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Pharmaceutical intervention assessment in the identification and management of drug interactions in an intensive care unit

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ABSTRACT

It is estimated there are thousands of combinations of drugs, which may generate various adverse drug events, including drug interactions (DI). To assess the contribution of pharmacist to identification and management of DI in an intensive care unit (ICU). A longitudinal study was conducted in the ICU of a private hospital in the city of Aracaju-SE, between 2008 and 2009. The prevalence and clinical relevance of DI was assessed by two clinical pharmacists. Demographic data and clinical information of patients hospitalized in the period of the study were obtained from medical records. At the end of the study 137 medical records were analyzed, with a predominance of female patients (55.4%), average age of 66 (±7.0) years. 6,085 prescriptions were collected during the study period, in which 2,455 drugs prescribed. Of these, 175 prescriptions contained clinically relevant DI, 178 of moderate severity and 35 of major severity, 213 DI in total. The clinical pharmacists prepared reports for the physicians, which enabled the reduction of 40% of all DI. Data from this study suggest that pharmacist's contribution may have reduced the incidence of DI, providing more familiarity of physicians on clinically relevant information and improving the quality of prescriptions in the ICU.

INTRODUCTION

In the last century, adverse events associated with the use of medicines became a major public health problem involving patients and health professionals (Almeida *et al.*, 2007). Among the adverse events, 30% are drug interactions (DI) (Grizzle *et al.*, 2007), which account for approximately 3% of hospital admissions in the United States (Mcdonnell, Jacobs, 2002; Peyriere, 2003). In the same country, the study of Aparasus et al. (2007) showed that over 11% of patients experience symptoms associated with DI, which led to increase of health care costs. According to Lapi et al. (2010), it is estimated that there are more than 100,000 combinations of drugs, which may be responsible for several adverse drug events. Hammes et al. (2008) defined DI as a specific type of adverse event that occurs when the effects of a drug are altered by the presence of another. Although their results can be both positive and negative, DI are often unpredictable and undesirable in pharmacotherapy. Despite advances in technology and information provided by health authorities to prevent clinically significant DI, hundreds of millions of these events occur annually, affecting millions of patients (Almeida *et al.*, 2007). As for the prevalence of DI, their occurrence within the hospital is highlighted, since patients are generally under multiple drug therapy (Becker *et al.*, 2006). In the hospital, the Intensive Care Unit (ICU) provides factors that create a favorable situation for DI occurrence (Reis, Cassiani, 2011; Rossignoli *et al.*, 2006). Among these factors, it is possible to highlight the use of medicines with narrow therapeutic index, the presence of patients with organ failure, especially kidneys and liver. Furthermore, at ICU there is a high frequency of elderly patients with pharmacokinetic and pharmacodynamics alterations common to the age (Lima, Cassiani, 2009). The study of DI becomes an important tool to optimize the therapeutic regimen, which may contribute to the safety, effectiveness and quality of pharmacotherapy in the ICU (Reis, Cassiani, 2011; Rossignoli *et al.*, 2006). Thus, it is essential that health professionals, such as pharmacists, are able to clinically assess possible DI, collaborating with the health staff and developing strategies for the management

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of patients (Abarca *et al.,* 2004; Saverno *et al.,* 2009). Thus, this study aimed to assess the pharmacist's contribution to identification and management of DI in ICU of a private hospital.

METHODOS

A longitudinal study was conducted from May 2008 to December 2009. All prescriptions from the ICU of a private hospital in the city of Aracaju (Brazil) were assessed. The hospital studied serves about 9,500 patients/year, representing 0.5% of the total population of the State. The ICU has 20 beds with 127 employees, including 36 doctors and 12 nurses. This unit receives patients who require intensive care, such as postoperative and those with chronic degenerative diseases that frequently use a large variety of medicines for a long period of time.

Data Collection

Demographic data of each patient (name, age, gender) were collected from medical records (nursing evolution and medical assessment). The identities of patients and prescribers have been kept confidential. This study was approved by the Ethics Committee for Research of Universidade Federal de Sergipe.

Prescribing patterns

Total number of medicines were analyzed, as well as those most widely used and the presence of polypharmacy. Polypharmacy was defined as multiple use of five or more medications (Flores, Mengue, 2005; Linjakumpu *et al.,* 2002). In order to identify substances and dosages from trade names, Guanabara Therapeutic Dictionary was used (Korolkovas, Ferrira, 2007). The active principles present in each pharmaceutical specialty were listed and classified according the *Anatomical-Therapeutical-Chemical Classification System* (ATC) (World Health Organization, WHO).

