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Article

Prevalence of potential drug-drug interactions in the intensive care unit of a Brazilian teaching hospital

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Patients in intensive care unit are prescribed large numbers of drugs, highlighting the need to study potential Drug-Drug Interactions in this environment. The aim of this study was to delineate the prevalence and risk of potential drug-drug interactions between medications administered to patients in an ICU. This cross-sectional observational study was conducted during 12 months, in an adult ICU of a teaching hospital. Inclusion criteria were: prescriptions with 2 or more drugs of patients admitted to the ICU for > 24 hours and age of ≥18 years. Potential Drug-Drug Interactions were quantified and classified through Micromedex™ database. The 369 prescriptions included in this study had 205 different drugs, with an average of 13.04 ± 4.26 (mean ± standard deviation) drugs per prescription. Potential Drug-Drug Interactions were identified in 89% of these, with an average of 5.00 ± 5.06 interactions per prescription. Of the 405 different pairs of potentially interacting drugs identified, moderate and major interactions were present in 74% and 67% of prescriptions, respectively. The most prevalent interaction was between dipyrone and enoxaparin (35.8%), though its clinical occurrence was not observed in this study. The number of potential Drug-Drug Interactions showed significant positive correlations with the length of stay in the intensive care unit, and with the number of prescribed drugs. Acknowledging the high potential for Drug-Drug Interactions in the ICU represents an important step toward improving patient safety and best therapy results.

Uniterms: Potential drug-drug interactions. Intensive care unit. Patient safety. University hospitals.

INTRODUCTION

A Drug-Drug Interaction is a pharmacological or clinical response to the administration of two or more drugs, which is different from the response triggered by the individual use of these agents (Tatro, 2012). Knowledge of the main characteristics of these interactions and access to databases with detailed information on them, including the mechanisms involved and their potential severity, can prevent the resulting adverse events and/or assist in their clinical management (Papadopoulos, Smithburger, 2010; Magro, Moretti, Leone, 2012; Dubova *et al.*, 2007).

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When the interactions present in the prescription are theoretically evaluated through databases and not by their actual occurrence, they are considered potential (Brunton *et al.*, 2011).

In clinical practice, potential Drug-Drug Interactions (pDDIs) can lead to serious problems, such as severe adverse events and ineffective drug therapy (Mannheimer, Eliasson, 2010; Reimche, Forster, Van Walraven, 2011). Patients in the intensive care unit (ICU) routinely receive large numbers of drugs with pDDIs, highlighting the need to study these interactions in this environment (Papadopoulos, Smithburger, 2010; Reimche, Forster, Van Walraven, 2011; Kopp *et al.*, 2006). Reducing unnecessary risks to the patient is improving patient safety. As the risks profiles are established, reduction of risks and avoidable adverse events can also improve patient safety.

(Benkirane *et al.*, 2009; Cullen *et al.*, 1997; Kopp *et al.*, 2006; Mcdowell, Ferner, Ferner, 2009).

PDDIs often are between drugs that are metabolized by the same cytochrome P450 (CYP450) enzymes, and/or due to the administration of drugs that inhibit or induce these enzymes systems (Spriet *et al.*, 2009; Klein, Gueorguieva, Aarons, 2012; Mouly, Meune, Bergmann, 2009). Drugs metabolized by this route include midazolam, tacrolimus, cyclosporine, and phenytoin, all of which are widely used in the ICU. CYP450 inducers and inhibitors include drugs such as amiodarone, fluconazole, and carbamazepine, which are often used in the ICU (Papadopoulos, Smithburger, 2010; Mannheimer, Eliasson, 2010).

The large number of pDDIs between drugs prescribed to ICU patients has been documented by several studies (Smithburger, Kane-Gill, Seybert, 2012; Smithburger *et al.*, 2010; Rivkin, Yin, 2011; Kane-Gill *et al.*, 2012). A recent study conducted in the USA showed that 46.3% of ICU prescriptions included pDDIs (Smithburger, Kane-Gill, Seybert, 2012), while Brazilian studies have reported a prevalence of 67% or 70% (Hammes *et al.*, 2008; Moreira, Cassiani, 2011). In addition, there are international differences in drug availability that may contribute to regional variations in the number of pDDIs (Moreira, Cassiani, 2011; Moura, Prado, Acurcio, 2011; Moura *et al.*, 2012).

Preventing adverse events caused by pDDIs and managing these interactions are central to the Clinical Pharmacy practice in an ICU (Rudis, Brandl, 2000). This justifies the elevated number of publications in this matter (Rivkin, Yin, 2011; Kane, Weber, Dasta, 2003; Moura *et al.*, 2012; Papadopoulos, Smithburger, 2010; Mannheimer, Eliasson, 2010.; Moreira, Cassiani, 2011).

