OBJECTIVE: To analyse the occurrence of potential high-risk drug-drug interactions in elderly individuals with dementia. METHODS: The sample was chosen from a geriatric outpatient clinic of the Multidisciplinary Center for the Elderly in the University Hospital of Brasilia. This cross-sectional study included patients aged 60 or older with a diagnosis of dementia. The prescriptions were analyzed using the Lexi-Interact® database to identify possible potential drug-drug interactions. RESULTS: The study included 97 participants. Sixty-one patients (62.9%) had at least one clinically important potential drug-drug interactions (risks C and D). Of the 264 interactions identified, 23 (8.7%) were classified as risk D, 14 were pharmacodynamics and nine pharmacokinetic. CONCLUSION: The results of this study suggest an increased frequency in the occurrence of clinically significant potential drug-drug interactions in dementia patients. This reinforces the need for drug-drug interaction studies in specific populations. KEYWORDS: aged; drug interactions; geriatrics; dementia.

RESUMO

OBJETIVO: Analisar a ocorrência de interações medicamentosas de alto risco, em indivíduos idosos com demência. MÉTODOS: A amostra foi selecionada em um ambulatório de geriatria do Centro Multidisciplinar do Idoso do Hospital Universitário de Brasília. Este estudo transversal incluiu pacientes com 60 ou mais anos, diagnosticados com demência. As prescrições foram analisadas utilizando-se a base de dados Lexi-Interact®, a fim de identificar possíveis interações medicamentosas potenciais. RESULTADOS: O estudo incluiu 97 indivíduos. Sessenta e um pacientes (62,9%) apresentaram pelo menos uma potencial interação medicamentosa clinicamente importante (riscos C e D). Das 264 interações identificadas, 23 (8,7%) foram classificadas como risco D, 14 como farmacodinâmicas e 9 como farmacocinéticas. CONCLUSÃO: Os resultados obtidos sugerem uma frequência aumentada de potenciais interações medicamentosas clinicamente significativas em pacientes com demência. Isso reforça a necessidade de mais estudos sobre a interação medicamentosa em populações específicas.

PALAVRAS-CHAVE: idoso; interações de medicamentos; geriatria; demência.
INTRODUCTION

Dementia is defined as a syndrome of diverse etiology. Alzheimer’s disease is considered its most common cause, thus affecting the brain structure and causing progressive deterioration of memory and of other brain functions. The World Health Organization estimates 35.6 million people living with dementia worldwide. In Brazil, population studies indicate a prevalence of 5.1 to 19% of dementia in the population aged 60 years or older. Comorbidities are common in the elderly, as well as in subjects with dementia, and are associated with a higher risk of polypharmacy and drug-drug interactions.

Drug-drug interactions are changes in the action of a drug, which are caused by the presence of another drug in the body. These can be pharmacokinetic if the drug concentration in its site of action is altered, or pharmacodynamics, when there is a change of the molecular activity in its site of action or in the expected physiological response. Drug interactions can result in therapeutic failure, adverse events, hospitalization, or even death.

From an economic outlook, drug-drug interactions alone can contribute to an increased frequency of adverse drug-related events and, consequently, to a high expense on health care. Cognitive impairment and age-related changes in pharmacokinetics and pharmacodynamics can contribute to the complexity of prescriptions. Furthermore, patients with dementia need to pay special attention to potential drug interactions. The present study aimed at analyzing the occurrence of potential and theoretical high-risk drug-drug interactions in elderly individuals with dementia.

METHODOLOGY

Study design and population

Due to convenience, the sample was selected from consecutive appointments in a geriatric outpatient clinic of a reference center called the Multidisciplinary Center for the Elderly at Universidade de Brasília (UnB), Brasília, Federal District, Brazil. Data collection was cross-sectional and occurred from January 2002 to December 2006, and the analysis was carried out from January to February 2011.

The study included patients aged 60 or older, of both genders, diagnosed with dementia, based on criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association. All participants signed an informed consent form. The Research Ethics Committee of the School of Health Sciences at UnB approved the study, under registration number 0261.0.012.000-05.

