REME • Rev Min Enferm. 2019;23:e-1226
DOI: 10.5935/1415-2762.20190074

RESEARCH

DRUG INTERACTIONS PREVALENCE INVOLVING HIGH-SURVEILLANCE DRUGS: A CROSS-SECTIONAL STUDY

PREVALÊNCIA DE INTERAÇÕES MEDICAMENTOSAS ENVOLVENDO MEDICAMENTOS DE ALTA VIGILÂNCIA: ESTUDO TRANSVERSAL

PREVALENCIA DE LA INTERACCIÓN DE DROGAS QUE INCLUYEN MEDICAMENTOS CONTROLADOS: ESTUDIO TRANSVERSAL

Ana Laura Biral Cortes [1]
Zenith Rosa Silvino [1]
Fernanda Barbosa Moreira Santos [1]
Juliana Aguiar Carvalho Pereira [1]
Graziela Silva Tavares [1]

[1] Universidade Federal Fluminense – UFF, Departamento de Fundamentos de Enfermagem e Administração. Niterói, RJ – Brazil.

Corresponding author: Ana Laura Biral Cortes
E-mail: analaurabiral@yahoo.com.br

Author´s Contribuitions:
Conceptualization: Ana L. B. Cortes; ***Data Collection:*** Ana L. B. Cortes, Fernanda B. M. Santos, Juliana A. C. Pereira, Graziela S. Tavares; ***Investigation:*** Ana L. B. Cortes; ***Methodology:*** Ana L. B. Cortes; ***Project Management:*** Ana L. B. Cortes, Zenith R. Silvino; ***Supervision:*** Ana L. B. Cortes, Zenith R. Silvino; ***Writing - Original Draft Preparation:*** Ana L. B. Cortes, Fernanda B. M. Santos, Juliana A. C. Pereira, Graziela S. Tavares; ***Writing - Review and Editing:*** Ana L. B. Cortes, Zenith R. Silvino, Fernanda B. M. Santos, Juliana A. C. Pereira, Graziela S. Tavares.

Funding: No funding.

Submitted on: 2018/07/04
Approved on: 2019/07/07

ABSTRACT

Objective: to estimate the prevalence of potential drug interactions (PDIs) related to the high-surveillance drugs (HSD) used by a sample of patients admitted to an intensive care unit (ICU). **Methods:** a cross-sectional, retrospective study with a quantitative approach. Research was based on the analysis of patients prescriptions admitted to the ICU over a one-year period (2014-2015) to identify potential drug interactions related to recurrent HSDs. For each medical record, they were analyzed from the first three to five prescriptions, depending on their availability and the period of individual hospitalization. PDIs identification was made by consulting the Trissels device from the Micromedex 2.0 database. **Results:** in the 244 drug prescriptions, 846 HSD-related PDIs and 112 different pairs of PDI involving the HSDs were identified. The main HSDs in PDI were: regular insulin, midazolam, fentanyl and tramadol. Of the 112 types of identified PDI, some were recurrent; namely: tramadol and ondansetron, fentanyl and midazolam, midazolam and omeprazole, regular insulin and hydrocortisone, as well as regular insulin and norepinephrine. HSD with PDIs prevalence in this sample was 0.96 (96%). **Conclusion:** most patients were exposed to PDI involving midazolam, fentanyl or regular insulin. Some vigilance should be established to avoid unnecessary interactions. Alternatively, when the joint administration of certain interactants is indispensable skills should be in place to manage this administration more appropriately and with the lowest possible risk to the patient.

Keywords: Patient Safety; Safety Management; Drug Interactions.

