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Evaluation of Potential Drug Interactions Detected in Critical Patients in Different Electronic Databases

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ABSTRACT

Objective: In clinical practice, electronic databases are used to detect drug interactions. In this study, it is aimed to identify potential interactions in the treatment of critically ill patients and to compare the severity category of these interactions according to 4 different electronic databases frequently used by clinicians.

Method: In this prospective and cross-sectional study; patients aged 18 years and older who were treated in the intensive care unit of a university hospital between December 6, 2021 and April 4, 2022, and who had at least two drugs in their treatment were included. The drug treatments of these patients were evaluated daily by a clinical pharmacist and 4 different databases were used to detect drug interactions (UpToDate®, Micromedex®, Medscape® and TEBRP®,).

Results: The compatibility of the severity categories of 419 different potential drug interactions detected in the UpToDate®, Micromedex®, Medscape® databases were compared according to the Fleiss Kappa statistic. According to this analysis; It was determined that the Kappa coefficient was 0.0493 and there was a low level of statistical agreement in terms of the severity categories specified by the electronic databases for drug interactions ($p<0.05$).

Conclusion: There may be differences between the databases in terms of the severity category and interpretation of the interactions. The involvement of clinical pharmacists who are specialized in the multidisciplinary team in intensive care units will contribute to the management of drug interactions.

Keywords: Drug interactions, critically ill, consistency, database

Introduction

Even if drug interactions can be used for therapeutic benefit, drug-drug interactions may jeopardize patient safety by leading to toxicity or reduced therapeutic benefit and increase mortality and morbidity due to increased complications, especially in critically ill patients (1). In a study, it was observed that the number of interactions increased significantly as the number of drugs increased and 1 clinically significant interaction requiring intervention occurred in the presence of ≥7 drugs in the treatment and there was a positive correlation between the number of drugs in the treatment and the potential drug interaction risk (2). The probability of occurrence of drug-drug interactions, one of the most important causes of drug-induced problems, rises with the increase in the number of drugs used (3). Clinically important drug-drug interactions are more likely to occur in intensive care unit patients with polypharmacy, undergoing complex treatment processes and with alterations in organ functions (4). Studies have shown that 33% of patients hospitalized in the ward and 67% of in intensive care unit (ICU) were exposed to drug-drug interactions at least once during their hospitalization (3).

Consideration of drug-drug interactions for patients in the ICU is of critical importance for the patient. Early reporting of potential drug-drug interactions can prevent many complications, which in turn improves patients' medication safety and increases the patient's quality of life. Evaluation of interactions only according to the ratings made by databases may lead to errors (5). The databases used in the determination of interactions may not reflect the clinical significance of interactions (the degree of reflection of the interaction in the clinic) alone. An interaction detected by drug interaction databases may not always be clinically significant or may sometimes be critical for the patient (2,3).

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In this study, it is aimed to identify potential interactions in the treatment of critically ill patients and to compare the severity category of these interactions according to 4 different electronic databases frequently used by clinicians.

Material and Methods

This prospective and cross-sectional study was carried out in the intensive care unit of a university hospital. Patients who were hospitalized in the intensive care unit between December 6, 2021 and April 4, 2022, aged 18 and over and had at least two drugs in their treatment were included in the study.

Within the scope of the study, the drug therapies of the included patients were monitored daily and recorded on the data collection form. Interactions between the drugs in the treatment were determined daily by a clinical pharmacist using UpToDate®, Micromedex®, Medscape® and TEBRP® (6–9) electronic databases. The number (n) and severity categories (e.g., contraindicated, serious, major, moderate and minor) of interactions identified from these 4 different databases were compared (Table 1).

Descriptive data of the patients were analyzed using Microsoft Excel 2021 Version 2204. The patients were followed daily during the study. As the patients were followed up for more than one day, the number of drugs varied between days. For this reason, the average values of the number of drugs of the patients were not specified. The minimum and maximum number of drugs used by the patients on the days of their follow-up treatment were stated.

Fleiss Kappa coefficient R 4.1.2 programming language was used for statistical analysis of drug interaction data determined within the scope of the study. A value of $p<0.05$ was considered significant in statistics. Fleiss Kappa is a measure of inter-rater reliability that eliminates the expected agreement by chance and is suitable for three or more raters. The kappa value ranges between -1 and 1, with 1 indicating complete agreement, -1 indicating complete disagreement, and 0 indicating agreement expected by chance (10). In Fleiss' interpretation of kappa values <0.0 is poor agreement, 0.0–0.2 is slight agreement, 0.21–0.40 is moderate agreement, 0.41–0.60 is moderate agreement, 0.61–0.80 is substantial agreement and 0.81–1.00 is almost perfect agreement. P values are calculated for Kappa and $p<0.05$ means that rater agreement is unlikely to be due to chance. High agreement between raters does not always mean that the answer is correct and low agreement does not always mean that the answer is incorrect. (11)

In case there was an intervention that needed to be made for the management of drug interactions detected in the patient's treatment (e.g., changing one of the two interacting drugs, giving the drugs at different times), this intervention was communicated to the patient's physician as a recommendation.