The aim of this study was to evaluate the prevalence of pDDIs in prescriptions in the ICU of a university hospital in the Brazilian public health system. Were quantified and classified the pDDIs per their degree of severity, to analyse the risks to patient management. Both pharmacokinetic and pharmacodynamic interactions were evaluated, as all PDDIs were included.

METHODS

This cross-sectional observational study was conducted for 12 months (from August 2014 to September 2015) in the adult ICU of Clinics Hospital of the State University of Campinas (HC-UNICAMP) that has 403 beds. Inclusion criteria were: prescriptions with 2 or more drugs of patients admitted to the ICU for > 24 hours and age of ≥ 18 years, one random prescription per patient. Patients that were admitted and discharged to the ICU on weekends did not have their prescriptions included in the study. Data was retrieved from patients' prescriptions and the hospital's database. This research received approval from the Ethics Committee of the School of Medical Sciences, University of Campinas (Campinas, São Paulo, Brazil); protocol number CAAE: 0882.0.146.000-10.

The search for pDDIs within the prescriptions was performed using the Micromedex™ database (MICROMEDEX, 2011), where pDDIs are classified as follows: contraindicated (the drugs are contraindicated for concurrent use); major (the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects); moderate (the interaction may result in exacerbation of the patient's condition and/or require an alternative therapy); or minor (the interaction would have limited clinical effects; manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major change in therapy) In addition, it was possible to correlate the presence of pDDIs with other parameters including length of stay, death in the ICU, the number of prescribed drugs, patient age, and gender. This analysis was conducted by critically analysing pDDI data with a database of ICU patient clinical records that was updated daily. The purpose of this database is to continuously monitor the safety and quality of the ICU and it provides a very useful research tool. The database was organized by admission number, assuring patient confidentiality. Only professionals and researchers directly involved had access to the records database.

All the analysed medication information was transposed to a Microsoft Excel™ spreadsheet and interaction information was constantly updated during the study, through frequent consultations of the Micromedex™ database (MICROMEDEX, 2011).

After analysis, these drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system that is recommended by the WHO for drug utilization studies (WHO Collaborating Centre for Drug Statistics Methodology, 2012). This study determined the frequency of usage of prescribed drugs that were monitored by the FAST HUG strategy. FAST HUG is a mnemonic used to facilitate the continuous monitoring of patients in relation to: Feeding; Analgesia; Sedation; Thromboembolic prophylaxis; Head-of-bed elevation; stress Ulcer prophylaxis; and Glycaemic control. These parameters should be monitored daily and relate to factors involving drug therapy, as well as non-pharmacological actions (Vincent, 2005).

To determine a statistically significant sample size, a

pilot study with 88 prescriptions was conducted for three months. Descriptive statistics were used to describe the sample profile. To analyse correlations between variables, the Spearman correlation coefficient (r_s) was used. The significance level for statistical tests was 5%, or $p < 0.05$. The Statistical Analysis System (SAS) for Windows, version 9.2 (SAS Institute Inc., 2002-2008, Cary, NC, USA), was used for statistical analyses.

RESULTS

During the study period, the prescriptions of 369 patients were analysed over one 24-h period, one prescription per patient. The study group (205 men and 164 women) represented approximately 37% of the population admitted into the ICU during this period. The study group was heterogeneous, comprising both surgical and clinical patients. Since this study was performed at a general ICU, the reasons for patient hospitalization were very diverse, including elective surgeries that demanded postoperative intensive care, grave clinical conditions that required life support, such as stroke, among others. During the assessed period, 205 different drugs were prescribed. Table I describes the clinical characteristics and demographics of the patients.

TABLE I - Patient clinical and demographic characteristics

Characteristics	Values
Number of patients	369
Age in years [median ± standard deviation]	57.0 ± 14.6
Gender [male n (%)]	205 (55.5)
Number of drugs per prescription [median ± standard deviation]	13.0 ± 4.3
Length of stay in the ICU in days [median ± standard deviation]	13.3 ± 16.5
Clinical Specialties [n (%)]	
Neurology	117 (31.7)
Cardiology	98 (26.5)
Gastroenterology	73 (19.8)
Vascular surgery	39 (10.6)
Others	42 (10.8)
Reasons for ICU admission [n (%)]	
Post-surgery	254 (68.8)
Septic shock	18(4.8)
Sepsis	10 (2.7)
Others	87 (23.6)

Many of the most commonly prescribed drugs were associated with standard protocols in ICU medicine, as illustrated in Table II. This Table shows the percentage of patients prescribed each of the indicated drugs and highlights their relation to FAST HUG protocols. Table II also shows the frequency of pDDIs present in prescriptions involving these drugs.

During the study, 1844 pDDIs were identified, quantified, and classified; these included 405 different pDDIs between the prescribed drugs.