RESUMO

Objetivo: *estimar a prevalência de interações medicamentosas potenciais (IMP) relacionadas aos medicamentos de alta vigilância (MAV) usados por uma amostra de pacientes internados em um centro de terapia intensiva (CTI).* ***Métodos:*** *estudo transversal, retrospectivo de abordagem quantitativa. A pesquisa apoiou-se na análise das prescrições dos pacientes internados no CTI no período de um ano (2014-2015) a fim de identificar as interações medicamentosas potenciais relacionadas aos MAVs nelas recorrentes. Para cada prontuário, foram analisadas das três às cinco primeiras prescrições, dependendo da disponibilidade destas e do período de internação do indivíduo. A identificação das IMPs foi feita a partir de consulta ao dispositivo Trissels da base de dados Micromedex 2.0.* ***Resultados:*** *nas 244 prescrições medicamentosas foram identificadas 846 IMPs relacionadas aos MAVs e 112 pares diferentes de IMP envolvendo os MAVs. Os principais MAVs nas IMP foram: insulina regular, midazolam, fentanil e tramadol. Dos 112 tipos de IMP identificados, algumas foram recorrentes; a saber: tramadol e ondansetrona, fentanil e midazolam, midazolam e omeprazol, insulina regular e hidrocortisona, bem como insulina regular e noradrenalina. A prevalência das IMPs com MAV nessa amostra foi de 0,96 (96%).* ***Conclusão:*** *grande parte dos pacientes foi exposta à IMP envolvendo midazolam, fentanil ou insulina regular. Há de se estabelecer certa vigilância no sentido de se evitar interações desnecessárias ou quando a administração conjunta de determi-*

How to cite this article:
Cortes ALB, Silvino ZR, Santos FBM, Pereira JAC, Tavares GS. Drug interactions prevalence involving high-surveillance drugs: a cross-sectional study. REME – Rev Min Enferm. 2019[cited ____ ___ ___];23:e-1226. Available from: _____ DOI: 10.5935/1415-2762.20190074

nados interagentes for indispensável, Deve-se possuir competências para manejar essa administração de forma mais adequada e com o menor risco possível para o paciente.

Palavras-chave: *Segurança do Paciente; Gestão da Segurança; Interações de Medicamentos.*

RESUMEN

Objetivo: *estimar la prevalencia de posibles interacciones farmacológicas (IMP) relacionadas con los medicamentos controlados (MAV) utilizados por una muestra de pacientes ingresados en una unidad de cuidados intensivos (UCI).* ***Métodos:*** *estudio retrospectivo transversal de enfoque cuantitativo. La investigación se basó en el análisis de las prescripciones de los pacientes ingresados en la UCI por un período de un año (2014-2015) para identificar posibles interacciones farmacológicas relacionadas con los MAV recurrentes. Para cada registro médico, se analizaron las primeras tres a cinco recetas, según su disponibilidad y el período de hospitalización del individuo. La identificación de las IMP se realizó consultando el dispositivo Trissels de la base de datos Micromedex 2.0.* ***Resultados:*** *en las 244 recetas de medicamentos, se identificaron 846 IMP relacionadas con MAV y 112 pares diferentes de IMP que involucran MAV. Los principales MAV en las IMP fueron: insulina regular, midazolam, fentanilo y tramadol. De los 112 pares de IMP identificadas, algunas fueron recurrentes; a saber: tramadol y ondansetrón, fentanilo y midazolam, midazolam y omeprazol, insulina regular e hidrocortisona, así como insulina regular y noradrenalina. La prevalencia de las IMP con MAV en esta muestra fue de 0,96 (96%).* ***Conclusión:*** *la mayoría de los pacientes estuvo expuesta a IMP que involucran midazolam, fentanilo o insulina regular. Se debe establecer cierta vigilancia para evitar interacciones innecesarias o cuando la administración conjunta de ciertos interagentes sea indispensable. Debe haber competencia suficiente para manejar la administración de drogas de manera más apropiada, con el menor riesgo posible para el paciente.*

Palabras clave: *Seguridad del Paciente; Administración de la Seguridad; Interacciones de Drogas.*

INTRODUCTION

Drug therapy relevance in the patients' clinical condition is widely recognized. However, there is a related problem that occurs frequently and causes to increase patient morbidity and mortality; adverse drug events (ADE), which constitute a new public health problem.[1]

Avoidable events that may compromise the quality of health care include drug interactions (DI). These are important patient safety events and may be due to errors that did not reach the patient or damage events.[2]

Medication errors (MEs) are defined as any preventable event that may cause or lead to inappropriate use of a medication or harm to the patient while the medication is under the control of healthcare professional, patient or consumer.[3] Drug adverse events (DAEs) are defined as any drug damage caused by their use or lack of use.[4]

Therefore, it is understood that MEs may or may not evoke ADE, depending on the existence of the damage arising from the drug. It is also important to recognize the so-called potential adverse events that occur when there is an error, but no harm to the patient. This type of event does not bring problems to the patient, but its identification is important in the therapy risk assessment.[2,5]

