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Interactions medicative and consequents interventions pharmaceutics in the unity of intensive therapy in a private hospital in Macapa, Amapa

Interações medicamentosas e consequentes intervenções farmacêuticas na Unidade de Terapia Intensiva de um hospital privado em Macapá, Amapá

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ABSTRACT

Introduction: Patients admitted to Intensive Care Units (ICU) are submitted to multiple drug treatments, considering the severity of their problems. Drug interaction is defined as an event caused by the modification of the effect or use of a drug in the body. The evaluation of potential drug interactions can help the multiprofessional team to promote a quality treatment, avoiding harmful interactions, reducing the length of hospitalization and consequently reducing costs. **Objective:** To evaluate the main drug interactions observed in the ICUs of a private hospital in the city of Macapá, Brazil, through the analysis of the prescriptions and the consequent interventions adopted in order to minimize their risks. **Method:** Prescriptions of patients admitted to the ICU were evaluated for the presence of potential drug interactions and their respective classification according to their risk and mechanism. A brief bibliographic study about the main interactions was carried out in order to highlight its mechanism and the measures adopted by the multidisciplinary team. **Results:** We observed that the majority of the interactions, both in the adult ICU and in the neonatal ICU, were considered of moderate risk. Pharmacokinetic interactions were more common in the adult ICU, while pharmacodynamics predominated in the neonatal intensive care unit. Management during the administration of medications was the most appropriate intervention for most cases of drug interactions. **Conclusions:** Monitoring of potential interactions in critically ill patients seeks to ensure patient safety in order to reduce the potential risks to which they are exposed.

KEYWORDS: Pharmacy Service Hospital; Drug Interactions; Pharmaceutical Services

RESUMO

Introdução: Pacientes internados em Unidades de Terapia Intensiva (UTI) são submetidos a tratamentos com múltiplos fármacos, visto a gravidade dos problemas que são tratados. A interação medicamentosa é definida como um evento causado pela modificação do efeito ou aproveitamento de um fármaco no organismo em virtude de outro. A avaliação das potenciais interações medicamentosas pode auxiliar a equipe multiprofissional a promover um tratamento de qualidade, evitando que estas interações sejam danosas ao paciente, diminuindo o tempo de internação e consequentemente auxiliando na redução de custos. **Objetivo:** Avaliar as principais interações medicamentosas observadas nas UTI de um hospital privado na cidade de Macapá (Amapá, AP) através da análise das prescrições e das consequentes intervenções adotadas a fim de minimizar seus riscos. **Método:** Foram avaliadas prescrições de pacientes internados em UTI quanto à presença de potenciais interações medicamentosas e sua respectiva classificação, segundo seu risco e mecanismo. As principais interações foram destacadas a fim de destacar seu mecanismo e medidas adotadas pela equipe multidisciplinar. **Resultados:** Observou-se que a maioria das interações, tanto na UTI adulto quanto na UTI neonatal, foram consideradas de

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risco moderado. As interações farmacocinéticas foram mais comuns na UTI adulto, enquanto as farmacodinâmicas predominaram na UTI neonatal. O manejo no horário de administração dos medicamentos foi a intervenção mais adequada para a maioria dos casos das interações medicamentosas. **Conclusões:** o monitoramento das potenciais interações em pacientes críticos procura garantir a segurança do paciente, buscando diminuir os riscos potenciais aos quais estes estão expostos.

PALAVRAS-CHAVE: Serviço de Farmácia Hospitalar; Interações Medicamentosas; Assistência Farmacêutica

INTRODUCTION

Patients admitted to an Intensive Care Unit (ICU) are submitted to treatments with several medications, which is justified by the clinical condition itself. However, these drugs may interact with each other, causing undesirable adverse reactions, increasing the time and cost of treatment.

Drug interactions are defined as Adverse Drug Reactions (ADRs). They occur when the effect of a drug changes in the presence of another, resulting in increased toxicity or reduced therapeutic effect[1].

