Exposure to potential drug-antimicrobial agent interactions in primary health care

Izloženost potencijalnim lek-antimikrobni agens interakcijama u primarnoj zdravstvenoj zaštiti

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Abstract

Background/Aim. Drug-drug interactions involving antimicrobials present important and often unrecognized complications of pharmacotherapy which can be prevented. The aim of the present study was to identify the frequency and type of potential drug-antimicrobial agent interactions among outpatients and to define recommendations for their management.

Methods. Cross-sectional prescription database study was conducted. The analysis randomly included 823 patients who visited Health Center Novi Sad over 1-month period (November 1–30, 2011) and had prescribed ≥ 2 drugs where at least one drug was antimicrobial agent for systemic use. All interacting drug combinations involving antimicrobials were identified according to Drug Interaction Facts. Additionally, based on the compendium, potential interactions were classified into categories: pharmacological mechanisms, potential clinical outcomes and management advice.

Results. Overall, 88 potential clinically significant drug-antimicrobial agent interactions were identified among 69 (8.4%) exposed outpatients [the mean age 61.7 years (SD ± 15.4); the mean number of prescribed drugs 7.5 (SD ± 2.9); 56.5% females]. The most common identified potential interacting pairs were benzodiazepines undergoing oxidative metabolism and clarithromycin or erythromycin, and aminophylline and ciprofloxacin. In 83.0% of all cases underlying mechanism was pharmacokinetic involving primary inhibition of metabolic pathways mediated by CYP3A4 and CYP1A2 isoenzymes. Excessive sedation (22.7%), cardiotoxicity (20.5%), miscellaneous aminophylline adverse effects (13.6%), and bleeding (10.2%) were the most frequently implicated potential clinical outcomes. Risk for adverse interactions could be managed by close monitoring of simultaneous administration of drugs (37.5%), different risk-modifying strategies (31.8%), and avoiding combinations (30.7%).

Conclusion. Among outpatients, there was common potential for clinically significant interactions involving antimicrobials. Information based on the results of the present study could be integrated in existing computerized physician order entry system in the Health Center as a form of clinical support.

Key words: drug therapy; anti-bacterial agents; drug interactions; outpatients; adverse drug reaction reporting systems; pharmacovigilance.

Apstrakt

Uvod/Cilj. Interakcije antimikrobnih lekova predstavljaju važne i često neprepoznate komplikacije farmakoterapije koje mogu biti prevenirane. Cilj prezentovane studije bio je da se identifikuje učestalost i tip potencijalnih interakcija antimikrobnih lekova kod ambulantnih bolesnika, i da se definišu preporuke za kontrolu istih.


Rezultati. Ukupno, 88 potencijalnih, klinički značajnih lek-antimikrobni interakcija identifikovano je kod 69 (8,4%) izloženih bolesnika [prosečna starost 61,7 godina (SD ± 15,4); prosječan broj propisanih lekova 7,5 (SD ± 2,9); 56,5% alata]. Najčešće identifikovane potencijalne interakcije konsistirale su između benzodiazepina koje se metaboliziraju oksidativnim putem i makrofilina, aminofilina i ciprofloksacina. U 83,0% kod svih slučajeva, podstaklo za interakciju bilo je farmakokinetičko medijirano između glavnih metabolizama CYP3A4 i CYP1A2 isoenzyma. Najčešće se pojavljive posledice potencijalnih interakcija bilo su ekstremna sedacija (22,7%), kardiotoksicitet (20,5%), misteriozne posledice vanredne metotrešnosti aminofilina (13,6%), i krvi (10,2%) bilo su najčešće potencijalna posledice za interakciju. Risk za neposrednu reakciju moglo bi se upravljati sledeće: blaga onemogućenja simultanog administracije lekova (37,5%), različite strategije modificiranja rizika (31,8%), i uklanjanje kombinacija (30,7%).

Završetak. Među ambulantnim pacijentima, alik je posljednji čovjek potencijal za izloženost interakcijama antimikrobnih lekova. Informacije bazirane na rezultatima prezentovane studije bi moglo se integrirati u postojeći sistem ordinacije lekova u zdravstvenom centru u obliku nadzora kliničke podrške.

