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Drug interactions in female oncologic inpatients: differences among databases

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ABSTRACT

The aim of the present study was to quantify drug interactions in prescriptions for women undergoing supportive therapy in an oncology setting at a women's hospital in Brazil and compare the information provided by different databases regarding these drug interactions. A convenience sample was selected of prescriptions for patients diagnosed with breast or gynecological tumors hospitalized in the clinical oncology and surgery wards from April to June 2009. DRUGDEX/Micromedex (Thomson Micromedex) was the main database used for the identification of drug interactions and was compared with two other databases: Drugs.com and Lexicomp. The search was performed by inputting all drug combinations found in the prescriptions in Micromedex and Drugs.com. All interactions identified and classified by Micromedex and/or Drugs.com as of major severity were then checked in Lexicomp. A total of 152 interactions were identified by Micromedex (61 major, 69 moderate and 22 minor). In Drugs.com, 614 interactions were identified (85 major, 464 moderate and 65 minor). Forty-four were classified as major drug interactions in at least one of the databases: 30 in Micromedex, 26 in Drugs.com and 14 in Lexicomp. The present findings reveal discrepancies among the three databases analyzed. Thus, standardization should be proposed. Moreover, both the pharmacist and multidisciplinary team should perform a critical analysis of prescriptions to promote safe practices in the use of medications and minimize potential complications caused by drug interactions.

Keywords: Drug interaction. Drug Prescriptions. Medical Oncology.

INTRODUCTION

A drug interaction consists of a clinical event in which the result of using a drug is altered due to simultaneous exposure to one or more other medications (Brunton et al., 2006). This is a common cause of adverse drug events (Reimche et al., 2011), the outcome of which can be dangerous, especially when causing an increase in toxicity or a decrease in efficacy. Many drug-drug interactions (DDIs) lead to delayed clinical manifestations that may be misjudged and interpreted as a new disease condition (Seymour & Routledge, 1998), further hampering their management. DDIs are significantly more likely to occur in the hospital setting, where patients are commonly on a multiple drug regimen (Moura et al., 2009). The incidence of DDI when taking five drugs is estimated to be 56% and this figure rises to 100% when eight medications are taken at the same time (Karas, 1981).

A number of studies recommend a peer review of prescriptions by the pharmacist as a preventive measure to minimize the number of medication errors and DDIs (Aronson, 2009; Dean et al., 2002; Vonbach et al., 2007). This activity is recommended by patient safety organizations and safe medication practices, such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the Leapfrog Group for Patient Safety. The development and implementation of guidelines and programs for the identification of drug interactions can help physicians and pharmacists prevent potentially dangerous DDIs and avoid harm to patients (Moura et al., 2009).

The database used for DDI screening programs should be updated and comprehensive to be useful in daily hospital practice (Barrons, 2004). Health professionals should know the limitations of these programs and the need for critical analysis when choosing a software program, considering the importance of establishing criteria of evidence, severity and clinical relevance (Reis & Cassiani, 2010). Vonbach et al. (2008) analyzed four programs for the identification of drug interactions and none was considered ideal with regard to specificity and sensitivity. The authors point out that each program has favorable and unfavorable points that are important to know (Vonbach et al., 2008). Moreover, disagreements between the information offered by DDI databases and textbooks are common, which underscores the need for further well-established criteria when choosing a software program (Fulda et al., 2000).

The aim of the present study was to quantify drug interactions in prescriptions for women undergoing supportive therapy in an oncology setting at a women's

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hospital in Brazil and compare the information provided by different databases regarding these drug interactions.

MATERIALS AND METHODS

Study design

A crossover descriptive study was carried out from April to June 2009 involving daily prescriptions for female inpatients managed at the Prof. Dr. José Aristodemo Pinotti Women's Hospital (Caism-Unicamp), Campinas, SP, Brazil. This study received approval from the Human Research Ethics Committee of the *Centro Universitário Hermínio Ometto* under protocol n. 063/2009.