Although often unidentified, the interactions are vertiginously present, especially in the hospital reality. In a multicenter study conducted in 2013 in Brazil, it was observed that in the first 24 hours of hospitalization in intensive care units, 70.6% of patients had at least one drug interaction. Drug interactions total number during the survey period was 2,299, with 350 types of drug-drug interactions.[6]

In the drug interactions sphere, drugs were established over which there should be more control. High vigilance (HSD) or potentially hazardous drugs (PHD) are those that have a high risk of causing significant harm when used wrongly. Due to measurement errors involving PHD damage severity, strategies to minimize these errors are recommended.[7]

Understanding the importance of these classes in safe drug therapy, it is recognized the need to satisfactorily manage the care developed with these drugs.

Objective: To estimate the prevalence of potential drug interactions related to high-surveillance medications used by patients in an intensive care center.

METHODOLOGY

A cross-sectional, retrospective study with a quantitative approach. Held in a university hospital (UH) with drug prescriptions for patients admitted to the intensive care center (ICU).

Research was based on the analysis of all prescriptions of patients admitted to the ICU within one year (2014-2015), in order to identify potential drug interactions related to HSDs in them. Based on a specific script, the 24-hour drug prescriptions were analyzed, collecting some information regarding patients and drug prescriptions for discussion, namely: drug names, dosage, way of administration and specific care, if any. In addition, patients' gender and age, main diagnosis, comorbidities, date of ICU stay, date of discharge, death or transfer.

As inclusion criteria, we analyzed the medical records that had at least three prescriptions related to the first days of hospitalization, where the necessary information for the collection was available. Daily drug prescriptions should have at least one HSD and be differentiated from each other.

As exclusion criteria, it was not used the prescriptions that were not properly dated, signed and readable.

All medical records related to the collection period were requested from the institution's medical file. Sixty documents were selected according to the inclusion criteria, as well as their availability in the medical archive, as 88 medical records were unavailable for analysis because they were digitized (not in the medical archive) in use at the hospital or outside the institution. Sixty-six were excluded because they did not have at least three different prescriptions; have illegible prescriptions; have no prescriptions for the first week of ICU admission; or a minimum of HSD prescriptions. Of the 60 charts selected, 244 drug prescriptions were verified.

Before the final data collection, a pilot test was conducted with a data collection script. However, as there was no change required and the number of medical records available was small, it was decided to use the data in the research. For each medical record, they were analyzed from the first three to five prescriptions, depending on their availability and the period of individual hospitalization. This period related to the first days of hospitalization was chosen due to the concentration of changes in the prescription during this period.

After selection, the prescriptions were transcribed and the potential drug interactions pairs were raised.

Definition of potential drug interactions and drug pair selection

Interactions identification, as well as their severity, scientific evidence, likely mechanism, PDI results, and actions for clinical management were performed by consulting the Trissel's device from the Micromedex 2.0 database.

Data processing

Variables were analyzed based on position statistics (mean, median, minimum and maximum) and scale (standard deviation and interquartile ranges). Medication use prevalence was expressed by absolute and relative frequencies. A 95% confidence interval was used.

Ethical aspects

It is noteworthy that the present study sought to meet all the determinations present in Resolution 466/12 of the National Health Council (*Conselho Nacional de Saúde*-CNS), being submitted to the Research Ethics Committee responsible for consideration and approval. Research did not require an informed consent, as it was retrospective and used only the drug prescriptions present in the medical records.

Results

Patient profile

As for gender, 25 (41.66%) patients were female, and 35 (58.33%) were male. The mean age of the patients was 58.6 years old.

Most patients (37, 61.66%) had as admission reason pre or postoperative of various surgical procedures, having a period of hospitalization of two to three days, which can be considered reduced. Many patients did not reach five days of hospitalization (Table 1).

Table 1 - Patients exposed to PDI characterization, according to demographic and clinical variables, *Niterói*, RJ, 2015

Characteristics	Total	Without HAM-related PDI	With HAM-related PDI
Gender			
Male	35	1	34
Female	25	1	24
Age in years old			
12 – 18	1	0	1
19 – 59	30	1	29
≥60	29	1	28
Excessive polypharmacy (over 10 medications)			
Yes	54	1	53
No	6	1	5
Comorbidities			
Yes	38	1	37
No	22	1	21
Surgical patient			
Yes	37	1	36
No	23	1	22
Length of hospitalization stay in days			
Up to 10	41	2	39
11-30	15	0	15
>30	4	0	4

Source: personal collection.

