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CLINICAL SCIENCE

Prevalence of potential drug interactions in patients in an intensive care unit of a university hospital in Brazil

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OBJECTIVES: To investigate the prevalence of potential drug interactions at the intensive care unit of a university hospital in Brazil and to analyze their clinical significance.

METHODS: This cross-sectional retrospective study included 299 patients who had been hospitalized in the intensive care unit of the hospital. The drugs administered during the first 24 hours of hospitalization, in the 50th length-of-stay percentile and at the time of discharge were analyzed to identify potential drug-drug and drug-enteral nutrition interactions using DRUG-REAX® software. The drugs were classified according to the anatomical therapeutic chemical classification.

RESULTS: The median number of medications per patient was smaller at the time of discharge than in the 50th length-of-stay percentile and in the first 24 hours of hospitalization. There was a 70% prevalence of potential drug interactions at the intensive care unit at the studied time points of hospitalization. Most of the drug interactions were either severe or moderate, and the scientific evidence for the interactions was, in general, either good or excellent. Pharmacodynamic interactions presented a subtle predominance in relation to pharmacokinetic interactions. The occurrence of potential drug interactions was associated with the number of medications administered and the length of stay. Medications that induced cytochrome P450, drugs that prolong the QT interval and cardiovascular drugs were pharmacotherapy factors associated with potential drug interactions.

CONCLUSION: The study showed that potential drug interactions were prevalent in the intensive care unit due to the complexity of the pharmacotherapies administered. The interactions were associated with the number of drugs, the length of stay and the characteristics of the administered medications.

KEYWORDS: Drug-drug interaction; Drug-enteral nutrition interaction; Critically ill; Intensive care units.

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INTRODUCTION

Drugs are one of the health technologies that are essential for the effectiveness of the care delivered at intensive care units (ICUs). Due to the complexity of the pharmacotherapy involved in the simultaneous use of several drugs and various therapeutic classes, critically ill patients are at an increased risk for drug interactions (DIs).[1-3]

ICU patients are particularly predisposed to the development of drug interactions, and this predisposition is complicated by disease severity and organ failure, both of which can change the pharmacologic response to medications.[4,5]

The number of prescribed drugs is a risk factor for the occurrence of a DI. Studies have demonstrated a positive correlation between polypharmacy and DIs.[6] Other determinant factors for the occurrence of a DI include the pharmacokinetic profile and the pharmacological characteristics of the medications.[1,7,8]

DIs can cause undesirable patient responses, with effects ranging from treatment inefficacy to serious adverse events.[1,4,9] However, the decision to prescribe two drugs simultaneously is sometimes intentional, with the aim of obtaining a specific pharmacological synergism.[10]

Thus, the objectives of the present study were to investigate the prevalence of DIs in the ICU of a university hospital in Brazil and to analyze the clinical significance of their interactions.

METHODS

Study design, patients, and data collection

This cross-sectional retrospective study was developed at Hospital das Clínicas, Federal University of Minas Gerais, which is a tertiary hospital in Brazil. The investigation was approved by the ethics committee at the university.

All patients admitted to the hospital ICU between January 2007 and December 2007 were identified using the hospital's information system. Patients who met the following criteria were included in the study: over 18 years of age, at least 5 days in the ICU and prescribed medications in the first 24 hours of hospitalization and in the 50th length-of-stay percentile and discharged with two or more drugs. Of the 1,361 patients admitted to the ICU during 2007, 299 met the inclusion criteria.

The demographic information, main diagnosis, comorbidities and laboratory and clinical data necessary to obtain the SAPSII were extracted from the patients' clinical history records. Information regarding medications and enteral nutrition administered at each of the three time points were collected from the medical prescription documentation, and other observations were obtained from the administration notes made by the nurse.

The drugs were classified according to the anatomical therapeutic chemical (ATC) classification. Drugs with the following characteristics were identified: narrow therapeutic index, cytochrome P450 inhibitor, cytochrome P450 inducer, cytochrome P450 substrate, activity over glycoprotein P, and those that prolong the QT interval.

