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Potential drug interactions prevalence in intensive care units

Prevalência de potenciais interações medicamentosas droga-droga em unidades de terapia intensiva

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ABSTRACT

Objectives: Drug interactions occur when effects and/or toxicity of a drug are affected by presence of another drug. They are usually unpredictable and undesirable. A study was conducted to verify the prevalence and clinical value of potential drug interactions in intensive care units

Methods: All patients, of three intensive care units were included in a cross-sectional study, over a period of two months. Patients with less than a 2 days length of stay were excluded. Data were collected from twenty-four hour prescriptions and all possible paired combinations drug-drug were recorded. Prevalence and clinical value (significance) were checked at the end of follow-up.

Results: One hundred and forty patients were analyzed, 67.1% presented with some significant potential drug interactions and of the 1069 prescriptions, 39.2% disclosed the same potential. Of 188 different potential drug interactions, 29 were considered highly significant. Univariate analysis showed that in the group with significant potential drug interactions a higher number of different drugs, drugs/day had been used, there were more prescribing physicians and extended stay in intensive care units. Adjusted to the multivariate logistic regression model, only the number of drugs/day correlated with increased risk of significant potential drug interaction (p = 0.0011) and, furthermore that use of more than 6 drugs/day increased relative risk by 9.8 times.

Conclusions: Critically ill patients are submitted to high risk of potential drug interactions and the number of drugs/day has a high positive predictive value for these interactions. Therefore, it is imperative that critical care physicians be constantly alert to recognize this problem and provide appropriate mechanisms for management, thereby reducing adverse outcomes.

Keywords: Pharmaceutical preparations/adverse effects; Drug interactions; Drug toxicity; Pharmacology

INTRODUCTION

A drug interaction takes place when the effects and/or toxicity of a drug are affected by another drug.[1,2] Although results may be positive (increased efficacy) or negative (decrease of efficacy, toxicity or idiosyncrasy), in pharmacotherapy they are usually unforeseen and undesirable.[3]

With the continued development of new drugs and subsequent prescriptions with increasingly more complex combinations it has become difficult for physicians and pharmaceutics to be familiar with all potential interactions.[4]

Risk of occurrence and severity rest upon several factors, among them

the number of drugs prescribed, duration of treatment, patient age and stages of disease. Patients that require a large number of drugs, long time of treatment, with physiological aging changes or certain diseases such as renal failure, shock, [5-8] hepatic disease such as cirrhosis or acute viral hepatitis,[9,10] are considered of high risk for severe drug interactions.

Results from the Harvard Medical Practice Study II [11] disclose that complications related to use of drugs are the most common type of adverse events in hospital care (9% of the patients). Of the hospitalized patients 2-3% experience reactions specifically caused by pharmacological interactions[12,13] In intensive care units (ICU) studies have disclosed that potential drug interactions may occur in 44.3 to 95% of patients.[14-16] However, studies are scarce and limited, regarding the real assessment of their clinical values.

Assessment of this potential (clinical value) must consider weighing the severity of the effect and the level of evidence. This study, based on medical prescriptions in three intensive care units in Joinville (SC), Brazil was carried out for the purpose of verifying the prevalence of potential drug interactions (PDI), ranking their clinical value and identifying eventual risk factors.

METHODS

All patients admitted to three ICU in Joinville (SC) in two different periods: October 1 to November 4, 2004 and March 7 to April 6, 2005 were identified. One was a neuro-surgical ICU, the second a general ICU, both in a public institution and the third was a general ICU in a private institution.

All patients with more than a 48 hours stay in the ICU were included in the study. Data were collected from medical records and prescriptions. In both public ICU collection was carried out in a prospective way during the above mentioned period. Later, research included the private ICU where data collection took place in a retrospective way, selecting all patients admitted to the ICU in the same period.

Registered information included age, gender, date of hospital admission, date of ICU admission, cause of admission, Acute Physiological Chronic Heatlh Evaluation (APACHE) II score, outcome at the end of follow-up (dismissal or death), 24 hour prescriptions and number of prescribing physicians. Confidentiality was maintained, patients and physicians were not identified for collection, informed consent was not considered necessary by the Ethics Committee of the involved institutions.