Potential drug interactions characterization

Potential drug interactions identified

In the 244 drug prescriptions, 846 HSD-related PDIs and 112 different pairs of PDI involving the HSDs were identified.

33 HSDs were identified in the 244 prescriptions. Of these 33 medicines, 21 participated in at least one PDI, of which two were unrelated to the Micromedex Health Care database (Table 2).

Table 2 - List of high-surveillance medicines identified with their respective interactants, *Niterói*, RJ, 2015

High-surveillance medication	Drug interactions identified
Fentanyl	Clarithromycin, Clonazepam, Nifedipine, Carbamazepine, Phenytoin, Fluconazole, Ranitidine, Haloperidol, Valproic Acid, Chlorpromazine, Azithromycin, Ciprofloxacin Linezolid, Voriconazole, Ritonavir, Atazanavir, Morphine, Tramadol, Midazolam, Propofol, Diazepam, Promethazine
Midazolam IV	Clarithromycin, Omeprazole, Phenytoin, Carbamazepine, Fluconazole, Ranitidine, Voriconazole, Atazanavir, Ritonavir, Propofol
Regular insulin	Hydrocortisone, Furosemide, Methylprednisolone, Losartan, Clonidine, Levofloxacin, Ciprofloxacin, Captopril, Aspirin, Hydrochlorothiazide, Chlorpromazine, Spironolactone, Mometasone, Solucortef, Symbicort, Levothyroxine, Noradrenaline, Clonidine, Noradrenaline, Clonidine, Saxagliptin, Prometazine IV, Dobutamine
Amiodarone	Clarithromycin, Ondansetron, Carbamazepine, Atenolol, Haloperidol, Fluconazole, Ciprofloxacin, Metronidazole, Clonazepam, Levofloxacin, Clopidogrel, Simvastatin, Voriconazole, Ranitidine, Fentanyl, Midazolam, Tramadol
Tramadol	Ondansetron, Metoclopramide, Carbamazepine, Haloperidol, Valproic Acid, Promethazine IV, Morphine, Digoxin
Morphine	Ipratropium, Spironolactone, Carvedilol, Furosemide, Captopril
Adenosine IV	Carbamazepine
Potassium chloride	Losartan, Captopril, Spironolactone
Diazepam IV	Phenytoin, Omeprazole, Propofol
Enoxaparin	Clopidogrel, Ketoprofen, Aspirin
Promethazine IV	Ondansetron, Tramadol, Insulin, Fentanyl
Noradrenaline	Linezolid, Insulin
Succinylcholine	Vancomycin
Digoxin IV	Spironolactone, Carvedilol, Furosemide, Captopril, Omeprazole, Tramadol
Dobutamine IV	Linezolid, Insulin
NPH insulin	Clonidine, Mometasone, Dexamethasone
Metoprolol IV	Clonidine, Ranitidine, Amiodarone
Clonidine IV	Insulin, Metoprolol
Propofol	Fentanyl, Diazepam, Midazolam
Dexmedetomidine	Fentanyl
Saxagliptin	Insulin

Source: personal collection.

The main HSDs in the PDIs were: regular insulin, which participated in 251 potential interactions; midazolam, which participated in 196 PDIs; fentanyl, bound to 171 PDIs; and, finally, tramadol, related to 150 PDIs.

Of the 112 types of PDIs identified, some were recurrent; namely, tramadol and ondansetron, identified 97 times in the prescriptions; fentanyl and midazolam, identified 74 times; midazolam and omeprazole, 67 times; regular insulin and hydrocortisone, which occurred 54 times, as well as regular insulin and norepinephrine, observed 51 times.

It is important to note that of the 60 patients in the database, only two had no case of PDI. Therefore, the prevalence of HSD PDIs in this sample was 0.96 (96%), with a 95% confidence interval.

Potential drug interactions classification

Of the 112 types of PDI, seven (6.25%) were considered contraindicated, 56 (50%) were considered important, 48 (42.8%) moderate and one (0.89%) secondary.