The Brazilian National Agency of Sanitary Surveillance (Anvisa) adopts the same concept of pharmacovigilance as the World Health Organization (WHO). It is the "science and activity related to the identification, evaluation, understanding and prevention of adverse effects or any problems related to the use of drugs". It includes, therefore, adverse events related to quality deviations, therapeutic ineffectiveness, medication error, abusive use, poisoning and drug interactions[2].

Drug interactions are important causes of hospital admissions and medical visits, accounting for up to 22.2% of the adverse reactions that lead to patients' hospitalization[3]. For this reason, patients receiving various drugs should be monitored for ADRs caused by drug interactions. It is important to assess what the main potential drug interactions are and how to avoid their associated risks.

Additionally, there are few pharmacoepidemiological studies on patient safety conducted in northern Brazil that can portray this particular reality and provide support to the practice and research in this area.

Given these circumstances, the objective of this study was to identify and classify the main potential drug interactions and pharmaceutical interventions observed in the ICU of a private hospital in the city of Macapá, AP, Brazil.

METHOD

A retrospective study was performed in a large private hospital with 180 beds. The hospital has an adult ICU and a neonatal ICU, with ten and nine beds, respectively. We analyzed the prescriptions issued between January and April 2014 in both ICUs. However, only patients who met the following criteria had their prescriptions evaluated in the study:

1. Patients taking medication through probe;
2. Patients submitted to insulin therapy;
3. Patients taking three or more antibiotics;
4. Patients taking Potentially Hazardous Drugs (PHD);
5. Patients with sepsis;
6. Patients with chest pain;
7. Patients on parenteral nutrition.

The reason why we chose these criteria is because they are the criteria used by the hospital to guide its own pharmacists, indicating what patients should receive a closer follow-up.

We assessed the gender, age, reason for admission, number of drugs prescribed and number of potential drug interactions to determine the profile of the prescriptions of the patients included in this study. The variables of gender and age were not considered in neonatal ICU patients.

Study and classification of interactions

The prescriptions analyzed were evaluated for the presence of drug interactions using the *Medscape*® and *Micromedex Healthcare Series*® databases.

Drug-drug interactions were counted by patients and classified according to their severity, following the criteria adopted by Cruciol-Souza and Thomson[4]. They were divided into severe, moderate or mild.

The interactions were also classified according to the classification of the National Therapeutic Form[5] in:

- Pharmacokinetic interactions;
- Pharmacodynamic interactions;
- Pharmaceutical interactions.

For this study, we chose the five most prevalent drug interactions, which were evaluated through a literature review of articles published in the PubMed, MEDLINE and SciELO databases.

This study was approved by the ethics committee of the Federal University of Amapá (Unifap) under CAAE n. 38712014.4.0000.0003.

RESULTS AND DISCUSSION

In total, we analyzed 388 prescriptions (Table 1), of which 235 were from the adult ICU, belonging to 70 patients with a mean age of 61.14 years, 56% of whom were male. The other 153 prescriptions of the neonatal ICU belonged to 33 patients accompanied by the clinical pharmacy service.

The main reasons for hospitalization were related to cardiac and circulatory diseases in the adult ICU (68.57%) and to specific respiratory and cardiovascular disorders of the perinatal period in the neonatal ICU (58.38%).

In a similar study on potential drug interactions in the ICU of a university hospital in Ceará conducted by Lima and Cassiani[6], a similar result was obtained. Of the 102 patients, 64.7% were males with a mean age of 60 years. The most frequent diagnostic classes were diseases of the circulatory system, in 24.9% of the cases.

When evaluating the number of drugs prescribed and the number of potential interactions in each prescription, we observed a greater number of interactions in the patients in the adult ICU than in the neonatal ICU.

Gastelurrutia et al.[7] studied the impact of the pharmacist on the multidisciplinary team of a clinic treating patients with heart failure. They detected a significant relationship between the number of drugs administered to each patient (10.2 ± 3.2) and the number of Negative Results Related to Drugs (DRP) and Potential Negative Results Associated with Medicines (PDRP), according to the committee of the Third Consensus of Granada[8].

