Prevalence of drug interactions in intensive care units in Brazil

Prevalência de interações medicamentosas em unidades de terapia intensiva no Brasil

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Abstract

Objective: To determine the prevalence of drug interactions in intensive care units and to analyze the clinical significance of interactions identified.
Methods: A multicenter, retrospective and cross sectional study conducted with 1124 patients in the seven intensive care units of teaching hospitals in Brazil. Information on drugs administered at 24 hours and 120 hours of hospitalization was obtained from the prescriptions.
Results: Within 24 hours, 70.6% of patients had at least one drug interaction; the number at 24h was 2299, at 120 h it was 2619. Midazolam, fentanyl, phenytoin and omeprazole were the drugs with higher frequency of drug interactions.
Conclusion: In this sample, moderate and severe drug interactions were more prevalent. In light of these findings, all actions of health professionals who provide care to these patients must be integrated in order to identify and prevent possible drug events.

Resumo

Objetivo: Determinar a prevalência de interações medicamentosas em Unidades de Terapia Intensiva-UTI brasileiras e analisar seu significado clínico.
Métodos: Estudo multicêntrico, retrospectivo, desenvolvido com 1.124 prontuários em sete UTI de hospitais de ensino brasileiros. As informações sobre os medicamentos prescritos e administrados em pacientes com 24 horas e 120 horas de internação foram obtidas baseadas nas prescrições.
Resultados: Em 24 horas, 70,6% dos pacientes de UTI tinham, pelo menos uma interação medicamentosa. O número total de interações detectadas foi de 2.299 em 24 horas, e 2.619 em 120 horas. Midazolam, Fentanyl, Phenytoin e Omeprazole foram os medicamentos que apresentaram maior frequência de interação medicamentosa.
Conclusão: Na amostra estudada, as interações medicamentosas graves e moderadas foram mais prevalentes. Neste sentido, todas as ações dos profissionais de saúde que prestam cuidados a esses pacientes devem ser integradas no intuito de identificar e prevenir possíveis eventos com medicamentos.

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Introduction

The patients from intensive care units (ICUs) have a higher risk of developing drug interactions (DI) than patients from other care units. In addition to the risk attributed to multiple drugs, there is risk resulting from the severity of the illnesses and organ failure. Studies have shown a positive correlation between the many different drugs and DI. Drug interactions contribute to the incidence of adverse reactions in ICU and often constitute an unrecognized complication in pharmacotherapy. The DI may be beneficial or harmful, depending on various factors related to the medication, the patient or the conditions under which the medication is used.[1] Beneficial or desirable interactions aim to treat diseases, reduce adverse effects, increase efficiency or allow the reduction of the dose. On the other hand, the harmful interactions are those that cause a reduction of the effect or results contrary to those expected, or that increase incidence and profile of adverse reactions and the cost of therapy, without an increase in therapeutic benefit.[2]

The prevalence of potential drug interactions in the ICU detected in observational studies ranged from 44.3% to 86%.[3-4] In the literature researched, the prevalence of drug-enteral nutrition interactions in intensive care was not identified.

Beyond the risk attributed to multiple drugs, patients in the ICU presented a risk due to the severity of illness and organ failure. Changes in the volume of drug distribution and other pharmacokinetic factors also contribute to a decrease in the safety of medicines in these patients. The activity of cytochrome P450 and the effect of P-glycoprotein are important determinants of the pharmacokinetic processes of a significant number of drugs, and are involved in the mechanisms of clinically important interactions in ICU.[2] In addition to the risk of drug-drug interactions, patients in ICUs have higher predisposition to drug-nutrient interactions. Due to their severe clinical status, these patients receive nutrition through nasoenteric feeding tubes, nasogastric tubes or stoma. However, these devices are not only used for the administering of food, but often are also used for the delivery of medication. The consequence of this practice is the risk of adverse events such as the obstruction of the tube, physicochemical incompatibilities and drug-nutrient interactions.[5]

Health professionals' knowledge about DI and their clinical significance, especially those responsible for prescriptions, could help predict DI and minimize the negative impacts through adequate monitoring, when the combination is unavoidable. This kind of attitude of the health care team contributes to the optimization and safety of pharmacotherapy in critically ill patients.