At least one pDDI was identified in 89% of the patient prescriptions included in this study, and those classified as moderate and major were present in 74% and 67% of the prescriptions, respectively. A wide variety of pDDIs types were identified. A total of 405 interactions were found: 12 contraindicated; 130 major; 225 moderate; and 38 minor. For 52 of these interactions, the management recommendations state that their concomitant use should be avoided and suggest the suspension of one drug, while monitoring is recommended for 306 of the pDDIs. Dipyrone was involved in the largest number of pDDIs. This analgesic and antipyretic drug is widely used in Brazil but has a restricted use in several countries and is not available in the USA. Table III provides information on the 10 most common pDDIs and their frequencies in the analysed prescriptions. The 12 contraindicated pDDIs observed have extremely careful management recommendations to either suspend use of one of the medications or when keeping both drugs, cautiously watch for adverse event signs.

The results were subjected to statistical analysis to evaluate the correlations between the number of pDDIs and the number of prescribed drugs, the length of stay in ICU (days), and patient age. There was a statistically significant correlation showing that the higher the total of pDDIs in a prescription, the longer the ICU stay ($p = 0.0027$), and major pDDIs were related to longer ICU stay ($p < 0001$). Also, there were more pDDIs in prescriptions with more drugs ($p < 0001$). The other variables analysed did not show statistically significant correlations.

DISCUSSION

With 89% of the analysed prescriptions including at least one pDDI, the need for their evaluation and monitoring is evident. Other studies, with different designs and sample sizes, have confirmed this alarmingly high number, which included all classes of pDDIs (from contraindicated to minor) (Papadopoulos, Smithburger, 2010; Reimche, Forster, Van Walraven, 2011; Kane-Gill *et al*., 2012; Arques-Armoiry *et al.*, 2010; Rodrigues *et al.*, 2015). The relationship between the number of prescribed drugs and the number of pDDIs has been reported

TABLE II - Prescribed drugs related to FAST HUG and their potential Drug-Drug Interactions (pDDIs)

FAST HUG	Drug	ATC class	Prescription frequency [n(%)]	pDDI frequency in prescription [n(%)]
(A) Analgesia	Dipyrone	Analgesic N02A	342(92.7)	239(64.8)
	Morphine	Analgesic N02B	172(46.6)	68(18.4)
	Fentanyl		52(14.1)	80(21.7)
	Tramadol		51(13.8)	7(1.9)
	Acetaminophen	Analgesic N02A	29(7.8)	5(1.3)
	Acetaminophen/Codeine	Analgesic N02B	9(2.4)	2(0.5)
	Meperidine		3(0.8)	14(3.8)
	Nalbuphine		2(0.5)	1(0.3)
(S) Sedation	Midazolam	Psycholeptic N05C	62(16.8)	95(25.7)
	Diazepam	Psycholeptic N05B	29(7.8)	24(6.5)
	Haloperidol	Antipsychotic N05A	17(4.6)	26(7.0)
	Chlorpromazine		7(1.9)	32(8.7)
(T) Thromboembolic prophylaxis	Enoxaparin	Antithrombotic agent B01A	151(40.9)	166(45.0)
	Heparin		35(9.5)	7(1.9)
(U) Stress Ulcer prophylaxis	Omeprazole	Peptic Ulcer Treatment A02B	148(40.1)	80(21.7)
	Ranitidine		160(43.4)	6(1.6)
(G) Glycemic Control	Insulin Regular Human	Antidiabetic A10A	334(90.5)	59(16.0)
	Insulin, Isophane		14(3.8)	9(2.4)

TABLE III - Most frequent relevant potential Drug-Drug Interactions

Drug interaction	Prescription Frequency [n (%)]	Severity	Potential risk	Recommendation
Enoxaparin + Dipyrone	132 (35.8)	Major	Bleeding	Suspension or monitoring
Insulin + Acetylsalicylic acid	64 (17.3)	Moderate	Hypoglycemia	Monitoring
Enalapril + Acetylsalicylic acid	43 (11.6)	Moderate	Decreased antihypertensive efficacy	Monitoring
Amlodipine + Simvastatin	34 (9.2)	Major	Myopathy and rhabdomyolysis	Monitoring
Miconazole + Warfarin	30 (8.1)	Major	Bleeding	Monitoring
Darunavir + Warfarin	29 (7.8)	Moderate	Alterations of Warfarin levels	Monitoring
Dipyrone + Metoprolol	28 (7.6)	Moderate	Decreased antihypertensive efficacy	Monitoring
Omeprazole + Midazolam	26 (7.0)	Moderate	Increased benzodiazepines toxicity	Monitoring
Amiodarone + Simvastatin	24 (6.5)	Major	Myopathy and rhabdomyolysis	Suspension or monitoring
Insulin + Octreotide	24 (6.5)	Moderate	Hypoglycemia	Monitoring

previously. This correlation illustrates the inherent risk of prescribing a wide range of drugs (Papadopoulos, Smithburger, 2010; Reimche, Forster, Van Walraven, 2011; Kane-Gill *et al.*, 2012).