Drug Interactions identification and management

Data collected were assessed according to the combinations of drugs observed within 24 hours. Topical medicines, eye medicines, herbal medicines, oxygen inhalation, parenteral nutrition, enteral nutrition and enemas were excluded.

In this study, DI were assessed by four sources of reference information: Stockley (2007), Medscape® (2010), Epocrates® (2010) and Micromedex® (2010) databases. These bases were selected due to data availability on the DI quality of information (excellent, good, fair and poor) and severity of the interaction (severe, moderate and light). All these variables were used to the calculation of the DI classification system.

DI were identified in two steps. First, two pharmacists (TNGA and CCS) ranked DI regarding their level of importance, according to the method described by Tatro (2009). According to the information contained in databases about the severity and quality of documentation found, a numerical value was assigned. In this study, potentially significant DI were those with clinical value ranging from 1 to 3, highly significant DI were those with clinical value ranging 1 or 2, corresponding to severe or moderate intensity and established or probable evidence. In the second step, all patients with DI identified and ranked as clinically relevant, in at least three databases, were assessed by the pharmacist to identify signs and symptoms due to DI. Hence, patient records and laboratory tests were reviewed in order to gather the information required to perform the interventions. Regarding pharmacist DI management, when a clinically relevant DI was confirmed, a written warning was generated in the form of a report, intended for the prescribing physician or the nursing staff. The reports were interventions developed by the clinical pharmacists, describing the effect, mechanism and severity of DI, as well as reference to a previous clinical case described in the literature, proposing a conduct based on evidence. For the assessment of interventions effect, all patients were monitored regarding the adverse reactions from DI, observing if the recommendations provided in the reports were accepted, until discharge from the hospitalization unit. If necessary, the physician or the ICU nursing coordination was contacted to inform the need for more specific care for that patient. Statistical analysis was performed using the software Statistical Package for Social Sciences™ (SPSS) version 15.0 for Windows. Descriptive statistics were used to prescribing patterns and demographic variables. The chi-square test was used for associations between demographic variables and the presence of DI. The confidence interval of 95% was used to measure the strength of association between variables and a p-value < 0.05 was considered significant.

RESULTS

In the study 6,085 prescriptions of 213 patients were analyzed, of which 175 (2.9%) had at least one clinically relevant DI. In this analysis there was a predominance of female patients (n=113, 55.4%), although, there was no statistically significant association between DI and the frequency of women ($\chi^2 = 61.01$, $p>0.1$). In the study group, the average age was 66 (±7.0) (Table 1) and association was found between the number of DI and age increase ($\chi^2= 532.55$, $p<0.05$). Although there has been less simple frequency of prescriptions with polypharmacy from 2008 to 2009, the percentage of these prescriptions with multiple medications has remained high. However, there was a decrease in the number of DI from 2008 (133) to 2009 (80), around 40%. Moreover, significant association was found ($\chi^2= 209.36$, $p<0.005$) between the number of medications and the degree of severity between the observed DI. Finally, an increase of 19% of interventions accepted by physicians from 2008 to 2009 was observed, with a significant association ($\chi^2 = 7.64$, $p<0.005$) between interactions identified and resolved by the clinical pharmacist. The major clinical managements were identified: monitoring of signs and symptoms of DI (92, 43.2%), monitoring of therapeutic response (86, 40.3%), adjusting the time of administration (08; 3.7%), avoiding the combination of medications (22; 10.3%) and replacing it with other medications (05; 2.3%).

Table 1: Distribution of study population according to socio-demographic and pharmacotherapeutic aspects in the ICU of a private hospital (Aracaju-SE), from May 2008 to December 2009.