Classification of potential drug interactions

The drugs administered in the first 24 hours of hospitalization, the 50th length-of-stay percentile and at the time of discharge were analyzed to identify potential drug-drug and drug-enteral nutrition interactions using DRUG-REAX® (Thomson Micromedex™, Greenwood Village, Co, USA) [11]. This software has the appropriate sensitivity and specificity to detect possible DIs.[12,13] The software identifies the interactions, provides information about the associated clinical consequences or adverse reactions to drugs and characterizes the interaction mechanism. The software classifies the interactions in five categories according to severity (contraindicated, severe, moderate, mild and unknown), time of onset (immediate and delayed), and six scientific documentation categories (excellent, good, fair, poor, unlikely and unknown). The mechanism is classified as pharmacokinetic or pharmacodynamic. For pharmacokinetic interactions, the researchers identified the process involved (absorption, distribution, metabolism or excretion) using the interaction monograph provided by DRUG-REAX® .

Statistical analysis

The descriptive data were presented using the median with the corresponding interquartile interval or as proportions. Numerical variables were tested for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilt tests. The Mann–Whitney non-parametric test was used for comparisons when the t test did not meet the usual criteria (normality and homoscedasticity). Comparisons between categorical variables were performed using the chi-square test without correction or with the Yates correction. The odds ratio was also calculated. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using R 2.7.1.

RESULTS

Patient characteristics

The characteristics of the 299 patients included in the study are presented in Table 1. The median age was 57 years, with most participants (57.2%) younger than 60 years of age. A little over half of the patients were female. The most frequent diagnoses at the time of ICU admission were circulatory system diseases. The average patient severity, measured using SAPSII, was 25. The length of stay in the ICU ranged from 5 to 72 days, with a median of 8 days.

Table 1 - Clinical and demographic characteristics of the 299 ICU patients.

Clinical and demographic data	Value
Age in years [median (interquartile interval)]	57(42–68)
<60 years [n (%)]	171(57.2)
>60 years [n (%)]	128(42.8)
Gender [female (%)]	151(50.5)
Length of stay in the ICU in days [median (interquartile interval)]	8 (6–14)
Diagnoses [n (%)]	
Circulatory system diseases	141(47.2)
Neoplasms	41(13.6)
Symptoms, signs and abnormal exam results not classified elsewhere	25(8.4)
Digestive system diseases	24(8)
Respiratory system diseases	20(6.7)
Congenital defects, deformities and chromosome aberrations	11 (3.7)
Others with a frequency ≤3%	37(12.4)
SAPS II [median (interquartile interval)]	25(19–34)
Charlson comorbidity index [median (interquartile interval)]	4(1–4)
Pharmacotherapy	
Number of medications administered within 24 hours of hospitalization [median (interquartile interval)]	12(10–14)
Number of medications administered in the 50th length-of-stay percentile [median (interquartile interval)]	12(10–14)
Number of medications administered at the time of discharge [median (interquartile interval)]	10(7–12)

Administered drugs

During 24 hours of hospitalization, 3,580 drugs containing 164 pharmacologically active substances were administered. This was the largest number obtained among the three hospitalization time points. The number of pharmacologically active substances used in the 50th length-of-stay percentile was 157, and this number decreased to 107 at discharge. Similarly, 3,575 drugs were administered in the 50th length-of-stay percentile, and this number diminished to 2,883 at the time of discharge.

A median number of 12 medications were administered per patient during the first 24 hours of hospitalization and in the 50th length-of-stay percentile; the median number was reduced to 10 at the time of discharge. The ATC system groups with the largest number of administered drugs at the three studied ICU time points were as follows: B-Blood and blood-forming organs, C-Cardiovascular system, N-Nervous system.

Potential Drug Interactions

The prevalence of potential DIs during the first 24 hours of hospitalization in the 50th length-of-stay percentile and at the time of discharge is shown in Table 2. There was no evidence of any statistically significant difference between the prevalence of DIs at the three studied hospitalization time points. The largest number of DIs was identified in the

Table 2 - Prevalence of potential drug interactions in the 299 ICU patients.