Prescriptions were selected through convenience sampling. Only prescriptions related to hospitalization period were included. No analysis was performed after discharge of the patients. The following were the inclusion criteria:

- Females aged 18 to 50 years;
- Patients diagnosed with breast and gynecological tumors, such as breast cancer, ovarian cancer, cancer of the cervix and others, and attended at clinical oncology (CLO) or surgical oncology (SUO) ward of the hospital;
- Patients who had not yet started chemotherapy or were in a gap period between treatment cycles;
- Patients hospitalized for at least 24 hours.

Analysis of prescriptions

Drug names and the number of drugs used were collected from all prescriptions. Patient age and medical chart number were also recorded. Patients were exclusively identified by their initials to maintain their anonymity.

DrugDex/Micromedex (Thomson Micromedex) was the main database used for the identification of DDIs due to the fact that it is a reliable database used in many countries. Comparisons of interactions were carried out using two other drug interaction databases: Drugs.com website and LexiComp. The website Drugs.com was included in this study for being a free compendium available on the Internet, which makes it an important tool for public health services. The LexiComp is available as a book and was chosen due to the fact that it can be used when no Internet access is available. (Lacy et al., 2009)

Searches were performed by inputting all drug combinations found in each prescription to both DrugDex/Micromedex (Thomson Micromedex) and Drugs.com for the generation of a list of recognized drug interactions. All major DDIs found in Micromedex and/or Drugs.com were verified in LexiComp. In addition to being quantified, interactions were classified regarding severity in all databases. All Micromedex interactions were sorted based on scientific evidence.

RESULTS

The sample comprised 87 female patients in the CLO (n = 22) and SUO (n = 65) wards, with a mean age of 41.2 ± 6.7 and 41.2 ± 8.4 years, respectively (Table 1).

The total number of prescriptions evaluated in the CLO ward was 45 (2.0 ± 1.2 prescriptions/patient). The total number of drugs in each prescription ranged from 4 to 27 (mean: 10.4 ± 3.9 drugs/prescription), 43 (91.9%) of which contained five or more drugs. Four hundred sixty-six drugs were prescribed in this ward (Table 1). The variation in the number of drugs in the 71 prescriptions (1.1 ± 0.4 prescriptions/patient) analyzed in the SUO ward ranged from 1 to 15 (mean: 6.1 ± 2.8 drugs/prescription), 49 (69.0%) of which contained five or more drugs. Four hundred thirty-one drugs were prescribed in the SUO ward (Table 1).

Table 1. Study population and prescriptions evaluated according to Micromedex database

	CLO	SUO
Number of patients	22	65
Age (mean ± SD, years)	41.2 ± 6.7	41.2 ± 8.4
Total number of drugs prescribed	466	431
Number of prescriptions (mean ± SD per patient)	45 (2.0 ± 1.2)	71 (1.1± 0.4)
Number of DDIs per prescription (mean ± SD)	2.8 ± 2.9	0.4 ± 0.7
Number of DDIs per patient (mean ± SD)	5.7 ± 4.9	0.4 ± 1.0
Number of drugs/prescription (range)	4-27	1-15
Number of drugs/prescription (mean ± SD)	10.4 ± 3.9	6.1 ± 2.8

SD: standard deviation; DDI: drug-drug interaction; CLO: clinical oncology; SUO: surgical oncology

The most prescribed drugs in the CLO ward were dipyrone (n = 39; 8.4%), metoclopramide (n = 35; 7.5%), amitriptyline (n = 33; 7.1%) and morphine (n = 25; 5.4%). The most common drugs prescribed in the SUO ward were nifedipine (n = 67; 15.5%), metoclopramide (n = 64; 14.9%), meperidine (n = 42; 9.7%), enoxaparin (n = 38; 8.8%), and tramadol (n = 34; 7.9%). A total of 152 interactions (61 major, 69 moderate and 22 minor) were identified in the Micromedex database (the main database used for this study) and classified as suggested (Table 2). In a more detailed approach, the major DDIs found in the Micromedex database involved haloperidol/amitriptyline (32.4%) and codeine/diazepam (11.8%) in the CLO ward as well as captopril/potassium chloride (33.3%) and diazepam/morphine (25.0%) in the SUO ward (Table 3).

