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EVALUATION OF POTENTIAL DRUG - DRUG INTERACTIONS IN INPATIENTS TREATED AT THE INTERNAL WARD

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Abstract

Concomitant multiple-drug usage often increases therapeutic effectiveness steadily, but certain combinations may result in a higher risk of adverse effects or loss of effect due to drug-drug interactions. Therefore, this study aimed to determine the prevalence, severity, and characteristics of potential DDIs as well as identify the drugs most often associated with possible serious DDIs prescribed in hospitalized patients. A retrospective cross-sectional study data was collected from the medical charts of patients admitted in the internal ward based on the inclusion criteria. Potential drug-drug interaction was analyzed using the Drug Interactions Checker and the online drug register of the Republic of North Macedonia. Major potential DDIs accounted for 12.2% of the total number of interactions detected, while moderate potential DDIs and minor potential DDIs were 71.3 % and 16.5 % . Enoxaparin (23.8%), acetylsalicylic acid and clopidogrel (8.8%) were the three most involved drugs in major potential interactions. The three most frequently occurring serious potential DDIs were enoxaparin and acetylsalicylic acid (15.4%), while a combination of heparin and enoxaparin as well as, ketoprofen with enoxaparin accounts for 10.3% of these interactions. The indicators of this study can be useful as data to understand the extent of the problem and take measures to improve the practice of managing drug interactions.

Keywords: Concomitant drugs, potential drug interactions, internal ward, inpatients.

1. Introduction

Multiple outcomes are expected when people use drugs. Patients generally benefit from drug therapy, although adverse events, should not be overlooked. Adverse drug events (ADEs) have been considered major main public health concerns.

Drug-drug interactions are one of the specific types of ADEs. It is defined as an event that occurs when the effects of a drug are modified by another drug that is taken concomitantly (Nidhi S, 2012). Approximately 3–26% of all adverse drug reactions that require hospital admission are caused by drug-drug interactions (Ferner & Aronson, 2006). DDIs are more frequent in patients who are elder, hospitalized for a longer period, and/or receive more drugs per day (Janković, et al., 2018; Obreli-Neto, et al., 2012; Romagnoli et al., 2017). This exponential increase in DDIs may be due to an increased life expectancy which leads to comorbid conditions, chronic therapeutic regimens, and polypharmacy. Studies conducted in hospital settings report prevalence rates ranging from 0.6 to 18.3%, and a study carried out in a primary health care unit reports a prevalence rate of 6.8% (Cruciol-Souza & Thomson, 2006; Silva, et al., 2010; Codagnone Neto, et al., 2010).

DDIs may result in either increase or decrease in efficacy, treatment failure, or increased toxicity of medications (Bjornsson, et al., 2003; Mozayani, et al., 2004). Only a few potential drug interactions do lead to 'manifest' outcomes and little information is available about the epidemiology of adverse outcomes. Most evidence is derived from case reports, volunteer studies, or investigations of potential drug interactions in hospitalized patients (Juurlink, et al., 2003) Most interactions go unnoticed by physicians due to the absence of new clinical signs and symptoms and because they often produce a worsening of already existing

symptoms (Picazo, et al., 2010). Chen, et al.,(2005) found an incidence of 1.9 per 1000 patient-years (95% confidence interval (CI) 1.5, 2.3) of prescribed potentially hazardous/contraindicated drug interactions. They identified multiple possible causes (e.g., lack of knowledge of the drug interaction or the patient medication history) and system failures (e.g., incomplete medication records, communication between primary and secondary care or between the prescriber and the patient) for the dispensing of contraindicated drug combinations. Pharmacists play an important role in protecting patients from the harmful effects that may be experienced due to these interactions (Kennedy-Dixon, et al., 2015). Therefore, integrated professional interaction should be encouraged between healthcare professionals to optimize drug safety (Netsanet Diksis, et al., 2019).

Since there were no clinical pharmacists in the Clinical Centre in Tetovo to be consulted in medication decision-making, to detect and manage potential DDIs, especially in the Internal Medicine ward frequented by a great number of patients with a wide range of disease conditions, it is possible to predict that DDIs may be prevalent in the inpatient settings. Therefore, this study sought to determine the prevalence, severity, and characteristics of potential DDIs as well as identify the drugs most often associated with possible serious DDIs prescribed in hospitalized patients in the internal ward at the Clinical Hospital in Tetovo.