We can infer that the greater the number of drugs prescribed to a patient, the greater the likelihood of drug interactions. In a study by Hammes et al.[9] that assessed the potential prevalence of drug-drug interactions, the mean number of different medications per patient at the end of the study was 13.10 ± 5.95 and the number of prescriptions was 7.64 ± 6.66 for each patient. In the same study, 1,069 24-hour prescriptions containing 159 drugs were evaluated, of which 775 (72.5%) had some interaction.

For this study, the five main interactions of each unit were chosen and are described in Table 2.

In the adult ICU, the most common interaction was between metoclopramide, indicated for gastrointestinal disorders and widely used in ICUs to avoid events such as gastroesophageal reflux, and tramadol, an opioid analgesic. In the neonatal ICU, the most common interaction occurred between gentamicin, an aminoglycoside-class antibiotic, and penicillin.

Table 1. Number of prescriptions, number of medicines and number of drug interactions in adult and neonatal ICU.

Adult ICU	Prescriptions	Drugs	Number of interactions
Average per patient	3.35 ± 3.66	17.22 ± 4.80	4.01 ± 2.40
Total	219	52	74
Neonatal ICU			
Average per patient	4.63 ± 4.20	9.30 ± 6.21	1.90 ± 1.58
Total	153	17	22

ICU: Intensive Care Unit.
Source:

Table 2. Most frequent drug interactions per unit.

Drugs involved	Number	%
Adult UTI		
Metoclopramide + tramadol	31	14.16
Furosemide + insulin	27	12.33
Acetylsalicylic acid + clopidogrel	17	7.76
Acetylsalicylic acid + enoxaparin	16	7.31
KCl + spironolactone	7	3.20
Other	121	55.24
Total	219	100.00
Neonatal ICU		
Gentamicin + penicillin	27	40.91
Piperacillin/tazobactam + amikacin	4	6.06
Captopril + furosemide	4	6.06
Phenobarbital + omeprazole	4	6.06
Omeprazole + midazolam	3	4.55
Other	24	36.36
Total	66	100.00

Metoclopramide and tramadol

Metoclopramide (or 4-amino-5-chloro-2-methoxy-n-(2-diethylaminoethyl) benzamide) has cholinomimetic and dopamine antagonist properties. It is useful in the treatment of gastrointestinal disorders and in the treatment and prevention of nausea and vomiting[10].

Tramadol is a centrally acting synthetic opioid analgesic, which appears to act at least partially through binding to μ opioid receptors, causing inhibition of the ascending pain pathway[11].

According to the survey conducted in the *Micromedex*[12] database, the use of tramadol with certain drugs increases the risk of seizures. Metoclopramide is not recommended in epileptic patients or in patients treated with drugs that may cause extrapyramidal effects since the frequency and severity of seizures may be aggravated.

Micromedex, however, classifies this interaction as having "poor documentation", that is, the available documentation is insufficient. However, pharmacological considerations make clinicians suspect the existence of the interaction.

Nonetheless, both drugs may be necessary to treat a patient, therefore, their suspension or substitution may not be the most adequate solution. For this reason, the clinical pharmacy team intervened during the administration of the drugs, so that they were not administered at the same time, according to the pharmacokinetics of each one. Thus, the peak concentration of each drug did not coincide, decreasing the risks associated with this interaction.

Still according to *Micromedex*[12], metoclopramide shows a peak concentration of 15 min after administration and a half-life of 5 to 6 h. Tramadol, in turn, has a peak concentration of 1 h 30 min,

with half-life of 6 to 8 h. Therefore, the intervention adopted by the team in these cases involves the drug administration times.

Furosemide and insulin

Furosemide is a loop diuretic that acts by inhibiting Na^+, K^+ e Cl^- ions of the apical membranes of renal cells in the ascending limb of Henle's loop. This inhibition results in an increase in the excretion of sodium and chlorine and indirectly of calcium and magnesium, reducing the reabsorption of water in the collecting tubule and increasing its excretion due to the drop in the concentration of solutes in the medullary interstitium[13].

Insulin is a hormone produced by ß-cells in the pancreas. Its role is to assist the passage of glucose from the blood into the cells. Type I diabetes occurs when these cells are destroyed by autoimmune processes, the body stops producing insulin, and exogenous insulin must be given immediately. Type II diabetes occurs when the body produces insulin, but this insulin is insufficient or deficient[14].