Variable	Value
First 24 hours of hospitalization	
Number of patients with a potential DI (%)	205(68.6)
Total number of potential DIs	552
Types of DIs	138
Number of potential DIs per patient [median (interquartile interval)]	1(0–3)
50th length-of-stay percentile	
Number of patients with potential DIs (%)	221(73.9)
Total number of potential DIs	753
Types of DIs	170
Number of potential DIs per patient [median (interquartile interval)]	2(0–4)
Discharge	
Number of patients with potential DIs (%)	208(69,6)
Total number of potential DIs	610
Types of DIs	151
Number of potential DIs per patient [median (interquartile interval)]	1(0–3)

50th length-of-stay percentile (753). The maximum number of DIs per patient was 22 in the 50th length-of-stay percentile, 17 at the time of discharge and 16 in the first 24 hours of hospitalization. The largest median number of interactions per patient (2) was observed in the 50th length-of-stay percentile.

In the 50th length-of-stay percentile, 170 types of potential DIs were detected, 168 of which were drug-drug interactions and two of which were drug-enteral nutrition interactions. There were 137 types of drug-drug interactions in the first 24 hours of hospitalization and 148 at the time of discharge. In the first 24 hours of hospitalization, only one type of drug-enteral nutrition interaction was detected, but that number increased to three at the time of discharge.

The number of drugs administered was higher in patients with potential DIs at the three investigated time points of hospitalization. In the first 24 hours of hospitalization, the median number of drugs administered to patients with a potential DI was 13, (range 5 to 25); patients without a potential DI were administered a median of 10 drugs(range 2 to 18). The median number of drugs administered to patients with a possible DI in the 50th length-of-stay percentile was also 13(range 4 to 25); patients without a potential DI were given a median of 10 drugs(range 2 to 16). At the time of discharge, the median number of drugs administered to patients with a potential DI was 11(range 3 to 19); patients without a potential DI were given a median of 7 drugs(range 2 to 14). The differences were statistically significant at all three time points (p value <0.001).

In terms of severity, most interactions were severe or moderate. With respect to onset, delayed interactions were the most prevalent, with frequencies of greater than 50% observed at the different times of hospitalization. Most of the scientific evidence supporting possible interactions was good or excellent. Pharmacodynamic interactions presented a subtle predominance in relation to pharmacokinetic interactions. The highest frequency (61.4%) was detected in the first 24 hours of hospitalization. Among the pharmacokinetic mechanisms of the potential DIs, the most frequent process was metabolism, which corresponded to up to 82.5% of the interactions identified in prescriptions of the first 24 hours of hospitalization. The frequency of interactions with the capacity to induce therapeutic failure ranged from 17.5–19.5% during the three time points, with the highest value detected among the discharge prescriptions.

The pharmacotherapy factors associated with the occurrence of potential DIs and their respective odds ratios are presented in Table 3. Only inducers of cytochrome P450, drugs that prolong the QT interval and drugs from group C of the ATC (cardiovascular system) were significantly associated with potential DIs at the three time points assessed during hospitalization. In the first 24 hours of hospitalization, a potential DI association was discovered between drugs with a narrow therapeutic index and drugs from ATC group N. The use of drugs from groups J, L, and N and those with a narrow therapeutic index was significantly associated with a potential DI in the 50th length-of-stay percentile. At the time of discharge, inhibitors of cytochrome P450, drugs that affect glycoprotein P and drugs from groups J and L were significantly associated with potential DIs.

The length of stay was significantly greater among patients who presented one or more potential DI in the first 24 hours of hospitalization than in those without a potential DI (average of 8 days compared to 7 days; $p<0.001$). The same trend was observed in the 50th length-of-stay percentile (average of 8 days compared to 6 days; $p<0.0010$).

The ten most frequent severe and moderate interactions are presented in Table 4. The severe interaction between fentanyl and midazolam was the most frequent DI during

Table 3 - Factors associated with the occurrence of potential DIs in the ICU.

