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Drug-drug interactions in an intensive care unit of a tertiary hospital in southern Chile: Evaluating databases agreement

[Interacciones farmacológicas en una unidad de cuidados intensivos de un hospital terciario en el sur de Chile: Evaluación de acuerdo con bases de datos electrónicas]

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Abstract

Context: Patients in intensive care units have a high risk of experiencing a pharmacological interaction due to complex pharmacotherapy, severe disease, and comorbidities; increasing the risk of adverse effects of medications. Electronic databases are useful sources to identify drug-drug interactions (DDI), especially when new therapeutic alternatives are added to conventional treatments.

Aims: To identify the frequency and severity of potential drug-drug interactions (pDDIs) in ICU patients using three electronic databases.

Methods: Clinical pharmacists collected data on medication dosage and route of administration, sex, age, length of stay, comorbidities, and APACHE II score using patient records. Micromedex, Medscape, and Lexicomp databases were used to identify and categorize pDDIs. Intensivists confirmed if a pDDI was clinically present. kappa concordance test was utilized as a measure of agreement among databases.

Results: Of the 93 ICU patients studied, pDDIs were identified in 89. A positive incremental relationship was found between number of medications, length of stay, and number of pDDIs. Patients with respiratory pathologies were most predisposed to presenting DDIs. Agreement among databases was mixed. Intensivists confirmed 5% of pDDIs.

Conclusions: Discrepancies among databases and in intensivist judgment highlight a significant information gap in the identification of DDIs.

Keywords: clinical pharmacist; drug interactions; intensive care unit.

Resumen

Contexto: Los pacientes hospitalizados en las Unidades de Cuidados Intensivos tienen un alto riesgo de experimentar una interacción farmacológica debido a la compleja farmacoterapia, a la gravedad del cuadro agudo y las comorbilidades; aumentando el riesgo de efectos adversos de los medicamentos. Las bases de datos electrónicas son útiles para identificar interacciones farmacológicas, especialmente cuando se agregan nuevas alternativas terapéuticas a los tratamientos convencionales.

Objetivos: Identificar la frecuencia y la gravedad de las posibles interacciones farmacológicas (pIF) en pacientes hospitalizados en la Unidad de Cuidados Intensivos mediante la utilización de tres bases de datos electrónicas.

Métodos: Se recopilaron datos de los registros de pacientes sobre dosis de medicamentos y la vía de administración, el sexo, la edad, la duración de la estancia, las comorbilidades y la puntuación APACHE II. Se utilizaron las bases de datos Micromedex, Medscape y Lexicomp para identificar y clasificar los pIF. Los intensivistas confirmaron si un pIF estaba clínicamente presente. La prueba de concordancia kappa se utilizó como medida de acuerdo entre las bases de datos.

Resultados: De los 93 pacientes de Unidad de Cuidados Intensivos estudiados, los pIF se identificaron en 89 de estos. Se encontró una relación incremental positiva entre el número de medicamentos, la duración de la estancia y el número de pIF. Los pacientes con patologías respiratorias estaban más predispuestos a presentar pIF. El acuerdo entre las bases de datos fue mixto. Los intensivistas confirmaron el 5% de los pIF.

Conclusiones: Las discrepancias entre las bases de datos y en el juicio intensivista resaltan una brecha de información significativa en la identificación de pIF.

Palabras Clave: farmacéutico clínico; interacciones farmacológicas; unidad de cuidados intensivos.

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INTRODUCTION

A drug-drug interaction (DDI) is defined as an action that a drug generates on another, causing a quantitative or qualitative change in its effects (Flynn, 2011). In order to achieve greater therapeutic effect, clinicians often administer multiple drugs simultaneously, which increases the risk of adverse drug effects (ADEs) due to DDIs or other variables (Smithburger et al., 2012). ADEs constitute a major problem in healthcare settings, leading to complications of clinical relevance, such as an increase in the number of days of hospitalization and the production of other disorders, and may even put the life of the patient at risk (Moura et al., 2011; Kapadohos et al., 2017).

