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RESEARCH ARTICLE

MEDICAL INTERACTIONS IN INTENSIVE CARE UNITS: NEGLECTED RISK

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ABSTRACT

Background: To evaluate the consequences of drug interactions prescribed in the intensive care unit (ICU) of a large public hospital. **Methods:** Cross-sectional and retrospective study, performed with medical records of patients admitted to the adult ICU of a large hospital in the city of Imperatriz Maranhão, from January to March 2018. The selected patients were older than 18 years, and had a length of stay in the ICU for a equal or superior period of 24 hours and prescription with at least two drugs. Potential drug interactions have been quantified and classified using the Micromedex™ database. **Results**: The 95 prescriptions included in this study contained 93 different drugs, with an average of 8.87 (± 2.28) drugs per prescription. Potential drug interactions were identified in 94.7% of prescriptions, with an average of 6.33 (± 4.01) interactions per prescription. From the 602 potential interactions identified, important and moderate interactions were present in 65.28% and 26.74%, respectively. The number of drug interactions showed a significant correlation with the number of drugs prescribed and the length of stay in the intensive care unit. **Conclusion:** Through the accomplishment of this study, it was demonstrated the high prevalence of potential drug interactions in the intensive care unit sector and its clinical consequences for the patient, highlighting the need to implement strategies to increase patient safety.

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INTRODUCTION

A drug interaction (DI) is an incident that ariseswhen the effects and / or toxicity of a drug are modified by the presence of another medicine used simultaneously. Although their results may be either positive (increased effectiveness) or negative (decreased defectiveness or toxicity), they are generally unpredictable and undesirable in the pharmacotherapy (Jankel, 1990; Hartshorn, 1982; Alvim, 2015). The prescription of multiple drugs to a patient may cause a DI, which can be identified when pharmacokinetics and pharmacodynamics or the response to the administration of a combination of two drugs is different than expected to the known effects of both drugs when individually prescribed. In medical practice, it is very common to use multiple drugs that may contain potential drug interactions (PDIs) between them, although not all of the detected PDIs may necessarily occur (Moreira *et al.,* 2017; Morales-Ríos, 2018). Patients hospitalized in the intensive care unit (ICU) services in general are critically unstable and with multiple comorbidities, they require a more complex prescription with multiple drugs, increasing the incidence of DI and consequently its unwanted effects, in addition they facilitate the incidence of factors that interfere with the disease healing process, which may clinically harm the patient (Alvim *et al.,* 2015; Ismail *et al.,* 2016; Rodrigues *et al.,* 2017). The large incidence of PDIs in ICU patient prescriptions has been documented by several studies. These studies reported a 70% to 89% predominance rate of PDIs in this hospital environment. In addition, a particularity of ICUs is the large number of drugs prescribed for interned patients, this circumstance increases the risk of PDIs (Ismail *et al.,* 2016; Rodrigues *et al.,* 2017; Tesfaye *et al.,* 2017; Vanham *et al.,* 2017). PDIs occur frequently among drugs metabolized by the same cytochrome P450 (CYP) enzymes, and/or due to the administration of drugs that inhibit or induce this enzyme system. Drugs metabolized by this route include midazolam, cyclosporine and phenytoin, all of which are widely used. CYP inducers and inhibitors include drugs such as amiodarone, fluconazole and carbamazepine, which are often used in ICU (Rodrigues *et al.,* 2017; Carvalho *et al.,* 2013). The present study aimed to evaluate the consequences of potential drug interactions on ICU prescriptions of a large public hospital, quantify and classify potential interactions by their degree of severity and clinical significance.