Therefore, the objectives of this study were to determine the prevalence of drug interaction in the ICUs of seven hospitals in Brazil, and to analyze the clinical significance of the interactions identified.

Methods

This was a multicenter, retrospective and cross sectional study conducted in the ICUs of seven teaching hospitals in Brazil. The hospitals were located in the west central, northeast and southeast regions of Brazil, all belonging to the Sentinel Network of Hospitals of the National Health Surveillance Agency.

The medical records of patients in 2007, hospitalized in the ICUs of the hospitals studied, were included in the research. The demographic information and main diagnosis were extracted from the patients' clinical history records. Information regarding medications and enteral nutrition administered at each of the two time points were collected from the medical prescription documentation.

The sample selection was random, with patients who met the following criteria participating in the study: over 18 years of age, and a length of stay in the ICU for a period of no less than 120 hours. Patients younger than 18 years or with length of stay less than five days, was excluded the study.

We constructed a specific instrument to assist in data collection. Using this data collection instrument, information was collected from patients, including: age, gender, length of hospitalization, primary diagnoses (according to the *International Statistical Classification of Diseases and Related Health Problems - ICD 10*), and information about drugs administered

at 24 hours and 120 hours of hospitalization. These time intervals were chosen because of the quantity of drugs prescribed on the first day of hospitalization in the ICU, and after the first week of hospitalization - the period of greatest therapeutic adjustment.[3]

Potential DI are interactions that could theoretically occur during the patient's pharmacotherapy treatment, and which may or may not be clinically manifested. In the present investigation the terminology "*drug interaction*" will be used to refer to the area that includes drug-drug interaction and drug-enteral nutrition interaction.

For the identification of potential drug-drug interactions and drug-enteral nutrition interactions, the *Drug Reax*® software was used, developed by *Thomson Micromedex* TM, *Greenwood Village*, CO, USA.[6] This software has the adequate sensitivity to detect drug interactions in the hospital.[7] The Drug Reax software provides information on clinical outcomes or adverse drug reactions resulting from the interaction, and characterizes the mechanism of action. It classifies the interactions in relation to severity in five categories (contraindication, severe, moderate, mild and unknown), onset (early and late), and level of scientific evidence (excellent, good, fair, poor, unknown and unlikely).[6] The mechanism of action of the interaction was classified as pharmacokinetic, pharmacodynamic or mixed. For the pharmacokinetic interactions the process involved was identified (absorption, distribution, metabolism or excretion).

The data was stored in *Microsoft*® *Access* 2007. For statistical analysis, *StatSoft*® version 8.0 was used.

Descriptive analysis was performed using frequency distribution for the categorical variables, and the central tendency measures (mean) and dispersion (standard deviation) were used for the quantitative variables.

The study followed the development of national and international standards of ethics in research involving humans.

Results

The study included 1124 patient records, 630 (56%) of which were from male patients. The mean age was 52.5 years (± 19.0), with a minimum age of 18 and a maximum of 96.8 years. The mean length of stay was 19.4 days (± 23.0). The most common diagnoses for both 120 hours and 24 hours were: circulatory diseases, respiratory diseases, injuries caused by poisoning, and certain other consequences of external causes. The number of drugs prescribed per patient in a 24 and 120-hour period was equivalent to 13.6 (± 45) and 13.2 (± 4.8), respectively.

The prevalence of potential DI at 24 and 120 hours of hospitalization is presented in table 1. In the first 24 hours, 70.6% of the patients had at least one DI. The total number of DI was 2299, with 350 types of drug-drug interactions and three types of drug-enteral nutrition interactions. The prevalence of interactions at 120 hours was 72.5%. The number of DI detected at 120 hours was higher, at 2619, with 419 types of drug-drug interactions and four drug-enteral nutrition interactions. The average number of DI per patient increased from 2.9 (24 hours) to 3.3 (120 hours).