Data were tabulated according to the combinations of drugs observed during the 24 hours period. Drugs that in the handwritten prescriptions were illegible, nutritional supplements, hydro-electrolytic components, insulin and vitamins were excluded.

Verification of potential drug interactions was carried out using the software *iFacts™ 2005* version for *Palm OS*, by the same author of the book *Drug Interaction Facts*[4] - a system chosen because of its high accuracy when compared to other models.[17]

If a drug could not be found in the *iFacts™ 2005* databank, the combination was considered without potential risk of interaction. In this case, no verification by the pharmacological class was performed, because not all drugs within the same class are equally susceptible to drug interactions.[18]

This verification procedure took place at the end of the follow-up, researchers were not aware of the potential drug interactions during data collection. The study did not envisage methods to investigate the actual occurrence of interactions.

Assessment of the clinical value of PDI was made by assessing severity of the effect (intensity) and level of evidence, information supplied by the *iFacts™ 2005*.[4]. The clinical value was ranked from 1 to 5 according to the plan proposed in chart 1 which agrees with literature.[4,5,19]

PDI were considered significant when the clinical value ranged from level 1 to 3 and highly significant were those with a clinical value of 1 or 2, correspon-

Chart 1 – Classification of the clinical value of drugs interactions

Intensity	Level of evidence				
	Established	Probable	Suspect	Possible	Implausible
Severe	1	1	1	4	5
Moderate	2	2	2	4	5
Mínimal	3	3	3	5	5

Recommendations 1 – avoid combination; 2 – usually avoid combination; 3 - minimize risk; 4 – no action required; 5 – there is no interaction.
Severity: severe (potential risk to life or irreversible damage; moderate (worsening of the clinical condition), minimal (light or imperceptible).
Source: (Adapted from Jansman, 2005)[20]

ding to severe or moderate intensity and established or probable evidence.

Statistical analyses were made using the software GraphPad Prism 4.0® and EPI Info 3.3.2®. Statistical differences between the group of patients that presented PDI of clinical significance and the group that did not present were first assessed by univariate analysis using the non parametric Mann-Whitney test – the confidence interval used was of 95%. Variables with p<0.05 were selected for a multivariate logistic regression model.

RESULTS

One hundred and forty patients were analyzed, 49 (35%) from the public general ICU, 44 (31%) from the public neurological-surgical ICU and 47 (34%) from the private general ICU. Mean age of the population studied was 53.34 ± 20.25, of which 92 were men and 48 women. The mean APACHE| II score was 18.22± 7.86. Mean of drugs per day was 6.76 ± 2.16 with a mean of 13.10 ± 5.95 different drugs per patient by the end of observation. The analyzed period was a mean of 10.71 ± 12.96 days and the number of prescriptions 7.64 ± 6.66 for each patient.

Regarding cause of admission, 68 (48.6% |) patients were surgical and 72 (51.4%) were clinical. Patients at postoperative of neurosurgery (15), polytrauma (13), cranio-encefaphalic trauma (12) and postoperative of general surgery (10) were more frequent among the first; followed by postoperative of cardiac surgery (7), postoperative of thoracic surgery (4) and other causes (7). For clinical patients the distribution was acute respiratory failure (20), stroke (14), septicemia (13), acute myocardium infraction (6) heart failure (6), neoplasia (3), extensive burns (3) and other causes (7).

A total of 1069, 24 hour prescriptions were assessed,

adding up to 159 drugs; 775 (72.5%) presented some PDI; 419 (39.2%) with at least one significant PDI, clinical value level 1 to 3 Tatro (2005). From the entire sample 123 (87.9%) patients were exposed to some PDI, 94 (67.1%) with a significant PDI and 49 (35%) with highly significant PDI. One hundred and eighty eight PDI were detected, 96 of them significant and 29 highly significant (Table 1).