In hospitalizations, some patients may require glycemic control with the help of insulin for a number of factors, ranging from pre-existing diabetes itself to the use of other drugs that may cause hyperglycemia, such as corticosteroids.

ICU patients are constantly monitored for their glycemic level. This work is usually done by the nursing team. The pharmacist is primarily responsible for verifying the safety of insulin use in patients according to their clinical condition and the other medications taken.

According to data from *Micromedex* and *Medscape*, furosemide does not interact directly with the use of insulin, however, this drug causes an increase in blood glucose, thus requiring a dose adjustment of the insulin. The dose is adjusted together with the clinical pharmacy staff, taking into account the blood glucose, the dose of furosemide and the type of feeding the patient is receiving. Moreover, glycemic levels are monitored daily by the pharmacist and the nursing staff.

Acetylsalicylic acid, clopidogrel and enoxaparin

Interactions between acetylsalicylic acid (ASA), clopidogrel and enoxaparin were the third and fourth most observed interactions in the adult ICU. In only one of the cases in which these drugs were prescribed, enoxaparin was not included in the prescription, which is why we decided to consider the interactions separately at the time of counting the interactions but to discuss them together.

ASA, also known as aspirin, is the oldest and most widely studied non-steroidal anti-inflammatory drug (NSAID). However, it is considered separately from the others because of its predominant use in the treatment of cardiovascular and cerebrovascular diseases in low doses[15].

The ASA mechanism of action occurs by the non-selective inhibition of the cyclooxygenase enzyme in its two isoforms. The COX-1 isoform is constitutively expressed in most tissues, whereas COX-2 is induced in inflammation by various stimuli[16].

In the ICU and in patients with cardiovascular problems, the use of ASA is justified by the reduction of platelet production of thromboxane A_2, due to the blockade of COX-1, preventing arterial thrombosis.

Clopidogrel, whose mechanism of action is based on the inhibition of platelet aggregation induced by ADP, is used to prevent thrombotic events in patients with cardiovascular problems and in ICU. This inhibition is dose dependent and can be detected 2 h after the ingestion of 400 mg, remaining stable for 48 h[17].

Enoxaparin sodium is an antithrombotic capable of inhibiting Factor Xa in the blood clotting cascade, generally without interfering with the prothrombin time and activated partial thromboplastin time tests[12].

Overall, these three drugs are used in association to prevent thrombotic events in patients admitted to the ICU, especially in cases of impaired cardiovascular function. The wide use of these drugs in the hospital is related to the high rate of patients diagnosed with cardiovascular disorders.

According to Oliveira[17], the addition of low doses of ASA and clopidogrel in the prevention of high-risk patients may reduce the risk of cardiovascular death associated with acute myocardial infarction and stroke in up to 1/5 of the patients and with refractory angina in 1/6 of the patients. There is also a decrease in recent revascularizations, severe ischemia and heart failure in 1/4 to 1/5 of the cases. However, an increase in the number of bleeding episodes is observed.

The use of these three drugs together, although often intentional in order to avoid further complications, can cause bleeding and severe bleeding in ICU patients, and should occur only when the benefits outweigh the risks.

In these cases, the hospital regularly performs blood coagulation tests on the patients who need to take these drugs. These tests are always accompanied by the clinical pharmacist, the nursing team and the physician in charge of the unit. When changes are noticed in these tests to the point of being harmful to the patient, the clinical pharmacist proposes to adjust the dose of one of the medicines or the suspension of at least one of them. This interaction is important, especially for patients who underwent or will undergo any type of surgical procedure.

Potassium chloride and spironolactone

Potassium chloride is one of the major constituents of the intracellular space, playing an important role in the maintenance of intracellular volume due to hydroelectrolyte balance and cell membrane stability. It is an activator of membrane ATPases in active transport[12].

According to research done on *Medscape* and *Micromedex*, spironolactone is an aldosterone-specific antagonist, acting through competitive binding at the aldosterone-dependent sodium and potassium exchange receptors, in the distal renal tubule. It is a potassium-sparing diuretic that causes an increase in the amount of water and sodium excreted.