Moderate pDDIs comprise much of interactions found in this study and are also the most frequently reported by other ICU researches (Smithburger, Kane-Gill, Seybert, 2012; Smithburger *et al.*, 2010; Hammes *et al.*, 2008; Rodrigues *et al.*, 2015). In this study, the interactions classified as contraindicated, major, and moderate by Micromedex™ were clinically relevant. In addition, the real impact of these pDDIs should be determined on an individual basis and this requires careful evaluation of the risk-benefit relationship between the suspension of therapy, or its maintenance with continuous monitoring. This approach is followed by most management guidelines, which always perform a risk-benefit analysis (MICROMEDEX, 2011). Moreover, it is worth remembering that drugs such as dipyrone are often prescribed "if needed" and are not usually administered concomitantly with the potentially interacting drugs.

Clinical relevancy of pDDIs in intensive therapy is not a subject with settled theoretical concepts. Although clinical decision support systems, as Micromedex™, contribute to this discussion, the inherent risk of each pDDI in clinical practice is individually evaluated using the theoretical information along with the specifics of each case. It is not possible to observe complete agreement among classification of severity of pDDI in intensive therapy publishing (Papadopoulos, Smithburger, 2010; Smithburger *et al.*, 2010; Rodrigues *et al.*, 2015).

The prescriptions analysed in this study demonstrated the major therapeutic drug classes are associated with standardized protocols employed in the ICU, highlighting the correlation between the frequency of these prescribed drugs and international guidelines that promote continuous checking of seven clinical parameters that are essential to the safety of critically ill patients, known by the mnemonic, FAST HUG (Vincent, 2005).

The ICU in the present study used international guidelines and FAST HUG, making its therapeutic profile very similar and comparable ICUs in the USA and Europe. However, there are some differences in the specific drugs used in ICUs in Brazil and other countries owing to international differences in drug licensing. An example of this difference is the use of dipyrone, which is widely prescribed in Brazil but is not marketed in the USA or in some European countries. The higher number of pDDIs in Brazil and in developing countries may reflect the more recent development of clinical pharmacy services with a focus on adverse events and their prevention, as compared to countries with well-established services (Dubova *et al.*, 2007; Hammes *et al.*, 2008; Moreira, Cassiani, 2011).

The significant correlation between the number of pDDIs and the length of stay in the ICU observed in this study was consistent with earlier studies (Moreira, Cassiani, 2011). Although this correlation exists, it is not obvious whether the pDDIs caused the increased stay, or vice-versa. It is possible that the number of pDDIs is elevated in patients with prolonged ICU stay because these patients tend to be seriously ill and therefore require a larger number of drugs. Again, greater exposure to adverse events caused by pDDIs may have increased the length of stay. This issue should be investigated in future studies.

Analgesics (dipyrone), antithrombotic (enoxaparin, warfarin), antifungal (miconazole), antidiabetics (insulin), beta blockers (metoprolol), ECA inhibitors (enalapril) drugs are involved in the 10 most occurring pDDI on this study, as were identified by other studies (Askari *et al.*, 2013; Uijtendaal *et al.*, 2014). The pDDI pair dipyrone and enoxaparin was the most prevalent in this study and is usually little noticed by the intensivists. However, it cannot be ignored since it is classified as a major pDDI and has good documentation (MICROMEDEX, 2011). Other pDDIs with acknowledged adverse events, such as antidiabetic agents, have an important clinical relevancy in an intensive care environment (Vanham *et al.*, 2016). Identifying which pDDIs are clinically relevant and manage their alerts to the multidisciplinary team is essential to improve patient safety (Rodrigues *et al.*, 2015).

The present study delineated the most common pDDIs in this ICU. This study had limitations, since it was not possible to randomize the data collection and a convenience sampling approach was used. In addition, the results of this research were based on the Micromedex™ version available during the study period.

The prescription of potentially dangerous drugs is more frequent in the ICU, where there is also a higher number of adverse events than in other hospital departments and reinforces the need for vigilance with respect to pDDIs (Manias *et al.*, 2014; Aljadhey *et al.*, 2013).

CONCLUSION

This study showed that the clear majority of ICU prescriptions had at least one pDDI and the most prevalent ones were classified as moderate. The theoretical risks of these pDDIs are known, but their real impact should be determined on an individual basis evaluating the risk-benefit relationship between the suspension of therapy, or its maintenance with continuous monitoring.

Acknowledging the high potential for Drug-Drug Interactions in the ICU represents an important step toward improving patient safety and best therapy results.

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CONFLICTS OF INTEREST

There are no conflicts of interest declared by any of the authors.

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