Ključne riječi: lekoterapija; antimikrobni agenti; lek-antimikrobna interakcija; ambulantni pacijenti; sistema poročanja o neposrednim posledicama lekova; farmakovigilansa.
Introduction

It is well known that adverse drug interactions (ADIs) involving antiinfective agents can be complication of pharmacotherapy. Thus, according to the World Health Organization Global Individual Case Safety Report (WHO Global ICSR) database, during the past 20 years, among the 15 most frequently reported adverse drug interacting combinations, 4 included antimicrobials. Molden and Andersson described two men with rhabdomyolysis, who received simvastatin 80 mg/day and who were hospitalized after the completion of short-term treatment with macrolide antibiotics (clarithromycin and erythromycin). Flockhart et al. reported on the case of a 27-year-old man who experienced a prolonged QT interval and sudden cardiac death two days after coadministration of pimozide and clarithromycin. Additionally, reports on fatal torsades de pointes induced by terfenadine during its coadministration with ketoconazole or erythromycin contributed to the withdrawal of terfenadine from the United States market. Also, antimicrobials can lead to a reduction or loss of therapeutic efficacy of concomitantly used drugs. Thus, ketoconazole affects formation of clopidogrel active metabolite causing reduced inhibition of platelet aggregation. Also, bioavailability of tetracyclines and quinolones can be significantly reduced in presence of aluminium, magnesium or calcium-containing antacids.

Besides safety aspect, interactions are important because they are often unavoidable or preventable adverse drug events (ADEs). Thus, Juurlink et al. estimated that at least 3.3% of hospital admissions due to hypoglycemia was caused by concomitant using of glibenclamide and cotrimoxazole, so as at least 2.3% of hospitalizations because of digoxin toxicity during its coadministration with clarithromycin could be prevented. The basis for the prevention of ADIs is possession of knowledge or possibility to predict situations when simultaneous administration of drugs presents risk for drug-mediated toxicity or therapeutic failure.

In literature a large number of interactions of antimicrobial drugs are listed and several reviews describe the ones which are clinically relevant. More specific, Spriet et al. gave overview of significant CYP450-mediated interactions involving antiinfective agents and drugs frequently received in the Intensive Care Unit (ICU) and Becker described adverse interactions of antibiotics commonly used in dental practice while Tey et al. reported on drug interactions with often prescribed antimicrobials in dermatological practice. However, differences in morbidity structure or complexity of healthcare contribute to specificity of study findings. Hence, as intention to improve the safety of pharmacotherapy in the Health Center, the primary aim of this study was to identify the frequency and type of clinically significant potential drug-antimicrobial agent interactions among outpatients and to define recommendations for their control subsequently based on this local reports.

Methods

The Ethics Committee of the Health Center Novi Sad (HCNS), Novi Sad, Serbia approved the protocol of the present study.

Study design and data collection

The prevalence and type of potential drug-antimicrobial agent interactions among outpatients at the HCNS were analyzed in the cross-sectional, single-center study. HCNS provides primary health care for population of approximately 340,000 people living in Novi Sad, the administrative seat of the northern Serbian province Vojvodina. Medical care is offered to outpatients within 45 Basic Health Units (BHUs) involving health promotion and education, prevention and early management of health problems as well as curative care. The study was carried out using data from all BHUs.

HCNS possesses a health information system certified by the European Institute for Health Records. Computerized medical record contains all relevant facts about patient and his/her therapy. Hence, study data were obtained from the electronic prescription database and their collection was done automatically by the computer server administrator. Data collection was described in detail by Nikolic et al.

compared to the WHO. 

Medical records of drug users in the HCNS during one-month observed period (November 1–30, 2011) were recruited to the study if patients had been prescribed two or more than two drugs where at least one of medicines was antibacterial for systemic use. Two researchers (BN and DR) were responsible for determination of subjects eligible for inclusion in the study. For each outpatient was assumed that using of medicines started at the same day when the medicine was prescribed and the duration of therapy for each medicine was calculated in days by multiplying a daily dose by the number of daily doses contained in the prescribed packs. Potential for the drug-antimicrobial agent interactions was studied when the exposure period for two medicines overlapped. Overlapping was defined as the presence of at least a day of co-prescription of two medicines. This definition is consistent with previous studies using administrative claims databases, evaluating the exposure of patients to potential drug-drug interactions (DDIs) rather than clinically manifest DDIs and their relative severity. Furthermore, monitoring of one-day overlap in therapy is beneficial in the cases when clinical effects are evident within 24 hours of administration of the interacting drugs (e.g. diazepam and clarithromycin, ciprofloxacin and iron salts) and when immediate action is necessary to avoid the effects of the interaction.