	First 24 hours			50th length-of-stay percentile			Discharge		
Predictive factors	**OR**	**CI 95%**	**p value**	**OR**	**CI 95%**	**p value**	**OR**	**CI 95%**	**p value**
Narrow therapeutic index	4.4	1.4–3.9	0.006[1]	3.6	0.9–4.1	0.039[3]	2.3	0.9–5.7	0.099[1]
Cytochrome P450 inducer	3.0	1.8–5.1	<0.001[1]	2.0	1.2–3.6	0.012[1]	2.2	1.3–3.9	0.003[1]
Cytochrome P450 inhibitor	1.5	0.2–11.0	0.651[3]	4.4	0.6–38.3	0.114[3]	6.6	2.3–20.0	<0.001[1]
Modulation of glycoprotein P	2.2	0.0–81.2	0.531[3]	8.8	0.8–223.0	0.056[3]	9.4	2.4–43.7	<0.001[3]
Drugs that prolong the QT interval	2.2	1.2–4.2	0.010[1]	1.9	1.1–3.5	0.030[1]	2.5	1.3–4.7	0.003[1]
ATC Group B	ND	ND	ND	8.8	0.8–223	0.056[3]	4.0	0.8–21.5	0.059[3]
ATC Group C	3.1	1.7–5.6	<0.001[1]	4.1	2.1–7.8	<0.001[1]	9.2	5.0–17.0	<0.001[1]
ATC Group J	1.3	0.8–2.3	0.293[1]	1.9	1.1–3.4	0.020[1]	1.8	1.1–3.1	0.029[1]
ATC Group L	1.7	0.6–4.4	0.359[1]	4.9	1.4–20.5	0.009[1]	9.3	2.1–57.3	0.001[1]
ATC Group N	6.4	3.3–12.5	<0.001[1]	2.8	1.5–5.2	0.001[1]	1.6	0.9–2.8	0.093[1]

ND – not determined because every patient in the study used at least one medication of this ATC Group. CI- Confidence interval
1: Chi-square test with Yates correction; 2: Chi-square test; 3: Fisher's exact test. OR - Odds ratio

Table 4 - The ten most prevalent potential drug interactions.

Drug Interaction	First 24 hours		50th length-of-stay percentile		Discharge	
Severe	n	%	n	%	n	%
Fentanyl + Midazolam	103	36.1	62	19.1	36	15.6
Captopril + Potassium Chloride	24	8.4	67	20.6	71	30.7
Acetylsalicylic Acid + Heparin	16	5.6	26	8.0	25	10.8
Clonazepam + Morphine	14	4.9	16	4.9	6	2.6
Clopidogrel + Enoxaparin	10	3.5	-	-	5	2.2
Fentanyl + Morphine	10	3.5	-	-	-	-
Midazolam +Morphine	10	3.5	-	-	-	-
Fentanyl + Morphine	10	3.5	-	-	-	-
Fentanyl + Prometazine	10	3.5	14	4.3	-	-
Morphine +Prometazine	6	2.1	-	-	-	-
Ciprofloxacin + Insulin	-	-	11	3.4	6	2.6
Fentanyl + Fluconazole	-	-	10	3.1	10	4.3
Amiodarone + Fentanyl	-	-	9	2.8	-	-
Sulfametoxazole +Trimetroprim + Fluconazole	-	-	9	2.8	-	-
Clonidine + Propranolol	-	-	7	2.2	-	-
Potassium Chloride + Spironolactone	-	-	-	-	8	3.5
Captopril + Spironolactone	-	-	-	-	5	2.2
Amiodarone + Ciprofloxacin	-	-	-	-	5	2.2
Moderate						
Furosemide + Hydrocortisone	12	6.9	22	7.1	7	2.4
Midazolam + Phenytoin	10	5.7	-	-	-	-
Ciprofloxacin + Hydrocortisone	9	5.2	16	5.1	6	2.1
Fentanyl + Phenytoin	Phenytoin 8	4.6	-	-	-	-
Acetylsalicylic Acid + Enoxaparin	8	5.6	9	2.9	8	2.8
Fluconazole + Midazolam	7	4.0	-	-	-	-
Midazolam + Omeprazole	6	3.4	-	-	-	-
Methylprednisolone + Tacrolimus	5	2.9	-	-	-	-
Furosemide + Gentamicin	5	2.9	-	-	-	-
Dexamethasone + Phenytoin	5	2.9	-	-	-	-
Captopril + Furosemide	-	-	17	5.4	21	7.3
Omeprazole + Tacrolimus	-	-	8	2.6	8	2.8
Fluconazole + Tacrolimus	-	-	8	2.6	8	2.8
Cyclosporine + Sulfamethoxazole+Trimethoprim	-	-	8	2.6	11	3.8
Hydrochlorothiazide + Propranolol	-	-	7	2.2	-	-
Captopril +Hydrochlorothiazide	-	-	7	2.2	8	2.8
Hydrocortisone + Phenytoin	-	-	6	1.9	6	2.1
Amiodarone + Clonazepam	-	-	-	-	6	2.1