The occurrence of some ADEs may be prevented by properly identifying relevant DDIs prior to treatment, considering the drugs' properties, routes of administration, and patient-specific variables (Janković et al., 2018). Electronic databases are useful sources for identifying DDIs. There are multiple databases available for health professionals that include information regarding medications and their possible pharmacological interactions. (Barrons, 2004; Roblek et al., 2015). Some of the most commonly used databases are Medscape®, Micromedex®, and Lexicomp®, which utilize an algorithm to determine the occurrence of DDIs.

While these databases can serve as a guide, it is necessary to monitor DDIs *in situ* in order to observe the effects of DDIs as a whole, especially when new therapeutic alternatives are added to formularies and incorporated with conventional treatments.

Patients in intensive care units (ICUs) are at elevated risk of experiencing DDIs because of complex pharmacotherapy, severe disease, and comorbidities. Existing studies suggest that risk factors for DDIs in ICU settings include polypharmacy, length of stay, and characteristics of the medication administered (Janković et al., 2018). To date, no studies of this kind have been conducted in Chile, a country where most hospitals do not utilize computerized DDI screening systems and where monitoring of patient profiles for DDIs is not part of common clinical practice. This study seeks to identify DDIs of clinical relevance by analyzing medical prescriptions in ICU patients at a Chilean hospital using three available databases and considering patient characteristics, treatments, frequency and severity of DDIs identified.

MATERIAL AND METHODS

Study setting and design

This prospective observational study included patients aged 18 years or older who were admitted for more than 72 hours to the ICU of a tertiary-care hospital in southern Chile. Data was collected for every patient hospitalized at the ICU during a course of three months from March to April 2018. Patients receiving less than two drugs on the third day of ICU admission were excluded. Clinical pharmacists were responsible for collecting data on medications prescribed, dosage, and route of administration. Also, data including sex, age, length of stay, comorbidities, and Acute Physiology and Chronic Health Evaluation (APACHE) II score were collected using the patient record.

Ethical approval

The local ethics committee approved the study and permission of the hospital authority was obtained to access patients' reports. Patient consent was waived due to the non-interventional design of the study. This study observed Helsinki Declaration of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

Procedures and definitions

Clinical pharmacists accessed three databases: Micromedex, Medscape and Lexicomp, using tablet computers to identify potential DDIs. These databases identify potential interactions and provide information regarding the mechanisms of possible adverse reactions and their clinical significance. A list of all DDIs was generated for each patient according to each database. Each DDI was,

according to the categorization system used by the database, categorized as 'Contraindicated' if the medications were contraindicated for simultaneous use; 'Major' if the interaction may put the patient's life at risk or cause permanent damage; 'Moderate' if the interaction may cause deterioration in the clinical condition of the patient, leading to additional treatment or prolongation of the hospital stay; and 'Minor' if the interaction is slight, undetected, or predicted, and without significant clinical involvement.

Once the interaction was classified, the patient was registered, and a follow-up appointment, emphasizing the monitoring of exam results and vital signs for evidence of pharmacological interaction, was conducted. In the event that an interaction was identified in one or more of the databases, two intensivists were asked to verify the potential DDI and to check its occurrence in the patients receiving the flagged drug combination.

Only the interactions between drugs used at doses for therapeutic, prophylactic or diagnostic purposes were studied. Each specific pair of drugs in a DDI was counted only once per patient. The drugs were classified in therapeutic classes according to the third level of the anatomical therapeutic chemical (ATC) classification.

Statistical analysis

The Cohen's kappa concordance test was utilized as a measure of agreement among databases and was classified as follows: $\kappa < 0$, no agreement; κ = 0-0.20; slight; κ = 0.21-0.40, fair; κ = 0.41-0.60, moderate; κ = 0.61-0.80, substantial; and κ = 0.81-0.99, almost perfect agreement (Landis and Koch, 1977).

Prevalence of DDIs and their severity levels were presented in the form of frequencies and percentages, whereas quantitative variables were presented as medians and interquartile ranges. Statistical analysis of the data was conducted using Stata 13.1 StataCorp LP, College Station Texas.

