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Analysis of potential drug interactions in the neonatal ICU of a public hospital in Bahia

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Abstract

Objective: To evaluate the profile of potential drug interactions in the Neonatal Intensive Care Unit (NICU) of a public children's hospital in the inland of Bahia. **Methods:** A descriptive study was conducted, with a cross-sectional design. The printed medical prescriptions (Rxs) of the NICU were collected and analyzed from May 1st, 2016 to October 31st, 2016. The Rxs included in this study were only those containing patient identification, date and the prescriber's signature and stamp, and which included two or more drugs. The data collected were analyzed using the Micromedex software, classifying the potential drug interactions (PDIs) according to severity, documentation, action mechanism, management of the interaction, and potential consequence. The statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS) 20.0 for Windows software. **Results:** A total of 1,476 Rxs were analyzed, and 83 PDIs were identified. In 99.4% of the Rxs, one or more PDIs were found, the following ones being the most frequent: fentanyl+phenobarbital (10.5%); fentanyl+ midazolam (10.5%); and midazolam+ phenobarbital (10.4%). The contraindicated interactions found and analyzed were as follows: domperidone + fluconazole (0.3%); epinephrine + linezolid (0.1%); calcium gluconate + ceftriaxone (0.1%); and dopamine + linezolid (0.1%). **Conclusion:** This study showed a high frequency of PDIs in the NICU Rxs.

Keywords: drug prescriptions; drug interactions; intensive care units; newborn.

Análise de interações medicamentosas potenciais na UTI neonatal de um hospital público da Bahia

Resumo

Objetivo: avaliar o perfil dos potenciais interações medicamentosas da Unidade de Terapia Intensiva Neonatal (UTI-Neo) de um hospital público infantil do interior da Bahia. **Métodos:** Foi realizado um estudo descritivo, com delineamento transversal. Foram coletadas e analisadas as prescrições médicas (PM) impressas da UTI neonatal no período de 01 de maio de 2016 a 31 de outubro de 2016. Foram incluídas somente PM contendo identificação dos pacientes, data, assinatura e carimbo do prescritor e que possuíam dois ou mais fármacos. Os dados coletados foram analisados no software *Micromedex*, classificando as interações medicamentosas potenciais (IMP) segundo gravidade, documentação, mecanismo de ação, manejo da interação e consequência potencial. A análise estatística foi realizada com auxílio do software IBM *Statistical Package for the Social Sciences* (SPSS) 20.0 for Windows. **Resultados:** Foram analisadas 1476 PM, sendo identificadas 83 IMP. Em 99,4% das PM foram verificadas uma ou mais IMP, sendo que as mais frequentes foram: fentanil + fenobarbital (10,5%); fentanil + midazolam (10,5%); midazolam + fenobarbital (10,4%). As interações contraindicadas encontradas e analisadas foram: domperidona + fluconazol (0,3%); epinefrina + linezolida (0,1%); gluconato de cálcio + ceftriaxona (0,1%); dopamina + linezolida (0,1%). **Conclusão:** Este estudo evidenciou alta frequência de IMP em PM na UTI-Neo.

Palavras-chave: prescrições de medicamentos; interações de medicamentos; unidades de terapia intensiva neonatal; recém-nascido.

Introduction

Children's physiology is quite different than that observed in adults. Neonates (newborns less than 28 days old) still do not have their organs fully developed, which results in pharmacokinetic and pharmacodynamic changes and, consequently, in a higher probability of adverse events resulting from the use of medications.[1]

Generally, the pharmacotherapy for neonates in Intensive Care Units (ICUs) is more complex. This is a critical area for the hospitalization of severe patients, who require continuous and specialized multiprofessional care and technologies needed for diagnosis, monitoring, and therapy.[2] Thus, these patients present a higher risk of developing adverse events resulting from Drug Interactions (DIs) since, in addition to the multi-drug treatment, there is the complication arising from the patient's severe health status.[1]

Drug-drug interactions, or Drug Interactions (DIs), occur when the effects of a drug are modified by the presence of another drug, with the possibility of causing treatment failures or development of adverse reactions, an important cause of increased mortality.[3] They can be classified as synergistic, when the effect of the interaction is greater than the individual effect of the medications; or as antagonistic, when the effect of the interaction is lower than the individual effect of the medications, or when there is a change in the pharmacological response.[4]