MATERIALS AND METHODS

This is a cross-sectional and retrospective study conducted with patients hospitalizedin the adult ICU of a public hospital in the city of Imperatriz, State of Maranhão in Brazil, which has 400 usable hospital beds with 20 adult ICU hospital beds and 10 pediatric ICUbeds. The research was conducted from January to March 2018. The project was submitted and approved by the Research Ethics Committee of the Federal University of Maranhão under the identification number CAAE 6774818.3.0000.5087. During the study, there were 130 hospitalizations in the general ICU of the Hospital undergoing this research. Of these, those that did not fit the inclusion criteria were not considered, leaving 95 patients included in the study. The identified Patients admitted to the general ICU were included in the research according to the following criteria: age above 18 years old, length of stay in the ICU for a period equal to or superior than 24 hours and prescription with at least two drugs. Medical records were excluded due to illegibility and prescription of nutritional supplements. The data were collected using a structured formulary for the following variables: age, gender, number of drugs prescribed at the end of 24 hours, hospitalization, length of hospitalization, main ICD-10 diagnosis and drugs administered at the end of 24 hours.

The search for potential drug interactions was performed using the Micromedex^{TM} database (Rodrigues *et al.,* 2017; Ismail *et al.,* 2016; de Paula, 2016; Hasanloei, 2014). In the case of eventual absence of the drug in the database, the combination has been considered to have no risk of potential interaction. The PDIs were classified according to the database[12]: contraindicated (simultaneous use of drugs is not indicated); important (the interaction is life threatening and/or requires medical intervention to reduce or prevent serious adverse effects); moderate (interaction may result in higher clinical risk and/or require alternative therapy); or secondary (interaction would have limited clinical effects; episodes may include an increase in the frequency or severity of side effects, but generally would not demand a significant change in the therapy). The rating regarding the level of documentation is segmented as excellent (controlled studies clearly demonstrated the existence of the interaction); good (documentation strongly suggests the interaction, but properly adequate controlled studies are lacking) and acceptable (the available documentation is insufficient, but pharmacological considerations lead clinicians to suspect the interaction; or the documentation is not good for a pharmacologically similar medicine). The data obtained were statistically analyzed using the IBM SPSS Statistics® software (v.23). A descriptive statistic was used to determine numerical frequencies and percentages. And with inferential statistics to correlate potential drug interactions with other variables including gender, age, number of drugs prescribed, length of hospitalization and diagnosis (95% CI; $p < 0.05$; Pearson's test).

RESULTS

The people subjected to this study had the average age of 56.2 years (18 to 96 years), 46 (48.42%) were elderly (60 years and over). Being 50 (52.6%) men. The average number of drugs per day was 8.87 (± 2.28). The lenght of hospitalization had in average 9.47 (± 9.02) days (Table 1).

Regarding the cause of admission, the studied group was heterogeneous, embracing clinical and surgical patients with widely diversified causes of hospitalization: 37 (38.95%) neurosurgical, 29 (30.53%) clinical, 17 (17.89%) orthopedic and 12 (12.63%) general surgery. In the first group, it was more frequent that patients were diagnosed with ischemic stroke (15), severe traumatic brain injury (5) and intracranial hemorrhage (4). In clinical patients, the most frequent diagnoses were in descending order: septicemia (9), respiratory insufficiency (4) and complications from diabetes mellitus (2). Orthopedic patients presented femur fracture (14) and tibia fracture (1). Surgical patients had intestinal obstruction (4) and ulcers (3). The reminding patients had different diagnosis. In the 95 evaluated prescriptions during 24 hours, 93 different drugs were observed. The amount of prescribed drugs varied from 5 to 16. Among the most prescribed drugs that lead to a DI, were metamizole (92.63%), ranitidine (68.42%), tramadol (53.68%), bromopride (49, 47%), cefriaxone (42.10%) and phenytoin (38.95%) (Table 2). Regarding potential drug interactions, a total of 602 potential interactions were identified: contraindicated 03 (0.5%), important 393 (65.28%), moderate 161 (26.74%) and secondary 45 (7.48%). With an average of 6.33 (± 4.01) interactions per prescription. At least one PDI was identified among 90 (94.7%) prescriptions included in the study (Table 3). There was a significant statistical correlation demonstrating the relation between the amount of prescribed drugs and length of hospitalization ($p < 0.05$), quantity of drugs and amount of potential interaction ($p = 0.01$) and cases of potential interaction and length of stay ($p < 0.05$) (Figure 1).