These two drugs, because of their own pharmacodynamic characteristics, increase the serum potassium level, which can result in hyperkalemia (or high blood potassium), if not properly monitored.

Hyperkalemia causes metabolic disorders, mainly for the neuromuscular system and heart. It frequently causes arrhythmia and leads to death from cardiac arrest whenever levels greater than 9 mEq/L are reached[18].

It is not always possible to avoid this combination depending on the patient's clinical condition. Because of that, strict monitoring of the potassium levels is necessary, especially when this interaction is detected. In these cases, some dose adjustment or other non-potassium-sparing diuretic is suggested.

Gentamicin and penicillin

Gentamicin is an aminoglycoside antibiotic widely used in Gram-negative bacterial infections in neonates. It interferes with bacterial protein synthesis through binding to ribosomal subunits 30s and 50s. Penicillin interferes with the synthesis of the mucopeptide cell wall during active multiplication, resulting in bactericidal activity against susceptible microorganisms[11,12].

The association between these two antimicrobials is very common and used in the hospital as treatment of choice in cases and infections typical of newborns and as a palliative solution.

The use of penicillin concomitant with the use of aminoglycosides may reduce the efficacy of the latter due to unknown mechanisms[19]. Like the interaction between metoclopramide and tramadol, its documentation is considered "poor" by *Micromedex*, but the existing clinical evidence leads us to believe it exists and is relevant.

Furthermore, aminoglycosides are generally known to be ototoxic and nephrotoxic and should be used with caution in patients with renal impairment, especially neonates. When aminoglycosides are administered together with penicillin, the kidneys suffer from their toxicity and are still responsible for eliminating the penicillin, which can cause greater stress to these organs, increasing the nephrotoxic potential of the drugs.

A study by Martins et al.[20] has some similarities with the present research, particularly regarding the main interactions, since 60% of the pediatric patients were exposed to the coadministration of antimicrobials, mostly the combination of oxacillin (belonging to the group of penicillins) with an aminoglycoside and associated with simultaneous timing, increasing the interaction potential.

Queiroz et al.[21] also detected the association of ampicilin, another drug of the penicillin class, in association with gentamicin, as the most common interaction (19.1% of the cases) in the neonatal ICU of a hospital in Mato Grosso, Brazil.

Therefore, the action of the clinical pharmacist in this case was to inform the nursing team about the interaction, so that the drugs were not administered at the same time. By separating the time of administration of these antimicrobials according to their pharmacokinetic characteristics, it is possible to avoid that the peak concentration of each drug is close to each other, which would decrease the possibility of interaction.

Piperacillin/tazobactam and amikacin

Piperacillin is a semisynthetic penicillin that demonstrates the same mechanism of action as described above. Tazobactam is a potent inhibitor of many ß-lactamases, including plasmid or chromosome-mediated enzymes that frequently cause resistance to penicillins and cephalosporins[22].

Amikacin is an aminoglycoside that acts similarly to gentamicin.

According to the search done on *Medscape*, piperacillin may increase the effect of amikacin by pharmacodynamic synergism, which may potentiate its ototoxic and nephrotoxic effects. However, Lacy et al.[19] refer to the interaction between these drugs as similar to the described interaction between gentamicin and penicillin, since the drugs are of the same pharmacological classes.

At any rate, like in the previous interaction, the clinical management was done through the non-administration of the drugs at the same time, thus avoiding the possible interaction.

Captopril and furosemide

The Renin-Angiotensin-Aldosterone system is responsible for maintaining long-term blood pressure. The renin enzyme is produced in the kidneys by the juxtaglomerular apparatus, through the action of baroreceptors known as Polkissen cells and the action of chemoreceptors that constitute the region known as macula densa. Additionally, there is a systemic extra-renal mechanism of renin production, through baroreceptors of the carotid sinus, located at the bifurcation of the carotid artery, and consequent sympathetic stimulation for the release of the enzyme[23].