2. Materials and methods

This retrospective study was carried out from June 01, 2018 to August 31, 2018 in the internal inpatient ward of the Clinical Centre in Tetovo, an urban city in the northwestern part of the Republic of North Macedonia.

Cross-sectional data were gathered from the medical charts of patients who were admitted to the ward during the study period and who had a drug profile containing two or more medications. If patients who were included earlier in the study came back to the ward later during the study period, they were excluded. Data regarding demographics such as age, sex, diagnosis, and the list of medications prescribed concurrently were recorded in a specially designed data entry form.

All medications prescribed for each patient were analyzed and checked for any potential interactions, using trusted online reference databases accessed from https://www.drugs.com/drug_interactions.html and https: //wwwrxlist.com/drug-interaction-checker.htm. Drug Interactions Checker is an online medical tool in which drugs prescribed in a given prescription are entered to predict the nature of the interactions based on severity (major, moderate, minor, or unknown). The online drug register of the Republic of North Macedonia was also used (https://lekovi.zdravstvo.gov.mk /drugs register/overview).

Table 1 presents the classification of possible drug interactions based on severity, according to Drug Interactions Checker - For Drugs, Food & Alcohol (http://www.drugs.com/drug_interactions.html).

Table1. Classification of possible drug interactions based on severity

Severity	**Explanation**
Major	Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.
Moderate	Moderately clinically significant. Usually, avoid combinations; use them only under special circumstances.
Minor	Minimally clinically significant. Minimize risk; assess risk and, consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.
Unknown	No interaction information is available.

Analysis by descriptive statistics was performed with the SPSS statistical software program. Data were expressed in terms of mean, standard deviation, or percentage frequency as appropriate.
The letter of approval for conducting the study was requested and obtained by the authorities of the Clinical Hospital Center in Tetovo. The study was exempted from patient consent since there was no direct involvement with patients. Thus, for reasons of confidentiality and to guarantee anonymity, codes were used for all files analyzed.

3. Results

A total of 87 drugs were prescribed for 51 medical charts qualified for review. The mean number of drugs prescribed per subject was 7.2±1.1. The minimum number of concomitant drugs per subject ranged from two to a maximum of fifteen, with 4 subjects having two drugs prescribed (7.8%) and 47 subjects (92.2%) having between 3 and 15 drugs The majority (86.3%) had more than two chronic conditions (Table 2). The most frequent diagnoses were hypertension (13.5%) and angina pectoris (11.2%).

Table 2. Clinical data of patients

Variables	**Frequency (%)**
Number of drugs prescribed per subject, mean ±SD	7.2±1.1
Two drugs prescribed	4 (7.8)
More than two drugs prescribed	47 (92.2)
Number of conditions	
2 or fewer conditions	44(86.3)
More than 2 conditions	7(13.7)
Potential DDI (n=327)	
Major	40(12.2)
Moderate	233(71.3)
Minor	54(16.5)

The most-prescribed drugs were antihypertensives (16.0%), followed by antibiotics, antihyperlipidemics and antacids (4.9%). Furosemide (26.2%) and bisoprolol (16.4%) are the most prescribed antihypertensives.
The overall prevalence of potentially drug-drug interactions (DDIs) of all categories was 94.1%. Of those, further examinations revealed that 71.3% of the interactions were moderate potential DDIs, potentially serious major drug-drug interactions accounted for 12.2%, while minor drug-drug interactions were at 16.5 % (Table 2).
The drugs most involved in the major DDIs were enoxaparin (23.8%), acetylsalicylic acid and clopidogrel (8.8%). Acetylsalicylic acid (12.3%) and methylprednisolone (7.6%) are considered drugs most involved in moderate interactions (Table 3).

Table 3. Drugs and severity of drug-drug interactions

Drugs	**Major**	**Moderate**	**Minor**
	%	%	%
Heparin	5	3.8	8.3
Ketoprofen	6.3	6.7	2.8
Enoxaparin	**23.8**	1.1	

