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Evaluation of potential drug-drug interactions of metformin using different software programs: A single-center retrospective study

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Abstract

Aim: Given that metformin is often recommended for the management of type 2 diabetes mellitus, it is clinically significant to consider the potential interactions between metformin and other medications. In this study, we aimed to identify potential drug-drug interactions associated with metformin by retrospectively analyzing the prescriptions of patients taking metformin.

Materials and Methods: Metformin-containing prescription data of five independent community pharmacies in Konya province for the year 2023 were analyzed retrospectively. Medscape®, Drugs® and LexiComp® software programs were used to detect potential drug-drug interactions. As a result of power analysis with the G Power program, 400 patients were included in the study with an effect size of 0.25, type 1 error of 0.05 and confidence interval of 0.95.

Results: Kendall's W value indicating the agreement between Medscape®, Drugs® and LexiComp® software programs was calculated as 0.061. In terms of potential drug-drug interactions of metformin, the agreement between the software programs was observed to be slight. The highest agreement between the progrmas was observed between Medscape® and LexiComp® (Kappa coefficient=0.44).

Conclusion: Since potential drug-drug interactions are common in prescriptions for patients taking metformin, these interactions should be carefully monitored. Clinicians should use multiple interaction programs to identify potential drug-drug interactions of metformin.

Introduction

Diabetes mellitus (DM) is a long-term metabolic illness marked by consistently high blood sugar levels caused by a decrease in insulin production and/or a decrease in the effectiveness of insulin, resulting in a severe reduction in quality of life. Chronic hyperglycemia in DM leads to functional damage in various organs and tissues, particularly the eyes, nerves, and blood vessels [1]. Diagnostic criteria for DM include a fasting plasma glucose level of ≥126 mg/dL (7 mmol/L), HbA1c ≥6.5%, or a random plasma glucose level of ≥200 mg/dL (11.1 mmol/L) [2]. According to the International Diabetes Federation (IDF) Atlas, approximately 537 million adults aged 20-79 years were living with DM in 2021. With the global prevalence of DM continuing to rise, this number is projected to reach 643 million by 2030 and 783 million by 2045 [3].

Metformin, a biguanide derivative, is an oral anti-diabetic agent that has been in clinical use for nearly 70 years and is commonly prescribed for the treatment of type 2 diabetes mellitus (DM) [4]. Metformin activates AMP-activated protein kinase in the liver, promoting hepatic glucose uptake and inhibiting gluconeogenesis, thereby enhancing glucose utilization in peripheral tissues [5]. It is favored as a first-line oral therapy for DM due to its efficacy in lowering glucose levels, good tolerability, accessibility, cost-effectiveness, promotion of weight loss, mild side effect profile, and low risk of hypoglycemia [6].

Drug-drug interaction is defined as a changing in drug efficacy resulting from synergistic or antagonistic effects due to the concurrent administration of two or more drugs. Pharmacokinetic interactions affect the absorption, distribution, metabolism, and elimination of drugs, whereas pharmacodynamic interactions involve alterations in the molecular signaling pathways of the drugs [7]. Since metformin is primarily excreted via the kidneys,

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drugs that influence renal function—such as loop diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, aminoglycosides, or angiotensin-converting enzyme inhibitors (ACE inhibitors)—may lead to metformin accumulation and increasing effects [8]. Metformin is actively transported into cells by organic cation transporters (OCTs). In silico studies have shown that proton pump inhibitors (PPIs), including omeprazole, pantoprazole, lansoprazole, rabeprazole, and tenatoprazole, are potent OCT inhibitors. These findings suggest that PPIs may inhibit the cellular transport of metformin [9].

Due to its widespread prevalence, diabetes mellitus (DM) is often associated with polypharmacy. Given that metformin is one of the most frequently prescribed medications for the treatment of type 2 DM, its interactions with other drugs are of significant clinical importance, particularly in patients on multiple medications. This study aimed to identify potential drug-drug interactions involving metformin by retrospectively analyzing the prescriptions of patients taking metformin and to statistically evaluate the agreement between 3 different interaction programs (Medscape®, Drugs®, and LexiComp®).