Consequently, DIs can be detrimental or favorable, depending on factors such as: drug, patient's characteristics, and circumstances in which the associations are used. DIs can also be clinically irrelevant (not requiring special measures for their management), cause transient or permanent harms to the patient, or be potentially fatal.[5]

A Potential Drug Interaction (PDI) is an event verified in the prescriptions and reported in the literature, although its clinical manifestation has not been investigated.[6] Therefore, knowing the occurrence of PDIs becomes important due to their relationship with the clinical manifestation, since there are indications that the potential risk is directly related to the actual occurrence of the DI.[6] DIs contribute significantly to the occurrence of Adverse Drug Reactions (ADRs) in the hospital context, possibly resulting in prolonged hospitalization and in increased costs with hospitalizations and deaths.[7]

It is imperative to monitor the Rxs in ICUs, since Drug-Related Problems are the most common type of adverse event (AE) during hospitalization, accounting for 3% to 5% of the ADRs, which can be prevented in this environment.[8] Computerized programs have been developed as an important tool in the review of Rxs and should be linked to the knowledge of the multiprofessional team pharmacist.[9]

There is scarcity of studies assessing PDIs in NICUs,[1] news studies being needed in this area. Therefore, the objective was to assess the profile of the potential drug interactions in the neonatal ICU of a public hospital, specialized in Pediatrics and located in the second largest municipality of the state of Bahia.

Methods

A descriptive study with a cross-sectional design conducted from May 1st to October 31st, 2016, in a large-size pediatric hospital located in the municipality of Feira de Santana, Bahia. This hospital provides public health care aimed at medium- and high-complexity specialties in Pediatrics, and its structure has a physical active capacity of 272 hospitalization beds. Of these, 20 are in the neonatal ICU (NICU), providing urgency, emergency, surgery and outpatient services, as well as support services for diagnosis and therapy.[10]

All the electronic prescriptions available in the NICU which met the following criteria were included: 1) Including the patient's identification (initials, bed number, age, gender, and length of stay) as well as the prescriber's (signature and stamp); 2) Prescription of two or more concomitant drugs (with due information: drug name, dosage, and administration route), including those administered in an irregular and intermittent manner (as needed); and 3) Having been elaborated during the study period.

The drug names were considered according to the Brazilian Common Denomination (*Denominação Comum Brasileira*, DCB) established by Law No. 9,787/99.[11]

The data were collected directly from the prescriptions with the aid of a form that was exclusively designed for documentary and retrospective collection. All the pharmaceutical presentations were included in the analysis, except those of topical use.

The drugs were classified according to pharmacological groups, as per the Anatomical Therapeutic Chemical (ATC), classification, adopted by the World Health Organization (WHO). Only Level 2 of the classification was taken into consideration, referring to the therapeutic subgroup.[12] For identification and classification of the PDIs, the Thomson Micromedex software[13] was used, which classifies the PDIs according to the following: 1) Severity; 2) Scientific verification of the findings; 3) Probable action mechanism; 4) Clinical management; and 5) Potential consequence, which were classified in this study. The queries in the software were made through institutional access to the CAPES Journals Portal (http://www.periodicos.capes.gov.br), a website that offers easy and reliable access.

Regarding severity, the PDIs were categorized as follows: 1 - Contraindicated*:* it presents risk of death for the patient; 2 - Major: it can represent risk of death and/or require a medical intervention to minimize or prevent severe adverse events; 3 - Moderate*:* it can worsen the patient's clinical condition and/or require changes in the treatment; 4 - Minor: it generally does not require significant changes in the therapy; and 5 - Unknown: no definition regarding severity.[13]

In relation to the documentation present in the scientific literature, the PDIs were classified as: 1 - Excellent*:* controlled studies clarified the presence of the PDI; 2 - Good: the documentation emphatically suggests the presence of the PDI, but controlled studies are scarce; 3 - Reasonable: unsatisfactory documentation, although pharmacological considerations lead to suspect that the PDI is present, or there is good documentation for a pharmacologically similar drug; and 4 - Unknown: the documentation on the PDI is unknown.[13]

The probable action mechanism refers to the way through which the drugs produce changes resulting in therapeutic effects, in their binding site.[14] Management of the PDI can occur through dose adjustment, monitoring, precaution, drug substitution and change in administration time, among others.[15] In addition, the potential consequence would be the outcome caused by the PDI.[15] In a complementary manner, searches in the literature were conducted in relation to the PDIs involving dipyrone, which is not included in Thomson Micromedex, referring to its probable action mechanism and to the consequence of the interaction.