Figures 1 and 2 respectively, show the distribution according to clinical value and the records. Regarding onset of effect, should they take place, 51.6% of the PDI detected could have had a late onset (after 24 hours) and 48.4% could have an early onset (within the 24 hours). Considering severity 39.7% would have minimal effects (imperceptible or light), 50.4% moderate (worsening of the clinical condition) and 9.8% (potential risk of life or irreversible damage).
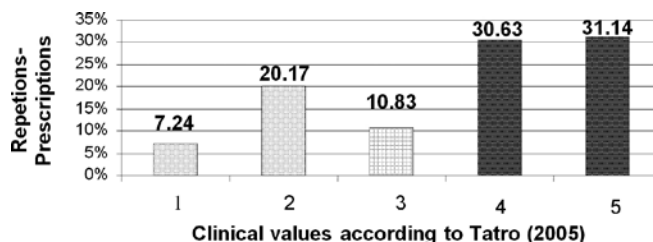
Figure 1 – Stratification of potential drug interactions according to clinical value.
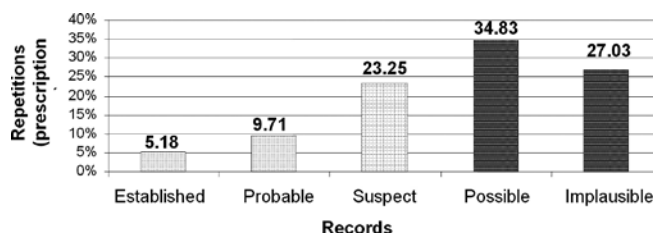
Figure 2 - Stratification of the potential drug interactions according to the level of evidence or records.

Table 1 - List of the ten more frequent highly significant potential drug interactions

	Potential interactions	Clinical value	Intensity	Records	Rep.	% (N)
1	Captopril – spironolactone	1	Severe	Probable	27	5.71 (8)
2	Pancuronium – vancomycin	2	Moderate	Probable	12	5.71 (8)
3	Amikacin – piperacillin-tazobactam	2	Moderate	Probabler	12	4.29 (6)
4	Digoxin – furosemide	1	Severe	Probable	11	3.57 (5)
5	ASA – hydrocortisone	2	Moderate	Probable	17	3.57 (5)
6	Dexamethasone – phenytoin	2	Moderate	Establishjed	24	3.57 (5)
7	Amiodarone – phenytoin	2	Moderate	Probable	11	2.86 (4)
8	Phenytoin – hydrocortisone	2	Moderate	Established	20	2.86 (4)
9	Amicacine – pancuronium	1	Severe	Probable	7	2.14 (3)
10	Amicacine – ampicilina-sulbactam	2	Moderate	Probable	5	2.14 (3)

Rep = Number of prescriptions

Among the highly significant PDI detected, the most prevalent pharmacological class was that of the antibiotics (23%) and the most representative were the aminoglycosides. The second most prevalent class was that of the anticonvulsivants (10.2%), with phenytoin as the chiefly involved drug; then the antihypertensives (10.2%) with ACE inhibitor and beta-blockers among the most present. Next ones were the corticosteroids (9%), neuromuscular blockers (7.7%, antiarrhythmics (6.4%) and anti-fungus (5.1%). With a prevalence of the 3.8% value, came the platelets antiaggregants, benzodiazepines and diuretics; 2.6% anticoagulants and bronchodilators and 1.3% for anesthetics, antiemetics, antipsychotics, barbiturics, opiates and sympathocomimetics.

Comparing the group exposed to some significant PDI with the control group without significant PDI using univariate analyses, the following results were found (Table 2).

The group of patients with significant PDI had a relatively higher mean length of stay (10.73 ± 11.96 *vs.* 10.65 ± 14,93, p=0.0292). The number of drugs was also higher in this group (14.95 ± 5.76 *vs.* 9.33 ± 4.38, p<0.0001); as was the number of drugs/day (7.59 ± 1.91 *vs.* 5.07 ± 1.60, p<0.0001). However the number of prescribing professionals involved was higher in the first group (5.41 ± 2.70 *vs.* 4.37 ± 2.79, p=0.0261).There was no difference in age, APACHE II and previous in hospital length of stay.