Renin, in turn, converts a protein called angiotensinogen produced by the liver into angiotensin I. The lungs produce the angiotensin converting enzyme (ACE), responsible for the conversion of

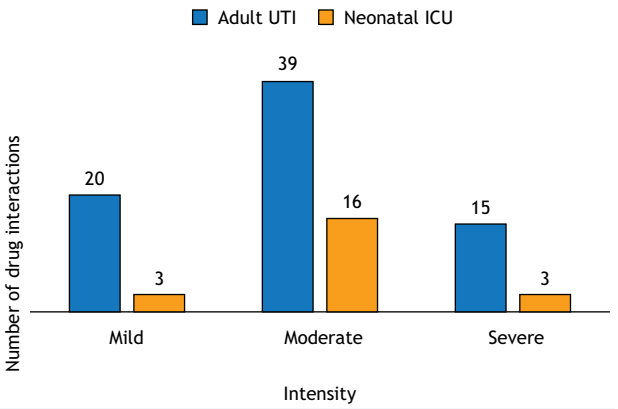

Figure 1. Classification of pharmacological interactions regarding severity in the units evaluated. ICU: Intensive Care Unit.

angiotensin I to angiotensin II. In addition, the ACE has the function of breaking down bradykinin, an endogenous vasodilator. The main functions of angiotensin II are vasoconstriction and the release of aldosterone through the cortex of the adrenal glands. Aldosterone increases sodium and water reabsorption by raising blood pressure[23].

One of the most commonly used classes for blood pressure control is ACE inhibitors, like captopril, which inhibit the conversion of angiotensin I to II, reducing the effects of angiotensin II, like vasoconstriction, aldosterone release, endothelial injury, and vascular and myocardial protein synthesis[24].

Patients taking captopril associated with furosemide have their blood pressure monitored constantly, since the association of these drugs can cause acute hypotension due to pharmacodynamic synergism.

Phenobarbital, midazolam and omeprazole

Phenobarbital is an anticonvulsant barbiturate that has low toxicity when compared to other drugs of the same class. It is one of the most used drugs for this purpose. It inhibits seizures probably by potentiating synaptic inhibition through action at the GABAA receptor[25].

Omeprazole is used to suppress the release of gastric acid by inhibiting the proton pump. It also inhibits the carbonic anhydrase of the gastric mucosa, which may contribute to its acid suppression properties[25].

There are indications that the metabolism of phenobarbital can be reduced by the action of omeprazole as an enzymatic inducer of cytochrome P4503A4. This induction also affects the metabolism of midazolam, increasing its time of action in the individual[19]. This increase in action time may result in exacerbation of toxic effects.

Midazolam is a sleep inducing benzodiazepine that promotes an increase in the frequency of ion channel opening at the same concentration of GABAA, enhancing its inhibitory effect and increasing the refractory period of the cell membrane to a new action potential[26]. With decreased metabolism, the depressant effect of the central nervous system is exacerbated and may cause exaggerated sedation in the patient.

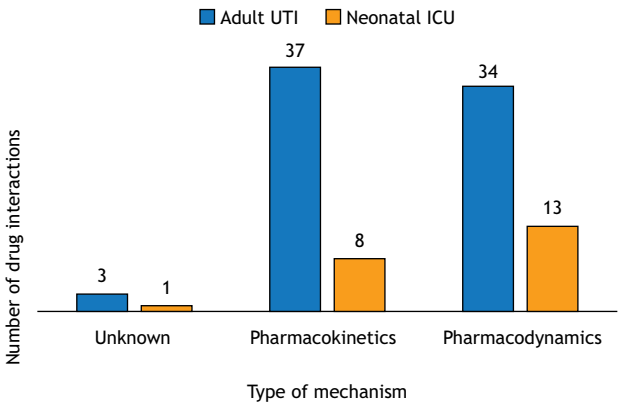

Figure 2. Classification of drug interactions regarding its mechanism in adult and neonatal ICU

The interaction between these drugs, however, although already reported by the clinical pharmacy team, is often desired by the medical staff and/or nursing staff, since patients in the ICU are usually sedated. This decrease in metabolism prevents an increase in the dose or frequency of administration of the drug. Even so, patients are carefully monitored for the degree of sedation.