The statistical analysis was performed with the aid of the Statistical Package for the Social Sciences (SPSS) for Windows software, version 20.0, consisting in descriptive analysis (calculation of absolute and relative frequencies for categorical variables; and calculation of mean, standard deviation, and maximum and minimum values for quantitative variables).

This research had previously been submitted to and approved by the Research Ethics Committee (*Comitê de Ética em Pesquisa*, CEP) of the State University of Feira de Santana (*Universidade Estadual de Feira de Santana*, UEFS), under Protocol No. 221,848 (Certificate of Presentation for Ethical Appreciation, CAAE: 11895712.3.0000.0053).

Results

A total of 1,476 Rxs of 111 patients were selected. Of these, 67 were newborns (0-28 days old) and 44 were patients in a transition process, who were admitted as newborns and reached the age of infants; with 51.4% (n=57) male and 48.6% (n=54) female subjects. The mean hospitalization time was 13.5 days, varying from 1 to 93 days.

The mean number of drugs prescribed in the Rxs was 18.57 ± 3.07, varying from a minimum of 5 to a maximum of 27 drugs per prescription. A total of 88 different drugs and three associations were identified, totaling 32 therapeutic subgroups (17 specified and 15 subgroups in "Others" in Table 1). The most prescribed types of drugs were as follows: mineral supplements (14.5%), cardiac stimulants (11.1%), and antibacterials (10.1%). The most frequent drugs were the following: calcium gluconate (5.3%, n=1,444), phenobarbital (5.2%, n=1,417), atropine (5.2%, n=1,414), epinephrine (5.2%, n=1,413) and adenosine (5.1%, n=1,399) (Table 1). A total of 83 PDIs were identified, with 99.4% (n=1,467) of the Rxs presenting some PDI, varying from 1 (n=22) to 21 (n=4), with a mean of 10.06 ± 3.286 PDIs per Rx. These associations were recurrent, accounting for a total of 13,362 PDI episodes.

The most frequent PDIs were fentanyl + phenobarbital (10.5%, n=1,409), fentanyl + midazolam (10.5%, n=1,407) and midazolam + phenobarbital (10.4%, n=1,394). The PDIs with contraindicated severity were the following: domperidone + fluconazole (0.3%, n=43), epinephrine+ linezolid (0.1%, n=10), calcium gluconate + ceftriaxone (0.1%, n=6) and dopamine + linezolid (0.1%, n=2) (Table 2).

Table 1. General characteristics of the patients (n=111) and distribution of the drugs prescribed in the NICU according to the Anatomical Therapeutic Chemical (ATC) classification. (Continue)

Information	All
Sociodemographic	**n (%)**
Male gender	57 (51.4)
Female gender	54 (48.6)
Age ≤ 28 days old	67 (60.4)
Age > 28 days old	44 (39.6)
Pharmacotherapy	**n (%)**
Mineral supplements	**3,969 (14.5)**
Calcium gluconate 10%	1,444 (5.2)
Sodium chloride 20%	1,294 (4.6)
Potassium chloride 19.1%	1,214 (4.4)
Zinc sulphate	8 (0.1)
Calcium polystyrene sulfonate	5 (0.1)
Magnesium sulfate	4 (0.1)
Cardiac stimulants	**3,041 (11.1)**
Epinephrine	1,413 (5.1)
Adenosine	1,399 (5.0)
Dobutamine	200 (0.6)
Norepinephrine	22 (0.2)
Milrinone	4 (0.1)
Dopamine	3 (0.1)
Psycholeptics	2,754 (10.0)
Midazolam	1,398 (5.1)
Thiopental	1,357 (4.9)
Antidotes	**2,377 (10.0)**
Flumazenil	1,377 (5.1)
Naloxone	1,356 (4.9)
Medications for functional gastrointestinal disorders	**2,174 (7.9)**
Atropine	1,414 (5.1)
Domperidone	525 (1.9)
Metoclopramide	227 (0.8)
Bromopride	8 (0.1)
Antiepileptics	**1,440 (5.2)**
Phenobarbital	1,417 (5.1)
Phenytoin	23 (0.1)
Psychoanaleptic	**98 (0.3)**
Caffeine	98 (0.3)
Antibacterials for systemic use	**2,726 (10.1)**
Vancomycin	621 (2.3)
Meropenem	462 (1.7)
Cefepime	326 (1.2)
Amphotericin B	284 (1.1)