Interacting combinations not involving antibacterial agents were not considered in the study.

Identification and analysis of potential drug-antimicrobial agent interactions

Potential drug-antimicrobial agent interactions were identified and classified according to the Drug Interaction Facts (DIFs). In the compendium, based on the Editorial Group's assessment of interaction severity (the magnitude of the effect of a drug interaction) and documentation (the quality and clinical relevance of the primary literature supporting the occurrence of an interaction), significance rating was assigned by number 1 through 5 to each interaction monograph. In the current study, interactions ranked as 1 and 2 were considered as potentially harmful and therefore clinically relevant. According to the compendium, these interactions have a reasonable probability of occurrence (proven to occur in well-controlled studies; or, very likely but not proven clinically; or may occur, they are some good data, but more studies are needed); their effects are potentially life-threatening or capable to cause permanent damage (significance rating 1); or, may cause a deterioration in patient's clinical status, hence additional treatment, hospitalization, or an extended hospital stay may be necessary (significance rating 2). For each subject exposed to overlapping prescriptions, all pairs of drug combinations were analysed for interacting potential by two independent researchers (BN and DR). In the case of disagreement among assessors, evaluation of potential drug-antimicrobial agent interaction was discussed until consensus view was achieved. The assessment of interrater agreement (determined before a consensus was reached) indicated acceptable consistency among observational ratings (kappa, 0.76; 95% confidence interval – 0.50 to 1.00).

Additionally, the drug-antimicrobial agent interactions were classified in "pharmacological mechanisms", "potential clinical outcomes" and “management advice” categories. The DIFs provide textual information about these parameters for each interaction. The compendium text was converted into aforementioned categories by three researchers (BN, JP, MB). Differences in classification were resolved by discussion. Interrater agreement (based on the estimation before a consensus was reached) was substantial for “pharmacological mechanisms” (kappa, 0.82; 95% confidence interval – 0.73 to 0.91), “potential clinical outcomes” (kappa, 0.95; 95% confidence interval – 0.91 to 0.99) as well as “management advice” (kappa, 0.76; 95% confidence interval – 0.66 to 0.86).

Statistical analysis

Descriptive statistics was used to describe patient characteristics. The mean and standard deviation were calculated for age and number of prescribed drugs, while proportion was calculated for sex. The selected sample for analysis was divided into two different groups, thus subjects with ≥ 1 potential drug-antimicrobial agent interaction were in the exposed group and those without potential drug-antimicrobial agent interaction were in the unexposed group. Intergroup differences in the continuous variables, age and number of drugs, were assessed applying nonparametric Mann-Whitney U test because they failed to show a normal distribution. A categorical variable, sex, was compared using χ² test of independence. Parameters of potential interactions (pis) (“pharmacological mechanisms”, “potential clinical outcomes”, and “management advice”) were evaluated by absolute and relative frequencies. For all of tests, p value < 0.05 was considered as statistically significant. Data were analyzed using Statistical Package for the Social Sciences (SPSS) 20.0 software.

Sample size calculation was based on assumption on 10% exposure to pls (variable derived from a small pilot study conducted within our population). Standard tabular values of 95% confidence limit factors for estimate of a Poison-distributed variable were used to assist in carrying out this computation. Thus, 800 outpatients (95% confidence interval, 384 to 1472) were needed for study to be confident. Additionally, calculated size was increased by 3% to account for potential losses.

Results

During the study period medication records for 823 patients were analysed, the mean age of subjects was 50.8 years (SD ± 23.3) ranged from 1 to 94 years, 520 (63.2%) were...
females, and the average number of prescribed drugs was 4.7 (SD ± 2.6). Overall, 88 clinically significant potential drug-antifungal interactions were identified among 69 (8.4%) outpatients. Exposed subjects were significantly older (p < 0.01) and they had more complex therapeutic regimen (p < 0.01), while risk for occurrence of pIs was not in line with patient sex (p = 0.285), (Table 1). The average number of interactions involving antibacterials per exposed patients was 1.3 (ranged 1–5), and 56 subjects had 1, and 13 subjects ≥ 2 pIs.

**Potential drug-antimicrobial interactions**

In total, 31 different interacting combinations were identified, the most common pIs were benzodiazepines undergoing oxidation and clarithromycin or erythromycin and aminophylline and ciprofloxacin (Table 2). The proportion of pIs involving antimicrobials was 44.3% for macrolides, 33.0% for quinolones, 9.1% for azole antifungals, 5.7% for aminoglycosides, 4.5% for penicillins, 3.4% for cephalosporins, and 2.3% for tetracyclines.