Of the 112 types of PDI, eight (7.14%) had excellent level of evidence, 23 (20.53%) had good scientific evidence and no PDI had unknown evidence. Vast majority (81, 72.32%) of PIMs have reasonable evidence.

DISCUSSION

Of the 60 patients analyzed (244 drug prescriptions), 58 had HSD-related PDIs and 54 reported excessive polypharmacy, which may be related to these PDIs. IMP prevalence was 96%. Polypharmacy is considered dangerous for patients, as it favors the emergence of drug interactions (DI), adverse drug reactions (ADRs), side effects, prolonged hospitalizations, iatrogenic diseases, and may also cause complications leading to death.[8] This practice is still related to care costs, linked to the medicines themselves and the repercussions of the events related to them.

Specifically in intensive care sectors, inpatients are particularly at risk for drug interactions for various reasons, such as impaired absorption, reduced metabolism, renal failure, and polypharmacy, which are common in these settings.[9]

Drug-drug interaction rates were reported to be twice as high for patients in intensive care settings compared to patients in other settings, with 40 to 80% of intensive care patients exposed to at least one PDI during their stay.[9,10]

In addition to polypharmacotherapy, the impact of HSD-related adverse events should be considered. In a recent study, it was identified that 12.1% of the events were related to HSDs, with a predominance of venous anesthetics.[11]

Prevalence of DI impact in the care context becomes more significant when accompanied by information that allows the identification of its clinical significance. Clinical significance is determined by severity, level of evidence and

clinical consequences.[6,12] In this study, 92.8% of the identified PDIs are in the severe or moderate group.

In a Brazilian multicenter study, the most frequent interaction, both at 24 hours and 120 hours, was midazolam + fentanyl, which are considered HSDs.[6]

In the present study, the main HSD-related PDIs during the analyzed period were associated with midazolam, fentanyl, insulin, amiodarone and tramadol.

Although the aforementioned drugs are frequently used by patients admitted to the sector, indicating that this association could be associated with the frequency of use, IV amiodarone was used by only nine of the 60 patients. Potential interactions of clinical significance occur with amiodarone due to its inhibitory activity of CYP4503A4 and glycoprotein P.[6]

Fentanyl and midazolam are widely used in intensive care so much that the current literature also brings the high frequency of DI involving these two drugs. Among the most interacting drugs, midazolam and fentanyl presented 45 (14.5%) of drug interactions identified in an ICU.[13]

A study conducted in intensive care with patients diagnosed with sepsis found that of the 15 most frequent DIs, nine involved midazolam or fentanyl. Harm caused by excessive sedation is known, such as decreased mobility in the bed, leading to increased thromboembolic factors, muscle weakness, and pressure injuries.[14,15]

Although the combination of midazolam with fentanyl is widely used in therapeutic intensive care settings, database classifies it as severe and relates it to adverse events such as hypotension, hypoventilation, and central nervous system (CNS) depression.

To combine the achievement of therapeutic goals with patient safety, a sedation monitoring strategy is important. The nurse is an essential professional in monitoring of sedated patients, assessing their state of consciousness from scales like Ramsay's, observing the need or not of sedation, thus promoting individualized and qualified care.[16] Table 3 lists the main identified PDIs with the relationship of Nursing care that can be implemented to prevent adverse events associated with PDI.

As a medication system safety proposal, specific HSD, there are procedures that can be adopted to prevent MS with these medications, such as making and disseminating a list of HSDs; implementation of guidelines for these inputs management; drug labeling with different colors or warning signs on the packaging; adoption of double checking, restriction of the number of presentations and concentrations in the institutions; removal of concentrated electrolyte solutions from wards and outpatient clinics, as well as measures such as a continuing education program on medications for the professionals involved; management of medication errors with HSD; implementation of a specific ICU patient safety program for drug use.[11]

Table 3 - Potential drug interactions: associated events and clinical management, *Niterói*, RJ, 2015

Potential drug interactions	Associated events	Nursing care
Tramadol and Ondansetron	Tramadol Efficacy Reduction	Monitor patient for signs and symptoms of increased pain (visual analog scale/numeric scale)
Midazolam and Omeprazole	Benzodiazepine toxicity (CNS depression, ataxia, lethargy)	Monitor patient for CNS depression (Glasgow coma scale, Ransey scale); monitor patient for respiratory depression
Insulin and Hydrocortisone	Possible hyperglycemia	Periodically perform hemoglycose test, monitor for signs and symptoms of hyperglycemia
Insulin and Noradrenaline	Impaired glucose regulation	Perform a hemoglobin test periodically
Fentanyl and Midazolam	Increased risk of CNS depression (hypotension, respiratory depression and deep sedation)	Monitor patient for CNS depression Monitor patient for respiratory depression

Source: personal collection.

