einstein
Official Publication of the Instituto Israelita de Ensino e Pesquisa Albert Einstein

ISSN: 1679-4508 | e-ISSN: 2317-6385

ORIGINAL ARTICLE

Drug interactions in maternal intensive care: prevalence, risk factors, and potential risk medications

Interações medicamentosas em terapia intensiva materna: prevalência, fatores e medicamentos de risco

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DOI: 10.31744/einstein_journal/2019AO4521

ABSTRACT

Objective: To characterize severe potential drug interactions in maternal intensive care, and to determine their frequency, risk factors and potential risk medications. **Methods:** An observational and longitudinal study conducted between December 2014 and December 2015 in a maternal intensive care unit. Clinical data were collected and severe potential drug interactions were identified on pregnant inpatients. The drug interactions were classified by type, prevalence and exposure rate. A multivariate logistic regression model was used to identify the severe potential drug interactions and the related drugs ($p<0.05$). **Results:** A total of 95.1% of patients were exposed to, at least, one potential drug interaction; in that, 91.7% 33.9% were related to, respectively, moderate and severe potential drug interactions. The patients were exposed, on average, on 69.2% of days they were in the intensive care unit. The main drugs involved in more severe drug interactions were magnesium sulfate, metoclopramide, propranolol and diazepam. **Conclusion:** The severe potential drug interactions were observed in almost all patients of the study, and, approximately one third of those interactions were related to greater severity and resulted in exposure during long hospital stay. The higher number of prescribed drugs and its previous use of medications at home increase the occurrence of severe potential drug interactions.

Keywords: Drug interactions; Intensive care units; Maternal health; Drug therapy; Pregnancy

RESUMO

Objetivo: Caracterizar as interações medicamentosas potenciais graves em terapia intensiva materna, e determinar sua frequência, os fatores e os medicamentos de risco associados à ocorrência dessas interações. **Métodos:** Estudo observacional e longitudinal executado entre dezembro de 2014 a dezembro de 2015, conduzido em uma unidade de terapia intensiva materna. Foram coletados dados clínicos e identificadas interações medicamentosas potenciais graves de gestantes admitidas. As interações medicamentosas foram caracterizadas quanto ao tipo, à prevalência e à taxa de exposição. Um modelo multivariado de regressão logística foi utilizado para identificação de fatores associados à ocorrência de interações medicamentosas potenciais graves e os medicamentos implicados ($p<0,05$). **Resultados:** Um total de 95,1% das pacientes foi exposto a, no mínimo, uma interação medicamentosa potencial, com 91,7% delas envolvidas com interações medicamentosas potenciais moderadas e 33,9% com as interações graves. As pacientes ficaram expostas, em média, em 69,2% dos dias que estiveram sob terapia intensiva. Os principais medicamentos implicados em interações medicamentosas de maior gravidade foram sulfato de magnésio, metoclopramida, propranolol e diazepam. **Conclusão:** As interações medicamentosas potenciais graves ocorreram na maioria das pacientes avaliadas. Aproximadamente um terço das

How to cite this article:
Pessoa TL, Clemente Junior WS, Costa TX, Bezerra PK, Martins RR. Drug interactions in maternal intensive care: prevalence, risk factors, and potential risk medications. einstein (São Paulo). 2019;17(3):eAO4521. http://dx.doi.org/10.31744/einstein_journal/2019AO4521

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Received on:
Apr 11, 2018

Accepted on:
Nov 12, 2018

Conflict of interest:
none.

interações foram graves e levaram à maior exposição por um longo período de internação. Maior número de fármacos prescritos e uso prévio domiciliar de medicamentos elevam a ocorrência de interações medicamentosas potenciais graves.