Acetylsalicylic acid	8.8	**12.3**	**15.7**
Clopidogrel	8.8	1.8	8.3
Ranitidine	1.3	2.2	4.6
Rosuvastatin	1.3	0.2	0.9
Enalapril	2.5	2.9	1.9
Bisoprolol	1.3	5.1	4.6
Ascorbic acid	1.3		
Diazepam	3.8	4.5	4.6
Ciprofloxacin		2	0.9
Dextriferron		0.2	
Losartan		0.2	
Ceftriaxone		0.2	0.9
Tramadol	3.8		
Acenocumarol		0.4	1.9
Fenofibrate	5		
Amlodipine	1.3	2	3.7
Hydrochlorthiazide		1.3	0.9
Repaglinide	3.8	3.4	0.9
Methylprednisolone	1.3	7.6	1.9
Aminophylline	5	2	5.6
Metoclopramide		0.7	
Pentoxifylline		2.2	
Insulin		1.1	
Furosemide	2.5	6.9	9.3
Amiodarone	2.5	0.2	0.9
Kalcium carbonat		2	1.9
Trospium chloride		2.5	
Lisinopril		1.3	1.9
Nifedipine		0.9	2.8
Carvedilol		2	1.9
Metformin		2.9	
Nebivolol	1.3	1.3	0.9
Perindopril		2.2	1.9
Nicardipine		0.4	
Digoxin		1.8	2.8
Spironolactone	2.5	4.7	4.6
Meloxicam	1.3	0.9	0.9
Atorvastatin		0.4	
Omeprazole	1.3	0.2	
Carbazochrome	1.3		
Prednisolone	1.3		

Alprazolam	1.3	0.2	
Escitalopram	1.3	1.8	
Pantroprazole		0.7	0.9
Ginkgo biloba		0.7	
Tamsulosin chlorid		0.2	0.9
Alendronic acid		0.2	
Telmisartan		0.7	

The interaction between enoxaparin and acetylsalicylic acid occurs in 15.4% of potentially serious interactions, while a combination of heparin and enoxaparin as well as ketoprofen with enoxaparin accounts for 10.3% of these interactions. Table 4 shows the percentages of the major potential DDIs along with the potential clinical consequences as a result of these combinations as stated on Drugs.com.
Most of the major potential DDI identified were associated with increased risk of bleeding (54.0%), followed by severe or fatal bronchospasm (7.7%).

Table 4. Drug class combinations of major potential interactions, potential adverse events and their frequency

Major potential DDI	**No**	**%**	**Potential clinical consequences**
Heparin < > Enoxaparin	4	10.3	Risk of bleeding, including severe and sometimes fatal haemorrhage.
Ketoprofen < > Enoxaparin	4	10.3	Bleeding complications
Ketoprofen < > Acenocoumarol	1	2.6	Risk of bleeding
Enoxaparin < > Acetylsalicylic Acid	6	**15.4**	Risk of bleeding complications
Enoxaparin < > Clopidogrel	3	7.7	Risk of bleeding, including severe and sometimes fatal haemorrhage
Enoxaparin < > Acenocumarol	2	5.1	Risk of bleeding, including severe and sometimes fatal haemorrhage
Acetylsalicylic Acid < > Acenocumarol	1	2.6	Risk of bleeding
Clopidogrel < > Repaglinide	3	7.7	Hypoglycaemia
Clopidogrel < > Omeprazole	1	2.6	May reduce the effectiveness of clopidogrel in preventing heart attack or stroke
Rosuvastatin < > Fenofibrate	1	2.6	Liver damage and rhabdomyolysis
Enalapril < > Spironolactone	2	5.1	Hyperkalaemia
Bisoprolol < > Aminophylline	2	5.1	Severe or fatal bronchospasm
Diazepam < >Tramadol	1	2.6	Sedation, respiratory depression, coma, and death
Ciprofloxacin < > Methylprednisolone	1	2.6	Tendinitis and tendon rupture
Ciprofloxacin < > Aminophylline	1	2.6	Increase the serum concentrations of theophylline and the associated risk of toxicity
Ciprofloxacin < > Prednisolone	1	2.6	Tendinitis and tendon rupture
Tramadol < > Alprazolam	1	2.6	Sedation, respiratory depression, coma, and death

Tramadol < > Escitalopram	1	2.6	Serotonin syndrome
Aminophylline < > Nebivolol	1	2.6	Severe or fatal bronchospasm
Furosemide < > Amiodarone	2	5.1	Elevated risk of ventricular arrhythmias, including ventricular tachycardia and torsades de pointes

4. Discussion

This retrospective study analyzed potential drug-drug interactions in a population of hospitalized patients in the internal inpatient ward of the Clinical Centre in Tetovo between June and August 2018.