the first 24 hours of hospitalization. In the 50th length-of-stay percentile and at the time of discharge, the most frequent severe interaction was between captopril and potassium chloride. Most of the ten most prevalent interactions in the first 24 hours of hospitalization involved drugs from ATC group N. Conversely, the most severe interactions at the time of discharge and in the 50th length-of-stay percentile involved drugs from groups C and J.

The main moderate interactions in the first 24 hours of hospitalization also involved midazolam. Moderate interactions prevailed in the 50th length-of-stay percentile and at discharge and were caused by drugs from groups C, J, and L.

The most prevalent severe and moderate interactions were those involving anticoagulants and platelet aggregation inhibitors, which are group B drugs.

DISCUSSION

This study demonstrated a 70% prevalence of potential DIs at the investigated ICU at all three time points of hospitalization; the prevalence of the DIs did not depend on the time point studied. Quantitative studies demonstrating the magnitude of DIs in the ICU are scarce.[14] The overall prevalence of DIs in the ICU, as described by other authors, has been shown to range between 44.3% and 87.9%.[14-16] Differences in study design, the studied casuistic, and software sensitivity and specificity make it difficult to compare our study with previous studies.

Within the context of intensive care, it is important to investigate potential drug-drug interactions as well as potential drug-enteral nutrition interactions. The present study showed a low incidence of drug-enteral nutrition interactions, with the highest occurrence observed in the 50th length-of-stay percentile and at the time of discharge. However, it should be stressed that the potential drug-enteral nutrition interactions have a clinical impact and can affect the pharmacotherapeutic outcomes planned for the patient. The drug-enteral nutrition interactions identified in this study involved three drugs with a narrow therapeutic index (phenytoin, levothyroxin and warfarin), which demonstrates the clinical importance of these potential interactions.[17,18]

The present study also showed that the prevalence of potential DIs was associated with the number of drugs administered. Although the number of drugs administered at the time of discharge was reduced, the association with the occurrence of interactions remained significant. The number of medications has been shown to be a predictive factor for the occurrence of DIs at hospitals, both in the ICU and in internal medicine units [6,15,19,20].

The administration of cytochrome P450 inhibitors and inducers and the drugs that affect glycoprotein P was

associated with the occurrence of DIs. The activities of cytochrome P450 and glycoprotein P are determinants of important pharmacokinetic processes in a significant number of drugs and are involved in the mechanisms responsible for DIs with clinical significance in the ICU. The integration between basic and clinical research is essential for identifying the mechanisms and the severity of those interactions, especially in the ICU.[1,7]

The administration of drugs with a narrow therapeutic index was an important predictor of DIs. The pharmacotherapy of critically ill patients requires the use of cyclosporine, tacrolimus, phenytoin, gentamicin and vancomycin, in addition to other drugs with narrow therapeutic indexes. The identified association was likely due to the use of these drugs.

The association discovered between the occurrence of DIs and the administration of drugs that prolong the QT interval should be stressed because there is a growing concern regarding these drugs due to the risk of cardiotoxicity with *torsade de points* and cardiac arrest.[21,22] These adverse events can be determined by potential pharmacokinetic interactions that inhibit the metabolism of drugs with this property or by pharmacodynamic synergism. The metronidazol+amidorane, fluconazole+sulfametoxazole+trimetroprim, fluconazole+haloperidol, and amiodarone+haloperidol interactions detected in this investigation can produce the mentioned adverse events.

