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ORIGINAL ARTICLE

Clinical relevancy and risks of potential drug–drug interactions in intensive therapy

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Abstract *Purpose:* Evaluate the potential Drug–Drug Interactions (pDDI) found in prescription orders of adult Intensive Care Unit (ICU) of a Brazilian public health system hospital; quantify and qualify the pDDI regarding their severity and risks to the critical patient, using the database from Micromedex®.

Methods: Prospective study (January–December of 2011) collecting and evaluating 369 prescription orders (convenient sampling), one per patient.

Results: During the study 1844 pDDIs were identified and distributed in 405 pairs (medication A × medication B combination). There was an average of 5.00 ± 5.06 pDDIs per prescription order, the most prevalent being moderate and important interactions, present in 74% and 67% of prescription orders, respectively. In total, there were 9 contraindicated, 129 important and 204 moderate pDDIs. Among them 52 had as management recommendation to "avoid concomitant

Abbreviations: pDDI, Potential Drug–Drug Interaction; ICU, Intensive Care Unit; ATC, Anatomical Therapeutic Chemical; CYP, Cytochrome P

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use'' or ''suspension of medication'', while 306 had as recommendation ''continuous and adequate monitoring''.

Conclusion: The high number of pDDIs found in the study combined with the evaluation of the clinical relevancy of the most frequent pDDIs in the ICU shows that moderate and important interactions are highly incident. As the majority of them demand monitoring and adequate management, being aware of these interactions is major information for the safe and individualized risk management.

1. Introduction

Due to the highly complex environment of ICUs and for the great number of medications that most critical patient need, their prescription orders are more predisposed to have potential Drug–Drug Interactions (pDDIs) (Cullen et al., 1997; Papadopoulos and Smithburger, 2010). The prevention of adverse events caused by potential interactions and their management are activities of the most importance in the practice of clinical pharmacy in Intensive Care Units, being seen as one of the first actions to be developed in the clinical pharmacy services (Chisholm-Burns et al., 2010; Leape et al., 1999).

Drug–drug interaction is defined as a pharmacological or clinical response to the administration of two or more drugs that is different from the response they initiate when individually administered (David and Tatro, 2012). The knowledge of the pharmacological characteristics of the drug interactions assists in their clinical management. The access to databases with detailed information on the pDDIs involved risks, their mechanism of action and management orientation largely collaborate with the prevention of adverse events (Blix et al., 2008; Duan et al., 2011; Papadopoulos and Smithburger, 2010).

Currently there are many evidences about the existence of an important relationship between the adverse events and the presence of drug interactions. A study developed by Plaza et al. (2010) in Chile pointed out in its results that 23% of clinically significant adverse events observed in the studied ICU during the research were related to drug interactions.

It was also demonstrated the need for continuous education actions linked to the presence of interactions and the use of computerized systems for their detection, which can result in satisfactory diminishing of prescription orders with potential interactions (Paterno et al., 2009; Smithburger et al., 2011; Wright et al., 2012).

Here is accentuated the necessary collaboration among the interactions alert systems and their critical evaluation by the intensivist team. The achievement of ideal results concerning the prevention of interactions combines alert systems with the pharmacist's professional evaluation, avoiding the exposure of the clinical team to the ''alert fatigue'', expression that represents the great number of interactions signaled by the systems while not all being clinically relevant. Even though the whole clinical decision is individualized and requires a judicious evaluation on a case by case basis, it is evident the need for the critical evaluation of the clinical relevancy of the prevalent pDDIs in ICU outlining their risk profile and collecting information about their management and frequency in ICU prescription orders (Smithburger et al., 2010a,b, 2011, 2012).

2. Materials and methods

This is an observational, transverse study with a prospective data compilation (January–December of 2011). This research was carried out in a general adult ICU, with 24 beds, of a tertiary university hospital with a total of 403 beds. This is a reference hospital in the area and it belongs to the public health system.

The study group is composed of patients admitted to the studied ICU during the data collection period. This is a general ICU, tending for potentially critical patients or patients with an unbalance of one or more organic systems due to high-complexity surgeries, grave infections and other clinical situations that demand intensive life support. The inclusion criteria were admission in ICU for more than 24 h, be 18 or older and have valid prescription orders with 2 or more drugs.