Table 1. General characteristics of the patients (n=111) and distribution of the drugs prescribed in the NICU according to the Anatomical Therapeutic Chemical (ATC) classification.(Continued)

Information	All
Pharmacotherapy	**n (%)**
Gentamicin	237 (0.9)
Ampicillin	230 (0.8)
Amikacin	200 (0.7)
Metronidazole	155 (0.5)
Oxacillin	91 (0.4)
Polymyxin B	37 (0.2)
Sulfamethoxazole + trimethoprim	34 (0.2)
Others	85 (0.1)
Blood substitutes and plasma protein fractions	**1,413 (5.2)**
Sodium bicarbonate	1,368 (5.0)
Albumin	45 (0.2)
Anesthetics	**1,379 (5.0)**
Lidocaine	1,377 (4.9)
Ketamine	2 (0.1)
Analgesics	**1,379 (5.0)**
Dipyrone	1,010 (3.7)
Tramadol	334 (1.1)
Morphine	29 (0.1)
Paracetamol	6 (0.1)
Analgesic, anesthetic	**1,315 (4.8)**
Fentanyl	1,315 (4.8)
Diuretics	**774 (2.8)**
Furosemide	689 (2.6)
Spironolactone	48 (0.1)
Hydrochlorothiazide	37 (0.1)
Drugs for acid-related disorders	**572 (2.1)**
Omeprazole	472 (1.7)
Ranitidine	100 (0.4)
Antihemorrhagics	**350 (1.2)**
Vitamin K	348 (1.1)
Tranexamic acid	2 (0.1)
Hypoglycemic	**12 (0.1)**
Regular insulin	12 (0.1)
Antiasthmatics	**268 (1.0)**
Aminophylline	127 (0.4)
Salbutamol	63 (0.2)
Beclomethasone	62 (0.2)
Fenoterol	11 (0.1)
Ipratropium	5 (0.1)
Others	**1,344 (3.7)**

Table 2. Most frequent potential drug interactions, identified in prescriptions made in the NICU of a public hospital from Bahia, from May to October 2016, with information extracted from Thomson Micromedex.[13] (Continue)