**Pharmacological mechanisms**

The reported mechanisms for pIs were classified as pharmacodynamic (11.4%), pharmacokinetic (83.0%), a combination of both types (2.3%) and unknown (3.4%). Pharmacodynamic pIs were in line with potentiation of pharmacological effects while pharmacokinetic pIs were associated primarily with inhibition of metabolic pathways mediated by CYP3A4 and CYP1A2 isoenzymes (Table 3).

**Potential clinical outcomes**

In 89.8% of cases there was an increased risk for ADEs including excessive sedation (22.7%), cardiotoxicity (20.5%), miscellaneous adverse effects of aminophylline (13.6%), bleeding risk (10.2%), miscellaneous adverse effects of corticosteroids (8.0%), etc. (Table 4). The potential for decreased effectiveness of antiinfective agents was reported in the 12.5% of cases (Table 4).

### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Exposed (n = 69)</th>
<th>Unexposed (n = 754)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>67.0 (19.0)</td>
<td>56.0 (33.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>39 (56.5)</td>
<td>481 (63.8)</td>
<td>0.285</td>
</tr>
<tr>
<td>Number of prescribed drugs, median (IQR)</td>
<td>7.0 (4.0)</td>
<td>4.0 (3.0)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

IQR – interquartile range; p value < 0.05 was considered as statistically significant.

### Table 2

The most common potential drug-antimicrobial agent interactions

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>pIs, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines/clarithromycin</td>
<td>17 (19.3)</td>
</tr>
<tr>
<td>Aminophylline/ciprofloxacin</td>
<td>12 (13.6)</td>
</tr>
<tr>
<td>Calcium channel blockers/clarithromycin</td>
<td>7 (8.0)</td>
</tr>
<tr>
<td>Digoxin/clarithromycin</td>
<td>5 (5.7)</td>
</tr>
<tr>
<td>Iron salts/ciprofloxacin</td>
<td>5 (5.7)</td>
</tr>
<tr>
<td>Antiarrhythmic agents/levofloxacin</td>
<td>5 (5.7)</td>
</tr>
<tr>
<td>Methylprednisolone/clarithromycin</td>
<td>4 (4.5)</td>
</tr>
</tbody>
</table>

pIs – potential interactions; BZs – benzodiazepines; CCBs – calcium channel blockers.

### Table 3

Overview of pharmacological mechanisms for identified drug combinations

<table>
<thead>
<tr>
<th>Overall mechanism</th>
<th>Mechanisms</th>
<th>pIs, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamic</td>
<td>Additive pharmacological effect</td>
<td>10 (11.4)</td>
</tr>
<tr>
<td>Pharmacokinetic</td>
<td>Drug absorption (^a)</td>
<td>7 (8.0)</td>
</tr>
<tr>
<td></td>
<td>Drug metabolism (^b)</td>
<td>55 (62.5)</td>
</tr>
<tr>
<td></td>
<td>Drug excretion (^c)</td>
<td>8 (9.1)</td>
</tr>
<tr>
<td></td>
<td>Other (^d)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td></td>
<td>Pharmacokinetic (total)</td>
<td>73 (83.0)</td>
</tr>
<tr>
<td>Pharmacodynamic/pharmacokinetic</td>
<td>2 (2.3)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (3.4)</td>
<td></td>
</tr>
</tbody>
</table>

pIs – potential interactions; \(^a\)Drug absorption: chelation (6 pIs), high gastric pH (1 pIs); \(^b\)Drug metabolism: CYP3A4 inhibition (36 pIs), CYP3A4 induction (1 pIs), CYP1A2 inhibition (17 pIs), CYP2C9 inhibition (1 pIs); \(^c\)Drug excretion: P-glycoprotein (Pgp) inhibition (5 pIs), glomerular filtration reduction (2 pIs), competition for organic anion transporter (1 pIs); \(^d\)Drug absorption/drug metabolism combination: Pgp/CYP3A4 inhibition (3 pIs).