Demographic characterization	**f (%)**	
	2008	**2009**
Gender		
Female	73 (55.4)	45 (56.3)
Male	60 (44.6)	35 (43.7)
Age		
≥60	83 (62.4)	54 (67.5)
≥60	50 (37.6)	26 (32.5)
Number of Prescriptions		
Assessed prescriptions	2,379 (100)	3,706 (100)
Prescriptions with interaction	106 (4.5)	69 (1.9)
Number of medicines per prescription		
1-4	1 (0.9)	0 (0.0)
5-8	11 (10.4)	3 (4.3)
9-12	23 (21.7)	18 (26.1)
13-16	39 (36.8)	28 (40.6)
17-20	29 (27.4)	18 (26.1)
21-24	3 (2.8)	2 (3.0)
Number of interactions		
Total	133 (100)	80 (100)
Mechanism of interactions		
Pharmacokinetic	64 (48.1)	38 (47.5)
Pharmacodynamic	66 (49.6)	37 (46.3)
Unknown	3 (2.3)	5 (6.3)
Severity of interactions		
Moderate	112 (84.2)	66 (82.5)
Major	21 (15.8)	14 (17.5)
Number of interventions		
Accepted	71 (53.4)	58 (72.5)
Not accepted	62 (46.6)	22 (27.5)

Table 2: Distribution of medicines used by the studied population, according to the ATC classification, at the ICU of a private hospital (Aracaju-SE), from May 2008 to December 2009.

Major classes and subgroups	**ATC Code**	**f (%)**		
		2008	**2009**	**Total**
Alimentary tract and metabolism	**A**	**320 (21.8%)**	**250 (25.4%)**	**570 (23,22%)**
Antacids/Antiulcer drugs/Antiflatulents	A02	103	68	171
Antispasmodic, Anticholinergic and Propulsive Agents	A03	92	77	169
Drugs used in Diabetes	A10	76	66	142
Vitamins	A11	22	14	36
Nervous system	**N**	**275 (18.7%)**	**211 (21.4%)**	**486 (19.80%)**
Anesthetics	N01	52	24	76
Analgesics	N02	86	96	182
Antiepileptics	N03	47	33	80
Psycholeptics	N05	81	47	128
Cardiovascular system	**C**	**262 (17.8%)**	**182 (18.5%)**	**444 (18.09%)**
Cardiac drugs	C01	83	58	141
Diuretics	C03	88	48	136
Inhibitors of the Renin-angiotensin System	C09	36	41	77
Hypolipidemic agents	C10	21	11	32
Respiratory system	**R**	**205 (14%)**	**108 (10.9%)**	**313 (12.75%)**
Nasal preparations	R01	79	47	126
Anti-asthmatics	R03	120	51	171
General anti-infectives for systemic use	**J**	**169 (11.5%)**	**119 (12 %)**	**288 (11.72%)**
Antibacterials for systemic use	J01	150	103	253
Antimycotics for systemic use	J02	19	15	34
Blood and blood forming organs	**B**	**140 (9.5%)**	**53 (5.4%)**	**193 (7.85%)**
Antithrombotic agents	B01	94	37	131
Blood substitutes and perfusion solution	B05	41	16	57
Systemic hormonal preparations, excluding sex hormones and insulins	**H**	**76 (5.2%)**	**54 (5.5%)**	**130 (5.30%)**
Musculoskeletal system	**M**	**8 (0.6%)**	**5 (0.5%)**	**13 (0.53%)**
Dermatologic agents	**D**	**8 (0.6%)**	**-**	**8 (0.83%)**
Genitourinary system and sex hormones	**G**	**2 (0.1%)**	**3 (0.3%)**	**5 (0.21%)**
Antineoplastics and agents Immunomodulators	**L**	**2 (0.1%)**	**1 (0.1%)**	**3 (0.12%)**
Various	**V**	**2 (0.1%)**	**-**	**2 (0.08%)**
Total		**1469 (100%)**	**986 (100%)**	**2455 (100%)**

Table 3: Main drug interactions clinically important, drugs used by the studied population at the ICU of a private hospital (Aracaju-SE), from May 2008 to December 2009.