This study was approved by a local Ethics Committee (Decision No: 117/51).

Results

Within the scope of the study, 112 patients (48.21% were female) who were treated in the reanimation unit during the specified periods were followed up and included in the study. The mean age of the patients in the study was 51.08±18.7 years. The minimum number of drugs prescribed to the patients was 6±2.6 and the maximum was 8±3.51 (minimum – maximum: 2–18). During the study period, a total of 785 potential drug interactions were identified, 419 of which were different. It was calculated that there was an average of 7.01±7.77 potential drug interactions in each patient followed up.

Potential drug interactions were evaluated from 4 different electronic databases and different numbers of interactions were detected in each database. Accordingly, 245 potential drug interactions were detected in UpToDate® database, 257 in

Table 1. Severity categorization of electronic databases

UpToDate®	Medscape®	Micromedex®	TEBRP®	Severity Degree
B - No Need for Amendment	Minor	Minor	Minor/Effect Unknown	1
C - Monitor Therapy	Closely monitoring	Moderate	Careful Use and Patient Monitoring	2
D - Requires a Change in Therapy	Serious - Use Alternative	Major	Treatment should be changed/ Patient should be closely monitored	3
X - Avoid Combination	Contraindicated	Contraindicated	Serious - Avoid Using Together or Consider Other Alternatives	4

Table 2. Severity category in databases of potential interactions detected

	UptoDate®	Medscape®	Micromedex®
Severity Category (%)	X (3.67)	Contraindicated (1.17)	Contraindicated (5.30)
	D (20.41)	Serious - Use Alternative (12.84)	Major (60.61)
	C (60.41)	Closely monitoring (70.43)	Moderate (31.06)
	B (15.51)	Minor (15.56)	Minor (3.03)
Total (n)	245	257	132

Tablo 3. Statistical analysis of the consistency levels of potential drug interactions identified from electronic databases

Severity Category	Kappa	z	p
0	0.017	0.589	0.556
1	-0.047	-1.677	0.094
2	-0.001	-0.037	0.970
3	0.254	9.019	0.000*
4	0.211	7.478	0.000*

*p<0.05

Medscape® database, 132 in Micromedex® database and 227 in TEBRP® database. Potential drug interactions were categorized according to their severity. Accordingly, most of the potential drug interactions detected in the UpToDate® database (60.41%) were at level C, most of the potential drug interactions detected in the Medscape® database (70.43%) were at 'Closely Monitoring'level, and most of the potential drug interactions detected in the Micromedex® database (60.61%) were at 'Major' level. Table 2 shows the distribution of detected potential drug interactions according to the severity levels of each electronic database.

The number of potential drug interactions identified from electronic databases and the severity categories of some interactions were found to be different. Fleiss Kappa coefficient R 4.1.2 programming language was used to statistically examine these differences (p<0.05 was considered significant). Accordingly, when the table below regarding the kappa coefficient at the category level is examined, it is found that there is a low level but statistically significant similarity (K=0.04; p<0.05). When the kappa coefficients related to the categories are analyzed, while the kappa coefficients in categories 0, 1 and 2 are not statistically significant (p>0.05), the kappa value in categories 3 and 4 is low and statistically significant (p<0.05) (Table 3).

All potential drug interactions identified in the treatment of patients were evaluated daily by a clinical pharmacist and 58 recommendations were made to the physicians for clinically significant drug interactions.

Discussion

Polypharmacy constitutes an important problem for critical patients and is associated with increased side effects, drug interactions and treatment costs (12,13). The prevalence of potential drug interactions among intensive care unit patients has been reported to be 46–80% (10). Studies have reported that the factors affecting the occurrence of drug interactions are the pharmacologic properties of the drug and the number of drugs in the treatment. Farzanagen et al. included a total of 195 patients treated in the cardiothoracic intensive care unit in their prospective study and reported that an average of 12 (minimum-maximum: 2–18) drugs were administered per patient (14). Reis and Cassiani reported that the median value of the number of drugs in the treatment of 299 patients followed up in the intensive care unit was 12 (minimum-maximum: 10–14) (15). In a prospective and observational study by Kopp et al., it was shown that the median number of drugs used by internal and surgical intensive care unit patients was 8 (minimum 0 – maximum 18) (16). In our study, it was observed that the mean ± SD number of drugs used in the treatment of 112 patients within the days of follow-up was minimum 6±2.6 and maximum 8±3.51 (minimum – maximum: 2–18). The similarity of the data between the studies suggests that polypharmacy is frequently seen in the treatment of critically ill patients.