Once the model of multivariate logistic regression was adjusted to the variables that had p<0.05 at the previous univariate analysis, it was perceived that only the number of drugs/day was related to the presence of significant PDI (p = 0.0011).

In this model, use of more than 6 drugs per day increased by 9.8 times the risk of significant PDI (sensitivity 75.5%, specificity 76.1%, positive predictive value 86.6% negative predictive value 60.3% and accuracy 75.7%).

Mean age of surgical patients was lower than that of clinical patients (49.78 ± 20.24 vs. 56.71 ± 19.75; p = 0.0398). The APACHE II was also lower in these patients (16.79 ± 8.03 vs. 19.57 ± 7.39; p = 0.0252). The number of drugs used during the time period analyzed was higher in clinical patients (14.61 ± 6.07 vs. 11.50 ± 5.45; p = 0.0027), as well as the mean of drugs per day (7.34 ± 2.01 vs. 6.15 ± 2.17; p = 0.0006).There were no differences between the two groups regarding prescriptions with significant PDI (3.22 ± 3.89 vs. 2.75 ± 5.01; p = not significant (NS) The number of professionals and time analyzed between groups was similar.

According to the nature of the institution, public or private ICU, mean of age was higher in the private group (58.06 ± 21.07 vs. 56.71 ± 19.80; p=0.0304). Hospital length of stay prior to admission to the ICU was lower in the private institution (5.23 ± 14.84 vs. 8.82 ± 16.17, p=0.0007) and also length of stay in the ICU (7.60 ± 8.61 vs. 10.65 ± 10.91; p = 0.0119). There were no differences in the APACHE II, total number of drugs, number of drugs/day and number of prescribing professionals. There was no difference between prevalence of potential drug interactions.

Regarding the group of surviving patients versus non-surviving, a higher daily exposure to drugs (drug/day) was detected in patients that died (7.58 ± 2.39 vs. 6.51 ± 2.03; p=0.0256). However, there was no correlation with presence of significant drug interactions. These patients were older 62.42 ± 17.94 vs. 50.54 ± 20.17; p = 0.0022) and had a higher APACHE II score (24.12 ± 7.48 vs. 16.40 ± 7.07; p < 0.0001).

Table 2 – Profile of patients according to presence or absence of potential drug interactions

Variables	Group of significant PDI	Group with no significant PDI	P value
Age (years)	50.65 ± 21.58 (46)	54.66 ± 19.55 (94)	NS
APACHE II	17.07 ± 8.90 (46)	18.79 ± 7.29 (94)	NS
Previous length of stay (days)	7.07 ± 13.01(46)	7.28 ± 15.36(94)	NS
Length of stay ICU (days)	10.65 ± 14.93 (46)	10.73 ± 11.96(94)	0.0292
Different drugs (N)	9.33 ± 4.38 (46)	14.95 ± 5.76(94)	<0.0001
Prescribing physicians (N)	4.37 ± 2.79 (43)	5.41 ± 2.70(88)	0.0261
Prescriptions (N)	6.39 ± 6.07 (46)	8.24 ± 6.88(94)	0.0187
Drugs per day (N)	5.07 ± 1.60 (46)	7.59 ± 1.91(94)	<0.0001

PDI – potential drug interaction; APACHE – Acute Physiological Chronic Health Evaluation; ICU– intensive care unit; N – number NS – not significant. Results expressed in mean± standard deviation (number of analyzed patients). Mann-Whitney Test

DISCUSSION

According to trials already carried out, the study also disclosed a high prevalence of PDI in the ICU.[14-16] Different from the previous observational studies, this potential risk was stratified to verify its real clinical value. A higher prevalence of PDI was observed with low clinical value (level 4 and 5) for which no interventions were needed, although an even higher number of significant PDI (level 1,2 and 3) have been found.