An enteral feeding was received by 320 (28.5%) patients with 24 hours of admission, and 504 (44.8%) with 120 hours. The prevalence of drug-en-

Table 1. Prevalence of potential drug interactions in seven intensive care units

Variable	n
24 hours of hospitalization	
Number of patients with drug interactions	793(70.6)
Total drug interactions	2299
Types of drug interactions	353
Drug-drug interactions	350
Drug-enteral nutrition interactions	3
Number of drug interactions per patient - mean (min, max)	2.92(1.18)
120 hours of hospitalization	
Number of patients with drug interactions	815 (72.5)
Total drug interactions	2619
Types of drug interactions	423
Drug-drug Interactions	419
Drug-enteral nutrition interactions	4
Number of drug interactions per patient - mean (min, max)	3.3 (1.18)

teral nutrition interaction among these patients was found to be 20 (6.3%) and 39 (7.7%), respectively.

Table 2 presents the characteristics of potential interactions with respect to severity, time of onset, mechanism of action, and the level of scientific evidence. The severe and moderate potential interactions, together, accounted for 86% of the interactions, at both periods investigated. The frequency of potentially serious interactions was 36.5% (24 hours) and 35.2% (120 hours), respectively. The level of evidence for approximately 60% of the interactions was good. There is a balance in relation to the mechanism of action of potential interactions in 24 hours, with 982 (42.7%) of the pharmacokinetic type and 946 (41.1%) of the pharmacodynamic type. At 120 hours there was already a slight predominance of potential interactions with a pharmacodynamic mechanism of action, with a frequency of 1104 (42.2%). The potential interactions of pharmacokinetic mechanisms totaled 1037 (39.6%). Analyzing the distribution of cases of potential pharmacokinetic drug-drug interactions, the metabolism process was identified as being responsible for 88.5% of the potential interactions at 24 hours, and 83.1% at 120 hours. The number of the processes was different because a pharmacokinetic interaction can be determined by more than one process.

The most frequent serious potential interactions at 24 and 120 hours, with absolute frequency greater than 10, are listed in table 3.

The potential interactions of moderate severity most prevalent at 24 hours were midazolam +ome-

Table 2. Classification of potential drug interactions identified in seven intensive care units

Classification	Prescription	
	24 hours n(%)	120 hours n(%)
Severity		
Contraindicated	2(0.1)	5(0.2)
Major	840(36.5)	922(35,2)
Moderate	1151(50.1)	1347(51.4)
Minor	306(13.3)	345(13.2)
Documentation		
Excellent	242(10.5)	342(13.1)
Good	1468(63.9)	1548(59.1)
Fair	589(25.6)	727(27.8)
Unknown	0(0)	2(0.1)
Mechanism of action		
Pharmacokinetic	982(42.7)	1037(39.6)
Pharmacodynamic	946(41.1)	1104(42.2)
Mixed	29(1.3)	42(1.6)
Unknown	342(14.9)	436(16.6)
Pharmacokinetic process		
Absorption	65(6.4)	94(8.7)
Distribution	3(0.3)	5(0.5)
Metabolism	895(88.5)	900(83.1)
Excretion	49(4.8)	84(7.7)
Onset		
Immediate	585(49.7)	841(32.1)
Late	1142(25.4)	1292(49.3)
Unknown	572(24.9)	486(18.6)

Table 3. Most frequent serious drug interactions in seven intensive care units

Drug-drug interaction	Prescription	
	24 hours n(%)	120 hours n(%)
Fentanyl + Midazolam	324(38.6)	215(23.3)
Captopril + Potassium Chloride	54(6.4)	97(10.5)
Salicylic Acid + Heparin	47(5.6)	80(8.7)
Clopidogrel + Enoxaparin Sodium	21(2.5)	15(1.6)
Amiodarone + Fentanyl	18(2.1)	28(3.0)
Fentanyl + Nimodipine	19(2.3)	14(1.5)
Clopidogrel + Omeprazole	16(1.9)	18(2.0)
Fentanyl + Fluconazole	16(1.9)	20(2.2)
Haloperidol + Tramadol	16(1.9)	19(2.1)
Fentanyl + Phenobarbital	15(1.8)	-(-)
Fentanyl + Nifedipine	14(1.7)	18(2.0)
Clopidogrel + Heparin	14(1.7)	17(1.8)
Ciprofloxacina + Insulin	14(1.7)	22(2.4)
Midazolam + Phenobarbital	13(1.5)	-(-)
Midazolam + Morphine	11(1.3)	-(-)
Captopril + Spironolactone	0(0)	17(1.8)
Clonidine + Propranolol	0(0)	13(1.4)
Insulin +Levofloxacin	12(1.3)	12(1.3)
Others	216(25.8)	317(34.4)
Total	840(100.0)	922(100.0)