Descritores: Interações de medicamentos; Unidade de terapia intensiva; Saúde materna; Tratamento farmacológico; Gravidez

INTRODUCTION

Care of critically ill patients in intensive care units (ICU) entails extensive use of medications and consequent polypharmacy. Prescription of several drugs increase occurrence of adverse events, especially drug interactions, leading to greater costs and longer hospital stay.[1-3] A potential drug-drug interaction (PDI) is defined as the concurrent administration of two potentially interactive drugs, with a prevalence of 46% to 80% among intensive care patients.[1,4-6] Because of clinical severity, critically ill patients have a lower capacity for drug elimination, increasing the risk of damage resulting from PDI.[3-5,7]

The treatment of pregnant women at ICU is associated with emergency obstetric care.[8,9] In developed countries, it is estimated that 2% or less of pregnant women are admitted to the ICU, while in developing countries this rate is approximately 10%.[9] The main reasons for admission in maternal ICU are related to hemorrhage and hypertensive disorders of pregnancy.[8-10] Other less common reasons include heart disease, genitourinary infection, obstetric complications, such as ectopic pregnancy and miscarriages, non-genitourinary infection, sepsis, cerebrovascular disease, and pulmonary embolism.[9,10]

The use of drugs in maternal ICU presents some peculiarities. Physiology changes during pregnancy, leading to modified actions of medications on the body.[11] Pregnant women present significant pharmacokinetic changes. The increase in adipose tissue increases the distribution volume and the half-life of lipophilic drugs. Other changes include increased activity of liver enzymes and glomerular filtration rate, with risk of fetal exposure to lipophilic drugs.[11-13]

Most studies on PDI are limited to characterizing the frequency of medications and therapeutic classes involved, without highlighting which factors contribute to the occurrence of PDI and their possible consequences. However there is scarce literature on frequency of clinically significant PDI in pregnant women, in addition to characterization of these events in patients admitted to maternal ICU.

OBJECTIVE

To characterize severe potential drug-drug interactions in maternal intensive care units and determine the frequency, risks factors, and potential risk medications.

METHODS

An observational, descriptive, cross-sectional study conducted at the 6-bed maternal ICU of the *Maternidade Escola Januário Cicco* (MEJC), with an average of 53 admissions per month. All patients admitted to the ICU during the study period who stayed for more than 24 hours, and had more than two drugs prescribed were considered eligible. Patients previously included in the sample were excluded. A total of 348 patients were evaluated between December 2014 and December 2015.

This project was approved by the Research Ethics Committee of *Hospital Universitário Onofre Lopes*, protocol 496.656, CAAE: 21536713.0.0000.5292.

Clinical data related to previous pregnancies, comorbidity score as per the Mortality Probability Model (MMP) upon admission, clinical diagnosis according to the International Classification of Diseases and Related Health Problems - Tenth Edition (ICD-10), and prescribed drugs were collected. All patients were daily monitored for occurrence of drug interactions, assessed as to the prescribed items and time of exposure to the PDI throughout the hospitalization period.

The software Lexi-Interact was used to identify PDI in medical prescriptions. It consists of a database with restricted online access, with updated information on more than 8,000 unique drug terms. The database enables classifying the PDI as minor, moderate or severe, according to severity level. Severe PDI can be life-threatening and/or require intervention to reduce or prevent damage; moderate interactions imply exacerbation of the clinical condition, and possible changes in the prescription; and minor PDI imply a limited clinical effect with the possibility of worsening, but with no need for intervention.[14]

Statistical analysis was carried out using Stata release 11 (Stata Corporation, College Station, TX, USA). In the descriptive analysis, the characteristics of the patients were presented as mean and standard deviation, or relative or absolute frequencies, when appropriate. The rate of exposure to drug interactions was calculated by the ratio between the number of days exposed to the event and the total length of hospital stay. For each variable studied, the number of drug interactions per day of hospitalization was obtained by multiplying the number of events by the exposure

rate. The identification of risk factors for severe drug interactions was conducted by univariate and multivariate analysis using logistic regression. Only the variables presenting a p value <0.10 were included in the multivariate model (p<0.05). To determine the prescription drugs at the highest risk of causing severe drug interactions we used regression adjusted by the risk factors identified and those already reported as being associated with drug interactions (number of medications, length of stay and age).

RESULTS

During the study, 348 patients were assessed (Table 1). The mean age was 26.4 years, with a mean of two pregnancies; 26.2% reported at least one miscarriage. In the sample, there was a predominance of cesarean section (57.8%), but roughly 37% were still pregnant. Gestational hypertension was characterized as the most frequent diagnosis (65.9%), followed by eclampsia (7.5%), and urinary infection (2.6%). Patients had a mean length of ICU stay of 3 days (standard deviation of 2.1 days).