Regarding the severity of the interactions, we used the parameters described by Cruciol-Souza and Thomson[4]. The results are shown in Figure 1.

In both the adult and neonatal ICUs, we observed a higher incidence of moderate interactions, in other words, interactions that may result in exacerbation of the patient's condition and/or change in therapy. For this reason, follow-up by the clinical pharmacist to manage these interactions, along with clinical follow-up with the multiprofessional team, is necessary.

Although there are fewer severe interactions in both units, they represent a greater danger to the patients. They may result in clinical complication or even lead to death and should therefore be avoided.

The most common severe interactions in the adult ICU were: metoclopramide and tramadol, already discussed before, with 31 cases; dopamine and phenytoin, which may result in an exacerbated increase in the hypotensive effect of phenytoin by pharmacodynamic synergism; and amiodarone and ondansentrone, with four cases each. The latter may lead to prolongation of the QT interval. Considering that most ICU patients have cardiac problems, the use of these drugs together can do severe harm to these patients.

The percentage of 52.70% (39) of moderate interactions can corroborate the study carried out by Carvalho et al.[27], in which 50.1% of the interactions were thus classified. Similarly, Lima and Cassiani[6] detected that 54.7% of potential drug interactions in ICU patients were also considered of moderate severity. In another study by Hammes et al.[9], an approximate number of moderate potential interactions was found, accounting for 50.4% of the total.

In all the aforementioned studies, the percentage of mild and severe interactions was consistent with that found in this study.

In the present study, 72.80% (16) of the cases were considered as "moderate" risk present in the neonatal ICU. In another study conducted by Queiroz et al.[21], 57% of the interactions were classified as "risk to be assessed" when there is drug interaction, but the benefits outweigh the risks. However, this study used different classification criteria, which would rate most of the interactions mentioned in the study as having "moderate" risk if the same criteria adopted here were used.

The drug interactions were also classified according to their mechanism, as per the National Therapeutic Form[5]. No "pharmaceutical" type interactions were detected during the research. The results are shown in Figure 2.

We observed that in the adult ICU pharmacokinetic interactions were the most frequent, unlike the neonatal ICU, where 59% (13) of the interactions were classified as pharmacodynamic.

Pharmacokinetic interactions also accounted for the majority of interactions in the study conducted by Carvalho et al.[27], with 42.7% of the total. In the same study, it was demonstrated that 88.5% of pharmacokinetic interactions occur due to the interference of one drug in the metabolism of the other. One of the most common examples in this study was the coadministration of omeprazole and diazepam. As previously mentioned, omeprazole is a strong enzyme inducer and may affect the metabolism of several drugs, including benzodiazepines such as diazepam.

The pharmacodynamic interactions were the majority in the adult ICU. This fact corroborates what was found by Queiroz et al.[21], when 77.58% of the interactions were thus classified.

The main ways of monitoring pharmacological interactions and their prophylactic and/or corrective measures in the hospital include monitoring the clinical and laboratory data of the patients. A good example is the monitoring of the glycemic level in the case of joint administration of furosemide and insulin, for possible dose adjustment. Another common case is the monitoring of electrolyte levels in cases of administration of potassium chloride and spironolactone.

The coexistence of other diseases and the attempt to avoid adverse effects of drugs may predispose to a high number of drugs, which in turn may lead to a greater number of drug interactions. An example of this is the administration of a proton pump inhibitor in order to avoid the gastrointestinal effects caused by the continuous use of NSAIDs.

Blockade of COX-1 in the gastrointestinal tract by ASA, for example, results in inhibition of gastric mucosal protection and increased acid secretion, which can lead to erosion, ulceration, perforation and hemorrhage. The likelihood of this occurrence may increase with concomitant administration of corticosteroids, anticoagulants, and old age[16]. In order to minimize these effects, medications such as omeprazole, lanzoprazole and ranitidine are prescribed. These, as potent inducers or enzyme inhibitors, may interact with other medicinal products.

It is up to the pharmacist, together with the physician and the nursing team, to evaluate the needs of each case, considering whether the drug interaction, when there is any, presents risks that may outweigh the benefits in the therapy of the patient.

