Prevalence and classification of drug-drug interactions in intensive care patients
Prevalência e classificação de interações entre medicamentos dispensados para pacientes em terapia intensiva

Silvana Maria de Almeida¹, Cinthia Scatena Gama², Nelson Akamine³

ABSTRACT

Objective: To identify, quantify and classify drug-drug interactions among the medications most frequently dispensed in the adult ICU of a large private tertiary care hospital over a period of 30 days. Methods: Collection of data from an electronic database on consumption and drug-drug interactions of the 50 most frequently dispensed medications. Results: During the period studied, 395 commercial brands were dispensed, representing 258 active ingredients, classified into ten large groups and 36 subgroups according to Anatomical Therapeutic Chemical criteria. Four hundred and nine drug-drug interactions were identified - 174 were severe and 235 moderate. The drug-drug interactions were classified as pharmacokinetic (30%), neurologic (22%), and cardiologic (18%), and together accounted for 70% of drug-drug interactions tracked with the Micromedex Healthcare Series® electronic database. The other interactions were classified as hematologic, renal, endocrine/metabolic, respiratory, muscular, gastrointestinal, hepatic, and others, comprising the remaining 30%. Conclusion: Drug-drug interactions are very common in ICU patients. They may potentially produce a significant economic and clinical impact. The use of electronic computerized systems allows a better approach for medical prescriptions making it possible to prevent and intervene in cases of harmful interactions and adverse events even before medications are dosed.

Keywords: Drug interactions; Prescriptions, drug; Intensive care units; Medical records systems, computerized

RESUMO

Objetivo: Identificar, quantificar e classificar as interações medicamentosas entre os medicamentos mais dispensados na UTI de adultos de um hospital privado, de grande porte e de atendimento terciário no período de 30 dias. Métodos: Coleta em base de dados eletrônica do consumo e de interações medicamentosas referentes à dispensação dos 50 medicamentos mais utilizados. Resultados: No período estudado foram dispensadas 395 marcas comerciais, representando 258 princípios ativos, classificados em 10 grandes grupos e 36 subgrupos segundo a Anatomical Therapeutic Chemical. Foram identificadas 409 interações medicamentosas, 174 de gravidade alta e 235 de gravidade moderada. As interações medicamentosas foram classificadas como farmacocinética (30%), neurológica (22%), cardiológica (18%) que somadas chegam a 70% das interações medicamentosas rastreadas por meio da base de dados eletrônica Micromedex Healthcare Series®. As demais interações classificadas como hematológica, renal, endócrino-metabólica, respiratória, muscular, gastrointestinal, hepática e outras detiveram os 30% restantes. Conclusão: As interações medicamentosas são muito comuns na UTI. Elas podem potencialmente produzir grande impacto econômico e clínico. A utilização de sistemas eletrônicos informatizados permite melhor abordagem da prescrição médica possibilitando prevenir e intervir sobre interações prejudiciais e eventos adversos mesmo antes da administração dos medicamentos.

Descritores: Interações de medicamentos; Prescrição de medicamentos; Sistemas computadorizados de registros médicos; Unidades de terapia intensiva

INTRODUCTION

The launching of a new drug on the market is a slow process that involves great financial and human investments. When a new active ingredient is conceived for therapeutic use in humans, first its efficacy and innocuousness must be demonstrated through preclinical and clinical investigations(1).

Initial or preclinical studies are carried out in experimental animals. After confirming drug safety, the first clinical trials are performed in humans in order to determine its pharmacokinetics, pharmacodynamics, dosage, safety, and efficacy. During the final stage before it is marketed, the most frequent undesirable effects are identified and quantified, taking into consideration the small number of subjects included in the research project compared to the general population. During commercialization of the new drug, the general

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population is studied, and adverse events, intolerance, and consequences of chronic use not described in the clinical studies are analyzed\(^2\).