The association of DIs with ATC group N drugs was greater in the first 24 hours of hospitalization and involved mostly drugs used for sedation. Knowledge regarding the epidemiology of excessive sedation and its determinants, both pharmacological and non- pharmacological, is essential for achieving excellent and safe sedation levels. Pharmacological factors include DIs and organic dysfunctions that can change the plasma concentration of the sedative.[23,24]

The use of immunosuppressive drugs in transplant patients being treated in the ICU explains the observed association of drugs from group L with the occurrence of interactions in the 50th length–of-stay percentile and at the time of discharge. Immunosuppressive therapy is a complex of drugs with narrow therapeutic indices and has characteristics that predispose it to interactions with other medications.[25]

The use of antimicrobials is common in critically ill patients due to the risk of nosocomial infection, and the occurrence of pharmacodynamic and pharmacokinetic interactions with this therapeutic class have been previously reported.[4,26,27] These factors contribute to the association between the administration of drugs from group J and the occurrence of interactions in the 50th length-of-stay percentile and at the time of discharge.

Cardiovascular drugs are often involved in drug-drug interactions.[19,28] The characteristics of cardiovascular drugs that predispose them to DIs and the prevalence of cardiovascular diseases in the ICU are factors that explain the identified association.

In agreement with a previous study performed in an ICU, we found that patients with DIs had longer lengths of stay at the ICU.[15] This can be explained by the knowledge that more drugs are administered during a prolonged hospitalization, which results in elevated chance for a DI. Nevertheless, the cross-sectional design of the present study did not allow the identification of any causal relationships between the occurrence of a potential DI and the variables studied.

The potential drug-drug interactions detected were mostly severe and moderate with excellent and good evidence. The drug-enteral nutrition interactions were all of moderate severity. The clinical significance of a DI is determined by the severity, the drug profile, the clinical consequences for the patient and the available evidence for the interaction.[29,30]

Among the mechanisms of the potential DIs, the pharmacodynamic mechanism showed a subtle predominance over the other possible mechanisms indentified among the ICU prescriptions. An analysis of the pharmacokinetic interactions showed that drug metabolism was the main determinant pharmacologic process responsible for these interactions. Therapeutic failures and adverse reactions are negative outcomes associated with the identified potential interactions. Considering this profile of interactions, the prevention measures at the studied ICU should include strategies such as adjustments of the drug dose, avoidance of group use, observation of the therapeutic response and clinical monitoring for the early detection of adverse effects.[31]

With respect to the time of onset, delayed interactions prevailed. The identification of these interactions at the time of discharge is important because the effect of an interaction may not appear until the patient has been transferred to another hospital unit. The greatest concern is that the effect will not appear until after hospital discharge. This situation highlights the importance of the medication reconciliation process for patient safety upon discharge from the ICU.

The severe fentanyl+midazolam interaction, classified by DRUG-REAX® as a pharmacodynamic interaction, is based on pharmacological synergism, in which an opioid analgesic (fentanyl) and a benzodiazepinic (midazolam) are used for sedation. In addition, this combination is used to provide comfort and anxiety relief to critically ill patients on mechanical ventilation. It is also used to synchronize the patient and the ventilator and to optimize oxygenation. Thus, this interaction is used in intensive care with a therapeutic goal.[23,32]

The current tendency is to classify this interaction as pharmacokinetic because fentanyl is a P4503A4 cytochrome inhibitor and midazolam is metabolized by this enzymatic system. An accumulation of alpha hydroxymidazolam glucuronide, the active metabolite of midazolam, was identified in patients with prolonged sedation who were treated with midazolam plus inhibitors of P4503A4 cytochrome or who had other risk factors that affect the elimination of midazolam.[23,24,32,33]

Among other potential interactions detected in this study that interfere with sedation or analgesia were fentanyl+fluconazole, fluconazole+midazolam, fentanyl+morphine, midazolam+morphine, clarithromycin+fentanyl and clarithromycin+midazolam.

Ensuring excellent sedation levels is one of the challenges in intensive care, and this goal should be pursued by the health team to avoid prolonged periods of mechanical ventilation and to reduce the risk for pneumonia, which can be acquired while on ventilation. To ensure the safety of sedation and analgesia in the ICU, the multidisciplinary team should implement the following evidence-based strategies: the use of validated scales to evaluate the level of sedation and delirium, the daily interruption of sedation

and the design of sedation protocols. The referenced sedation protocols should include DI identification and monitoring.[24,32]

The severe captopril+potassium chloride interaction was the most prevalent interaction at the time of discharge and in the 50th length-of-stay percentile. The clinical consequence of this interaction is hyperkalemia, which mainly occurs in individuals with cardiac insufficiency, the elderly and patients with renal insufficiency. A study performed at a Swiss Hospital also demonstrated that the interaction between potassium and angiotensin-converting enzyme (ACE) inhibitors was included among the most prevalent DIs at the time of discharge.[34] Another study, which determined the rate of development of hyperkalemia in hospitalized patients, found a statistically significant difference between the rate of development in patients using an ACE inhibitor and those using ACE inhibitors + a potassium supplement.[35] Hyperkalemia can also be caused by other potential interactions detected in the present study, including captoptril+spironolactone, potassium chloride+spironolactone or losartam+potassium chloride.