Considering that patients in the ICU often are aged and have physiological alteration, summing up to unfavorable clinical conditions for drug metabolism such as shock, renal failure and hepatic disease, it might be inferred that relevance of potential interaction, even if not very significant, is relevant for prevention of undesirable adverse effects.

Corroborating former statements,[5] it was perceived that patients from the group of significant PDI received a higher number of drugs during stay, a higher number of drugs/day and had a longer length of stay in the ICU, possibly due to increased load of drug exposure and possibility of more complex combinations. Unexpectedly, the group of patients with significant PDI also presented a higher number of prescribing professionals during treatment, a factor that merits consideration.

Based upon multivariate analysis, the only independent risk factor for greater risk of significant PDI was the number of drugs/day, a risk substantially increased when more than 6 types of drugs are used.

An individualized discussion of the approach of PDI should not be addressed here, although it is known that the majority may be controlled, not only by interrupting the combination but also by adjusting doses and monitoring possible adverse events, that is to say, an individualized assessment of risk and benefit.

Among the existing confusion factors found in this survey, some were not controlled. The arrangements drug-drug of a 24 hour prescription suppose that all drugs would be simultaneously used, but administration takes place at different times of the day and there are differences in the velocity of their metabolism. Drugs that are not registered in the iFacts™ 2005, regardless of their pair, were considered as without PDI, therefore prevalence of PDI may have been underestimated. The survey assessed the situation of patients in the study period, many were analyzed only at one point of their stay, therefore no reliable inference on the length of stay can be made.

There are evidences that the potential risks are directly related with the actual occurrence of drug interactions. In a previous study involving patients in the surgical ICU, it was noted that 44.3% of patients were exposed to PDI, 19.3% effectively had analytical alterations related to drug interaction and 6.4% developed clinical manifestations. [14] Although the study had ranked the interactions regarding severity and records their actual occurrence was not envisaged in the survey. Severe PDI such as captopril-spironolactone and furosemide-dygoxin, drugs of habitual association, do not frequently occur in clinical practice. In this context, new clinical trials must be carried out.

CONCLUSION

Patients in ICU have a high prevalence of potential drug interactions. The number of drugs/day is the independent risk factor for increase of this possibility. Fortunately, most PDI is not a contraindication to use of the drug, in the sense of replacement or interruption of use, nevertheless the high frequency of interactions with a significant clinical value (level 1 to 3) must always be recognized and its effect monitored.

Even though it is known that they can be disclosed in the prescription, release and administration of drugs, it is recommended that greater relevance be given to the subject and that support systems in this sense should become habitual in the practice of pharmacological therapies in order to prevent iatrogenies. The decision support systems based on evidences have their place in this domain and deserve a greater practical applicability.

RESUMO

Objetivos: Interações medicamentosas ocorrem quando os efeitos e/ou a toxicidade de um fármaco são alterados pela presença de outro. São geralmente imprevistas e indesejáveis. Realizado estudo com objetivo de verificar a prevalência e o valor clínico das interações medicamentosas potenciais em unidades de terapia intensiva.

Métodos: Incluídos todos pacientes de três unidades de terapia intensiva em um período de 2 meses, analisados transversalmente. Foram excluídos aqueles com tempo de permanência menor que 2 dias. Os dados foram tabulados de acordo com as combinações de fármacos observadas no período de 24 horas. A presença e o valor clínico das interações medicamentosas potenciais foram conferidos ao final do seguimento.

Resultados: Analisados 140 pacientes, 67,1% apresentaram alguma interações medicamentosas potenciais significativa e das 1069 prescrições, 39,2% tiveram este achado. De 188 interações medicamentosas potenciais diferentes, 29 foram consideradas altamente significativas. Por análise univariada, observou-se no

grupo que apresentou interação significativa maior quantidade de medicamentos, fármacos/dia, número de médicos prescritores e tempo de internação na unidade de teapia intensiva. Por modelo de regressão logística multivariada, apenas o número de fármacos/dia correlacionou-se com o aumento do risco de interação medicamentosa potencial significativa (p = 0.0011); o uso de mais que 6 medicamentos/dia aumenta em 9.8 vezes este risco.