Data collection and analysis

A single trained researcher (pharmacist) collected data, and a clinical pharmacist monitored him/her, through semi-structured interviews with caregivers and consultation on systematic and standardized medical records. Sociodemographic variables such as age, gender, education, household income, and use of prescription drugs were collected.

The prescriptions for each patient were analyzed using the Lexi-Interact® database, to identify possible potential drug-drug interactions (PDDI). These interactions were classified as risk A (no known interaction), risk B (no action needed), risk C (monitored therapy), risk D (consider therapy modification), and risk X (avoid combination). This database was used in this study because it was free.

The identification was non-exclusive, thus the same elderly person could present more than one PDDI. Risk D interactions were selected and divided into pharmacokinetic or pharmacodynamics, depending on the mechanism of action. The pharmacodynamics interactions were subdivided into synergistic adverse effects (increased toxicity) and pharmacological antagonism (reduced effectiveness). The pharmacokinetic interactions were also subdivided into interaction during absorption, distribution, metabolism or excretion. All the drugs were classified according to the Anatomical Therapeutic Chemical (ATC) 2011, accessed on October 3rd, 2011.

Some drugs, such as dipyrone, mianserin, propargyl nitrate and diosmin, did not have their possible PDDI accounted for they were not listed in the Lexi-Interact® database.

In this study, the clinical outcome of these interactions was not evaluated, only the risk of potential adverse events associated with these drugs.

The statistical analysis was conducted using Microsoft Excel®. The statistical test used to determine the p-value for the population was the two-tailed z-test at a level of significance of 0.05 or lower.

RESULTS

The study included 97 participants aged between 60 and 94 years, mean age 78.0 ± 7.7 years, mostly women (69.1%). There was no statistically significant difference between the mean age of male (77.2 ± 7.8) and female (78.2 ± 7.7) (p = 0.595) participants.

The number of medications used by the patients ranged from one to nine, an average of 4.0 ± 2.2 drugs per patient. Among men, the mean number of medications was 3.8 ± 1.9 and among women 4.3 ± 2.4, with no statistical difference between the means (p = 0.436).
Sixty-one patients (62.9%) had at least one clinically important PDDI (risks C and D). Of the 264 interactions identified, 23 (8.7%) were classified as risk D, 8 (3.0%) as risk A, 27 (10.2%) as risk B, and 206 (78.3%) as risk C. The 23 risk D interactions were subdivided according to their mechanisms of action, being 14 pharmacodynamics and 9 pharmacokinetic.

We identified 26 drugs responsible for risk D interactions and classified them according to the ATC: 12 of which act on the central nervous system; three on the cardiovascular system; three on the musculoskeletal system; two on the blood and hematopoietic organs; two on the gastrointestinal tract and metabolism; one was classified as dermatological; one as systemic hormonal preparations, excluding sex hormones and insulin; and one as systemic anti-infective. Garlic extract could not be classified by ATC.14

All of the pharmacodynamics PDDI presented potential synergistic adverse effect. Among the potential adverse effects that were added or maximized in such interactions, eight might enhance the risk of prolonging cardiac repolarization (QT interval), four can lead to an increased bleeding time, one can increase central nervous system depression and one heightens the risk of Serotonergic Syndrome. The drug most often associated with these interactions was risperidone (Table 1).

Of the nine pharmacokinetic interactions, four involved absorption, three inhibition of cytochrome P450, and one induction of metabolism. There was one drug interaction involving an unidentified mechanism. The drug responsible for the greatest number of interactions was calcium carbonate, which acted as a precipitating agent in all four absorption interactions (Table 2).

**DISCUSSION**

Elderly people are susceptible to polypharmacy, and accordingly, to adverse effects from potential drug interactions.15 The most important result in our study was the high prevalence of at least one clinically significant PDDI in elderly patients with dementia, when compared with literature data. In our research, the prevalence of this PDDI type was of 62.8%. In a cross-sectional study with a population of 12,343 elderly in the region of Ourinhos, São Paulo State, Obreli Neto et al.16 found a prevalence of around 47.4%, but not in dementia patients. Thus, dementia may be an associated factor for the occurrence of PDDI. Other studies have showed that PDDIs are more likely to occur in hospital settings, where multiple drugs are regularly prescribed concomitantly.17