prazol and fentanyl + phenytoin in this category, while at 120 hours it was midazolam + omeprazole and omeprazole + phenytoin.

Discussion

The identification of interactions using a retrospective software approach detects potential interactions, which does not mean that the possible adverse events manifested clinically in all patients with those potential drug-drug or drug-enteral nutrition interactions.

The software is an important tool to verify potential DI, but it generally produces a high signal level that may indicate a higher prevalence of potential interactions.[8] Therefore, it is important to consider the magnitude of the interaction in the clinical area of ICU, in terms of severity and associated adverse events, in addition to the overall prevalence.

The frequency of potential interactions detected at 24 hours and 120 hours of patient exposure was approximately 70% (Table 1). The prevalence in the sample studied was lower than in other national studies, where the prevalence was over 85%.[4,9] In the design of this study, which evaluated medication prescriptions at two periods of hospitalization, variations in the complexity of ICU care, as well as differences in the level of sensitivity and specificity of the methodologies used in identifying the potential interactions may explain the discrepancy and minimize the value of comparisons between different studies. The average number of drugs prescribed per patient is one of the determinants of percentage of interactions.

Another distinguishing feature of the present study, which also may explain the lower prevalence, is the employment of a selective criterion for potential interactions with aspirin. Potential interactions were excluded that, according to the Drug Reax software, occured at doses above 300 mg. This criterion was used because in the pilot study it was verified that these doses were not frequent in the ICUs investigated. Aspirin is usually used in doses of 100mg with an objective that is therapeutically anti-platelet.

The impact of the prevalence of DI in healthcare settings gains greater importance when coupled with information identifying its clinical significance. The clinical significance is determined by severity, level of evidence and clinical consequences.[6] Potential interactions detected in the two time periods studied were predominantly moderate and severe (Table 2).

The most frequent interaction, at 24 hours and 120 hours, was midazolam + fentanyl. This pharmacodynamic interaction is an example of an interaction that is used therapeutically. The efficacy of the combination of midazolam + fentanyl sedation in mechanically ventilated patients was compared with the use of midazolam in a randomized, unblinded clinical trial. The researchers found that joint administration by continuous infusion provided more adequate sedation and ease of dose titration than with midazolam alone, with no difference in the rate of adverse occurrences.[10] However, it is important to note that in the midazolam + fentanyl group, adverse events were detected: hypotension and hypoventilation, which justifies the classification of this interaction as severe.

To combine therapeutic goals and patient safety, one important strategy for monitoring sedation is the use of appropriate scales such as the Ramsay Sedation Scale, and the development of protocols for sedation. The nursing role is important in the monitoring of patients to ensure safe and effective sedation.[10]

Potential pharmacodynamic interactions showed a significant prevalence in the study and demonstrated characteristics of causing clinically significant adverse events in the respiratory and cardiovascular systems: midazolam + morphine, fentanyl + morphine, fentanyl + phenobarbital.

Fentanyl + nimodipine and fentanyl + nifedipine were other potentially serious interactions, because of the risk of hypotension. At 120 hours of hospitalization fluconazole + fentanyl was the most frequent interaction. This antimicrobial is an inhibitor of CYP4503A4, increasing blood levels of fentanyl and the risks of sedation and its adverse effects. In this case, the adherence to sedation protocols is also an appropriate strategy in identifying and monitoring the effects of the interaction.