Sürmelioğlu and Demirkan found 161 potential drug-drug interactions using the UpToDate® database in 65 patients with sepsis and septic shock treated in the ICU, and the number of drug-drug interactions requiring clinically meaningful intervention was 19 (11.8%). they have determined (4). Reis et al reported that 40 (23.2%) of 172 medication errors were clinically significant in their prospective study on internal and surgical ICU patients (15). In the study conducted by Kara et al. in internal ICUs, 42, 112 and 91 drug interactions in 62 patients were determined by Micromedex, Medscape and Drugs. com, respectively. When the clinical significance of these interactions was evaluated, 15 (35.7%) of the drug interactions detected with the Medscape database were found to be clinically significant (17). In our study, recommendations were made to the physician following the patient in only 58 (13.84%) of 419 drug interactions. Considering the results of different studies, it is seen that the frequency of potential drug interactions is high in ICUs, and the rate of clinically significant ones varies between 11–35%.

In clinical practice, electronic databases are used to detect drug interactions. It has been observed that the severity category of potential drug interactions detected from databases are different. Monteith et al. calculated the Kappa coefficient as 0.142 using the general Fleiss Kappa statistic to compare the severity of 125 potential drug interactions detected from Micromedex®, Lexicomp®, Epocrates®, Drugs. com® and Medscape® databases in their study evaluating the interactions of antipsychotic drugs. In line with this value, it was reported that there was a low level but statistically significant (mildly concordant) concordance between the databases they used for couples with all main categories (11). Vivithanaporn et al. determined the severity levels of 292 potential drug interactions in Micromedex®, Drugs. com®, Liverpool® databases in their study including antiretroviral and antibiotic interactions. They reported that the agreement between the severity reports of the three databases determined by the Fleiss Kappa value was 0.129 and was accepted as a slight agreement between the three databases (18). In this study, UpToDate®, Micromedex®, Medscape® and TEBRP® databases were used to identify potential drug interactions. When the agreement of the

severity categories of 419 different potential drug interactions in UpToDate®, Micromedex® and Medscape® databases was compared according to the Fleiss Kappa statistic, it was found that the Kappa coefficient was 0.0493, which was low but statistically low level of agreement ($p<0.05$).

In our study, when the kappa coefficients related to the severity categories were analyzed, the kappa coefficients in categories 0, 1 and 2 were not statistically significant ($p>0.05$), while the kappa value in categories 3 and 4 was low and statistically significant ($p<0.05$). Previous studies have shown that the agreement between electronic databases increases as the degree of seriousness increases (17,18). Clinically significant drug interactions are usually seen in those with a high degree of severity, such as 3 and 4. Differences between databases, especially in the 3rd and 4th degrees, may pose a risk for the interpretation and management of drug interactions.

In addition to the severity ratings and severity ratings of potential drug interactions in electronic databases, differences were also observed in the information provided on interactions, drug selection, choice of dosage form (inhaler, nebulizer, etc.), and usage patterns such as membership or fee requirements. UpToDate® and TEBRP® databases were available with membership, Micromedex® was available with a paid password, and Medscape® was accessible without membership or fee. While UpToDate® database references articles on drug interactions and management, this was not the case in Micromedex®, Medscape® and TEBRP® databases. While UpToDate®, Micromedex® and Medscape® databases can be searched by active substance or preparation (limited quantity), TEBRP® database can only be searched by preparation name or QR code. TEBRP, one of the databases, is easier to utilize in our country because it is available in Turkish. In addition, it was observed that the TEBRP® database indicates the severity of interaction when accessed via mobile application, but does not indicate the severity of interaction when accessed via computer, which reduces its practicality in terms of use. During the working period, the TEPRP application was accessed via the web page. For these reasons, the severity categories of interactions over TEBRP are not specified.

Conclusion

In critically ill patients with frequent polypharmacy, the risk of drug interactions is quite high. There may be differences between the databases in which these drug interactions are evaluated in terms of the severity category and interpretation of the interactions. The involvement of clinical pharmacists who are intensively trained and specialized in pharmaceuticals in the multidisciplinary team in ICUs will contribute to the management of drug interactions.

AUTHOR CONTRIBUTIONS:

Concept: NS, DO; **Design:** NS, DO; **Supervision:** DO; **Data Collection and/or Processing:** NS; **Analysis and/or Interpretation**: NS; **Literature Search:** NS; **Writing Manuscript**: NS, DO; **Critical Review:** DO.

Ethics Committee Approval: The necessary approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Cukurova University Faculty of Medicine for the realization of the study (Decision No: 117/51).

Informed Consent: Consent form was obtained from the patients included in the study or from their relatives.

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors have no conflicts of interest to declare.

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