Approximately 8±3.5 medications were administered during hospitalization. About 95.1% of patients were exposed to at least one PDI; in that, 52.9% of minor, and 91.7% of moderate severity (Table 2). About one-third of patients (33.9%) had a more severe PDI. Table 2 also emphasizes that during hospital stay patients were, on average, 69.2% of period exposed to at least one severe PDI.

In the univariate logistic regression analysis, the occurrence of PDI was significantly associated with number of drugs administered, use of medications at home before hospitalization, age and diagnosis of urinary infection. These variables were included in the multivariate model (Table 3), in which a significant association was found between the occurrence of severe PDI and the number of drugs administered (odds ratio - OR: 1.106; 95% confidence interval - 95%CI: 1.073-1.139). There was also a significant association between the occurrence of severe PDI and the medications used at home (OR: 1.317; 95%CI: 1.022-1.696). The diagnosis of urinary tract infection was, however, less likely to be associated with occurrence of severe PDI (OR: 0.334; 95%CI: 0.136-0.854).

Among the drugs related to severe PDI, diazepam, magnesium sulfate, propranolol, and metoclopramide presented greater risk in pregnant women under

Table 1. Characteristics of the population (n=348) and profile of the potential drug interactions in relation to type and exposure rate of patients

Characteristics	Mean±Standard deviation
Age, years	26.4±7.7
Prenatal care visits	25±2.7
Number of gestations	2.2±1.6
MPM upon admission	2.2±2.2
Length of stay, days	3.0±2.1
Medications	8.0±3.5

MPM: mortality probability model.

Table 2. Profile of the potential drug interactions in relation to type and exposure rate of patients

PDI	n (%)	Mean±Standard deviation	95%CI
Patients with PDI during hospitalization	331 (95.1)		92.3-97.1
Patients with PDI			
Minor	184 (52.9)		47.5-58.2
Moderate	319 (91.7)		88.3-94.3
Severe	118 (33.9)		28.9-39.1
Days exposed to severe PDI, %		69.2±30.6	

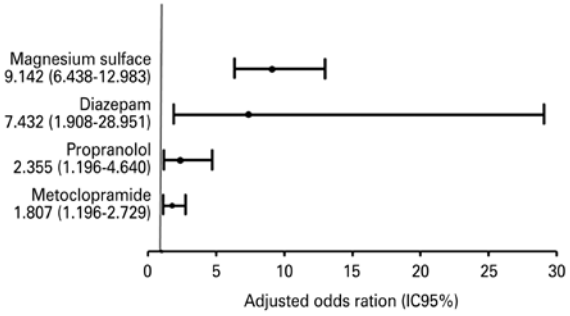
95%CI: 95% confidence interval; PDI: potential drug interactions.

Table 3. Univariate and multivariate logistic regression analysis of risk factors for occurrence of severe drug interactions

Parameters	Univariate analysis			Multivariate analysis		
	Odds ratio	95%CI	p value	Odds ratio	95%CI	p value
Age, years	1.019	1.004-1.034	0.014	1.002	0.986-1.018	0.817
Prenatal care visits	1.009	0.970-1.051	0.650	-	-	-
Number of gestations	1.045	0.974-1.121	0.219	-	-	-
History of miscarriage	1.015	0.781-1.319	0.913	-	-	-
Mode of delivery						
Vaginal	Reference			-	-	-
Cesarean section	1.472	0.732-2.959	0.278	-	-	-
Not performed	1.463	0.720-2.971	0.293	-	-	-
MPM score upon admission	1.015	0.972-1.061	0.524	-	-	-
Length of stay, days	1.035	0.986-1.086	0.164	-	-	-
Diagnosis						
Gestational hypertension	1.216	0.946-1.564	0.128	-	-	-
Eclampsia	0.984	0.632-1.530	0.942	-	-	-
Urinary infection	0.440	0.177-1.091	0.077	0.340	0.136-0.854	0.022
Diabetes mellitus	1.318	0.667-2.603	0.427	-	-	-
Preexisting hypertension	0.947	0.428-2.093	0.892	-	-	-
Medications taken before admission	1.634	1.281-2.085	0.000	1.317	1.022-1.696	0.000
Medications given	1.111	1.080-1.143	0.000	1.106	1.073-1.139	0.000

95%CI: 95% confidence interval; MPM: mortality probability model.

intensive care (Figure 1), representing 66.5% of interactions. Magnesium sulfate accounted for 37.8% of severe PDI and presented the highest frequency, as depicted in table 4. Although it is a potentially dangerous drug, diazepam was only responsible for 7.1% of severe PDI detected, whereas propranolol and metoclopramide accounted for 4.9% and 16.6%, respectively.