Potential drug interaction	Prevalence N=13,362 n (%)	Severity	Documentation	Mechanism	Management of the interaction	Potential consequence
Fentanyl Phenobarbital	1,409 (10.5)	Major	Reasonable	Additive CNS depression Induction of fentanyl metabolism mediated by CYP3A4	Monitoring Dose adjustment	Reduction of fentanyl efficacy Respiratory depression CNS depression
Fentanyl Midazolam	1,407 (10.5)	Major	Reasonable	Additive CNS depression	Monitoring Dose adjustment of one or both	Respiratory depression CNS depression
Midazolam Phenobarbital	1,394 (10.4)	Major	Good	Additive CNS depression	Monitoring Airway management	Respiratory depression CNS depression Exacerbation of the drug effect
Fentanyl Thiopental	1,386 (10.4)	Major	Reasonable	Additive CNS depression	Monitoring Dose adjustment of one or both	Respiratory depression CNS depression
Midazolam Thiopental	1,386 (10.4)	Major	Good	Additive CNS depression	Monitoring Support of the vital functions Airway management	Respiratory depression CNS depression Exacerbation of the drug effect
Phenobarbital Thiopental	1,386 (10.4)	Major	Reasonable	CNS depression	Monitoring	CNS depression Toxicity
Dipyrone Furosemide	499 (3.7)	Moderate	Unknown	Dipyrone may hinder the arrival of furosemide at the site of action	Avoid simultaneous use	Control of the patient's diuresis
Midazolam Omeprazole	420 (3.1)	Moderate	Reasonable	Delayed metabolism and clearance of the benzodiazepines	Monitoring Dose adjustment	Toxicity CNS depression
Phenobarbital Tramadol	318 (2.4)	Major	Reasonable	Additive CNS depression Induction of tramadol metabolism mediated by CYP3A4	Monitoring Dose adjustment	Respiratory depression Reduction of tramadol therapeutic efficacy
Fentanyl Tramadol	313 (2.3)	Major	Reasonable	Additive CNS depression Additive serotonergic effects	Monitoring Use of lower dose and less duration necessary	CNS depression Respiratory depression Serotonergic syndrome
Midazolam Tramadol	306 (2.3)	Major	Reasonable	Additive CNS depression	Monitoring Use of lower dose and less duration necessary	CNS depression Respiratory depression
Thiopental Tramadol	296 (2.2)	Major	Weak	Additive CNS depression	Monitoring Use of lower dose and less duration necessary	CNS depression Respiratory depression
Ampicillin Gentamicin	225 (1.7)	Minor	Good	Chemical inactivation of the aminoglycoside	Monitoring regarding aminoglycoside efficacy	Therapeutic ineffectiveness
Fluconazole Midazolam	207 (1.5)	Moderate	Excellent	Inhibition of midazolam metabolism mediated by CYP450 3A4 due to fluconazole	Reduction of the midazolam dose Monitoring of toxicity	Increase of the midazolam concentrations Toxicity Increase of the psychomotor effects
Metoclopramide Thiopental	206 (1.5)	Moderate	Excellent	Addition of the pharmacological effect	Monitoring	CNS depression
Fluconazole Phenobarbital	190 (1.4)	Major	Weak	Inhibition of the metabolism mediated by CYP2C19 due to fluconazole	Monitoring	Increase of the CYP2C19 substrate plasma concentrations
Domperidone Fluconazole	43 (0.3)	Contraindicated	Reasonable	Inhibition of domperidone metabolism mediated by CYP3A4 due to fluconazole Additive effects in QT interval prolongation	Contraindicated use	Increased exposure to domperidone Increased risk of QT interval prolongation

Table 2. Most frequent potential drug interactions, identified in prescriptions made in the NICU of a public hospital from Bahia, from May to October 2016, with information extracted from Thomson Micromedex.[13] (Continued)

Potential drug interaction	Prevalence N=13,362 n (%)	Severity	Documentation	Mechanism	Management of the interaction	Potential consequence
Epinephrine Linezolid	10 (0.1)	Contraindicated	Reasonable	Unknown	Monitoring Dose adjustment	Increase in blood pressure
Calcium gluconate Ceftriaxone	6 (0.1)	Contraindicated	Good	Physical incompatibility	Use contraindicated in newborns	Risk of formation of ceftriaxone-calcium precipitates Fatal reactions in newborn's lungs and kidneys
Dopamine Linezolid	2 (0.1)	Contraindicated	Reasonable	Sympathomimetic metabolism reduced by linezolid	Monitoring Dose adjustment	Increase in blood pressure
Others	1,953 (14.7)	-	-	-	-	-

Discussion

The patients' hospitalization time in this period is similar to that found in other studies, with means of 13.5[16] and 19.6[17] hospitalization days. It is important to note that hospitalization time is a risk factor for hospital infections and adverse effect, a factor that increases by 6% after each hospitalization day,[16] especially in sectors such as the one under study, since the occurrence of procedures and manipulations is relatively greater, as well as polypharmacotherapy. It was also possible to verify that a higher percentage of boys were admitted to the NICU, a result that is similar to that of other papers, with 51.8%[18] and 50.6%[1] of male children admitted to hospital units. These results can be due to the rate of male births when compared to that of female births. In 2015, the rate of male births was 51.10% in the state of Bahia and, in the same period, it was 51.08% in the micro-region of Feira de Santana.[19]

Treatments with multiple drugs are common in ICUs; however, the mean of drugs per prescription found in this study is higher than in others conducted in NICUs: 3.16[20] and 10.00[18] drugs. This discrepancy can be considered due to the methodology used in each study. A number of research studies evidenced that, if the number of medications exceeds five, the risk of AEs is higher; in addition to this, it is closely related to the occurrence of PDIs and to prolonged hospitalization.[5]

The concomitant use of different drugs and various pharmacological classes is common due to the complexity of the study setting. Mineral supplements are intended to maintain/reestablish homeostasis, since most of the patients admitted to this sector have one or more decompensated organ systems.[21] Cardiac stimulants, in turn, are prescribed for situations in which the patient presents cardiopulmonary arrest (CPA).[22] The consumption of antibacterials for systemic use by the NICU patients was high, which can portray their critical condition, probable infections (acquired inside or outside the hospital setting), and greater number of invasive procedures performed.[23]