Materials and Methods

Study design

In this study, prescription data from five independent community pharmacies in Konya province, containing metformin or metformin in combination prescriptions from the year 2023, were retrospectively analyzed. Only prescriptions of outpatients were included in the study; prescriptions of hospitalized patients were excluded. Prescriptions dated between January 1, 2023, and December 31, 2023, were included in the study. Demographic information, including age, gender, polypharmacy status, and medications used by the patients, was recorded. Potential drug-drug interactions were identified using the Medscape®, Drugs®, and LexiComp® software programs. Interactions were classified as contraindicated, serious, monitor closely and minor in according to Medscape®; major, moderate and minor according to Drugs® and A, B, C, D, or X according to LexiComp®. Drugs not covered by these software programs were excluded from the study. The concurrent use of five or more drugs was considered polypharmacy [10, 11].

Statistical analysis

The sample size for this study was calculated to be 400 patients, based on a power analysis conducted using the G Power program with an effect size of 0.25, a type I error rate of 0.05, and a confidence interval of 95%. Statistical analysis was performed using IBM SPSS 22.0, with the threshold for statistical significance set at $p < 0.05$ Kendall's W analysis was conducted to assess the concordance between the different software programs. Kendall's W test is used to test whether there is consensus, especially when more than one rater ranks the same group.

Results

Among the 400 patients included in the study, 249 were female (62.25%) and 151 were male (37.75%). The mean age of the patients was 57.78 ± 13.34 years, with the youngest patient being 18 years old and the oldest 91 years old. Polypharmacy was observed in 184 patients (46%), while 216 patients (54%) did not exhibit polypharmacy. The mean number of medications used per patient was 5.62 ± 3.91. The highest number of medications used by a single patient was 33, while the lowest was 2. The total number of medications analyzed in the study was 2.248 (Table 1).

Table 1. Demographic and clinical characteristics of the participants.

Variable	N (%)	Mean (±SD)
Gender		
Female	249 (62.25)	
Male	151 (37.75)	
Age		57.78 ± 13.34 (Min 18, max 91)
Polypharmacy		
Yes	184 (46)	
No	216 (54)	
Number of drugs used		5.62 ± 3.91 (Min 2, max 33)

Min: Minimum; Max: Maximum.

Table 2. The most common medicines encountered in patient prescriptions.

Commonly used drugs	N (%)
Antidiabetic drugs	
Glifor® 1000 mg 100 tablets	74 (19.5)
Galvus® Met 50/1000 mg 60 tablets 50 (13.1)	
Janumet® 50/1000 mg 56 tablets	42 (11)
Matofin® 500 mg 100 xr tablets	37 (9.7)
Forziga® 10 mg 28 tablets	30 (7.9)
Diaformin® 1000 mg 100 tablets	31 (8.2)
Other drugs	
Ecopirin® 100 mg 30 enteric tablet	33 (8.7)
Coraspin® 100 mg 30 tablet	29 (7.7)
Parol® 500 mg 30 tablet	27 (7.2)
Panocer® 40 mg 28 enteric tablet	26 (6.9)

All medications used by the patients were analyzed, and the most commonly prescribed drugs were identified. Details are given Table 2.

The study identified a total of 277 interactions between metformin and other drugs out of the 2,248 medications used by 400 patients according to the Medscape®, 442 interactions according to the Drugs® and 307 interactions according to the LexiComp®. Specifically, the Medscape® identified 3 serious interactions, 165 monitor closely and 109 minor interactions. The Drugs® reported 6 major, 414 moderate, and 22 minor interactions, while the LexiComp® identified 2 category B, 300 category C, and 5 category D interactions. Details are given Table 3.

In this study, Kendall's W value, indicating the level of

Table 3. Potential drug interactions in patient prescriptions for metformin according to different software programs.