RESULTS

Of the 93 hospitalized patients in the ICU of the tertiary-care hospital during the three-month study period, possible DDIs were identified in 89 of them. Demographic and clinical characteristics of these patients are shown in Table 1. Main causes for admission were respiratory (32%), infectious (20%), and cardiovascular disease (14%).

A total of 1,310 medications were administered to the patients included in the study, averaging 14 ± 6 medications per patient. Each drug, regardless of whether it was administered once or multiple times, was counted only once for each patient. 1,061 possible DDIs were detected in 89 patients. In the 67 patients who received more than 10 drugs each, 987 possible interactions were registered. In the 28 patients who were hospitalized for more than 10 days, 521 possible interactions were registered. Patients who entered the ICU with respiratory pathologies were the most predisposed to presenting potential drug interactions and having a longer stay, which could increase the risk of acquiring a nosocomial infection, among other complications. On the other hand, patients with renal pathology received the highest average number of medications and were identified as having the highest number of possible interactions. This was because these patients were usually transferred to the ICU after kidney transplantation, and immunosuppressant drugs prescribed post-transplantation have a high profile of interaction with other medications.

There was a positive and incremental relationship between number of medications, length of hospital stay, and number of potential DDIs, as shown in Fig. 1. The more days the patient stayed in the ICU or the more medications they received, the greater the likelihood that a DDI would occur.

As described in Table 2, agreement among the databases used to identify potential DDIs was mixed, ranging from 0.10 to 0.35 for DDIs classified as contraindicated; from 0.52 to 0.71 for DDIs

classified as severe; and from 0.23 to 0.64 for DDIs classified as moderate. In terms of contraindicated medications, Lexicomp and Micromedex were more often in agreement and were more likely to recognize the interactions. Medscape was less likely to identify these DDIs, though Medscape matched more times with Micromedex than with Lexicomp. In terms of severe interactions, the three databases were in better agreement. Lexicomp and Micromedex coincided in their predictions, while Medscape identified a greater number of interactions. In terms of moderate and minor interactions, the databases matched with different intensities (Fig. 2).

Of the total number of possible DDIs, 51 (5%) could be confirmed clinically, affecting a third of the total number of patients admitted to the study (33 patients); that is, one out of every three patients had a clinically proven interaction.

The potential DDIs identified in the study included the following: risk of central nervous system (CNS) depression with concurrent use of fentanyl and propofol; risk of acute kidney injury with concurrent use of piperacilin/tazobactam and vancomycin; enhanced adverse/toxic effect of combining two sympathomimetics, such as albuterol-salmeterol; beta2-agonists potentially enhancing the hypokalemic effect of loop diuretics with a furosemide-albuterol combination; QTc-prolonging agents potentially enhancing the QTc-prolonging effect of other QTc-prolonging agents with a droperidol-ondansetron combination; CYP3A4 inhibitors, such as clarithromycin, potentially increasing the serum concentration of fentanyl; pyrimethamine potentially enhancing the adverse/toxic effect of trimethoprim; the interaction between phenytoin and ritonavir potentially decreasing the serum concentration of ritonavir or the serum concentration of phenytoin. Other potential DDIs are presented in Table 3.

DISCUSSION

ICU patients are at an increased risk of experiencing DDIs due to their critical clinical conditions, extended lengths of stay, and polypharmacy. The situation becomes more worrying in settings, such as that of this study, where DDI detection is not considered a part of routine clinical practice.