Due to the critical condition of the NICU patients, the occurrence of CPA is common. The consumption of calcium gluconate can be justified by the CPA episodes resulting from hyperkalemia or hypermagnesemia.[24] In addition to that, electrolyte disturbances are common after CPA events, due to lack of circulation and to the methods applied to resuscitate the patient, including the administration of solutions and of adrenaline.[24] Seizures may occur after CPA, being recorded in nearly 30% of the patients[25] in a previous study, which may justify the high frequency of phenobarbital prescriptions, since it is indicated for seizure episodes in neonates.[26] Atropine is used for emergency endotracheal intubation, in order to prevent bradycardia.[22] Epinephrine is used as a vasopressor during CPA in pediatrics.[22] Adenosine, in turn, is recommended in the initial diagnosis and treatment of undifferentiated regular monomorphic wide-complex tachycardia, both in cardiovascular advanced life support and in pediatrics.[27]

In one of the studies that were compared, it was found that the frequency of PDIs per prescription corresponded to 51.26%, accounting for 170 PDIs, with a mean of 2.78 PDIs per prescription,[20] whereas another study found 197 PDIs.[18]

The more frequent PDI resulted from the fentanyl + phenobarbital association, with major severity, reasonable documentation, and pharmacokinetic and pharmacodynamic mechanism.[13] Fentanyl, an opioid analgesic, has respiratory depression as an adverse event.[28] Phenobarbital, an antiepileptic, also has respiratory depression as an adverse event and, when in overdose, it can also cause respiratory failure.[28] Consequently, the association of these drugs can lead to additive respiratory depression. The management of this interaction involves monitoring the signs of respiratory depression and/or opioid withdrawal, was well as dose adjustment. In case the use of phenobarbital exceeds 15 days, the pharmacological activity of fentanyl can be reduced. If combined use is necessary, signs of respiratory depression must be observed, with the possibility of dose adjustment.[13] Due the nature of the unit in which the study was conducted, this type of interaction can be recurrent since, in another study in a pediatric ICU, this PDI was the third most frequent interaction of major severity.[29]

The second most frequent PDI is associated with the concomitant use of fentanyl + midazolam, with major severity, reasonable documentation, and pharmacodynamic mechanism.[13] This PDI can result in increased risk of Central Nervous System (CNS) depression as a consequence of pharmacodynamic synergism, since both drugs cause CNS depression by acting on different molecular targets. The concomitant use of an opioid analgesic and a CNS depressant can cause respiratory depression, hypotension, and deep sedation, with the possibility of leading to coma or even patient's death.[30] The management of this interaction requires patient monitoring and dose adjustment.[13] This interaction was the most frequent of major severity in a study conducted in a pediatric ICU,[29] and may be justified by its common use for intubation procedures; however, it is emphasized that this procedure ensures the patient's respiratory function, minimizing the harms caused by the potential interaction.

The PDI resulting from the midazolam + phenobarbital association presents major severity, with good documentation and pharmacodynamic emergence mechanism through synergism.[13] The result of this PDI can promote additive respiratory depression, sedation, dizziness, confusion, and difficulty concentrating, due to the exacerbated effect of both drugs. This is justified by the concomitant use of a benzodiazepine and a barbiturate, which act increasing the formation of inhibitory postsynaptic potentials in the CNS and may lead to respiratory depression, in addition to hypotension and deep sedation.[30] The management of this interaction is related to patient monitoring and to airway management.[13]

Among the PDIs of contraindicated severity, the most frequent was the one resulting from the domperidone + fluconazole association, with reasonable documentation.[13] Concomitant use can result in increased exposure to domperidone and higher risk of QT interval prolongation in the electrocardiogram. Domperidone is metabolized by enzymes of the CYP3A4 subfamily and fluconazole, on its turn, is a potent enzymatic inhibitor. Therefore, with the inhibition of this subfamily, there is greater exposure to domperidone, which may lead to the emergence of its adverse events, in addition to the additive effect of QT interval prolongation, which can trigger arrhythmia and sudden cardiac death.[13]

