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ORIGINAL ARTICLE

Determination of Potential Drug-Drug Interactions in Patients Using Quinolone Group Antibiotics

Kinolon Grubu Antibiyotik Kullanan Hastalarda Potansiyel İlaç-İlaç Etkileşimlerinin Belirlenmesi

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ABSTRACT

Aim: The aim of the study was to determine the potential drug drug interactions of patients receiving inpatient treatment in the intensive care unit and infectious diseases ward and using quinolone group antibiotics by using different interaction software programs.
Material and Methods: The prescriptions of 100 patients who received inpatient treatment in infectious diseases service and intensive care unit at Selçuk University Faculty of Medicine Hospital between January 2022 and December 2022 and who were treated with quinolone group antibiotics during treatment were analyzed retrospectively.
Results: Of the patients included in the study, 62 were male and 38 were female. The mean age of men was 65.76 ± 16.22 years, while the mean age of women was 68.63 ± 16.29 years. While Medscape® detected a total of 1776 interactions, this number was 1432 in Lexicomp® and 1693 in Drugs®.While 0.33% of the interactions detected in the Medscape® software program were contraindicated, 3.77% of the interactions were contraindicated in Lexicomp®. Kendall W coefficient 0.94, Chi-Square test 281.12, p <0.001 were found to be statistically significant. The software programs used to detect pDDIs are highly compatible with each other.
Conclusion: High agreement was found between software programs used to detect potential drug-drug interactions. Interaction classifications between software programs are different. Therefore, clinicians may benefit from different software programs.

Keywords: Drug interactions, Software, Quinolone, Antibiotics

ÖZ

Amaç: Çalışmanın amacı, yoğun bakım ünitesi ve enfeksiyon hastalıkları servisinde yatarak tedavi gören ve kinolon grubu antibiyotik kullanan hastaların potansiyel ilaç etkileşimlerinin farklı etkileşim yazılım programları kullanılarak belirlenmesidir.
Yöntem: Ocak 2022-Aralık 2022 tarihleri arasında Selçuk Üniversitesi Tıp Fakültesi Hastanesi Enfeksiyon Hastalıkları Servisi ve Yoğun Bakım Ünitesi'nde yatarak tedavi gören ve tedavi sırasında kinolon grubu antibiyotiklerle tedavi edilen 100 hastanın reçeteleri retrospektif olarak incelenmiştir.
Bulgular: Çalışmaya dahil edilen hastaların 62'si erkek, 38'i kadındı. Erkeklerin yaş ortalaması 65,76 ± 16,22 iken kadınların yaş ortalaması 68,63 ± 16,29'dur. Medscape® toplam 1776 etkileşim tespit ederken, bu sayı Lexicomp®'ta 1432, Drugs®'ta ise 1693'tür. Medscape® yazılım programında tespit edilen etkileşimlerin %0,33'ü kontrendike iken, Lexicomp®'ta etkileşimlerin %3,77'si kontrendike bulunmuştur. Kendall W katsayısı 0.94, Ki-Kare testi 281.12, p<0.001 istatistiksel olarak anlamlı bulunmuştur. Potansiyel ilaç-ilaç etkileşimlerini tespit etmek için kullanılan yazılım programları birbirleriyle yüksek uyum içerisindedir.
Sonuç: Potansiyel ilaç-ilaç etkileşimlerini tespit etmek için kullanılan yazılım programları arasında yüksek uyum bulunmuştur. Yazılım programları arasındaki etkileşim sınıflandırmaları farklıdır. Bu nedenle, klinisyenler farklı yazılım programlarından faydalanabilirler.

Anahtar Kelimeler: İlaç etkileşimleri, Yazılım, Kinolon, Antibiyotik

Introduction

Drug-drug interaction is defined as the situation that occurs when drugs are used together and their pharmacological effects are altered by other drugs (1). Drug-drug interactions (DDIs) are mostly encountered at the pharmacokinetic level (2). As a result of the interactions of drugs with each other, results such as decreased efficacy in treatment and adverse drug reactions (ADRs) may occur (3). Potential drug-drug interactions (pDDIs) are among the leading preventable causes of ADRs. It is estimated that approximately 1% of hospitalized patients experience an ADRs due to DDIs (4). Quinolone group antibiotics have bactericidal effect on gram-negative and gram-positive microorganisms. They may interact with other drugs. They may inhibit the metabolic elimination of warfarin, theophylline and caffeine. Absorption of quinolones may be reduced by antacids, sucralfate, iron and zinc salts. They may interact with some Non-steroidal anti-inflammatory drugs (NSAIDs) and cause adverse effects in the central nervous system (CNS). As

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a result of these interactions, toxicity may be observed or treatment may fail. It is important for clinicians to manage interactions well (5-7).