The omeprazole + midazolam pharmacokinetic interaction was the most prevalent in the study. Moderate in severity, the mechanism of this interaction is to reduce the metabolism of midazolam by omeprazole, an inhibitor of cytochrome P4503A4. The scientific evidence is reasonable, because studies that demonstrated this interaction were in vitro. However, considering the context of the ICU it is important to monitor the level of sedation and, if necessary, to adjust the dose of medication in patients on concomitant use of these drugs.[6]

Phenytoin is a drug of narrow therapeutic index and a potent enzyme inducer, with pharmacological characteristics which are predisposed to potential DI, with significant clinical consequences. The determination of plasma levels is a suitable tool for monitoring the evolution of the successful management and interaction with dose adjustment.[2] The diversity of potential interactions with phenytoin, together with their pharmacotherapy characteristics, are aspects which suggest that nurses and other health team members should consider the likelihood of potential interactions with this drug in patients undergoing multiple drug therapy.

Interactions with omeprazole, nifedipine or amiodarone are examples in which the drug phenytoin is the object of interaction. The consequence is the increased plasma levels of phenytoin, the clinical manifestations of which are ataxia, nystagmus, shivering and hyperreflexia.[6]

On the other hand phenytoin can be a precipitating agent of the interaction, reducing the plasma levels of any other drug that participates in the interaction. The reduction in plasma levels occurs due to the inducing activity of phenytoin, and helps to decrease the effectiveness of the drug that is under the effect of enzyme induction, which may lead to therapeutic failure.[6]

A serious frequent interaction in the two periods of hospitalization was that of captopril + potassium chloride, which could result in hyperkalemia with serious clinical consequences, especially in the elderly, and patients with heart failure or renal insufficiency. Hyperkalemia can also arise from other potential interactions detected in this study, such as spironolactone + captoptril, and spironolactone + potassium chloride.[6]

Potential interactions of clinical significance occur with amiodarone because of its inhibiting activity of P-glycoprotein and CYP4503A4. Amiodarone is used to treat supraventricular arrhythmias such as atrial fibrillation, which constitutes the most frequent arrhythmia in ICU.[2,6] This therapeutic measure explains the widespread use of this drug in the ICU, and the frequency of potential interactions with amiodarone detected in this study. Given the risk of potential interactions, it is important to identify and monitor them to achieve the expected results and ensure the safety of the therapy.

Thus, the joint treatment of amiodarone + fentanyl requires close monitoring because of the risk of cardiotoxicity and the increased toxic effects arising from the interaction of fentanyl pharmacokinetics. Simultaneous use with nifedipine and other drugs that increase atrioventricular block may exacerbate bradycardia and signs of heart blockage. Use of amiodarone + simvastatin increases the risk of myopathy or rhabdomyolysis because of the increased plasma concentration of simvastatin, due to the inhibition of its metabolism by amiodarone. The inhibition of the P-glycoprotein by amiodarone implies reduced digoxin clearance, increasing the plasma level and the chances of digitalis intoxication. Dose reduction and periodic monitoring of plasma digoxin is essential to minimize the effects of this interaction. These potential interactions were more frequent with amiodarone in this study.[2,6]

There is an increasing concern with drugs that have the property of prolonging the QT interval, because of the risk of cardiotoxicity with *torsade de points* and cardiac arrest.[11] These adverse events may be determined by potential pharmacokinetic interactions that inhibit the metabolism of drugs with this property or pharmacodynamic synergism. The potential interactions between amidorane + metronidazole, fluconazole + sulfamethoxazole / trimethoprim, fluconazole + haloperidol, haloperidol + amiodarone detected in this study may produce the adverse events cited. Thus, the health care team must be knowledgeable of the drugs that prolong the QT interval, as well as other risk factors that

contribute to this phenomenon, in order to adopt appropriate strategies to manage and monitor the effects of potential interactions.

Recently, observational studies have identified negative results in patients using the clopidrogrel + omeprazole interaction after their discharge from hospitalization for acute coronary syndrome. The main negative outcomes evaluated were death and hospital readmissions for myocardial infarction or unstable angina. A retrospective cohort study demonstrated an association between the risk of adverse outcomes and the concomitant use of omeprazole + clopidrogrel in patients after hospitalization for acute coronary syndrome.[12] Equivalent results were found in a Canadian study with patients hospitalized for acute myocardial infarction.[13] These studies confirmed hypotheses generated from experimental studies that showed that omeprazole acts on cytochrome P4502C19, inhibiting the bioactivation of the prodrug clopidogrel to its active form, reducing its antithrombotic effect.