### Table 4

<table>
<thead>
<tr>
<th>Overall risk</th>
<th>Risks</th>
<th>pIs, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk for ADEs</td>
<td>Bleeding risk</td>
<td>9 (10.2)</td>
</tr>
<tr>
<td></td>
<td>Cardiotoxicity</td>
<td>18 (20.5)</td>
</tr>
<tr>
<td></td>
<td>Excessive sedation</td>
<td>20 (22.7)</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids adverse effects</td>
<td>7 (8.0)</td>
</tr>
<tr>
<td></td>
<td>Aminophylline adverse effects</td>
<td>12 (13.6)</td>
</tr>
<tr>
<td></td>
<td>ABs adverse effects</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics adverse effects</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>7 (8.0)</td>
</tr>
<tr>
<td>Risk for decreased effectiveness</td>
<td>Failure of ABs effectiveness</td>
<td>79 (89.8)</td>
</tr>
</tbody>
</table>

**Note:** Percentages do not add up to 100% because one pI could have multiple clinical outcomes.

### Table 5

<table>
<thead>
<tr>
<th>Overall recommendation</th>
<th>Recommendations</th>
<th>pIs, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring</td>
<td>Clinical monitoring of toxicity</td>
<td>22 (25.0)</td>
</tr>
<tr>
<td></td>
<td>Monitoring of physiological markers</td>
<td>11 (12.5)</td>
</tr>
<tr>
<td></td>
<td>Monitoring (total)</td>
<td>33 (37.5)</td>
</tr>
<tr>
<td>Adjust dose as needed</td>
<td></td>
<td>33 (37.5)</td>
</tr>
<tr>
<td>Avoid combination</td>
<td></td>
<td>27 (30.7)</td>
</tr>
<tr>
<td>Risk-modifying strategy</td>
<td>Separate administration</td>
<td>6 (6.8)</td>
</tr>
<tr>
<td></td>
<td>Therapeutic alternative</td>
<td>20 (22.7)</td>
</tr>
<tr>
<td></td>
<td>Supplements</td>
<td>2 (2.3)</td>
</tr>
<tr>
<td></td>
<td>Risk-modifying strategy (total)</td>
<td>28 (31.8)</td>
</tr>
<tr>
<td>Contraindicated combination</td>
<td></td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

**Note:** Percentages do not add up to 100% because one pI could have multiple management advice.

**Management advice**

To control the ADI risk, common recommendation was monitoring of simultaneous administration of drugs (37.5%) and in that case advice also included dose adjustment as needed (37.5%). Additionally, frequent advice were to avoid combination (30.7%) as well as different risk-modifying strategies (31.8%), and as a part of latter, significant proportion related to the choice of therapeutic alternative (22.7%) (Table 5).

**Discussion**

In the study, of the 823 patients included, 69 (8.4%) were exposed to a risk for the clinically significant ADIs involving antimicrobial agents. In the literature there is a lack of reports about frequency of these type of pIs. One study was conducted in the Netherlands among home-dwelling patients aged ≥ 75 years who used ≥ 4 drugs and the prevalence of pIs involving anti-infectives for systemic use was 14.3%.

Lower prevalence of pIs in our study could be explained by general characteristics of study population, given that outpatients in the HCNS were younger (50.8 vs 81 years in the Dutch study) and had less number of prescribed drugs on average (4.7 vs 6.8 medicines, respectively). According to the results of previous studies, both variables contribute to a greater risk for exposure to pIs. Further comparison is difficult with regard that the primary aim of the Dutch study was to determine the nature, volume and clinical relevance of prescription-related points of attention in the main ATC groups and there were no more information in line with prescriptions of anti-infectives for systemic use.

In the present study, the proportion of potential benzodiazepine and macrolide interactions was the most frequent (17 cases), thus co-administration of dazepam and clarithromycin, alprazolam and clarithromycin, and diazepam and erythromycin represented an increased risk for excessive sedation. Reis' et al. study showed that excessive sedation was ADE which was most frequently related to clinical manifestations of DDIs in the ICU, and among others, it was caused by administration of the interacting pair midazolam and clarithromycin. Benzodiazepines metabolized by oxidation were recognized as substrates of CYP3A4 isoenzyme, and macrolide antibiotics can inhibit their metabolism.

However, Yeates et al. reported that azithromycin did not affect midazolam metabolism. Hence, to prevent the risk, it is necessary to caution patients about over-sedation and to reduce the benzodiazepine dose as needed, or, to consider the use of benzodiazepines metabolized by conjugation (e.g.