Table 4 presents a comparison of the total number of major, moderate and minor drug interactions found in the 116 prescriptions analyzed in both the CLO and SUO wards according to the Micromedex and Drugs.com databases. Drugs.com showed a total of 395 more moderate drug interactions in comparison to Micromedex.

Forty-four DDIs were classified as major in at least one database analyzed, among which 30 were listed in the Micromedex database, 26 were listed in the Drugs.com database and 14 were listed in the LexiComp database. Table 5 displays the most common DDIs classified as major in at least one database analyzed and the six interactions common to all three databases.

Table 2. Classification of drug-drug interactions identified according to Micromedex database

	Prescriptions	Drug-drug interactions		
		Major	Moderate	Minor
SUO	71	12 (46.2%)	7 (26.9%)	7 (26.9%)
CLO	45	49 (38.9%)	62 (49.2%)	15 (11.9%)

CLO: clinical oncology; SUO: surgical oncology

Table 3. Major drug-drug interactions identified according Micromedex database

Drug interaction	Possible outcome	Onset	Documentation
Tramadol x amitriptyline	Increase in tramadol plasma levels	Rapid	Fair
Tramadol x fluoxetine	Increase in serotonin concentration in central and peripheral nervous system	Rapid	Good
Captopril x ringer lactate potassium chloride	Low concentrations of aldosterone	Delayed	Good
Morphine x diazepam	Central nervous system depression	Not specified	Good
Scopolamine x potassium chloride	Prevents or slows down potassium chloride passage through gastrointestinal tract	Rapid	Fair
Haloperidol x amitriptyline	Additive cardiac effects	Not specified	Fair
Codeine x diazepam	Respiratory depression	Not specified	Good

Table 4. Comparison of total number of major, moderate and minor drug-drug interactions according to Micromedex and Drugs.com databases

	Major	Moderate	Minor	Total
Micromedex	61 (40.1%)	69 (45.4%)	22 (14.5%)	152
Drugs.com	85 (13.8%)	464 (75.6%)	65 (10.6%)	614

Table 5. Comparison among most common major interactions

Major drug-drug interactions		Micromedex	Drugs.com	LexiComp
Diazepam	Codeine	X		X
Diazepam	Morphine	X		X
Fluoxetine	Amitriptyline	X	X	X
Haloperidol	Amitriptyline	X	X	X
Haloperidol	Fluconazole	X	X	X
KCl	Captopril	X	X	X
Tramadol	Amitriptyline	X	X	X
Tramadol	Fluoxetine	X	X	X
Tramadol	Metoclopramide		X	X
Tramadol	Promethazine	X	X	

Classification consistent with three databases analyzed: Micromedex, Drugs.com and LexiComp

DISCUSSION

When considering the differences between the CLO and SUO wards, the former had a larger number of major interactions due to the clinical profile of the patients. Clinical oncology does not focus on specific treatment/prophylaxis and a variety of disease states are treated at the same time, such as infections, prophylaxis for deep vein thrombosis and supportive care for pain, nausea/vomiting and circulatory conditions. The simultaneous use of a large number of different medications in this ward implies a greater risk rate for drug interactions.

Drugs that can cause central nervous system (CNS) depression/respiratory depression, such as diazepam, morphine and codeine, are also involved in important, well-documented drug interactions (Table 3). When used together, these drugs tend to have additive or synergistic effects and, even though the clinical objective may be precisely to depress the CNS, constant monitoring for the exacerbation of these effects is required, especially in debilitated patients. The Micromedex and LexiComp databases described these DDIs as major, whereas Drugs.com classified these DDIs as moderate. Interactions between tramadol and serotonin modulators (amitriptyline and fluoxetine) could be avoided by exchanging tramadol for codeine or morphine. Despite being classified as major, some drug interactions, such as captopril with ringer lactate and potassium chloride with scopolamine, require only simple monitoring measures: serum electrolytes and systemic blood pressure. Other drug interactions that have the potential to depress CNS function, such as opioid analgesics and benzodiazepine, are well known, clinically appropriate and used as intentional treatment, requiring proper patient monitoring. Thus, the clinical pharmacist should analyze each patient and suggest the best therapeutic option available.