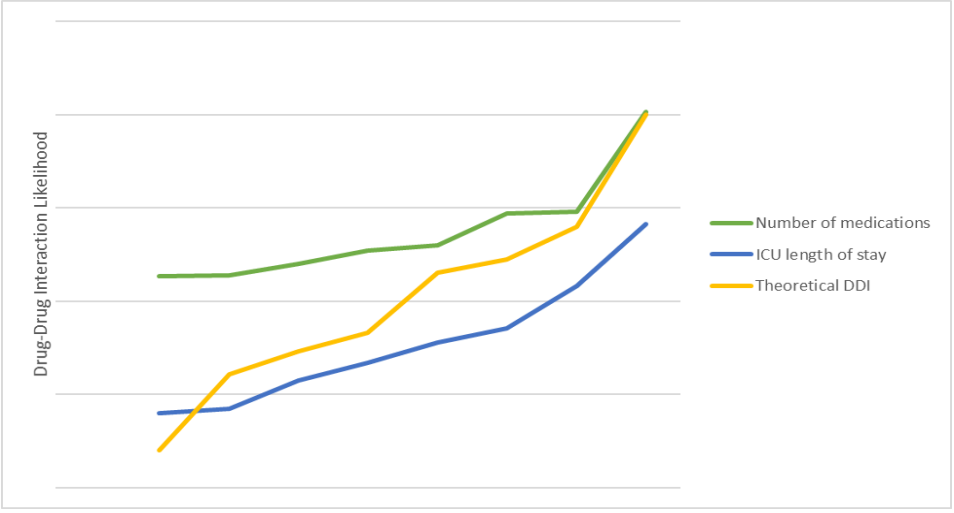

Figure 1. Relationship between length of stay, number of medications, and theoretical DDIs observed in the ICU patients admitted to the study.

ICU: Intensive Care Unit; DDI: Drug-Drug Interaction. Increase in number of medications in critical patients is related directly with the occurrence of a theoretical DDI and increase in the length of stay in the unit.

Table 1. Characteristics of Intensive Care Unit (ICU) patients admitted to the study (n=93).

Variable	Mean ± standard deviation (range) or number (%)
Age (years)	61.0 ± 15.1 (22 - 88)
Gender	Female: 40 (43%)
	Male: 53 (57%)
Length of hospitalization (days)	9.6 ± 11.0 (3 - 46)
Number of prescribed drugs	14 ± 6 (2 - 33)
APACHE II	7.4 ± 7.0 (3 - 34)
Number of comorbidities	2.5 ± 1.6 (0 - 7)
Reasons for admission to ICU [number of patients(%)]	
Respiratory system diseases	30 (32)
Infectious diseases	19 (20)
Circulatory system diseases	13 (14)
Genitourinary system diseases	7 (8)
Nervous system diseases	6 (6)
Endocrine and metabolic diseases	4 (4)
Hepatic diseases	1 (1)
Other diseases	13 (14)

APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive Care Unit.

Table 2. Agreement between classifications of DDIs identified according to the categorization system used by three databases.

DDI classification	Database	Medscape	Micromedex
Contraindicated			*
	Micromedex	0.3212	
	Lexicomp	0.1070	0.3474
Severe			
	Micromedex	0.5181	*
	Lexicomp	0.7121	0.5181
Moderate			
	Micromedex	0.2271	*
	Lexicomp	0.6368	0.4304
Minor			
	Micromedex	0.2127	*
	Lexicomp	0.2346	0.7291

*The Cohen's kappa concordance test; DDIs: Drug-Drug Interactions. Higher agreement within databases were observed for Severe and Moderate categories. Lexicomp and Micromedex showed better agreement in all categories.