Conclusões: Pacientes em unidades de terapia intensiva es-

tão submetidos a alto risco de interações medicamentosas potenciais e o número de fármacos/dia é condição com alto valor preditivo positivo para tal. Os intensivistas devem ser alertados para o reconhecimento do problema e criados mecanismos para o manejo adequado e prudente, diminuindo iatrogenias.

Descritores: Preparações farmacêuticas/efeitos adversos; Interações de medicamentos; Farmacologia; Toxicidade de drogas

REFERENCES

1. Jankel CA, Speedie SM. Detecting drug interactions: a review of the literature. DICP. 1990;24(10):982-9.
2. Hartshorn EA. Drug interactions. Fam Community Health. 1982;5(2):45-57.
3. Streetman DS. Metabolic basis of drug interactions in the intensive care unit. Crit Care Nurs Q. 2000;22(4):1-13.
4. Tatro DS, editor. Drug interaction facts. St. Louis: Facts and Comparisons; 2005.
5. Hansten PD, Horn JR, editors. Hansten and Horn's drug interactions. St. Louis: *Facts and Comparisons*; 2001.
6. DiPiro JT, Hooker KD, Sherman JC, Gaines MG, Wynn JJ. Effect of experimental hemorrhagic shock on hepatic drug elimination. Crit Care Med. 1992;20(6):810-5.
7. Park GR. Molecular mechanisms of drug metabolism in the critically ill. Br J Anaesth. 1996;77(1):32-49.
8. Kennedy JM, Riji AM. Effects of surgery on the pharmacokinetic parameters of drugs. Clin Pharmacokinet. 1998;35(4):293-312.
9. Wilkinson GR, Branch RA. Effects of hepatic disease on clinical pharmacokinetics. In: Benet LZ, Massoud N, Gambertoglio JG, editors. Pharmacokinetic basis for drug treatment. New York: Raven Press; c1984.
10. Keiding S. Drug administration to liver patients: Aspects of liver pathophysiology. Semin Liver Dis. 1995;15(3):268-82.
11. Leape LL, Brennan TA, Laird N, Lawthers AG, Localio AR, Barnes BA, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. N Engl J Med.1991;324(6):377-84.
12. Hallas J, Harvald B, Worm J, Beck-Nielsen J, Gram LF, Grodum E, et al. Drug related hospital admissions. Results from an intervention program. Eur J Clin Pharmacol. 1993;45(3):199-203.
13. Gosney M, Tallis R. Prescription of contraindicated and interacting drugs in elderly patients admitted to hospital. Lancet. 1984;2(8402):564-7.
14. Sierra P, Castillo J, Gómez M, Sorribes V, Monterde J, Castaño J. [Potential and real drug interactions in critical care patients]. Rev Esp Anestesiol Reanim. 1997;44(10):383-7. Spanish.
15. Nielsen EW, Dybwik K. [Drug interactions in an intensive care unit]. Tidsskr Nor Laegeforen. 2004;124(22):2907-8. Norwegian.
16. Meneses A, Monteiro HS. Prevalência de interações medicamentosas "droga-droga" potenciais em duas UTIs (pública X privada) de Fortaleza, Brasil. Rev Bras Ter Intensiva. 2000;12(1):4-7.
17. Barrons R. Evaluation of personal digital assistant software for drug interactions. Am J Health Syst Pharm. 2004;61(4):380-5.
18. Herman RJ. Drug interactions and the statins. CMAJ. 1999;161(10):1281-6. Review.
19. Sjoqvist F. FASS 2000. Stockholm: LINFO Drug Information Ltd; 2000. P.1481-6.
20. Jansman FG, Jansen AJ, Coenen JL, de Graaf JC, Smith WM, Sleijter DT, Browers JR. Assessing the clinical significance of drug interactions with fluorouracil in patients with colorectal cancer. Am J Health Syst Pharm. 2005;62(17):1788-93.