Another difference in DDI was found between tramadol and metoclopramide, the interaction of which was classified as major in Drugs.com and did not even appear in Micromedex and LexiComp. Moreover, no articles were found on this DDI and no additional information on this interaction was found in Drugs.com. Due to this lack of information, Drugs.com is not the first choice for the identification of DDIs.

The present findings demonstrate important differences among the databases analyzed regarding the identification and grading of DDIs. Drugs.com classified nearly six-fold more moderate and minor DDIs than the Micromedex database. Furthermore, Drugs.com identified more major DDIs and a fourfold greater total number of DDIs in comparison to Micromedex. Previous studies have also found considerable discrepancies among drug compendia (Vitry, 2007; Vonbach et al., 2008; Fulda et al., 2000). Indeed, Fish (2007) found little agreement among drug interaction databases. This lack of standardization may disrupt clinical actions and ultimately affect the patient. Beyond the divergence between existent and nonexistent interactions, the databases list many drug interactions with no clinical relevance or DDIs that go against well-established treatment guidelines. These findings underscore the importance of a multiple reference research when analyzing drug interactions as well as the standardization of the information provided by these databases. In this

context, the clinical judgment of pharmacists can help improve the evaluation of drug interactions.

The most important finding involves discrepancies between Micromedex and Drugs.com regarding major DDIs. These differences continued even after checking the LexiComp database. As Drugs.com and Micromedex are updated daily, these compendia are considered to be better databases than LexiComp. Moreover, since they are Internet databases, both Micromedex and Drugs.com are easier, faster and more updated tools for the identification and classification of DDIs. Micromedex is an accepted international database. While the Brazilian Ministry of Health provides access to Micromedex, this access is greatly simplified and much information remains unavailable, making it financially unviable for Brazilian public health services. Drugs.com (2012) is a suitable tool for DDI management, as it is a free online database, but different DDI classifications could lead to uncertain clinical decisions. Due to the fact that LexiComp is a book, it should not be the first option to check for DDIs, as it is updated less often than the Internet databases. However, LexiComp is an internationally recognized reference and should be the first option when Internet access is unavailable.

The findings demonstrate the need for a health professional in hospital wards who can understand all the information contained in the databases and choose the best option for each patient. For every DDI found, a review performed by a clinical practitioner is indispensable. Moreover, pharmacists must check all prescriptions before the drugs are dispensed to patients and warn the prescriber of any inconsistencies. These practices help minimize the occurrence of negative outcomes related to drugs and allow the evaluation of clinically important DDIs. Actions to improve safety in medication management include the creation of a drug information center where the analysis of prescriptions could be performed and the presence of a pharmacist on duty with the multidisciplinary team in the different wards for immediate intervention in cases of error (Kaboli et al., 2006).

The use of dipyrone (metamizole) was constant in nearly every prescription. However, drug interaction databases do not contain this medication due to the fact that it has been withdrawn from the American market. Significant drug interactions (Baxter, 2008) involve dipyrone with cimetidine (increase in the area under the curve (AUC) of dipyrone), rifampin (increase in rifampin peaks) and methotrexate (increase in AUC of methotrexate). However, none of the prescriptions in the present study had these drugs used together. Another study on drug interactions suggests using dipyrone cautiously with phenothiazine derivatives due to the increased risk of severe hyperthermia and states that dipyrone may induce CYP3A4, decreasing the efficacy of the drug metabolism for some medications, such as benzodiazepines, tramadol, codeine, fentanyl, methadone, acetaminophen and corticosteroids (Worón et al., 2008). When dipyrone is necessary (based on clinical or economic issues), it is essential to monitor the patient and perform a thorough search of the literature for possible interactions.