95%CI: 95% confidence interval.

Figure 1. Medications at risk of severe drug-drug interactions raves in pregnant women under intensive care (multiple regression model adjusted for age, number of prescribed medications, length of stay, use of medications before hospitalization, and diagnosis of urinary infection)

Table 4. Profile of detected severe potential drug interactions

Severe PDI associated to high-risk medications	n (%)	Clinical effect
Magnesium sulfate		
Nifedipine	70 (37.8)	Hypotension, hypocalcemia, neuromuscular block, myocardial depression and pulmonary edema
Metoclopramide		
Levomepromazine	26 (14.1)	
Chlorpromazine	1 (0.5)	Extrapyramidal effects and, in extreme cases, neuroleptic malignant syndrome
Haloperidol	1 (0.5)	
Promethazine	1 (0.5)	
Amiodarone	1 (0.5)	Syncope, polymorphic ventricular tachycardia, ventricular fibrillation and cardiac sudden death
Fluoxetine	1 (0.5)	Extrapyramidal adverse events
Propranolol		
Methyldopa	7 (3.8)	Hypertensive reaction, tachycardia and arrythmia
Cabergoline	2 (1.1)	Hypertension and peripheral ischemia
Diazepam		
Phenobarbital	4 (2.2)	Somnolence, irritability and hyperactivity
Phenytoin	4 (2.2)	Headache, nystagmus, diplopia and ataxia
Carbamazepine	3 (1.6)	Reduced therapeutic effectiveness of diazepam
Levomepromazine	2 (1.1)	Extrapyramidal adverse events
Total	123 (66.5)	

PDI: potential drug interactions.

DISCUSSION

The occurrence of PDI in maternal intensive care is observed in almost all patients, and the exposure time covers 69.2% of hospitalization period. Compared to other intensive care modalities, the prevalence of PDI detected in pregnant women was markedly higher. For adult and cardiac ICU, *e.g.*, the prevalence of patients exposed to at least one PDI ranges from 50 to 80%, and severe PDI occur in percentages lower than those found in this study.[3-5] A systematic review included nine studies and 3,150 intensive care patients evaluated, found that about 63% of patients were exposed to at least one PDI.[15]

It is important to emphasize that prescription of drugs with potential drug interactions does not necessarily imply harm to patients. Nonetheless, the risk is higher when PDI are classified as severe.[5] In this study, about one-third of pregnant women had at least one severe PDI and were exposed for more than two-thirds of the hospitalization period. Obstetric patients present physiological changes that alter the pharmacokinetics and pharmacodynamics of numerous drugs, thus increasing the risk of harm associated with use of drugs, especially when there is interaction between them, which may affect the dyad mother-fetus.[11,12,16] Therefore, considering the prevalence and duration of exposure, severe PDI should be considered in the pharmacological approach of these patients.

Approximately 33.9% of patients presented severe PDI, and the prior use of medications before hospitalization and a high number of drugs prescribed during the hospitalization period were identified as risk factors for these events. Polypharmacy is a risk factor already described, and is related to the occurrence of drug interaction and other incidents associated with the use of medications.[17] The use of medications at home as a risk factor probably indicates greater clinical severity, leading to the use of multiple drugs during hospitalization. In contrast, urinary tract infection appeared as a reducing factor, which may be justified by the treatment approach applied in those cases in which a smaller number of drugs related to severe PDI are used.