Interactions	Repetitions	Severity	Mechanism	Interaction Effects	Intervention Report	Significance*
Bromopride x ipratropium	38 (29.5%)	Moderate	Dynamic	Effects of bromopride on gastrointestinal motility are antagonized by anticholinergic drugs	Accepted (20) Not accepted (18)	NA
Insulin x hydrocortisone	17 (13.2%)	Moderate	Dynamic	Hydrocortisone decreases effects of insulin by pharmacodynamic antagonism	Accepted (11) Not accepted (6)	NA
Dexamethasone x phenytoin	17 (13.2%)	Moderate	Kinetic	Concurrent use of dexamethasone and phenytoin may result in decreased dexamethasone effectiveness	Accepted (8) Not accepted (9)	Grade 2
Furosemide x hydrocortisone	11 (8.5%)	Moderate	Kinetic	Concurrent use of furosemide and hydrocortisone may result in hypokalemia	Accepted (7) Not accepted (4)	NA
Moxifloxacin x amiodarone	9 (7.0%)	Major	Dynamic	Concurrent use of amiodarone and moxifloxacin may result in an increased risk of QT interval prolongation	Accepted (7) Not accepted (2)	Grade 1
AAS x furosemide	8 (6.2%)	Moderate	Kinetic	AAS decreases effects of furosemide.	Accepted (4) Not accepted (4)	Grade 2
Dexamethasone x insulin	8 (6.2%)	Moderate	Dynamic	Dexamethasone decreases effects of insulin by pharmacodynamic antagonism	Accepted (3) Not accepted (5)	NA
Domperidone x ipratropium	8 (6.2%)	Moderate	Dynamic	Domperidone may antagonize the effects of anticholinergic drugs on gastric motility	Accepted (7) Not accepted (1)	NA
Fluconazole x phenytoin	7 (5.4%)	Moderate	Kinetic	Concurrent use of fluconazole and phenytoin may result in an increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremors)	Accepted (4) Not accepted (3)	Grade 2
Amiodarone x fentanyl	6 (4.7%)	Major	Kinetic	Concurrent use of amiodarone and fentanyl may result in cardiac toxicity (low cardiac output) and an increased risk of fentanyl toxicity (central nervous system depression, respiratory depression).	Accepted (5) Not accepted (1)	Grade 1

* Classification criteria TATRO, 2009. Note that the lower the value the greater the clinical significance of the interaction.
* NA = when the degree of significance is not in the reference.

The average of different medications per prescription was 14.0 ± 3.8. Table 2 provides a detailed description of the most used medications, according to the anatomical (Level 1) and therapeutical (Level 2) classification of the ATC. Among the most prescribed therapeutic classes, medications that act in the alimentary tract and metabolism are highlighted (23.22% - antacids/antiulcer drugs/antiflatulents); nervous system (19.80% - analgesics) and the cardiovascular system (18.09% - cardiac drugs and diuretics). Table 3 provides a detailed description of DI identified with regard to mechanism and severity degree. The number of clinically relevant DI per prescription ranged from one to five with an average of 1.22. Of these, the most frequent DI in the study sample were *Bromopride x ipratropium* (38; 29.5%), *insulin x hydrocortisone* (17; 13.2%) and dexamethasone x phenytoin (17; 13.2%).

DISCUSSION

This study showed a predominance of female patients, this is corroborated by the literature that demonstrates the feminization in the Brazilian population aging (Flores, Mengue, 2005; Dias Junior *et al.,* 2006). Although Lima and Cassiani (2009) claim that females receive more medicines and are more likely to DI, this study found no association between the frequency of women and DI.

In Brazil there has been a considerable growth in the population of Brazilian citizens with more than 60 years old (Cruciol-Souza, Thomson, 2006). In this study, an association between elderly people and the presence of DI was found (Lima, Cassiani, 2009; Bleich *et al.,* 2009; Blix *et al.,* 2008). According to the literature, age is a risk factor for DI, since elderly people have more physiological alterations and chronic health conditions that favor a longest ICU stay and increased use of drugs/day, enabling the prescription of more complex pharmacotherapeutic combinations (Hamms *et al.,* 2008; Lima, Cassiani, 2009).

In this study, the average of medications per prescription was similar to that found by Hammes and colleagues (2008) and Ibáñez (2009). The existence of multiple diseases in patients hospitalized in ICUs has contributed significantly to the increased use of polypharmacy in recent years, which favors a higher incidence of DI and therapeutic duplicity (Cruciol-Souza, Thomson, 2006; Bleich *et al.,* 2009; Locatelli *et al.,* 2010). Thus, the analysis and monitoring of prescriptions by the clinical pharmacist in the ICUs could be an important safety collaborator for the patient. Unlike the results found in international studies conducted in hospitals (Blix *et al.,* 2008; Cremades *et al.,* 2009),

the majority of prescribed drugs was alimentary tract and metabolism agents, followed by drugs for the nervous and cardiovascular systems. However, the data are similar to other studies conducted in ICUs in Brazil (Hamms *et al.,* 2008; Lima, Cassiani, 2009). The use of medications that act in the alimentary tract and metabolism has been a common practice in stress ulcer prophylaxis in critically ill patients, since several diseases that require hospitalization in the ICU are directly associated with gastric mucosal lesions (Araujo *et al.,* 2010; Pompilio, Cerconello, 2010). This fact may explain the findings in this study.