It is important to highlight that about 80% of the measures that can minimize or even avoid the effects of drug interactions can be performed by the assisting nurse, including: observation of signs and symptoms, monitoring of therapeutic response, adjustment of the time of administration of the drug and avoid the combination.[13]

Therefore, it is believed that these medications in drug prescriptions may pose a potential risk for interactions with ADE for the patient if they are not individually and constantly monitored.

In addition to patient monitoring as a strategy for their safety, ADE reporting systems constitute a foundation for a patient safety program, a quality assurance strategy, recently structured in Latin American countries.[17]

However, in hospital institutions, only severe ADEs are identified and eventually become public domain, as they cause serious harm to the patient. ADEs small-scale are usually not notified due to the lack of processes aimed at their identification, notification and registration or because of the professionals' fear of exposure and punishment.[18]

CONCLUSION

Most patients were exposed to PDI involving midazolam, fentanyl or regular insulin. This fact, although it may be influenced by the widespread use of these agents in the intensive care setting, represents its relevance when dealing

with errors related to the medication system. This is also true when looking at current literature. Errors and ADE related to these medications are frequent in several studies in ICU. Because of its pharmacodynamics, the repercussions may be even more severe, considering the patient admitted to the ICU; usually polymedicated, elderly, presenting comorbidities and with the possibility of inefficiency in the processes of drugs metabolization and excretion. Thus, some vigilance should be established to avoid unnecessary DI or when the joint administration of certain interactants is indispensable and one must have the skills to manage this administration more adequately with the minimum possible risk to the patient.

This research is relevant regarding to patient safety and medication use, as there are few studies focused on drug interactions related to HSDs, especially regarding the intensive care public, whose literature reports being more subject compared to patients in medical clinics due to their complex characteristic. Considering that DIs can configure medication errors if they are preventable, it is indispensable that healthcare staff work with strategies to manage better the medication system. To establish strategies, in turn, studies that characterize DIs are needed. In this sense, this research finds its value.

Limitations of the study

The software used is a tool used to identify potential DIs, which does not mean that they have occurred or culminated in ADE. It should also be considered that the study is retrospective.

It is noted that some drugs – bamifiline, dipyrone, bromopride, 50% glucose, fenoterol, AD elemet, domperidone and deslanoside – were not identified in the Micromedex software therefore, the possible DIs involving them were not considered. This fact may then underestimate the prevalence of PDIs.