Another contraindicated PDI, with reasonable documentation,[13] is linked to the epinephrine + linezolid association, which can result in increased hypertensive effects. Epinephrine is metabolized by monoamine oxidase (MAO), whereas linezolid presents reversible weak inhibitory effects of this enzyme. This PDI has an unknown emergence mechanism; however, it is suggested that the effects of epinephrine are intensified due to the increased serum concentration of this drug, caused by the inhibition of its metabolizing enzyme by linezolid. As a recommendation, the use of these drugs must be intercalated, avoiding their simultaneous administration.[31]

The concomitant use of calcium gluconate + ceftriaxone can result in a PDI contraindicated for newborns due to the physical incompatibility of the drugs, promoting ceftriaxone precipitation, in addition to a risk of fatal reactions in the lungs and kidneys.[13] It is not indicated either to combine solutions containing ceftriaxone and calcium (including parenteral nutrition) or to administer them by the same infusion route. This interaction presents good documentation.[13] This incompatibility was found with a percentage of 8.89% in another study conducted in a pediatric ICU[32] and of 20%[33] in a study in an adult ICU. It can be seen that the increased percentage in the ICU for adults can be justified by the fact that the contraindication only refers to newborns.

The PDI resulting from the dopamine + linezolid association can also result in increased hypertensive effects. Linezolid is a non-selective reversible inhibitor of MAO, and dopamine is an adrenergic agent, thus increasing dopamine serum concentration, favoring the occurrence of more hypertensive events, in addition to the sympathomimetic metabolism being reduced by linezolid.[13,31] This interaction is considered as contraindicated, with reasonable documentation.[13]

The management and monitoring strategies for respiratory depression involve monitoring the respiratory function and oxygenation and, depending on the patient's clinical condition, the dose will have to be adjusted, in case the drug combinations are necessary. Reversion of hypoventilation must be sought; put the patient on artificial ventilation; and, if needed, add calcium ions to the treatment, favoring the increase of muscle contractions.[13]

In the patients who presented CNS depression, the respiratory function and arterial pressure must be monitored, as well as their sedation level. It is important to avoid the association of the drugs that could cause these events but, in case it is the only option, dose and dosage must be adjusted, and monitoring should continue.[13]

For the association of drugs that can cause toxicity, their serum concentrations must be monitored, as well as the patient's sedation level, blood pressure and respiratory function. Concomitant use of the drugs must be avoided but, if inevitable, it is necessary to readjust the dose and monitoring must also be maintained.[13]

The analysis of potential drug interactions is a good tool to guide the multidisciplinary team in the management of medical prescriptions; however, the use of programs to identify drug interactions requires knowledge on the pharmacological aspects of the drugs' action, since the program only shows the possible implications of simultaneous use. Thus, the team must use the necessary resources for the due control of the emergence of the drug interactions. When analyzing this fact, it is noticed that a study of such nature with the description of PDIs has limitations for not deepening on the description of the actual emergence or not of the drug interaction; such limitation can be partially overcome if data analysis was performed together with the assessment of more data from the medical prescription. The scarcity of information about some drugs, such as dipyrone, can represent another problem since its analysis cannot be approached in the same way as the other medications involved. Other study limitations are related to the fact that the prescriptions are practically the same daily; thus, some PDIs were repeated for the same patient during the study period; as well as the fact that the number of patients exposed to each specific PDI was not analyzed.

Conclusion

This study found a high number of prescriptions that presented some PDI, with predominance of the PDIs classified as major, which can impose risks to the patients' lives. The number of PDIs classified as contraindicated was also high, since these associations should not occur; however, depending on the patient's situation, considering the risk-benefit ratio and the need of the associations, these events must be constantly monitored.

The importance of raising awareness among the multidisciplinary team members involved in the rational use of medications is evident, who must be attentive to the information about PDIs, and be able to identify them and to suggest appropriate interventions. Consequently, PDIs must be identified in the prescription, dispensing and administration of the drugs, aiming to minimize the occurrence of those that can cause harms to the patients' health.

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Collaborators

TRC: conception, design and analysis, data interpretation, writing of the article. ARC: conception, design and data analysis and interpretation, writing of the article. KVA: writing of the article and relevant critical review of the intellectual content. MCS: writing of the article and relevant critical review of the content.

Conflict of interest statement

The authors declare that there are no conflicts of interest regarding this article.

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