It is common to use spironolactone and ACE inhibitors simultaneously in the therapeutic arsenal for the treatment of cardiac insufficiency.[36] A pharmacoepidemiological study performed at an internal medicine unit of a hospital in Switzerland demonstrated a four-fold increase in hyperkalemia when ACE inhibitors were combined with spironolactone, as compared to isolated uses.[36] Monitoring of the plasma levels of potassium is a strategy used to observe this interaction, which can cause severe arrhythmias. A study performed at an ICU in South Brazil showed that the captopril+spironolactone interaction was among those with the most significant clinical importance.[15]

The interaction between ACE inhibitors and potassium during hospitalization presents smaller risks than in ambulatory, provided that continuous monitoring of potassium levels and renal function is performed. Consequently, this interaction is acceptable within the hospital environment. The risk of hyperkalemia increases when this combination is prescribed to patients upon discharge from the hospital, because they will be without laboratory monitoring. Therefore, for these patients, it is recommended that replacements for one of the drugs be evaluated to avoid this DI.[38]

The combination of platelet aggregation inhibitors (low-dose aspirin or clopidogrel) with heparins is associated with an increased risk of bleeding, as compared to isolated treatments. The risk-benefit relationship of this association is positive due to improvements in anti-thrombosis efficacy in patients with acute coronary syndrome and atrial fibrillation.[39,40] To assure the safety and effectiveness of this treatment, patients should be monitored continuously.[39] The association between the occurrence of a DI and the administration of group B drugs is probably determined by the frequency of this type of interaction in the ICU.

Concerning the complexity of the analyzed data and the cross-sectional study design used in the present study, the results should be considered with an awareness of their limitations. Retrospective data collection can cause bias due to the possibility of incomplete patient records. The present study was developed at a single ICU, and therefore, it may be difficult to generalize the results.

The probability of pharmacokinetic interactions involving metabolism depends on the time of enzymatic inhibition or induction. The inhibition of drug metabolism is immediate (24–48 h), whereas induction is a slower process (7–10 days).[10,41] Because the analysis was performed without considering the doses administered or the time of treatment, it is possible that the prevalence of DIs was overestimated.

This investigation employed restrictive criteria for potential interactions with acetylsalicylic acid, which helped to avoid overestimations of the interactions. In intensive care practice, acetylsalicylic acid is usually used in low doses and as a platelet aggregation inhibitor. Potential interactions were excluded if the DRUG-REAX® software indicated that they occurred at acetylsalicylic acid doses above 300 mg. Some studies have not considered the heparin + aspirin association to be clinically significant due to the low doses used and minimal chances of bleeding.[19,38] Based on studies showing a risk of bleeding with low doses of aspirin, these associations were included in the present study.[42,43]

The clinical manifestations of the DIs were not evaluated in the present study, and therefore, the *potential drug interaction* expression was used. Another limitation of the current study was the use of software to identify potential interactions. Drug interaction screening software typically produces strong signal levels that can indicate a greater prevalence of potential DIs. Therefore, it is important to consider, in addition to the overall prevalence of DIs, the magnitude of the interaction in the clinical context of intensive health care, as well as in terms of severity and associated adverse events.

CONCLUSION

This study demonstrated a high prevalence of potential DIs in the ICU due to the complexity of pharmacotherapy. The severe interaction between fentanyl and midazolam was the most frequent interaction that occurred during the first 24 hours of hospitalization. In the 50th length-of-stay percentile and at the time of discharge, the most frequent severe interaction was captopril and potassium chloride.

Positive associations were observed between the occurrence of a potential DI and the number of drugs, the length of stay and the characteristics of the administered medications.

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