Despite all trials drugs are submitted to before marketing, it is not possible to detect rare adverse reactions or those associated with prolonged use\(^3\). Additionally, there are differences between clinical research and clinical practice, and post-marketing follow-up is vital.

According to Brown\(^3\), over the period of two years, approximately 80 new drugs are introduced on the American market and many deaths occur as a direct result of combinations of these drugs. On the other hand, only a small number of drugs are removed from the market due to adverse reactions or drug interactions. According to Nassar, from 1964 to 1999, approximately 8% of drugs approved by the FDA were removed from the American market\(^4\).

The Brazilian National Health Surveillance Agency (ANVISA), created in 1999, consolidated the National Drug Surveillance System. In 2001, Brazil was included as a member of the International Drug Monitoring Program coordinated by the Uppsala Monitoring Centre, in Sweden. It is a collaborating center of the World Health Organization – WHO, and since then, efforts have been directed towards the notification of adverse events to drugs by health care professionals and institutions. The Sentinel Network is a project created by the Sentinel Service Surveillance, part of the Adverse Event and Technical Complaint Surveillance area of ANVISA. One of the spheres of operation of the Sentinel Network is drug surveillance that operates directly in problems related to medications (PRMs).

In Brazil, according to ANVISA there are currently about 12,700 different drug forms available on the market. From 2000 to 2006, 305 medications were removed from the Brazilian market\(^5\), but there is no specific information available on cases related to adverse events. The Drug Surveillance sector has a future project intended to systematize all information pertinent to drugs.

According to the Institute of Medicine\(^6\), 44,000 to 98,000 deaths occur annually caused by error, and about 7,000 of these deaths result from adverse reactions to medications. In hospitalized patients, approximately 6.7% experience severe adverse reactions to drugs, and 0.32% of these lead to death. Adverse reactions to drugs represent the fourth leading cause of death in the United States, after cardiovascular disease, diabetes, and AIDS.

A potential drug-drug interaction refers to the possibility of a drug altering the effect of another drug administered simultaneously, and may occur before they are dosed (physical-chemical interaction or incompatibility) or after they are dosed.

The potential for development of drug-drug interactions increases with age, with the number of medications in use, and with the number of physicians who treat the same patient. It is believed that the potential for drug-drug interaction reaches 100% when the number of drugs prescribed reaches eight.

It is estimated that most hospitalized patients receive at least six medications simultaneously; therefore, recognition of the beneficial effects or undesirable reactions requires a thorough knowledge of the effects intended and of the possibility of the drugs causing untoward reactions\(^1,4\).

As Vincent\(^7\) pointed out, our efforts should be focused on reducing errors, and this suggests the concept of “FAST HUG” (Feeding, Analgesia, Sedation, Thromboembolic prevention, Head of the bed elevated, Stress Ulcer prophylaxis, Glucose control) referring to the seven components that should be checked by the Intensive Care Unit (ICU) team in all patients (diet, analgesia, sedation, prevention of thromboembolism, elevated head, stress ulcer prophylaxis, and glucose control).

In order to determine the degree of safety in using drugs, a series of factors are analyzed related to the physical-chemical, pharmacodynamic, and pharmacokinetic characteristics of the drugs as well as the individual characteristics of patients, and the risks associated with the disease itself. Nevertheless, it is still not possible to establish absolute safety in using drugs\(^1,4\). Many studies on medication errors associate the importance of the pharmacist in the multidisciplinary team and during clinical rounds, demonstrating a positive impact of this professional’s work in affording a higher quality of health care delivered especially regarding adverse events, inconsistencies in medical prescriptions, and economic impacts\(^8-14\).

The use of drugs in ICU is high. In large tertiary care hospitals, the average number of items prescribed may reach up to fifteen different drugs, and this justifies a study to identify, quantify, and recognize the severity of interactions among these medications.

**OBJECTIVE**

To identify, quantify and classify drug-drug interactions among the medications most frequently dispensed by the pharmacy for patients in the adult intensive care unit of a large private tertiary care hospital.

