Results: Overall, 1192 (62%) of the patients experienced drug-drug interactions. Of these, 30% had major interactions, 37% moderate interactions, whereas 33% manifested minor interactions. Main adverse outcomes included liver damage, treatment failure, kidney damage, hemorrhage, anemia, nerve damage, or a decrease in treatment efficacy.

Conclusions: Our study highlights the main adverse effects of drug-drug interactions among adult patients in a regional hospital of Kosovo. Health professionals in transitional Kosovo should be aware of the importance of a careful selection of drugs and a proper pharmaceutical care for their patients in order to avoid negative consequences of drug-drug interactions.

Keywords: adverse outcomes, drug-drug interactions, Gjilan region, hospitalized patients, Kosovo, severity.

Introduction

In the past decades, drug-drug interactions are progressively recognized as a very important area of medical services in most of the countries worldwide (1). This situation is due to the abundant evidence which has indicated a considerable negative effect and serious clinical damage of various types of drug-drug interactions (2,3). Indeed, different drug-drug interactions have been linked to a whole array of negative health consequences such as treatment inefficacy up to full failure, as well as increased toxicity including liver damage, kidney damage, or anemia (4,5).

In Kosovo, notwithstanding the information scarcity, there is some evidence, not well-documented though, pointing to a high degree of drug interactions which is linked to serious toxic effects and other negative health consequences especially in the adult population (6). In addition, the circumstances involving the elderly people in Kosovo are particularly worrying because this population subgroup is extremely dependent on multiple drug use due to the high degree of co-morbidity (6).

We have recently reported about the prevalence and socioeconomic and clinical correlates of drug-drug interaction among the adult population of Kosovo (7). According to this fairly recent report, the prevalence of drug-drug interaction among adult patients from the regional hospital in Gjilan was about 62% (7). Main demographic and socioeconomic correlates of drug-drug interaction in this study population of Kosovo adult patients included older age and a lower educational level. On the other hand, the most important clinical "determinants" included an excessive length of hospitalization, presence of co-morbidity and especially the excessive number of drug intake (7).

In any case, the information about the severity and the exact adverse outcomes of drug-drug interactions in the population of Kosovo is scarce. In this framework, the aim of this study was to determine the severity and the potential adverse outcomes of drug-drug interactions among the adult hospitalized patients in Gjilan region, Kosovo.

Methods

In this cross-sectional study, conducted in the regional hospital of Gjilan, Kosovo in 2011-2013, there was included a large representative sample of 1921 patients aged $\geq$18 years (50.3% women; overall response rate: 96%) hospitalized at the departments of Internal Medicine, Cardiology, or Infectious Diseases (7). Complete details about the study population and sampling have been described elsewhere (7).

All patients' records were carefully checked according to a structured checklist including clinical characteristics of the patients and other relevant data related to their hospitalization (7).

Potential drug-drug-interactions were assessed employing the Drug Interactions Checker within www.drugs.com database (7,8). The drug-drug interactions identified in this study sample were then classified as major, moderate and minor, depending on their severity of clinical significance and crossover checked manually for the presence of identified interacting agents, according to a few recent reports (9,10). Thus, in our study sample, drug-drug interactions were identified and classified based on the profile of medications prescribed, as suggested by the recent literature on this area of research (9,10).

Other important clinical data in our study included type of diagnosis (infectious diseases, cardiovascular diseases, endocrine diseases, respiratory diseases, gastrointestinal diseases and other diseases), length of hospitalization (dichotomized into: 1-6 days vs. $\geq$7 days), number of drugs administered (dichotomized into: 1-3 vs. $\geq$4) and presence of co-morbid conditions (yes vs. no) among patients included in the study.

In addition to clinical information, demographic and socioeconomic data were retrieved from all the patients' records and further verified (double-checked) by re-interviewing the patients (regarding selected socioeconomic factors such as educational attainment, employment status, income level, or social status). Demographic factors included sex (men vs. women) and age (categorized into:<40

years, 40-59 years and ≥60 years) of the patients, place of residence (urban areas vs. rural areas) and marital status (dichotomized into: married vs. single/divorced/widowed) at the time of hospitalization. Socioeconomic characteristics included educational attainment (years of formal schooling, trichotomized into: low, middle and high), employment status (categorized into: employed, unemployed and retired), self-perceived income level (trichotomized into: low, middle and high) and self-perceived social status (categorized into: low, middle and high) (7).

This study was approved by the Kosovo Board of Biomedical Ethics. All individuals who agreed to participate in this study gave their informed consent. Absolute number and their respective percentages were calculated for different types of severity of drug-drug interactions (major, moderate and minor severity). Adverse outcomes were identified for each type of severity of drug-drug interactions.