References

1. Rommers MK, Teeepe-Twiss IM, Guchelaar HJ. Preventing adverse drug events in hospital practice: an overview. Pharmacoepidemiol Drug Saf. 2007[cited 2015 Apr 23];16:1129-35. Available from: https: https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.1440
2. Frederico PM. Interações medicamentosas potenciais dos anti-hipertensivos: uso perigoso entre idosos. Rio de Janeiro: Fundação Oswaldo Cruz, Escola Nacional de Saúde Pública; 2012[cited 2015 Apr 23]. Available from: https://www.arca.fiocruz.br/handle/icict/24287
3. National Coordinating Concil for Medication Error Reporting and Prevention. Taxonomy of Medication Errors. 1998-9[cited 2015 Apr 25]. Available from: http://www.nccmerp.org/about-medication-errors
4. American Society of Healthy System Pharmacists. Suggested definitions and relationships among medication misadventures, medication errors, adverse drug events and adverse drug reactions.1998[cited 2015 Apr 23]. Available from: htpp://www.ashp.org/public/proad/mederror
5. Institute of Medicine of the National Academies. National safety patient agency. U.S. Department of Health and Human Services. Preventing Medication Errors: Quality Chasm Series; 2006[cited 2015 Sep 11]. Available from: http://psnet.ahrq.gov/resources/resource/4053/preventing-medication-errors-quality-chasm-series--
6. Carvalho REFL, Reis AMM, Faria LMP, Zago KSA, Cassiani SHB. Prevalência de interações medicamentosas em unidades de terapia intensiva no Brasil. Acta Paul Enferm. 2013[cited 2017 May 09];26(2):150-7. Available from: http://www.scielo.br/pdf/ape/v26n2/v26n2a08.pdf
7. Instituto para Práticas Seguras no Uso de Medicamentos. Medicamentos Potencialmente Perigosos de uso Hospitalar e Ambulatorial. Belo Horizonte: ISMP Brasil; 2015[cited 2016 Jan 08]. Available from: http://www.ismpbrasil.org/site/wpcontent/uploads/ 2015/12/V4N3.pdf
8. Rodrigues MCS, Oliveira C. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. Rev Latino-Am Enferm. 2016[cited 2017 May 09];24:e2789. Available from: http://www.scielo.br/pdf/rlae/v24/0104-1169-rlae-24-02800.pdf
9. Vanham D, Spinewine A, Hantson P, Wittebole X, Wouters D, Sneyers B. Drug-drug interactions in the intensive care unit: Do they really matter? J Crit Care. 2017[cited 2016 Oct 15];38: 97–103. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0883944116305330
10. Uijtendaal EV, Harssel LL, Hugenholtz GW, Kuck EM, Zwart-van RJE, Cremer OL, *et al*. Analysis of Potential Drug Interactions in Medical Intensive Care Unit Patients. Pharmacotherapy. 2014[cited 2016 Oct 15];34(3):213-9. Available from: https://www.onlinelibrary.wiley.com/doi/abs/10.1002/phar.1395
11. Bohomol E. Erros de medicação: estudo descritivo das classes de medicamentos de alta vigilância. Esc Anna Nery Rev Enferm. 2014[cited 2016 Oct 15];18(2):311-6[citado em 2015 abr. 23]. Available from: http://www.scielo.br/pdf/ean/v18n2/1414-8145-ean-18-02-0311.pdf
12. Drug-Reax® System. Greenwood Village (CO): Thomson Reuters; 2008[cited 2015 Apr 25]. Available from: https://www.thomsonhc.com
13. Lima REF, Cassiani SHB. Interações medicamentosas potenciais em pacientes de unidade de terapia intensiva de um hospital universitário. Rev Latino-Am Enferm. 2009[cited 2016 Oct 15];17(2):222-7. Available from: http://www.scielo.br/pdf/rlae/v17n2/pt_13.pdf
14. Caribé RA, Chaves GR, Pocognoni JD, Souza IA. Potenciales interacciones medicamentosas en pacientes con sepsis internados en la unidad de terapia intensiva. Farm Hosp. 2013[cited 2015 Mar 09];37(5):383-7. Available from: http://www.scielo.isciii.es/pdf/fh/v37n5/07original05.pdf
15. Godoy LM, Pino PA, Córdova GL, Carrasco JAO, Castillo AM. Sedación y analgesia para procedimientos invasivos en los niños. Arch Argent Pediatr. 2013[cited 2015 Jan 09];111(1):22-8. Available from: http://www.scielo.org.ar/pdf/aap/v111n1/es_v111n1a06.pdf
16. Oliveira FA, Cruz ICF. A sedação e seus efeitos na segurança do paciente: revisão sistematizada da literatura para um protocolo clínico. J Speci Nurs Care. 2016 jun.[cited 2016 Oct 15];8(1). Available from: http://www.jsncare.uff.br/index.php/jsncare/rt/printerFriendly/2805/681
17. Organización Panamericana de la Salud (OPAS). Sistemas de notificación de incidentes en América Latina. Washington: OPS; 2013[cited 2015 May 20]. Available from: https://www.paho.org/hq/dmdocuments/2013/HSS-HS-SistemasIncidentes-2013.pdf
18. Silva LD, Santos MM. Interações medicamentosas em unidade de terapia intensiva: uma revisão que fundamenta o cuidado do enfermeiro. Rev Enferm UERJ. Rio de Janeiro, 2011[cited 2015 Mar 09];19(1):134-9. Available from: http://www.facenf.uerj.br/v19n1/v19n1a22.pdf