**METHODS**

Study design: retrospective study on quantitative use of medications.
A survey was carried out using a consumption report of medications dispensed by the pharmacy over the period of one month for patients of the adult intensive care unit.

Based on this list, the 50 most frequently used drugs in that period were identified and classified as per Anatomical Therapeutic Chemical (ATC) criteria\(^{(15)}\).

Using a tool available at the hospital, Micromedex Healthcare Series\(^{(16)}\) electronic databases, the drug-drug interactions were identified for each of the medications consumed during that period.

The interactions observed were classified according to severity and undesirable effect (Chart 1).

**RESULTS**

Based on the consumption report of drugs dispensed by the pharmacy of the adult ICU during the month of November 2006, we observed 395 commercial brands that represent 258 different active ingredients. Of this list, the 50 most consumed items of the month were selected and divided into ten large groups and 36 subgroups using the ATC classification\(^{(15)}\) (Table 1 and Chart 2).

<table>
<thead>
<tr>
<th>Severe</th>
<th>The interaction is life threatening and/or requires medical treatment or intervention to minimize or prevent severe adverse effects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>The interaction may result in exacerbation of the disease of the patient and/or change in therapy.</td>
</tr>
<tr>
<td>Mild</td>
<td>The interaction would limit the clinical effects. The manifestations may include an increase in frequency or severity of adverse effects, but usually they do not require change in therapy.</td>
</tr>
</tbody>
</table>

**Classification per severity**

According to the survey made with the electronic database, for the 50 most consumed drugs we identified 513 severe drug-drug interactions and 863 moderate drug-drug interactions (Table 2).

Upon cross-referencing these 50 active ingredients with the total 208 active ingredients consumed over the entire month, 174 (33.92%) severe interactions and 235 (27.23%) moderate serious interactions were identified (Table 2).

During the study period, there were 212 admissions and 699 patient-days, representing approximately two interactions per admission and 0.6 interactions per patient-day considering the list of the 50 most consumed medications over that period, and 6.5 interactions per admission and two interactions per patient-day considering all drugs used over that period.

**Classifications of interactions**

After identification, the drug-drug interactions were grouped according to the resulting effect into the following groups: pharmacokinetic, neurologic, cardiologic, hematologic, renal, endocrine/metabolic, respiratory, muscular, gastrointestinal, hepatic, and others (Table 3).
Economic impact

According to the report of drug consumption for the month of November 2006, there was no correlation between the ten most consumed medications and the ten most expensive medications (Chart 3 and 4).

There were 37,617 units of medications dispensed, resulting in a total expenditure of R$ 1,132,971.53, and generating a cost of R$ 5,344.20 per patient (Chart 5 and 6).

**Chart 3. Most consumed medications (per units dispensed)**

<table>
<thead>
<tr>
<th>Main ingredient</th>
<th>Units Dispensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>3909 ap</td>
</tr>
<tr>
<td>Phentanyl</td>
<td>3457 ap</td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td>1499 ap</td>
</tr>
<tr>
<td>Diprone</td>
<td>1321 ap</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1287 ap</td>
</tr>
<tr>
<td>Furosemide</td>
<td>816 ap</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>750 ap</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>647 fap</td>
</tr>
<tr>
<td>Morphine</td>
<td>522 fap</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>494 fap</td>
</tr>
</tbody>
</table>