Safe and accurate medication timing is an important responsibility of the nursing professional, who often performs it manually, following a fixed-time routine that rarely considers the characteristics of the prescribed medication and/or the patient's clinical condition. Through proper timing, it is possible to organize the therapeutic plan established for the patients; however, in most hospitals, the pattern of time intervals is closely associated with the routine of nurses, physicians and pharmacy service. The distribution of schedules in standardized and fixed moments contributes to the fact that several drugs are administered at the same time, to the same patient, and this may lead to drug interactions[28].

In the hospital we studied, we observed that many pharmaceutical interventions were related to timing, so that the drugs that have interaction are not administered at the same time, thus avoiding the possibility of the interaction occurring and causing severe adverse effects.

One proposal to facilitate the follow-up of ICU patients is the adoption of the *FAST HUG* concept, a mnemonic way of identifying and verifying some of the fundamental aspects in the general care of critically ill patients.

The *FAST HUG* was proposed by Vincent[29] and is now used by several hospitals in Brazil and worldwide. This method consists in evaluating seven fundamental factors:

- F (feeding): Can the patient be nourished orally? If not, can he/she be fed enterally? If not, is it possible to initiate parenteral nutrition?;
- A (analgesia): The patient should not suffer pain, but analgesia cannot be excessive;
- S (sedation): The patient should not feel discomfort, but excessive sedation should be avoided;
- T (thromboembolic prophylaxis) [DVT]): DVT is associated with high morbidity and mortality, so all patients should be evaluated as to the benefit-risk of the therapy;
- H (head-of-bed elevation): head elevation between 30° and 45° reduces the incidence of gastroesophageal reflux in mechanically ventilated patients. It may be contraindicated in some patients, such as those at risk of cerebral perfusion;
- U (stress ulcer prophylaxis): prevention of stress ulcer;
- G (glucose control or glycemic control): we should always maintain the individuals' glycemia within the stability standards.

Another proposal would be to evaluate the plasma concentration of some drugs for possible dose adjustment. Patients with renal disorders may have the elimination rate of these drugs compromised, which may increase the drug's action time in the body.

The renal clearance of penicillin, for example, is considerably lower in neonates and babies. Consequently, the drug persists in the blood longer, especially in premature babies due to incomplete development of renal function. In patients with impaired renal function, the half-life of penicillin of approximately 30 min may reach 10 h. In these situations, about 7% to 10% of the drug is inactivated by the liver every hour[25].

Thus, the evaluation of the excretion rate of these drugs associated with the renal function of the patient can be an important tool of pharmaceutical intervention, in order to avoid greater harm to patients.

CONCLUSIONS

We observed that the majority of the interactions, both in the adult ICU and in the neonatal ICU, were considered of moderate risk. This points to the need to follow up the patients in whom these interactions are identified, in order to avoid further harm. Pharmacokinetic interactions accounted for most cases in the adult ICU, unlike the neonatal ICU, where pharmacodynamic interactions prevailed.

Management during the administration of the drugs according to their pharmacokinetics was the most appropriate intervention for most cases of drug interactions, since, according to the multiprofessional debate, the drugs involved in these interactions are essential for the treatment, so their suspension or replacement may not be recommended even though simultaneous use will cause harm.

We proposed the adoption of the *FAST HUG* concept, a mnemonic form that describes fundamental care for the follow-up of critical patients. Although this concept does not influence the direct detection of drug interactions, it may help the pharmacist and the multidisciplinary team take care of the patient in a more comprehensive fashion, with more seamless integration among the professionals.

Another intervention and monitoring proposal was to maintain the dose of drugs according to the renal function of the patients, in order to avoid subtherapeutic doses or toxic doses resulting from the malfunction of the kidneys.

Follow-up by the clinical pharmacy service, evaluation and pharmaceutical intervention in ICU prescriptions can help reduce the risks associated with medications.

This study enabled the collection of pharmacoepidemiological data in the region. Although this is still incipient, we are now more able to subsidize new studies and/or services about patient safety.

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.