There are few studies that evaluate PDDIs in geriatric patients, especially in dementia. Using a similar method but with different data base, Hosia-Randell et al.18 evaluated all nursing home residents aged $\geq$ 65 years in Helsinki. From 1,987 studied subjects, 69.5% were diagnosed with dementia and 4.8% were susceptible to a clinically significant PDDI. The most common potential PDDIs were related to the use of potassium-sparing diuretics, carbamazepine, and codeine.18 Another European study reported a prevalence of class D (“clinically significant interaction and the combination should be avoided”) PDDI among elderly outpatients ranging from 4.1 to 11.9%.19 We observed an approximate number, risk D, in 8.7% of our sample.
Among the interactions found, there was a predominance of the risk C type, a result consistent with similar studies.\textsuperscript{16,20} Such interactions, despite being more frequent, offer less risk to the patient.\textsuperscript{21} This research did not identify any risk X interactions, probably because it involved prescribers from a teaching center.\textsuperscript{22,23} It is noteworthy that the increase in drug intake is directly proportional to the increase in PDDI.\textsuperscript{16}

Since in many situations the occurrence of PDDI cannot be avoided, much can be done to prevent or reduce the damage they may cause. Having tools to screen potential interactions is important to prevent them. Databases such as Lexi-Interact\textsuperscript{®} are useful as means of flagging patients susceptible to PDDIs.\textsuperscript{18} Once the interaction is detected, prevention and management strategies can be employed based on the knowledge of the interaction mechanism — pharmacodynamics or pharmacokinetic.

All the pharmacodynamics PDDI found presented potential synergistic adverse effect. Their clinical management involves observing adverse effects and if there is exacerbation of these effects, reduction of dosage, replacement of one or more drug therapies or monitoring of lab tests should be considered.\textsuperscript{24} Eight (57\%) of the pharmacodynamics PDDI showed potential to increase the QT interval. Such an event, should it occur, might be considered particularly serious in elderly patients, who are more susceptible to arrhythmias, and also in those subjects using medications to control behavioral and psychological symptoms of dementia, which are among the main causes of QT prolongation.\textsuperscript{25,26} Recommendations are that patients with this type of interaction require periodic ECGs.\textsuperscript{27}

The pharmacokinetic PDDI occurred during metabolism, through enzymatic induction or inhibition. Literature suggests that the prescriber take into consideration which cytochrome is responsible for the metabolism in order to avoid possible interactions.\textsuperscript{24}

As to management, the replacement for other drugs that have different metabolic pathways is suggested. Other pharmacokinetic PDDI occurred when the drugs were administered with calcium carbonate, which is mainly used in the treatment of osteoporosis, it reduces the absorption of other medications and, therefore, the bioavailability of various drugs.\textsuperscript{28,29} The pharmacokinetic interactions during absorption are easy to manage. In most cases, it can be done simply by changing the medication administration timing to ensure the absorption of both drugs.\textsuperscript{30} The pharmacist’s participation in this context is important to determine the more adequate administration timing.\textsuperscript{31,22}

Despite the importance of our findings, data extrapolation and application are limited. Similar studies are scarce and, to date, there has not been a standardized approach to the detection and assessment of the interactions, since the different databases available provide different information.

An important element that was not considered in this study was the dosage of the drugs used. Although different doses present different safety margins, we have chosen to analyze only the potential risk of interactions. The clinical events resulting from these drug interactions were not analyzed. With regard to the analysis of interactions, certain drugs were excluded from the PDDI analysis because some commonly used drugs in Brazil are not included in the Lexi-Interact\textsuperscript{®} database.

**CONCLUSIONS**

The results of this study suggest an increased frequency in the occurrence of clinically significant PDDI in dementia patients. Drug-drug interactions are a frequent cause of preventable adverse drug events and medication-related hospitalizations. As commented by Maher, Hanlon and Hajjar, practitioners should keep the possibility of a drug-drug interaction in mind when prescribing any new medications.\textsuperscript{19} This reinforces the need of studies about such subject in specific populations, which may assist in the adoption of strategies for risk reduction and management of adverse effects resulting from these interactions.

**CONFLICT OF INTERESTS**

The authors reported no conflict of interests.

**REFERENCES**