**Chart 4. Higher cost medications (per unit)**

<table>
<thead>
<tr>
<th>Main ingredient</th>
<th>Market value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levothyroxine ap</td>
<td>R$ 297.52</td>
</tr>
<tr>
<td>Linezolide fr</td>
<td>R$ 249.46</td>
</tr>
<tr>
<td>Meropenem fap</td>
<td>R$ 165.87</td>
</tr>
<tr>
<td>Dexamethasemine ap</td>
<td>R$ 138.18</td>
</tr>
<tr>
<td>Tazobactam fap</td>
<td>R$ 112.56</td>
</tr>
<tr>
<td>Ciprofloxacin bol</td>
<td>R$ 99.76</td>
</tr>
<tr>
<td>Sertraline cp</td>
<td>R$ 81.11</td>
</tr>
<tr>
<td>Nimodipine fap</td>
<td>R$ 80.40</td>
</tr>
<tr>
<td>Cefepime fap</td>
<td>R$ 59.83</td>
</tr>
<tr>
<td>Ondansetrone ap</td>
<td>R$ 48.18</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The increased risk of adverse events in critical care units is related to the large number of medications administered and acute changes in organic functions (alterations of the drug pharmacokinetics), and leads to longer hospital stays.(17)

The incidence of drug-drug interactions in ICU is markedly higher than the general rates of the hospital environment as a whole, possible due to the type of medication used and the profile of patients admitted to this sector. We observed approximately 34% of severe drug-drug interactions and 27% of moderate interactions, different from what was verified by Cruciol-Souza(18), that is, 12.8% for severe interactions and 78% for moderate interactions at a general hospital.

The morbidity and mortality potential of drug-drug interactions is serious to the point of justifying systematic tracking performed by the clinical pharmacist.(19-20)

Among the 50 most consumed medications, we observed that most drugs were administered intravenously and a smaller proportion was used orally. The intravenous route provides a rapid effect with an immediate access to the circulatory system, and allows high doses and high concentrations to be given centrally. On the other hand, it is also related to a more rapid installation of adverse events due to administration errors, which are more difficult to correct. Besides the points mentioned above, the intravenous route is also associated with the risk of tissue infiltration or leakage, drug-drug interactions by direct contact, risks of contamination, and pyrogenicity.

The interactions classified as pharmacokinetic, neurologic, and cardiologic constitute the large majority of all interactions. Many pharmacokinetic interactions occur at the metabolic level and generally involve alterations in the activity of the primary drug-metabolizing enzyme, cytochrome P450(21). Co-administration of inhibitors or inducers of the enzyme responsible for metabolism may modify the plasma concentration, decreasing or increasing the effects of the drugs. Many drugs, such as phenobarbital, phenytoin, rifampin, and carbamazepine(22) may increase the synthesis or activity of these enzymes, while others, such as amiodarone, fluoroquinolone, trimethoprim, chlorpromazine, fluoxetine, and diltiazem inhibit its activity. Severe cases reported indicate that the concomitant use of fluoxetine and phenytoin may result in significantly increased serum levels of phenytoin, leading to toxicity.

The combination of potentially inappropriate drugs may occur with a higher frequency in the ICU, whether by
the patient’s own conditions or by the high level of drug consumption, justifying the presence of a knowledgeable pharmacist who is qualified and well trained. In this way, it is important that the pharmacist accompany the consumption of the drugs in order to contribute towards their rational use and prevent the occurrence of adverse events related to medications\(^{(18-20)}\).

The cost of medications in the ICU is extremely high. This results from a combination between the simultaneous use of many drugs and a greater use of expensive medications. According to Kane-Gill\(^{(23)}\), costs of medications in the ICU can contribute to at least 38% of total expenditure with medications in the entire hospital\(^{(24-25)}\).

In the hospital studied, the cost of medications was equivalent to the cost of one day in the ICU, which resulted in doubling the cost/day of patients admitted to this unit\(^{(24-25)}\).

The use of computerized systems made it possible to intervene and prevent many complications before initiating treatment, conferring greater safety to the medical prescription and to the patient\(^{(26-28)}\).

### CONCLUSIONS

By means of identification, quantification, and classification of drug-drug interactions among medications most frequently dispensed for adult ICU patients, we observed 1.9 interactions/patient during the period, and 0.6 interaction/patient day.

Medications represented a significant portion of the costs of a patient hospitalized in the ICU, and proper management of drug administrations may have a significant economic impact.

The use of computerized systems allows the pharmacist a better analysis of the medical prescription relative to drug-drug interactions and adverse events.

### REFERENCES