Every included patient had only one prescription order analyzed, selected among the valid prescription orders on the day of the data collection. The prescription orders were assembled from the central dispensation pharmacy of the institution and were not screened by admission date. The researchs database included prescription orders of different stages of admission in the ICU (day one of admission, day 15, day 45, etc.). The compilation was always done in the mornings, once a week, respecting the maximum limit of 10 prescription orders per day, a number permitting a full analysis by just one professional. Prescription orders were collected only when the researcher was present at the institution, characterizing a sampling by convenience. For ethical and professional reasons, there were made isolated interventions in a verbal form to the medical team when clinically relevant pDDIs were identified (moderate to contraindicated).

Quantification and classification of the pDDIs was done using the database from Micromedex® (Thomson Reuters 2011). The information used for the identification and classification of the pDDIs in this study was those available at Micromedex in 2011, when the data were analyzed. It is important to accentuate that this database is daily updated, indicating that the information used in this study may not be the same available by the current version from Truven 2014. The pDDIs were classified according to the information contained in this database, which regards the interactions whose drugs are contraindicated for concomitant use as ''contraindicated'', the pDDIs that can represent life threat and/or require medical intervention to diminish or avoid serious adverse effects as ''important'', those that can result in aggravation of the patients health problem and/or require a treatment alteration as ''moderate'' and those that could result in limited clinical effects that include increase in frequency or severity of colat-

eral effects that usually do not require an important treatment alteration as "secondary".

In this study, only the interactions classified as moderate, important or contraindicated in the clinical decision support system Micromedex® are considered clinically relevant.

Descriptive statistics was used to delineate the sampling profile. Statistical analysis was performed using the SAS System for Windows (Statistical Analysis System), version 9.2 SAS Institute Inc. 2002–2008, Cary, NC, USA. This project fulfilled all the ethical requirements for research involving human beings, having the approval of the Ethical Committee in Research of the institution.

3. Results

From January to December of 2011 were analyzed prescription orders of 369 patients (1 prescription per patient), mean age of 57.03 ± 14.62, admitted for at least 24 h in the adult Intensive Care Unit of HC – UNICAMP (average of hospitalization in adult ICU = 13.34 ± 16.49 days). The study group (205 men and 164 women) represents approximately 37% of the population admitted in the ICU during this period, which has 24 beds and receives about a thousand patients per year. In the assessed period 205 different types of drugs were prescribed, (13.04 ± 4.26 per prescription order). Table 1 shows the distribution of the drugs observed in this study according to the Anatomical Therapeutic Chemical (ATC) Classification.

During the study there were 1844 pDDIs identified, quantified, classified and distributed in 405 combinations among the prescribed drugs. In the analyzed prescription 89% presented at least one pDDI, the emphasis being on the prevalence of moderate and important interactions, present in 74% and 67% of prescription orders, respectively. Table 2 shows interactions distribution by ATC classification, their total frequency in prescription orders and the frequency of the considered clinically relevant interactions.

It was observed a number of potential interactions classified as contraindicated representing 7% of pDDIs found in the analyzed prescription orders. Metoclopramide is the drug most involved in this severity class of pDDIs, being present in 6 out of 12 listed types. By analyzing the risks associated with the observed pDDIs it was possible to determine the frequency for each physiological system, as presented by Table 3.

The pDDIs present in prescription orders analyzed in this study that are considered clinically relevant have different types of mechanism of action. The most prevalent are the ones with additive pharmacological effects ($n = 69$) that potentially lead to an exacerbation of the therapeutic function or of the undesired adverse effects. The next most frequent are 68 interactions caused by Cytochrome P450 (CYP450) induction or inhibition, which alters the drug metabolism, then the ones that lead to a possible therapeutic efficacy loss or the release of toxic metabolites that totalizes 65 interactions. Creatinine clearance alteration mechanism accounts for 18 interactions, and 17 point to a possible drug absorption reduction. Fifty interactions still do not have their mechanisms enlighted.

Most observed pDDIs (316) have as management orientation the careful monitoring of the patients that need concom-

Table 1 Frequency of prescription per ATC Class.