DISCUSSION

With 94% of prescriptions analyzed including at least one potential drug interaction, it is evident the importance of knowledge related to drug interactions in clinical practice. ICU drug interactions have a much higher incidence than the overall rates of the hospital environment as a whole, mainly due to the large number of drugs administered and the profile of patients admitted to this sector (Alvim, 2015). Other studies with different projects and sample sizes have shown high numbers of PDI. (7,12) Also methodologically similar studies in Brazil and abroad show a variable prevalence with rates of 32% to 89%. The lowest prevalence in Brazil was reported in the study in a teaching hospital in the interior of the state of Rio Grande do Sul. In contrast, the highest prevalence was reported in the Hospital das Clinicas in Campinas. The reason for this inconsistency is due to the study design, since the first study analyzed only contraindicated and important interactions with excellent level of scientific evidence (Morales-Ríos, 2018; Ismail, 2016; Rodrigues, 2017; Tesfaye, 2017; Vanham , 2017; Garske, 2017; Smithburger, 2012). The average age of patients was 56.2 years (18 to 96 years), converging with other studies conducted in Brazil with average ages between 57 and 60 years (Alvim, 2015; Rodrigues, 2017). In the present study, 48.42% of patients analyzed were elderly (60 years or older). People over 60 years of age have pharmacokinetic and pharmacodynamics changes such as decreased hepatic metabolism and renal excretion, factors that contribute to the occurrence of drug interactions. Additionally, most of these individuals have chronic diseases, which necessitate leads to the necessity ofdifferent drugs associations (de Araujo, 2013). When hospitalized in the ICU, these patients use polypharmacy, receiving a mean of 8.87 drugs per day.

The indicated average is within a range found in studies where the monitored patients presented an average of 6.8 drugs per prescription, ranging from 01 to 17 drugs and in another study,the monitored patients had an average of 13.3 drugs prescribed per day. with a maximum of 21 and a minimum of 6 medications per day (Garske, 2017; Piedade, 2015). The severity rating of PDIs is important for managing adverse effects caused by drug interactions. In the present study, most PDIs were severe; however, moderate also represent a considerable number of interactions. These results diverge from other studies conducted in ICU wards. One study had 416 patients and of the total interactions identified, most were of moderate severity (49%) and significant severity (33%) (Ismail *et al.,* 2016). Similarly, another study included 369 patients, with 405 interactions found. Most of these interactions were of moderate (74%) and significant (67%) severity (Rodrigues *et al.,* 2017). Despite the most prevalent reversal of rating between the significant and moderate, most prescriptions in these ratings are life-threatening and / or require medical intervention to decrease or prevent DI related serious adverse reactions. Therefore, proper monitoring of the parameters, regardless of severity, should be developed to minimize damage.