The number of DI identified in this study was lower than in similar studies (Reis, Cassiani, 2011; Lima, Cassiani, 2009; Cruciol-Souza, Thomson, 2006). According to Saverno (2009) and Abarca (2004) researchers usually record all DI detected by software, without worrying about their clinical relevance. As a result, an overestimation occurs in the identification of theoretically found DI, without reflecting the clinical practice reality. Tatro (2009) argues that differences between the results obtained and literature data may be associated with different concepts of clinical relevance used by each member of the assessment group, and with databases used by DI identification *software.*

Previous studies confirm that the majority of DI identified was also of moderate severity (Lima, Cassiani, 2009; Bleich *et al.,* 2009; Aspinall *et al.,* 2007). After the pharmaceutical interventions, the number of moderate DI halved in this study. However, the percentage of interactions of moderate severity was maintained from one year to another, similarly to other studies in the literature (Reis, Cassiani, 2011; Dinesh *et al.,* 2007). Therefore, it is critical that the clinical pharmacist monitors the specific cases of DI, managing pharmacotherapy when necessary, and minimizing the deterioration of the patient's clinical condition. In the first year of this study most of the DI identified was pharmacodynamics interactions, as confirmed by the study of Dinish (2007), in a teaching hospital at Nepal. After the pharmacist's interventions, there was an inversion in the predominant mechanism of DI found, with higher frequency of pharmacokinetic interactions. In a study conducted by Lima (2009), at the ICU of a teaching hospital in Brazil, a greater frequency of this mechanism was also found. According to Reis (2011), adverse events can be determined by the potential for pharmacokinetic interactions that inhibit the metabolism of drugs. Given this profile of interactions, prevention measures for patient safety in the ICU should include strategies as the adjustment of medications dose, observation and clinical monitoring of the patient in order to detect or prevent adverse events.

An increasing number of pharmacist's recommendation reports accepted by the prescribing physician were observed in this research, contributing to the reduction of DI from one year to the other. In the study of Grizzle et al. (2007), it was observed that most interventions were accepted and 89.4% of clinically significant DI were replaced by the prescriber. According to Bleich (2009), DI assessment, made by the clinical pharmacist, seems to improve the quality of prescriptions in hospitals. Thus, it is essential that risk factors and clinical relevance of DI be identified and disseminated among health professionals, providing the choice of safe dosage regimens, improvement of quality of care and prevention of harm to the patient.

As for the clinical management, the most frequent intervention was monitoring of signs and symptoms, and this is corroborated by the literature (Lima, Cassiani, 2009; Vonbach *et al.,* 2007). To Locateli (2010), most of the DI can be controlled by other means than the suspension of drugs combination, such as dose adjustment and monitoring of possible adverse events, i.e., the individualized assessment of risk and benefit for each DI. In this sense, the pharmacist can disseminate information about medicines to multidisciplinary team, monitoring the possible effects of DI and assisting ICU physicians in the pharmacotherapy effectiveness and safety.

Benefits and limitations were observed in this study. Among the benefits, it is possible to mention the sampling dimension and standardization of the method used for DI detection, with the use of four sources of reference information, increasing data sensitivity and the degree of documentation, which are important features for clinical relevance. Another advantage was the clinical investigation of DI with patients, which contributed to the effect and acceptance of pharmacist's interventions performed during the assessment.

On the other hand, this study has some limitations. First, some data were not collected, as total number of admissions in the ICU, duration of patient stay and absence of clinical outcomes assessment. Also, it should be noted that the light severity DI were not considered, for their lack of relevance in clinical practice. This fact may have contributed to the underestimation of the number of identified DI. Another limitation is related to the study in a single ICU, which hinders the generalization of results.

CONCLUSION

The results of this study suggest that pharmacist's contribution may have reduced the identified DI. Moreover, the pharmacist management might have enabled greater familiarity of physicians regarding clinically relevant DI, optimizing the quality of prescriptions, especially in the ICU. In this context, the effect of clinical pharmacist interventions in a multidisciplinary team may promote health, preventing and monitoring adverse events, intervening and contributing for pharmacotherapy effectiveness and patient safety.

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