ATC class	Drugs types (*n* (%))	Prescription frequency (*n* (%))
A – Alimentary tract and metabolism	30 (15.4)	1152 (24.8)
B – Blood and blood forming organs	19 (9.4)	771 (16.6)
C – Cardiovascular system	34 (16.9)	779 (16.7)
D – Dermatologicals	5 (2.5)	14 (0.3)
G – Genitourinary system and sex hormones	1 (0.5)	1 (0.0)
H – Systemic hormonal prep, excluding sex hormones	7 (3.4)	147 (3.2)
J – General antiinfectives for systemic use	39 (19.4)	433 (9.3)
L – Antineoplastic and immunomodulating agents	7 (3.4)	41 (0.9)
M – Musculo-skeletal system	6 (2.9)	20 (0.4)
N – Nervous system	37 (18.4)	1007 (21.7)
R – Respiratory system	11 (5.6)	275 (5.9)
S – Sensory organs	1 (0.5)	3 (0.0)
V – Various	1 (0.5)	3 (0.0)

Table 2 Frequency of total pDDIs and Clinically Relevant pDDIs per ATC Class.

ATC Class	pDDI types (*n* (%))	pDDIs frequency (*n* (%))	Clinically relevant pDDIs (*n* (%))
A – Alimentary tract and metabolism	73 (9.7)	367 (10.4)	361 (10.21)
B – Blood and blood forming organs	90 (11.9)	613 (17.3)	570 (16.1)
C – Cardiovascular system	185 (24.6)	840 (23.8)	705 (19.9)
D – Dermatologicals	6 (0.8)	37 (1.0)	36 (10.0)
H – Systemic hormonal prep, excluding sex hormones	25 (3.3)	87 (2.5)	56 (1.6)
J – General antiinfectives for systemic use	87 (11.6)	321 (9.1)	274 (7.7)
L – Antineoplastic and immunomodulating agents	27 (3.6)	62 (1.7)	62 (1.7)
M – Musculo-skeletal system	23 (3.0)	152 (4.3)	70 (2.0)
N – Nervous system	215 (28.6)	981 (27.8)	831 (23.5)
R – Respiratory system	20 (2.6)	73 (2.1)	34 (0.9)
S – Sensory organs	1 (0.1)	1 (0.0)	1 (0.0)

Table 3 Prevalent Risks among the found pDDIs.

Risks for each system associated to the pDDIs	pDDI types (*n* (%))	pDDI frequency (*n* (%))
Respiratory (respiratory depression or bronchospasm)	17 (5.5)	83 (6.0)
Central nervous system alterations	62 (20.0)	284 (20.6)
Cardiovascular risk (alterations in QT, alterations in pressure control and other)	94 (30.3)	334 (24.3)
Hepatotoxicity	1 (0.3)	1 (0.07)
Renal (nephrototoxicity and/or ARI)	4 (1.3)	16 (1.2)
Coagulation alterations	50 (16.1)	313 (22.7)
Other	82 (26.5)	345 (25.1)

itant use of drugs that present interaction(s) described on their monographies. In addition, possible dose adjustment need was recommended for 31 pDDIs, while 52 had the instruction to ''avoid concomitant use'' or ''suspend the use of one of the two drugs involved''.

4. Discussion

With 89.1% of the prescription orders presenting at least one pDDI, it is evident the need for evaluation and accompaniment of the risks associated with drug therapy. It is important to notice that this number includes all pDDI classes from the contraindicated to the secondary (usually with no clinical relevancy). All four classes are present in the studied pDDIs and the most frequent interactions are those called ''important''. The most recurrent ''important'' pDDI observed was the interaction between dipyrone and enoxaparin. Its clinical management states the suspension of dipyrone or if maintained, that a continuous monitoring of bleeding episodes is carried out (Micromedex®, 2011). Despite this instruction, little is known about the real incidence of this interaction, being necessary the judicious evaluation done in a case by case basis to establish the risk benefit relation between the suspension or maintenance with continuous monitoring of this drug therapy. This example is followed by most management orientations, that always aim for the risk benefit relation concerning the drug therapy and the patient́s health.

One of the findings of this study was the observation of contraindicated interactions, highlighting the presence of metoclopramide in most of them (79.4%). These interactions call attention to the gravity of their possible consequences, such as interactions between metoclopramide and neuroleptic agents, when the risk of the rare syndrome known as Malignant Neuroleptic Syndrome is enlarged. Considering this risk, this class of interactions is to be avoided and symptoms monitored and treatment protocol of possible adverse events if this combination is inevitable must be known (Micromedex®, 2011). These interactions represent an example of maximum severity pDDI. When these are detected in ICU's prescription orders they must be cautiously analyzed to determine the risk benefit relation to the patient.