Statistical Package for Social Sciences, version 17.0, Chicago, Illinois, was used for the quantitative data analysis.

Results

Overall, 1192 (62%) of the patients experienced drug-drug interactions in this representative sample of hospitalized patients in Gjilan region (7).

Table 1 presents the degree of severity of drug-drug interactions and their potential adverse effects among the hospitalized patients of Gjilan region during 2011-2013. In the overall sample of 1921 patients, there were 576 (30%) major drug-drug interactions, 713 (37%) moderate drug-drug interactions and 632 (33%) minor drug-drug interactions. The main adverse outcomes pertinent to the major severity of drug-drug interactions included serious liver damage, a complete treatment failure, severe hemorrhage and serious kidney damage. As for the moderate severity of drug-drug interactions, the main adverse effects consisted of severe anemia, nerve damage, moderate hemorrhage and a significant decrease of treatment efficacy. On the other hand, the main adverse effects related to the minor severity of drug-drug interactions included mild anemia, mild hemorrhage and a slight decrease of treatment efficacy (Table 1).

Table 1. Severity of drug-drug interactions and their potential adverse outcomes among hospitalized patients (N=1921) in Gjilan region, Kosovo, 2011-2013

Severity of drug-drug interactions	Frequency*	Adverse outcomes
Major	576 (30.0)	- Serious liver damage - Complete treatment failure - Severe hemorrhage - Serious kidney damage
Moderate	713 (37.1)	- Severe anemia - Nerve damage - Moderate hemorrhage - Significant decrease of treatment efficacy
Minor	632 (32.9)	- Mild anemia - Mild hemorrhage - Slight decrease of treatment efficacy
Total	*1921 (100.0)*	

* Absolute numbers and their respective percentages (in parentheses).

Table 2 displays selected drug-drug interactions and their respective adverse outcomes in the overall sample of hospitalized patients in Gjilan region. The combination of Rifampin and Isoniazid was associated with liver damage in this study population, similar to the simultaneous administration of Rifampin and Pyrazinamide. Conversely, the combination of Phenytoin with Artemether was linked to a reduction of the blood levels of artemether. On the other hand, administration of Warfarin and Heparin was related to an increased risk of bleeding, a situation which resembled also the simultaneous administration of Ceftriaxone and Heparin. Furthermore, the combination of Cotrimoxazole and Leucovorin was related to an increased risk of treatment failure. Ceftriaxone and Leucovorin, in turn, were associated with precipitation of ceftriaxone-calcium salt. Sulfadiazine and Pyrimethamine were related to an increased risk of anemia, whereas Isoniazid and Ethambutol were linked to an increased risk of nerve damage. Finally, Furosemide and Doxycycline were associated with a decrease in renal function (Table 2).

Table 2. Selected drug-drug interactions and their respective adverse outcomes among hospitalized patients (N=1921) in Gjilan region, Kosovo, 2011-2013

Type of drug-drug interactions	Adverse outcomes
Rifampin + Isoniazid	Liver damage
Rifampin + Pyrazinamide	Liver damage
Phenytoin + Artemether	Reduction of the blood levels of artemether
Warfarin + Heparin	Bleeding
Cotrimoxazole + Leucovorin	Increased risk of treatment failure
Ceftriaxone + Leucovorin	Precipitation of ceftriaxone-calcium salt
Sulfadiazine + Phenytoin	Increase of the effect of phenytoin
Leucovorin + Phenytoin	Decrease of the blood level and effects of phenytoin
Ceftriaxone + Furosemide	Increased risk of kidney damage by cephalosporin
Sulfadiazine + Pyrimethamine	Increased risk of anemia
Isoniazid + Ethambutol	Increased risk of nerve damage
Digoxin + Spironolactone	Reduction in the tubular secretion of digoxin
Furosemide + Doxycycline	Decrease in the renal function
Ceftriaxone + Heparin	Bleeding

Discussion

Main findings of our study which involved a large representative sample of adult patients from the regional hospital of Gjilan include a high degree of the overall drug-drug interactions, with about one-third exhibiting a major severity, and about 40% further displaying a moderate severity. The most important adverse outcomes in this study population included liver damage, treatment failure, kidney damage, hemorrhage, anemia, nerve damage, or a decrease in treatment efficacy.

The major drug combinations which were linked to negative health consequences in our study included the co-administration of Rifampin and Isoniazid; Rifampin and Pyrazinamide; Phenytoin and Artemether; Warfarin and Heparin; Ceftriaxone and Heparin; Cotrimoxazole and Leucovorin; Ceftriaxone and Leucovorin; Sulfadiazine and Pyrimethamine; Isoniazid and Ethambutol; and Furosemide and Doxycycline.