The use of antimicrobial drugs in hospitals is progressively growing. Quinolones, in particular, are widely prescribed to treat respiratory tract infections, including tuberculosis, urinary tract infections, intra-abdominal infections, skin and skin structure infections, sexually transmitted diseases, and bone and joint infections. National use of quinolones in US intensive care units increased steadily (8-10). Quinolones are among the most commonly prescribed antibiotics in hospital. In two different researches conducted in inpatients, the rates of quinolone group antibiotic use were 14.4% and 15%, respectively (11, 12). The use of inappropriate combined antimicrobials can cause ADRs and economic burden (13, 14).

pDDIs are commonly observed as a result of polypharmacy, particularly in intensive care units (ICU) (15). Antibiotics used in intensive care units, especially macrolides and quinolones, can often cause clinically significant interactions (16).

Multiple software programs can be used to detect pDDIs. It is recommended to use different software programs at the same time to make the most accurate decision (17, 18). Software programs used for interaction detection may not reflect the clinical significance of interactions on their own. Various deficiencies in drug interaction databases make it necessary to manage the process according to the clinical significance of the interaction by making an individual assessment for each patient (19, 20).

The aim of the study was to determine the pDDIs of patients receiving inpatient treatment in the intensive care unit and infectious diseases ward and using quinolone group antibiotics by utilizing different interaction software programs.

Material and Methods

Study design

The prescriptions of 100 patients, who received inpatient treatment in infectious diseases service and intensive care unit at Selçuk University Faculty of Medicine Hospital between January 2022 and December 2022 and were treated with quinolone group antibiotics during treatment, were analyzed retrospectively. Patients' demographic information such as age and gender were recorded, and orders containing medications not covered by the software programs were excluded. Software programs Medscape®, Drugs®, and Lexicomp® were used to detect pDDIs in patients.

Statistical analysis

By analyzing each pDDIs using Kendall W values, the link between prospective pDDIs software was verified based on the outcomes of three severity degrees of interaction. Kendall W calculates a correlation coefficient that indicates agreement between multiple raters. Kendall W values range from 0-0.2, which denotes a little agreement, to 0.21-0.40, fair, 0.41-0.60, considerable, 0.61-0.80, significant, and 0.81-1.0, perfect (21). To do the statistical analysis, IBM SPSS 22.0 was used. The threshold of statistical significance was set at $p<0.05$.

Ethical Approval

This study was approved by the Selcuk University Faculty of Medicine Local Ethics Committee (Ethics committee approval number: E-70632468-050.01.04-486873. Date: 15/03/2023).

Results

Of the patients included in the study, 62 were male and 38 were female. The mean age of men was 65.76 ± 16.22 years, while the mean age of women was 68.63 ± 16.29 years. Men used an average of 15.73 ± 6.18 drugs while women used an average of 14.50 ± 4.27 drugs. Details are given in Table 1.

Table 1. Patient demographic status

	Male (n=62)	Female (n=38)
Age (mean, SD)	65.76 ± 16.22	68.63 ± 16.29
Number of medications (mean, SD)	15.73 ± 6.18	14.50 ± 4.27
Number of comorbidities (mean, SD)	1.79 ± 1.31	2.42 ± 1.50

SD: Standard deviation

Medscape® detected a total of 1776 interactions whereas this number was 1501 in Lexicomp® and 1693 in Drugs®.While 0.33% of the interactions detected in the Medscape® software program was contraindicated, 3.66% of the interactions were contraindicated by Lexicomp®. Details are given Table 2.

When pDDIs of quinolone group antibiotics were examined, the most frequently detected by the Lexicomp® software program was the Moxifloxacin / Ipratropium and Albuterol interaction (3.42%). In the

Table 2. Total potential drug-drug interactions detected in different software programs

	Medscape®					Lexicomp®						Drugs®			
	C (n) (%)	S (n) (%)	Monitor closely (n) (%)	Minor (n) (%)	Total	X (n) (%)	D (n) (%)	C (n) (%)	B (n) (%)	A (n) (%)	Total	Major (n) (%)	Moderate (n) (%)	Minor (n) (%)	Total
Total	6 %0.33	154 %8.67	1382 %77.81	234 %13.17	1776	55 %3.66	210 %13.99	953 %63.49	283 %18.85	- -	1501	286 %16.89	1141 %67.39	266 %15.71	1693

C: Contraindicated

S: Serious

Table 3. Potential drug-drug interactions most frequently detected with quinolones