This study presented many PDIs with clinical relevance in the theoretical analysis being rated as important or moderate, although in clinical practice do not offer significant risks to patients. Among the risks involved in these interactions, events related to respiratory depression are highlighted, a kind of risk that has a different approach in intensive care, because a significant number of patients may be under assisted ventilation and all patients are under cardiovascular and respiratory monitoring. This type of analysis clarifies that these interactions, from a broader perspective, have a lower risk and clinical relevance in the ICU than in other hospital wards [3,18]. The theoretical concept about the clinical relevance of PDIs is not well settled. Although clinical practice support systems such as Micromedex ™ contribute to this discussion, the typical risk of each PDI in clinical practice is individually rated using theoretical information, along with the specifics of each patient. It is not possible to observe a complete agreement between the severity of PDI classifications and the real occurrence of drug interactions in intensive care publications (Moreira, 2017; Rodrigues, 2015). The significant correlation between the number of PDIs and the length of ICU hospitalization observed in the present study was consistent with previous studies (Rodrigues *et al.,* 2017; de Paula, 2016). Although this correlation exists, it is not clear whether PDIs caused an increase in the length of hospitalization, or vice versa. It is possible that the number of PDIs is high in patients with extended ICU stay, as these patients tend to be severely ill and therefore require a higher amount of medication. Contrarily, increased exposure to events caused by PDIs may have increased the length of hospitalization. The need for analysis in future studies is evident. Consequently, the correlations observed in the study interdepend on each other. The relationship between the number of drugs prescribed and the amount of potential drug interactions shows that the more drugs prescribed, the higher the prevalence of drug interactions. The high number of drugs prescribed for ICU patients indicates an increase in PDIs, where the number of drugs is directly proportional to the development of drug interactions and adverse effects, increasing the length of hospitalization (Cedraz, 2014). As a result of these facts, the health care system increases its burden and the clinical management of these patients is impaired. As the stay increases in the hospital, the intended costs for patients also increases, as the costs can reach up to R$ 800.00 (eight hundred Brazilian reals) patients / day at the ICU (Ministério da Saúde, 2011; Mwamakamba, 2014) As identified by other studies, metamizole, furosemide, tramadol and captopril are drugs that are also involved in the 10 most frequent PDIs in this study (Askari, 2013; Uijtendaal, 2014). Interaction between metamizole and furosemide when administered concomitantly may result in reduced diuretic efficacy and possible nephrotoxicity. This risk increases with the combined use of non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics due to dose-dependent reduction of NSAIDs in prostaglandin formation and renal blood flow. During concomitant use of NSAIDs and diuretics, it is recommended monitoring for signs of worsening renal function to ensure diuretic efficacy, including appropriate effects on blood pressure (Micromedex, 2011; Brunton, 2012; Katzung, 2017; Rang, 2016). Patients admitted to the ICU have a high incidence of 20 to 40% and predisposition to acute kidney injury (AKI), having as risk factors infections, sepsis, major surgeries and low cardiac output. Studies have shown that the most common comorbidities in AKI patients were pulmonary complications such as edema, pleural effusion and infections. Therefore, critically ill patients need precise intervention in drug interactions that may lead to some degree of nephrotoxicity, with volume expansion being the fundamental element of prevention and therapeutic management, as it contributes to the restoration of peripheral perfusion and attenuates drug nephrotoxicity (Ávila, 2014; Moura, 2017; Guedes, 2017; Luft, 2016). Another common PDI found is due to the concomitant use of tramadol and ranitidine, with a significant severity rating with the possibility of increasing tramadolplasma concentrations and may lead to prolonged opioid effects including respiratory depression. If use of a CYP3A4 inhibitor such as ranitidine is required in a patient taking tramadol, it is essential to reduce the tramadol doses and to monitor seizures, serotonin syndrome or respiratory depression (Micromedex, 2011; Brunton, 2012; Katzung, 2017; Rang, 2016).

Just as important interactions, the moderate ones also require attention and different management, as in PDI due to the simultaneous use of captopril and metamizole, due to the decreased antihypertensive and natriuretic effect of angiotensin converting enzyme inhibitors from metamizole. In addition, co-administration may result in deterioration of kidney function, including possible acute kidney failure. When the need for simultaneous use, proceed with periodically monitor of kidney function for signs of deterioration and antihypertensive efficacy, while ensuring that patients are adequately hydrated (Micromedex, 2011; Brunton,2 2014; Katzung, 2017; Rang, 2016). An important finding of this study was the observation of contraindicated DI, highlighting the presence of metoclopramide. These interactions draw attention to the severity of their possible consequences, such as interactions between metoclopramide and neuroleptic agents (chlorpromazine, promethazine, haloperidol, and risperidone) when the risk of the rare syndrome known as neuroleptic malignant syndrome is increased. Given this risk, this type of interactions should be avoided and it's symptoms monitored as well as the protocol for treatment of possible adverse events, if this combination is unavoidable, should be known. When they are detected in ICU prescription orders, they should be carefully analyzed to determine the risk-benefit ratio for the

patient (Micromedex, 2011; Rodrigues, 2015; Katzung, 217; Rang, 2016). When the use of potential interacting drugs is indispensable, the analysis of the possible effects of drug interactions and the careful monitoring of patients undergoing therapy are recommended. Most PDIs can be controlled by means other than withdrawal of the drug combination, such as dose adjustments and monitoring of possible adverse events, individually evaluating risk and benefit (de Paula, 2016; Alvim, 2015). Prescription efficiency plays a key role in preserving the effectiveness of available drugs, highlighting the role of health professionals to improve the currentconditions. It is emphasized the importance of a multitasking clinical team is, since pharmaceutical interventions can contribute to the reduction of avoidable adverse events (Andrade, 2015; de Lima Neto, 2017).