The prevalence of potential drug-drug interactions in this study was 94.1%. This percentage agrees with the findings of a study in Iran (Shafiekhani, Tarighati, Mirzaei & Namazi, 2020), which showed that (89.97%) of patients experienced at least 1 DDIs and was higher than the findings of studies conducted in Southwest Ethiopia (74.41%) (Netsanet Diksis, et al., 2019), as well as a study conducted in Romania (78.03%) (Bucşa, Farcaş & Cazacu, et al., 2013) and in two teaching hospitals in Quetta, Pakistan (68.3%) (Qadeer, et al., (2020). A much lower prevalence value was reported by a study conducted in Thailand (27.9%) (Janchawee, et al., 2005).

This broad difference in the prevalence of potential DDIs may be explained by factors, such as differences in the availability of alternative drugs and the absence of clinical pharmacists and drug information software to provide drug information in the inpatient settings of TASH during the study period. The involvement of pharmacists in reviewing hospitalized patients' medication prescriptions would significantly reduce the prevalence and harmful effects of DDIs. Pharmacists contribute to better treatment outcomes by early detection of medication errors, monitoring treatment outcomes, and by recommending treatment modification (Lopez-Martin, et al., 2014; Leape, et al., 1999; Kaboli, et al., 2006).

Most of the potential DDIs identified were moderate (71.3%), but 12.2% were classified as major potential DDI. In the study conducted at the Internal Medicine ward of Tikur Anbessa Specialized Hospital, Ethiopia, most of the potential DDIs were moderate (53.5%), followed by 33.4% of minor and 13.1% of serious (major) interactions (Tesfaye & Nedi, 2017). In the study conducted in southern Brazil, the majority of potential DDIs were moderate (70.2%), followed by 10.6% of minor and 19.2% were potential serious DDIs (Teixeira, et al., 2012). Venturini et al. reported a moderate DDIs prevalence of 69.9%, and a 21.2% prevalence of major DDIs. The difference in the results may be attributed to the use of different DDIs analysis database; DDIs categories differ according to the databases used, the difference in the population characteristics, and the sample size of these studies (Venturini, et al., 2011).

Various studies have reported the most common drug pairs with pDDI and different results have been reported. In the Aljadani and Aseeri (2018) study, atorvastatin was responsible for four pDDI, as was aspirin. Hypoglycemic agents, proton pump inhibitors, and calcium were each responsible for three pDDI. In the Dinesh, et al., (2007) study, aspirin ranks fourth among the 10 drugs with the highest potential for interactions. In our study, acetylsalicylic acid is also considered the drug involved in all types of potential DDIs (major, moderate, and minor). Other drugs that are involved in a higher percentage of interactions are enoxaparin (anticoagulant) clopidogrel (antiaggregant) and methylprednisolone (anti-inflammatory).

The most frequently occurring major potential DDI in this study was between enoxaparin and acetylsalicylic in 15.4%, while a combination of heparin and enoxaparin as well as ketoprofen with enoxaparin accounts for 10.3% of these interactions. According to Drugs.com, concomitant use of these drugs may increase the risk of bleeding. Close monitoring is needed for patients with identified major and moderate DDIs. In patients with multiple chronic diseases, the concomitantly prescribed drugs have the potential of causing adverse events as a result of drug-drug interactions. It is the responsibility of health care professionals to the

patient's drug list and to weigh the risk of potential adverse events versus the benefit from combinations of prescribed drugs.
Healthcare providers can use their practical knowledge of the pharmacological mechanism to minimize the risks from potentially DDIs and as well can reduce exposure to concurrent administration and should collaborate to develop educational programs and improve patients' counseling.
The limitation of this study is the small number of participants covering only the Internal Medicine ward which limits the ability to make our findings more generalizable to other settings or different populations. Second, the interactions found were only potential which does not always mean that the interactions occurred in the patients. Despite its limitations, the results of this study can help in overcoming this occurrence by understanding the extent of the problem and by taking adequate measures to improve the practice of managing drug interactions.

5. Conclusion

DDIs are common among patients, especially in those with multiple chronic diseases, due to the complexity of pharmacotherapy. This study demonstrated a high prevalence of potential DDIs among hospitalized patients in the internal ward. Most of the interactions were of moderate severity, even though we encountered potentially major interactions which are considered clinically important and should be avoided. Therefore, the use of cautionary guidelines, different education tools, or DDI software could help healthcare workers to avoid serious side effects on patients by preventing potentially dangerous DDIs.
The indicators of this study can be useful as data to understand the extent of the problem and take measures to improve the practice of managing drug interactions.

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