Patients who were prescribed magnesium sulfate, diazepam, propranolol and metoclopramide were at increased risk for severe PDI. Magnesium sulfate is not commonly used in other intensive care modalities and is indicated for hypertensive disorders of pregnancy. The other drugs are more frequently related to more severe PDI in intensive care in general.[6,18]

Magnesium sulfate is the drug with the highest risk of causing severe PDI, especially when it is associated with nifedipine. The association can cause hypotension, hypocalcemia, neuromuscular blockade, myocardial depression, as well as pulmonary edema.[19,20] The mechanism of interaction involves the reduction of flow in the calcium channels in myocardial cells, in addition to blocking the adrenal release of norepinephrine, antagonizing the vasopressor effects.[21]

The association of propranolol and methyldopa is not recommended, since it may cause hypertensive reaction, tachycardia or arrhythmia due to peripheral blockade of beta-adrenergic receptors, warranting the effect of vasoconstriction by alpha adrenergic receptors.[22] Propranolol should also be avoided with cabergoline, due to block of normal sympathetic vasodilatation stimulated by beta-2 receptors, resulting in excessive vasoconstriction, and may cause hypertension or even peripheral ischemia.[23,24]

Severe PDI involving diazepam are associated with depression of neural activity and significant changes in drug metabolism. Diazepam and phenobarbital act to potentiate the gamma-aminobutyric acid (GABA) inhibitory effect, favoring the opening of the chlorine channels in the neural membrane.[25-27] Simultaneous use of these drugs may lead to potentiation of neuronal inhibition and, clinically, to central nervous system depression.[27] Benzodiazepine, when associated with antipsychotic drugs, like levomepromazine, causes increased blocking of dopaminergic receptors, which may lead to extrapyramidal adverse events or other effects associated with these receptors.[28]

Drug interactions between diazepam and phenytoin occur at the pharmacokinetic level, with hydantoin being metabolized by hepatic isoenzymes CYP2C9 and CYP2C19.[29,30] Benzodiazepines are metabolized by a distinct isoform (CYP3A4), however, diazepam is specifically metabolized extensively by CYP2C19.[31] Diazepam may, therefore, compete with the metabolizing enzyme and significantly increase phenytoin concentrations, inducing toxicity.[29,30] Carbamazepine, may compromise the therapeutic action of diazepam through metabolic activity of the CYP3A4 isoenzymes.[31-34]

Metoclopramide also had a high frequency of more severe PDI, especially when used simultaneously with antipsychotics. The antiemetic action of metoclopramide is due to dopamine antagonism in D2 receptors.[35] The association with neuroleptics can cause intense dopaminergic blockade in the striatum and hypothalamus, favoring the occurrence of extrapyramidal effects and, in extreme cases, neuroleptic malignant syndrome.[36]

It is important to emphasize that this study characterizes PDI in pregnant women in intensive care, and data on this topic is scarcely found in the literature. Likewise other intensive care modalities, drug interactions are a major concern in medical practice, since they may have detrimental consequences for health care.[4,6,7] The identification, description and monitoring of potential interactions are, therefore, important in order to minimize pharmacotherapy-related risks. Similar studies may contribute to establishing automated alert systems aimed to the multiprofessional team at ICU, enabling less exposure of patients to severe drug interactions. The findings also indicated that a clinical pharmacist should monitor the patients, adequately evaluating the occurrence of PDI in the prescription and making it possible to prevent damage.[1,37]

This paper presents some limitations. Data was collected in one single center, which may compromise generalizing the findings. Despite the prospective collection, some information may have been missed due to failures in the process of medical records. It is important to emphasize that the interactions described are potential, that is, they were classified from the medical prescription, and did not necessarily imply the occurrence of negative clinical outcomes. The detection of PDI, even those classified as severe, should be contextualized with the patient's clinical presentation, and the risk-benefit of the treatment should always be considered. Another aspect that may decrease the capacity of generalizing the results involves possible disagreement between the databases and compendia regarding the class and severity of drug interactions.[38] However, the literature indicates that the software used in this study is solidly based on clinical evidence and is constantly updated.[38,39]

New investigations should be conducted in order to evaluate clinical outcomes related to drug interactions, especially correlating them with clinical parameters, length of stay, and mortality.

CONCLUSION

Almost all pregnant women in maternal intensive care are exposed to at least one potential drug-drug interaction. More than one-third of potential drug-drug interactions are severe and occur during most of the hospitalization period. The factors associated with severe potential drug-drug interactions are prior and use of medication at home, as well as a greater number of drugs prescribed during hospitalization, whereas the diagnosis of urinary tract infection

is inversely related to the occurrence of potential drug-drug interaction. The drugs most implicated in potentially severe drug-drug interaction were magnesium sulfate, metoclopramide, propranolol and diazepam. It is important to emphasize that the identification, description, and monitoring of potential interactions are important to ensure safety of pregnant woman under intensive care.

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