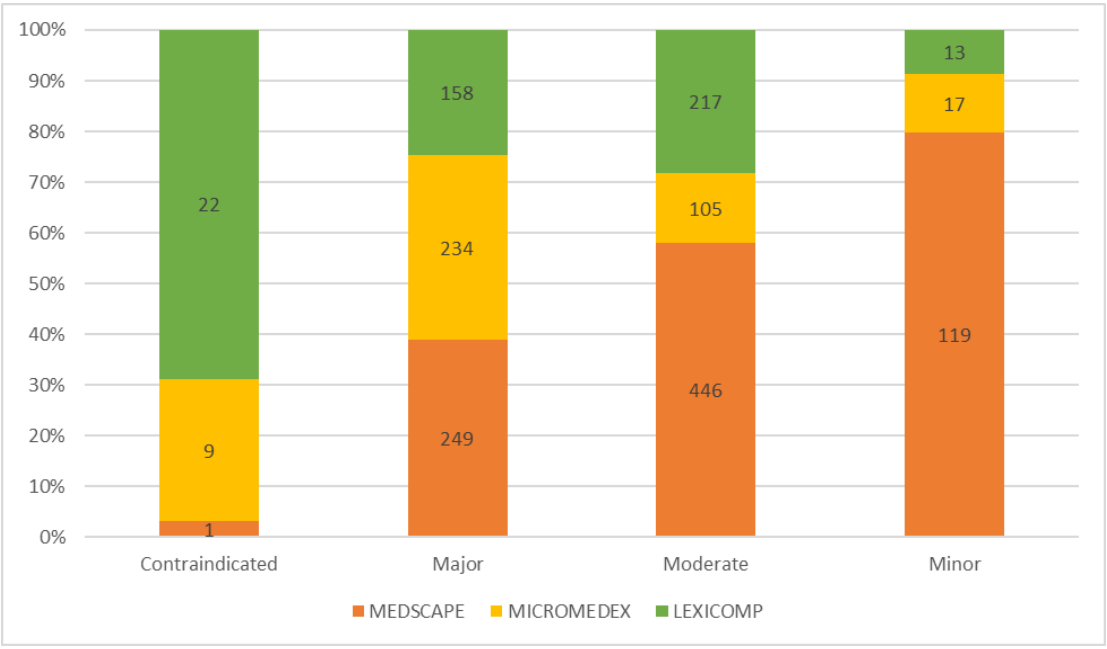

Figure 2. Severity of potential drug-drug interaction observed during the study by database.

Medscape identified more DDI under minor and moderate categories if is compared with Micromedex and Lexicomp. Micromedex and Lexicomp based their algorithm on evidence-based content, using peer-review scientific journals.

The number of potential DDIs identified is affected by the method of screening employed. (Kannan et al., 2016) Using these databases could translate into more potential DDIs being flagged, which may not have major clinical implications. Evaluating these alerts based on their clinical impact would support better clinical decision-making. However, the final determination regarding the clinical implications of a flagged DDI and the need to modify treatment would be at the physician's discretion considering the patient´s pharmacotherapy and health condition.

The databases utilized in this study were able to identify potentially DDIs. However, there were differences in the classification of the severity of DDIs among the databases. This was likely due to the fact that in its classification system, Medscape places less of an emphasis on contraindicated medications and more of an emphasis on severe, moderate, and mild interactions, whereas Micromedex and Lexicomp place more emphasis on contraindicated medications and severe interactions and less emphasis on moderate and mild interactions (Saverno et al., 2011).

The differences in the number of interactions identified by each database can also be explained by the fact that databases are powered by autonomous information suppliers; however, the Micromedex and Lexicomp databases contain published data on evidence-based content, using peer-review scientific journals and evaluation of the quality of the documentation. This approach is not follow by Medscape in terms of providing the source of evidence. Identifying DDIs with no precise presentation of clinical significance or relevance could affect the screening of this phenomenon.

To better recognize the connection between potential DDIs in prescriptions and the clinical effect arising from DDIs, future studies are necessary to explore DDIs and their consequences. By emphasizing the medications commonly used in ICUs and the possible specific interactions, it could increase the understanding and awareness of the medical team in this regard, and thus increase patient safety.

Table 3. Corroborated drug-drug interactions found in the ICU patients in study and pairs of drug involved.

First Drug	Second Drug	Medscape	Micromedex	Lexicomp	Frequency (%)
Fentanyl	Propofol	S	S	S	8 (15)
Piperacillin/tazobactam	Vancomycin	M	S	M	7 (13)
Albuterol	Salmeterol	M	X	M	5 (10)
Furosemide	Albuterol	M	M	M	5 (10)
Fentanyl	Midazolam	X	S	S	5(10)
Clarithromycin	Fentanyl	S	S	S	3 (6)
Furosemide	Salmeterol	M	X	M	3 (6)
Droperidol	Ondansetron	S	S	S	3(6)
Trimethoprim/sulfamethoxazole	Pyrimethamine	M	S	M	1 (2)
Phenytoin	Fentanyl	M	S	S	1 (2)
Phenytoin	Lopinavir/ritonavir	M	CI	S	1 (2)
Omeprazole	Ferrous sulfate	M	M	M	1 (2)
Midazolam	Morphine	M	S	S	1 (2)
Aspirin	Furosemide	X	S	M	1 (2)
Linezolid	Norepinephrine	CI	CI	S	1 (2)
Furosemide	Hydrochlorothiazide	M	X	M	1 (2)
Carvedilol	Albuterol	S	X	CI	1 (2)
Haloperidol	Quetiapine	M	S	CI	1 (2)
Amiodarone	Digoxin	S	S	S	1 (2)
Amiodarone	Fentanyl	S	S	X	1 (2)