In a recent study conducted in Ethiopia, the bulk of the major drug-drug interactions reported included Rifampin with Pyrazinamide which resulted in severe hepatic injury (9). Similarly, according to this study, simultaneous administration of Rifamipin and Isoniazid was linked to a higher risk of hepatotoxicity compared with the single administration of either drug alone (9). The authors reported that such drug combinations are commonly employed in their practice due to their therapeutic value (9). In any case, these combinations should

be administered with extreme caution in patients with liver damage, those with a poor nutritional status, as well as older individuals who are particularly vulnerable (9). Therefore, in case of simultaneous administration of such drug combinations, patients should be closely monitored for clinical symptoms of liver toxicity including fever, anorexia, vomiting and jaundice (4,9,10).

Our study provides useful evidence about the severity and types of drug-drug interactions in Kosovo, similar to the previous reports from studies conducted elsewhere (11,12). However, our study may have some limitations mainly related to the possibility of selection bias and information biases. Although we included a large and representative sample of adult patients, our findings are confined to hospital settings and, therefore, cannot be generalized to the overall adult population of Gjilan region in Kosovo. As for the possibility of information bias, we collected the clinical information based on the patients' files and charts which are assumed to be filled out in a similar manner. Hence, there is no reason to assume a differential recording of clinical data for different patients distinguished by their diagnosis, or other medical conditions. In any case, future studies in Kosovo should additionally and fully assess the degree of severity and the resultant health consequences of drug-drug interactions in the population of Kosovo.

In conclusion, our report provides useful information about the main adverse effects of drug-drug interactions among adult patients in a regional hospital of Kosovo. Health professionals in transitional Kosovo should be aware of the importance of a careful selection of drugs and a proper pharmaceutical care for their patients in order to avoid negative consequences of drug-drug interactions.

Conflicts of interest: None declared.

References

1. Zwart-van Rijkom JE, Uijtendaal EV, ten Berg MJ, van Solinge WW, Egberts AC. Frequency and nature of drug-drug interactions in a Dutch university hospital. Br J Clin Pharmacol 2009;68:187-93. DOI: 10.1111/ j.1365-2125.2009.03443.x.

2. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA.Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 2003;289:1652-8.

3. Bagheri H, Michel F, Lapeyre-Mestre M, Lagier E, Cambus JP, Valdiguie P, Montastruc JL. Detection and incidence of drug-induced liver injuries in hospital: a prospective analysis from laboratory signals. Br J Clin Pharmacol 2000;50:479-84.

4. Baxter K, editor. Stockley's drug interactions. London, UK: Pharmaceutical Press; 2010.

5. Hansten PD, Horn JR. Drug interactions analysis and management. St. Louis, MO, USA: Facts and Comparisons; 2009.

6. Shabani D, Bozalia A, Hudhra K, Bara P, Malaj L, Jucja B. Drug interactions and their potential toxic effects among patients in Gjilan region, Kosovo. Alban Med J 2014;2:104-7.

7. Shabani D, Tahiri Z, Bara P, Hudhra K, Malaj L, Jucja B, Bozalia A, Burazeri G. Prevalence and correlates of drug-drug interactions in the regional hospital of Gjilan, Kosovo. Mater Sociomed 2014;26:248-52.

8. Cerner Multum, Inc. Drug Interactions Checker. USA: Cerner Multum, Inc.; 2013. Available from: http:// www.drugs.com/ drug_interactions.html (accessed: August, 2014).

9. Bhagavathula AS, Berhanie A, Tigistu H, Abraham Y, Getachew Y, Khan TM, Unakal C. Prevalence of potential drug-drug interactions among internal medicine ward in University of Gondar Teaching Hospital, Ethiopia. Asian Pac J Trop Biomed 2014;4(Suppl 1):S204-S208.

10. Ismail M, Iqbal Z, Khattak MB, Javaid A, Khan TM. Prevalence, type and predictors of potential drug-drug interactions in pulmonary ward of a tertiary care hospital. Afr J Pharm Pharmacol 2011;5:1303-9.

11. Vonbach P, Dubied A, Krähenbühl S, Beer JH. Prevalence of drug-drug interactions at hospital entry and during hospital stay of patients in internal medicine. Eur J Intern Med 2008;19:413-20.

12. Becker ML, Kallewaard M, Caspers P, Visser LE, Leufkens H, Stricker B. Hospitalisations and emergency department visits due to drug-drug interactions: a literature review. Pharmacoepidemiol Drug Saf 2007;16:641-51.