Software Programs	Number of Interactions	Type of Interaction	Description
Medscape®	3	Serious	Alternative drug should be used
	165	Close monitoring	The patient should be closely monitored
	109	Minor	Interaction is low risk
Drugs®	6	Major	Combination should be avoided
	414	Moderate	The combination should be used in special cases
	22	Minor	Low-risk interaction
LexiComp®	2	B	No need for any action
	300	C	The patient should be closely monitored
	5	D	Change of treatment should be considered

Table 4. Assessing the compatibility between software programs.

Database	Kendall's W	p
Medscape®-Drugs®-LexiComp®	0.061	p<0.05

agreement between the Medscape®, Drugs®, and LexiComp® software programs was calculated to be 0.061. This suggests that the agreement between the databases regarding potential drug-drug interactions involving metformin is poor. Details are given Table 4.

The highest agreement between the software programs was observed between Medscape® and LexiComp® (Kappa coefficient=0.44).

Discussion

Diabetes mellitus (DM) is a chronic disease with an ever-increasing incidence, leading to a corresponding rise in the use of diabetes-related medications. This trend underscores the importance of monitoring drug-drug interactions. Given that metformin is one of the most frequently prescribed medications for patients with DM, this study focused on analyzing its potential drug-drug interactions. A significant proportion of patients taking metformin are also on multiple medications, which heightens the risk of interactions. The study's findings highlight critical considerations for the use of commonly prescribed drugs like metformin. Espacially, 46% of the patients in this study were identified as being on polypharmacy, a common scenario in DM treatment that substantially increases the risk of drug-drug interactions. As polypharmacy is more prevalent among elderly patients, special attention should be given to the prescriptions of geriatric patients to carefully manage and minimize the risks associated with polypharmacy [12-14].

A cross-sectional retrospective study using the LexiComp® software program identified one or more potential drug-drug interactions in 43.8% of the patients included in the analysis. Of these interactions, 68.6% were categorized as category D, indicating that a change in treatment should be considered [15]. Another study, utilizing the Micromedex® software program and involving 649 patients, found that 56% of the patients had polypharmacy, and 48% of those taking two or more medications had at least one potential pharmacokinetic drug-drug interaction [16]. In a separate study focusing on the geriatric population, which included 209 patients, the most common type of interaction, observed in 68.33% of cases, was categorized as category C (moderate risk), requiring monitoring of treatment [17]. Consistent with these findings, the present study on potential drug-drug interactions involving metformin also concluded that the most common type of interaction was of moderate risk.

In a study conducted in a community pharmacy involving 120 patients using oral antidiabetic drugs, it was found that 138 of the 591 medications used by the patients were oral antidiabetics, with metformin being associated with the highest potential for drug-drug interactions. The study identified 134 interactions for metformin, resulting in an interaction rate of 74% [18]. Another prospective study, which included 110 outpatients aged ≥65 years, evaluated potential drug interactions using software programs. For metformin, 16 drug-drug interactions were identified in the Medscape® software program and 14 were found according to LexiComp® [19]. Additionally, a retrospective study examining drug-drug interactions in 690 patients over 65 years of age attending family medicine outpatient clinics identified 181 (8.7%) potential interactions according to Medscape® and 141 (6.3%) according to Drugs® for metformin [20].

In the present study, which investigated potential drug-drug interactions involving metformin across different software programs, 276 interactions were identified according to the Medscape®, 441 according to the Drugs® and 307 according to the LexiComp®. The agreement between these three databases was found to be slight (Kendall's W = 0.061). This slight agreement is likely attributable to differences in the information sources, classification criteria and interpretation methods used by each database. The study's limitations include its retrospective design and the use of data from only five pharmacies in Konya. Future research should involve larger sample sizes and data from different regions. Additionally, prospective studies should focus on examining the clinical consequences of interactions between metformin and other drugs in greater detail.

Conclusion

This study shows that potential drug-drug interactions are common in prescriptions for patients taking metformin

and that these interactions should be carefully monitored. Clinicians should be utilize multiple interaction software programs when identifying potential drug-drug interactions of metformin.

Ethical approval

This retrospective study was approved by the Local Ethics Committee of Selçuk University Faculty of Medicine on 27.02.2024 with decision number 2024/131.

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