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lorazepam), which are unlikely to interact, or, to take into consideration azithromycin as therapeutic alternative for erythromycin and clarithromycin. To facilitate health professionals detection of pharmacokinetic interactions as well as interventions for reducing adverse events, numerous information about CYP450 substrates, inhibitors and inducers could be implemented in CYP450-based software.

In the study, among commonly reported pl's, there was the interaction between aminophylline and ciprofloxacin (12 cases). The inhibitory effects of quinolones on aminophylline metabolism were mediated by CYP1A2 isozyme. But, among quinolones there were significant differences in pharmacokinetic features. Thus, enoxacin was the most potent inhibitor of theophylline metabolism (reduced clearance by more than 50%), pipemidic acid, ciprofloxacin and pefloxacin reduced theophylline clearance to a smaller extent (approximately 20% to 30%), norfloxacin, ofloxacin and nalidixic acid had minimal effects. Finally, there was no pharmacokinetic interaction between orally administered levofloxacin and intravenously administered theophylline. When theophylline toxicity was studied in a 19-year period concomitant drug and/or substance exposure was positive in 87.8% of patients admitted to the Department of Emergency Medicine, and antimicrobials were among commonly co-administered medicines. The choice of therapeutic alternative without or with a limited potential for interaction with theophylline as well as monitoring its plasma concentration and clinical response can prevent adverse effects. However, considering an intermittent contact and an infrequent communication between clinicians and patients in primary healthcare settings, it is very important to advise patients to report unexplained abdominal pain, nausea, vomiting, tachycardia, palpitations, headache or insomnia.

In the current study, antimicrobial drugs (benzylpenicillin, ceftriaxone, clarithromycin, ciprofloxacin, and fluconazole) had potential for interactions with warfarin (9 cases; 10.2% of all pl's) increasing the risk of bleeding. Thus, co-administration of specified antibiotics or oral azole antifungals and warfarin were considered as indicator of a high risk when prescribed in primary care patients because of the consistency in article reportings about clinically significant bleeding. Macrolides, quinolones and metronidazole were defined as interacting antibiotics. Furthermore, according to the data on spontaneous reported ADEs to the WHO Global ICSR database decreased prothrombin level, increased International Normalized Ratio (INR), and haematuria, there were commonly noted adverse events during administration of interacting combinations involving warfarin and antimicrobials. There were several pharmacodynamic and pharmacokinetic factors which may potentiate warfarin's effect. Thus, beta-lactams modifying gut flora reduced endogenous vitamin K production, additionally penicillins and warfarin were considered as indicator of a high risk when prescribed in primary care patients because of the consistency in article reportings about clinically significant bleeding. Macrolides, quinolones and metronidazole were defined as interacting antibiotics. Furthermore, according to the data on spontaneous reported ADEs to the WHO Global ICSR database decreased prothrombin level, increased International Normalized Ratio (INR), and haematuria, there were commonly noted adverse events during administration of interacting combinations involving warfarin and antimicrobials. There were several pharmacodynamic and pharmacokinetic factors which may potentiate warfarin's effect. Thus, beta-lactams modifying gut flora reduced endogenous vitamin K production, additionally penicillins induced inhibition of adenosine diphosphate-mediated platelet aggregation. Fluconazole was identified as an inhibitor of CYP2C9 isoenzyme which mediated in oxidative biotransformation of 

be avoided in case when it was recommended to separate administration of iron salts and fluoroquinolones.

Authors did not focus on clinically manifested drug-antimicrobial interactions. It would be interesting for further research to consider common percentage of outpatients exposed to pls involving antiflaccitive agents. Additionally, in the present study frequently reported interacting combinations (benzodiazepines and clarithromycin, digoxin and clarithromycin, aminophylline and ciprofloxacin, calcium channel blockers and clarithromycin, warfarin and antimicrobials) were listed in recent literature as risk factors associated with pharmacotherapy problems. Considerable frequency of pls as well as strong epidemiological evidence about risk co-prescription of antimicrobials pointed out the importance of interactions with this drug class using for short-term intercurrent diseases.

In spite of its limitations, our study discussed the prevalence and type of potential drug-antimicrobial agent interactions in primary medical care which could cause a deterioration in a patient’s clinical status. For assessment of interacting combinations, the parameters as quality of evidence, rating of clinical significance, pharmacological mechanisms, clinical outcomes and management strategies were considered. By evaluation of these features for each potential interaction, we got the set of information which could be the base for taking measures to their prevention and consequently reduction of harming the patient.

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