Knowledge regarding the profile of DDIs allows the development of strategies to limit the risks and considerably improve pharmacotherapy in terms of patient morbidity/mortality and cost. The presence of a clinical pharmacist on the healthcare team constitutes one such strategy, as a pharmacist can act on different levels of the therapeutic process (i.e., identification of drug interactions based on research in the scientific literature as well as the clinical manifestations of interactions and their management) (Kaboli et al., 2006; Calop et al., 2008). Moreover, pharmacists should be involved in the standardization of the drug interaction database used within a hospital, since the available databases are not completely interchangeable and should be used in conjunction. Clinical pharmacists should be responsible for investigating interactions between two drugs in a prescription even in the absence of an initial clinical manifestation, since the suspicion of a interaction allows the healthcare team to be prepared in the case of undesired reactions (Gray & Felkey, 2004).

The short period of investigation (April to June 2009) was one of the limitations of the present study and occurred due to the lack of personnel available for a larger analysis. Moreover, the study was merely descriptive in nature; no interventions regarding the drug interactions identified were suggested/performed and the patient cases were not entirely considered, as only prescriptions were verified. The effect of drug interactions on patient outcomes was not considered as well, since all DDIs identified were interactions with the potential of occurring according to the literature and not actual interactions.

Despite the aforementioned limitations, the present study contributes important information on the prevalence and severity classification of drug interactions according to different databases. Based on the discrepancies found, standardization should be proposed. The following are further suggestions for more efficient pharmacotherapy and fewer complications caused by drug interactions: the promotion of safe medication practices, improvement in communication between patients and healthcare professionals and effective action of a multidisciplinary team. The establishment of video conference discussion groups of clinical cases among different institutions could be used to discuss conduct in cases of major interactions, which would assist in the creation of protocols and the standardization of evidence-based guidelines. However, more focused and larger studies should be carried out to obtain adequate validation and develop standardized methodologies for drug interaction analysis and management.

RESUMO

Interações medicamentosas em mulheres internadas com câncer: diferenças entre bases de dados

O objetivo deste estudo foi quantificar as interações medicamentosas em prescrições de mulheres submetidas à terapia de suporte no setor de oncologia de um hospital universitário brasileiro especializado na saúde da mulher e comparar as informações fornecidas por diferentes bases de dados em relação a estas interações medicamentosas. Foram selecionadas, por amostra de conveniência, prescrições de pacientes diagnosticadas com tumores mamários ou ginecológicos internadas nas unidades de Oncologia Clínica (CLO) e Cirúrgica (SUO),

durante o período de abril a junho de 2009. A principal base de dados utilizada foi a DrugDex/Micromedex (Thomson Micromedex), a qual foi comparada com outras duas bases de dados: Drugs.com e LexiComp. A busca foi realizada inserindo todas as combinações de drogas encontradas nas prescrições, na Micromedex e na Drugs.com. Todas as interações classificadas como de severidade maior identificadas pela Micromedex e/ou Drugs.com foram verificadas na LexiComp. Um total de 152 interações foram identificadas na Micromedex (61 maiores, 69 moderadas, 22 menores). Utilizando-se a Drugs.com, 614 interações foram identificadas (85 maiores, 464 moderadas, 65 menores). Quarenta e quatro interações medicamentosas foram classificadas como maiores em pelo menos uma das bases de dados: 30 pela Micromedex, 26 pela Drugs.com e 14 pela LexiComp. Estes resultados evidenciam discrepâncias entre as três bases de dados analisadas e, por isso, considera-se necessária uma padronização, além da análise criteriosa das prescrições por um farmacêutico junto à equipe multidisciplinar, a fim de promover práticas seguras no uso dos medicamentos, reduzindo, desta forma, possíveis complicações causadas por interações medicamentosas.
Palavras-chave: Interações de Medicamentos. Prescrições de Medicamentos. Oncologia.

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