CI: contraindication; S: major; M: moderate; X: unknown. The results show the frequency of patients that presented the interaction, and the severity according to the categorization system used by the database.

In terms of standardizing the interactions seen in this study and following databases and intensivist judgement, the following guidelines are suggested (Drew et al., 2010; Baniasadi et al., 2015):

1. Avoid the concomitant use of opioid analgesics and benzodiazepines or other CNS depressants if possible and only combine them when alternative treatment options are inadequate. If using both, it is necessary to limit the doses or duration of each drug to a minimum, controlling the desired clinical effect and closely monitoring for adverse effects in the ICU.
2. Control renal function and monitor patients for evidence of kidney damage if using a combination of antibacterial drugs such as piperacillin/tazobactam, especially if patients require combination with vancomycin.
3. Monitor possible sympathomimetic effects, such as an increase in blood pressure or heart rate during concomitant albuterol, salmeterol and norepinephrine use even if provided by a non-parenteral route. Higher doses of these products could yield high systemic concentrations.
4. The use of two QTc-prolonging drugs must be avoided when possible to avoid the risk of developing torsades de pointes (TdP) or other significant ventricular tachyarrhythmias. Patients with risk factors such as older

age, bradycardia, hypokalemia, hypomagnesemia, and heart disease, would be at a higher risk of these potentially life-threatening toxicities. If it is necessary to use these combinations, patients should be monitored for evidence of QT prolongation or other alterations of cardiac rhythm (e.g., ondansetron-droperidol).

5. When interaction involves an alteration in drug metabolism, it is necessary to closely monitor patients for several days following initiation of the combination. For example, patients receiving fentanyl and any CYP3A4 inhibitor should be closely monitored for several days following initiation of the combination, and fentanyl dosage should be reduced as necessary. Dose adjustments of phenytoin may be necessary when using these agents in combination.

6. Polypharmacy is a reality in ICU patients, so based on our results, we recommend using at least one of these databases, privileging Micromedex or Lexicomp, which are based on real world evidence.

The key strength of this study is that it was performed in a general ICU of an academic hospital with a large and diverse patient population, which increases the generalizability of the results to other ICUs. A limitation of this study is that outcomes resulting from potential DDIs were not studied. Although theoretically it would be worthwhile to measure the clinical consequences of potential DDIs, in practice it is almost impossible to attribute clinical outcomes to potential DDIs in complex and severely ill ICU patients. Another limitation is the relatively small sample size of 93 patients; a larger sample size and wider inclusion criterion could enhance the generalizability of the results. However, this is the first study in Chile comparing three different databases to detect DDIs. Therefore, this study provides a broader perspective on DDIs and assessment of reliability between databases.

CONCLUSIONS

This study shows that while numerous potential DDIs can be identified using databases, few can be clinically proven in an ICU setting. Discrepancies in different databases and judgment of intensivists highlight that important information to help identify clinically relevant DDIs, may be lacking. Identifying possible DDIs relevant to an intensivist's practice is a complex task, and adaptation to the local setting and delivery of care is necessary to avoid excessive information. Future studies may explore this information gap further.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Contribution	Zhiel EA	Cordova PM	Fernandez PB	Morales FE	Villa LA
Concepts or ideas		x			x
Design			x	x	
Definition of intellectual content					
Literature search	x	x		x	
Experimental studies					
Data acquisition	x		x		
Data analysis	x		x		x
Statistical analysis					x
Manuscript preparation		x	x		x
Manuscript editing		x			
Manuscript review	x	x	x	x	x

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