Software program	Potential drug-drug interactions	Interaction classification	Number of interactions (n) (%)	Comments
Lexicomp®	Moxifloxacin / Ipratropium and Albuterol	B	49 %3.42	Increased ECG monitoring may be considered in patients at high risk for QT interval prolongation.
	Moxifloxacin / Methylprednisolone	C	40 %2.79	Monitor closely for tendon or joint pain.
	Tramadol / Moxifloxacin	C	33 %2.3	Monitor for evidence of hypo- or hyperglycemia during concomitant administration of agents with blood glucose-lowering effects and quinolone antibiotics.
	Moxifloxacin / Acetylsalicylic acid	C	20 %1.39	Aspirin may decrease the serum concentration of quinolones.
	Moxifloxacin / Dexamethasone	C	18 %1.25	Monitor closely for tendon or joint pain.
Medscape®	Albuterol / Moxifloxacin	Monitor closely	52 %4.42	May increase QTc interval
	Methylprednisolone / Moxifloxacin	Monitor closely	41 %2.30	Monitor closely for tendon or joint pain.
	Dexamethasone /Moxifloxacin	Monitor closely	18 %1.01	Monitor closely for tendon or joint pain.
	Moxifloxacin / Midazolam	Minor	18 %1.01	Moxifloxacin may increase midazolam levels
Drugs®	Albuterol / Moxifloxacin	Moderate	50 %2.95	Can cause arrhythmia
	Methylprednisolone / Moxifloxacin	Major	39 %2.3	Monitor closely for tendon or joint pain.
	Tramadol / Moxifloxacin	Major	34 %2	Can cause arrhythmia
	Acetylsalicylic acid / Moxifloxacin	Moderate	22 %1.29	The patient should be monitored for central nervous system side effects.

ECG: Electrocardiogram

QT: Time from the beginning of wave Q to the end of wave T

Medscape® software program, the most common interaction Albuterol / Moxifloxacin percentage was 4.42%, while this rate was 2.95% in the Drugs® software program. Moxifloxacin/ Methylprednisolone interaction was also among the frequently observed interactions (2.79%) by LexiComp®. The observation rate of the same major interaction by the Drugs® is 2.30%. The rate of observation of this interaction in the Medscape® was determined as 2.30%. Details are given in Table 3.

Kendall W coefficient 0.94, Chi-Square test 281.12, p <0.001 were considered statistically significant. The software programs used to detect pDDIs are highly compatible with each other. Details are given in Table 4.

Table 4. Comparison of software programs

Program	Kendall W	Chi-Square	p
Lexicomp®-Medscape® -Drugs®	0.94	281.12	<0.001

Discussion

Especially in intensive care units, ADRs can be observed frequently due to polypharmacy. Some of the ADRs occur due to pDDIs. Up to 79% of patients in intensive care units may be exposed to drug-drug interactions (22). Clinicians can prevent pDDIs by using different software programs.

In a multicenter study by Kuscu et al. quinolone group antibiotics accounted for 10% of pDDIs in inpatients. Moxifloxacin/Methylprednisolone pDDI are among the most common interactions (23). Also in our research, Moxifloxacin/Methylprednisolone interaction was among the most frequently detected pDDIs. In another study evaluating the interactions of antibiotics with other drugs in intensive care patients, the highest number of interactions was found by the Medscape® software program. (24). In our research, the highest number of interactions was by Medscape®.The reason for this is thought to be that the same interaction is shown again in different categorizations.

There are many research comparing software programs used for interaction detection to determine the most clinically appropriate software programs. In a multicenter observational study examining interactions and their consequences in intensive care patients reported that quinolone group antibiotics caused arrhythmia by interacting with other drugs and this constituted 3% of total interactions. Quinolone group antibiotics are among the drugs that most frequently cause DDIs (25). In our research, it was determined that 3.42% of the common interactions of quinolone group antibiotics could cause arrhythmia by the Lexicomp® software program. This rate was 4.42% by Medscape® and 4.95% Drugs®.

In a research conducted in patients hospitalized in the internal medicine ward, the interaction rate detected by the Lexicomp® software program per patient was determined as 2.62 (26). In our research, this rate was 15.01. The difference is thought to be due to the inclusion of patients receiving treatment in the intensive care unit in our research and therefore the high number of drugs used by the patients. In another research, Medscape® software program detected 4.33% serious interaction (27). In our research, this rate was determined as 8.67%. It is thought that the reason for the difference in the high rate found in our research is that the patients participating in our study used more drugs. Software programs used to support clinicians

should have high compatibility with each other. Liu et al. found moderate agreement (weighted kappa=0.473) between LexiComp® and Micromedex®. Additionally, the most interaction was detected by the LexiComp® software program (28). In a research comparing Drugs® and Micromedex® software programs, Drugs® was more sensitive in detecting pDDIs. It was stated that both software programs can be used to detect pDDIs (29). In this research, high compatibility (Kendall W= 0.94) was determined between three different software programs. Multiple research assessing the efficacy of DDI screening software tools have consistently established that Lexi-Interact exhibits a high level of sensitivity and specificity (30, 31). In a research conducted in a community pharmacy setting and comparing three different software programs, it was stated that Lexicomp®, Drugs®, and Medscape® programs showed weak compatibility with each other (32). This study was conducted in a free pharmacy setting and in a larger population. Therefore, it is thought to give different results from our study.

The most important limiting factor is that this study was conducted retrospectively. Since the study was conducted retrospectively, clinically significant interactions could not be detected. Prospective and multicenter studies are needed to eliminate this limitation.

High agreement was identified between the software programs used to detect pDDIs. The interaction classifications between software programs are different. Therefore, clinicians should use different software programs for pDDIs detection.

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