In the context of the ICU, it is important to investigate both the potential drug-drug interactions as well as potential drug-enteral nutrition interactions. In the sample researched the incidence was low, but it is noteworthy that the potential drug-enteral nutrition interactions have clinical impact, and may interfere with the results of the pharmacotherapeutic plan developed for the patient. In the literature studied, no studies were found evaluating this type of interaction in the ICU. Among the interaction analysis software that exists, the detection of potential drug-enteral nutrition interactions is a peculiarity of *Drug Reax*.

Potential drug-enteral nutrition interactions identified in the study involved four drugs: hydralazine and three with a narrow therapeutic index (phenytoin, warfarin, and levothyroxine), which points to the clinical importance of these potential interactions. The investigations regarding the potential drug-enteral nutrition interactions are insufficient, and few in number.[14,15]

The mechanisms of potential drug-nutrient interactions involve physical and chemical reactions of drugs with dietary components that lead to a reduction of bioavailability. Another factor that contributes to reducing the plasma concentration of drugs is absorption in the walls of the enteral feeding tubes.[15]

A strategy identified to reduce the effects of potential drug-enteral nutrition interactions is planning the schedule of drug administration with consideration of the frequency and type of enteral nutrition administration. This aspect is more easily handled when the drug is administered in a single dose while nutrition is administered via bolus or intermittently. A complexity arises with multiple schemes of drug administration and continuous nutritonal infusion, since discontinuation of the feeding is required to administer medication, thereafter adjusting for dietary administration to ensure the prescribed caloric intake.[15] Normally, it is recommended to stop the feedings one to two hours before and after the administration of drugs.[14,15]

The role of the nurse, together with the physician, pharmacist and nutritionist, includes an outlining of the timetable, and care in the administration of these drugs to avoid drug-enteral nutrition interaction.

Potential interactions involving absorption were limited in this study, with greater frequency at 120 hours when the patient was clinically stable and had less need for using the parenteral route. The potential interactions identified in the study that involved reactions that reduced absorption were: levothyroxine + sevelamer, ketoconazole + ranitidine, omeprazole + atazanavir, and, calcium carbonate + captopril.

This multicenter study contributed significantly to the practice of critical care nursing by presenting the profile of DI in the ICU within Brazil, building an important tool for planning and interventions for improving patient safety in ICU. To increase the safety of patients, it is essential to implement strategies that help the healthcare team to identify potential interactions and implement prevention and monitoring of patients at risk of developing DI, before they manifest.

The nurse, as the individual responsible for the scheduling of the drugs and enteral nutrition, is key to the prevention of potential drug-enteral nutrition interactions and potential interactions in-

volving the absorption process, contributing to the pharmacotherapy effectiveness for patients.[16]

However, planning the schedule has little impact in the prevention of potential pharmacokinetic interactions that involve either the metabolism process or pharmacodynamics. For these categories, the main preventative measures are related to strategies such as: avoiding using them together, adjusting the dose of the drug object of interaction and clinical monitoring for early detection of adverse effects. The performance of the nurse can contribute to patient safety and prevent unwanted DI. However, the impact of actions will be most effective if developed in an interdisciplinary manner.

Conclusion

In this sample, the moderate and severe DI were more prevalent, in virtue of the profile of the patients and the complexity of the pharmacotherapy, requiring the integrated execution of the health team to better identify and prevent their occurrence.

Knowledge of the pharmacological mechanisms and the main risk factors of drug-drug interactions and drug-enteral nutrition interactions contributes to adequate programs in helping to prevent them, enables the optimization of the drug therapy and, as a result, increases the safety and effectiveness of the treatment.

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Collaborations

Carvalho REFL; Reis AMM; Faria LMP; Zago KSA and Cassiani SHB contributed to study conception, analysis and interpretation, the literature review, research design, interpretation of data, data collection, input, analysis and interpretation, drafting of manuscript and final approval of submitted manuscript.

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