One of the limiting factors of the research is related to the database used, as it is not able to take into calculate individual patient aspects such as doses, sequence and time of drug administration. In addition, the conduct of the doctor regarding dose adjustment is not evaluated. Although the study classified interactions according to severity and level of evidence, the actual occurrence of the interaction was not investigated in the research.

Conclusion

The study reiterates the risk of drug interactions arising directly from polypharmacy, a routine situation in intensive care units. The prescriptions of this therapeutic require increased attention. Furthermore, the knowledge of all health professionals about the drug therapy of each patient requires extra attention in order to prevent a DI. Knowledge of the key features of interactions and database access with specific information, including their mechanisms and severity potential, can minimize and / or prevent resulting adverse events and contribute to better clinical management of patients. In addition, the need for a multitasking clinical team and development of protocols ensures greater safety in prescriptions in this environment. In conclusion, this is a single center study, with the inclusion of a small number of patients. The high number of PDI in critically ill patients highlights the need for research in this area and shows the importance of the attention of health professionals involved in the care process of ICU patients.

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Key Points

- Knowledge of the main characteristics of interactions and the possibility of accessing a database with specific information on drug interactions can contribute to better clinical management of patients.
- The importance of vigilance of prescriptions in the intensive care unit, contributing to the reduction of adverse effects and days of hospitalization.
- The need for discussions about drug interactions in medical schools. Graduating doctors who know about this problem and decrease this percentage of interactions between medications.

ABBREVIATION LIST

DI – Drug Interaction
PDI - Potential Drug Interactions
ICU - Intensive Care Unit
ICD 10 – International Classification of Diseases 10th
AKI – Acute Kidney Injury

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APPENDIX

Table 1. Clinical information of medical records from the intensive care unit in the city of Imperatriz – Maranhão, Brazil

Variables [n(sd)]	Patients n=95
Drugs per medical prescription	8,8 (± 2,2)
Time of hospitalization (days)	9,4 (± 9,0)
Amount of drug interactions per prescription	6,3 (± 4,0)
sd- standard deviation	

Table 2. Clinical data classified by diagnosis specialty, severity of drug interactions and most frequent medications from the medical records of the intensive care service in the city of Imperatriz – Maranhão, Brazil

Diagnosis Specialty [n(%)]	
Neurosurgery	37 (39,0)
Clinic	29 (30,5)
Orthopedics	17 (17,9)
General surgery	12 (12,6)
Drug interaction classification [n(%)]	
Contraindicated	03 (0,5)
Important	393 (65,3)
Moderate	161 (26,8)
Secondary	45 (7,4)
Medicamentos [n(%)]	
Metamizole	88 (92,6)
Ranitidine	65 (68,4)
Tramadol	51 (53,6)
Bromopride	47 (49,4)
Ceftriaxone	40 (42,1)

Table 3. Most frequent potential drug interactions from the intensive care unit records in the city of Imperatriz – Maranhão, Brazil

Drug	Frequency [n(%)]	Severity	Levelofevidence	Clinicalrisk
Metamizole+ Furosemide	33	Important	Good	Reductiondiureticeffectiveness
Tramadol+ Ranitidine	32	Important	Acceptable	Respiratorydepression
Phenytoin+ Ranitidine	28	Secundary	Good	IncreasedPhenytoinConcentrations
Bromopride+ Tramadol	24	Important	Acceptable	Potentiationofsedativeeffects
Captopril + Metamizole	20	Moderate	Excellent	Renal Dysfunction / Increased Blood Pressure
Dexamethasone+ Metamizole	20	Important	Acceptable	Gastriculcerorbleeding
Metoclopramide+Tramadol	19	Important	Acceptable	Central Nervous System Depression
Midazolam + Ranitidine	18	Moderate	Acceptable	Increasedmidazolambioavailability
Phenytoin + Tramadol	17	Important	Acceptable	Reductionoftramadolexposure
Midazolam + Phenytoin	15	Moderate	Good	Decreasedefficacyofmidazolam

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