Even though a great number of drug interactions are classified by the clinical decision support systems as important, many of them do not present clinical relevancy in a closely monitored environment such as an Intensive Care Unit. For instance, this study presented many pDDIs found in prescription orders that have clinical relevancy in the theoretical analysis being classified as Important or Moderate, yet in practice do not offer significant risks to the patients. Among the involved risks of these interactions the adverse events related to respiratory depression are highlighted (23.5%), a kind of risk that has a different approach in intensive therapy, since a great amount of the patients could be under mechanic ventilation and all patients have close cardio and respiratory monitoring. This type of analysis shows that these interactions when looked under a broader perspective represent a smaller risk and clinical relevancy in an ICU than in other wards of the hospital. It is important to remember that other interactions, involving the same drugs requires a more detailed analysis on dose adjustment or pharmacotherapy alteration, such as Fentanyl that is dealkylated by CYP3A4 with high-hepatic-extraction ratios. The pharmacokinetics does not change when administered with inhibitors, but requires a greater dose when patients are in a long-term treatment with inducers (carbamazepine, phenytoin), being clinically relevant (Spriet et al., 2009).

Askari et al. (2013) study, conducted from 2002 to 2009 followed 9644 admissions in a 30-bed ICU and 3892 (11.2%) of these presented pDDIs. When the intensive therapy team analyzed the interactions, only 36 unique pairs of pDDIs were considered relevant out of a total of 85. The difference between the clinical relevancy classifications of the clinical decision support systems and the ones attributed by the ICU multidisciplinary team is demonstrated by the difference in the averages of pDDIs found: our study had an average of (5.0%) pDDIs per prescription order and the previously mentioned study had an average of 1.67 pDDIs per admission (Askari et al., 2013).

In the same manner as our study, Uijtendaal et al., 2014 retrospective study in a 32-bed ICU with 1659 patients and 35,784 prescription orders, indicated a high number of pDDIs that require only continuous monitoring as clinical management action (81%). The prospective study of Hasan et al. (2012), that assessed pDDIs incidence in a 13-bed ICU in Malaysia, evaluated the adverse events together with monitoring of laboratory test, physical and mental examinations of the patients with DDIs. It was also equally pointed out a great number of pDDIs (402, average of 6.5 per patient) however; few of them were clinically relevant (64, 15.9%). In this study the prevalence of moderate DDIs (68.9%) corresponds with the number found in our study (74.0%) (Hasan et al., 2012).

In the 2010 and 2012 studies completed by Smithburger et al. it is possible to observe the difference between the clinical relevancy pDDIs classification attributed by intensivist doctors and pharmacists and the severity classification applied by the databases. It is evident in the literature as well as in this research that the high number of moderate, important and contraindicated pDDIs found in prescription orders does not necessarily correspond to the clinical relevancy of these interactions in intensive therapy (Smithburger et al., 2010a,b,

2012). Studies like these testify to the need of correlation of the interactions present in the prescription orders, the laboratory tests and the patient's clinical parameters.

The information about the pDDIs helps in their critical analysis avoiding that an excess of non-relevant alerts reach the multidisciplinary team. The analysis and screening of these pDDIs by the intensivist pharmacists make their discussion with the prescribers more objective and effective, what prevents the alert fatigue of the team.

5. Conclusions

Therefore it is possible to conclude that it is extremely important to analyze the more frequent pDDIs in ICU, expanding the information about them which contributes to the appropriate management of the pharmacotherapy used in intensive therapy. Acknowledging that the elevated number of pDDIs would probably be significantly reduced when clinically analyzing them in an intensive environment evidences the need to confront the theoretical information from databases and the literature to the knowledge of the multidisciplinary team and the patient's parameters. The ultimate goal of gathering more information about the incidence of adverse events caused by DDIs and the judicious analysis of these interactions when present in ICU prescription orders, is the safety of the patient and the optimization of their pharmacotherapy.

Disclosure

There is no conflict of interest in this study.

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