Interactions between antidepressants and antihypertensive and glucose lowering drugs among patients in the HIPERDIA Program, Coronel Fabriciano, Minas Gerais State, Brazil

Interações entre antidepressivos e medicamentos e anti-hipertensivos e hipo-glicemiantes em pacientes do Programa HIPERDIA em Coronel Fabriciano, Minas Gerais, Brasil

Paula Vieira Coelho [1]
Carla de Arêdes Brum [1]

[1] Curso de Farmácia, Centro Universitário do Leste de Minas Gerais, Coronel Fabriciano, Brasil.

Correspondence
P. V. Coelho
Curso de Farmácia, Centro Universitário do Leste de Minas Gerais.
Rua Polônia 172, Timóteo, MG 35182-260, Brasil.
paulavcoelho@yahoo.com.br

Abstract

The aims of this study were to investigate the prevalence and to describe the most frequent potential interactions between antidepressants and antihypertensive and glucose lowering drugs in the HIPERDIA Program at two primary care units in Coronel Fabriciano, Minas Gerais State, Brazil. Data were collected through the patient registry in the HIPERDIA Program and the local psychoactive drug dispensing system. Interactions were classified as due to pharmacokinetic and/or pharmacodynamic mechanisms. Prevalence of antidepressant use in the HIPERDIA Program was 4.37% (29 of patient 663 records). Of the HIPERDIA patients in treatment with antidepressants, 19 were exposed to 47 interactions, 23.4% of which involving pharmacokinetic, 61.7% pharmacodynamic synergy, and 15.9% simultaneous pharmacokinetic and pharmacodynamic mechanisms. Complications can arise from drug-drug interactions, a situation that can escape the attention of prescribing health professionals.

Drug Interactions; Antihypertensive Agents; Hypoglycemic Agents; Antidepressive Agents

Introduction

Polytherapy is a useful tool for treating coexistent diseases, but drug combination may reduce efficacy and/or favor the appearance of adverse reactions with different degrees of severity [1]. Brazil is the fifth country in the world in consumption of medicines and the first in Latin America, and the Oswaldo Cruz Foundation estimates 24 thousand deaths per year from poisoning with medication [2]. New drugs, new indications, and new interactions appear daily, and *drug-drug interactions* are thus an everyday issue in medical practice [3].

Irrational use of medicines is a major public health problem worldwide. According to estimates, incorrect prescription leads to costs involving 50 to 70% of government funds earmarked for drugs [4]. Meanwhile, when used correctly, medicines are the most cost-effective therapeutic resource [5].

Several studies in recent years have shown a strong correlation between depression and such clinical diseases as diabetes and hypertension. Patients with diabetes showed an increased risk of depression, and those with diabetes and depression appear to have a higher risk of complications, as well as more difficult blood glucose control. Evidence also indicates that the reverse may occur, namely depression increases the risk of diabetes [6].

Due to the high incidence of simultaneous hypertension, diabetes, and depression, it is common to find patients that use antidepressants and antihypertensive and glucose lowering drugs concurrently. This polytherapy requires increased knowledge of these drug classes, particularly in relation to drug-drug interactions. "*Due to the pathophysiological characteristics of these clinical entities and the complexity and narrow therapeutic index of these drugs, severe complications can be triggered by their interactions if they are selected or managed inadequately*" [7] (p. 135).

In order to promote better quality of life for patients with diabetes and/or hypertension and allow monitoring of drug dispensing, the Brazilian Ministry of Health developed the HIPERDIA Program. The program's objective is to register and monitor patients with hypertension and diabetes captured by the National Plan for Reorganization of Care for Arterial Hypertension and Diabetes Mellitus in all the outpatient units of the Unified National Health System (SUS), generating information for local, Municipal, State, and Ministry of Health administrators (HIPERDIA: System for Registering and Monitoring Individuals with Hypertension and Diabetes; http://hiperdia.datasus.gov.br).

Numerous studies on medication errors, including drug-drug interactions, are currently underway worldwide, analyzing the medication systems in various hospitals and systematically assessing the errors. A hospital study by Cassiani et al. [8] suggests that factors contributing to medication errors include lack of concern by health staff towards the treatment plan adopted by prescribers. The authors found a striking lack of drug information centers and revision of medical prescriptions by pharmacists and nurses to evaluate the treatment, excessive doses, and drug-drug interactions [8]. Wiltink [1] highlights the pharmacist's importance in controlling and evaluating the prescribed drugs, since interactions pose a permanent risk that deserves investigation.

Serious adverse events (SAEs) are the sixth most common cause of death in hospitalized patients in the United States, while the most frequent form of SAE results from drug-drug interactions [3]. This emphasizes the need for studies on prescriptions to identify and establish the prevalence of drug-drug interactions that can cause disorders for patients and expenses for the health system.

In this study, we analyze data for patients in the HIPERDIA Program in primary care units in the neighborhoods of Caladinho and Centro in Coronel Fabriciano, Minas Gerais State, Brazil, and from the electronic registry of psychoactive drugs to identify possible drug-drug interactions involving antidepressants and antihypertensive and glucose lowering drugs during treatment.

Materials and methods

The sample selection included a representative number of patients for an error less than 5%, based on the total number of patients registered in the HIPERDIA Program in the primary care units in the neighborhoods of Caladinho and Centro in the city of Coronel Fabriciano. Systematic random sampling was used to select individuals for the sample.

The representative sample was calculated according to Barbetta [9]:

(1) $n_0 = 1/E_0^2$

(2) $n = N \times n_0 / N + n_0$

Where: n_0: approximation for sample size; E_0: tolerable sampling error = 0.05 or 5%; N: population size; n: sample size (number of elements); (1): sample size (n_0) as a function of the tolerable sampling error; (2): correction of the sample calculation as a function of n_0.

Based on the above calculation, we analyzed the records of 663 patients in the HIPERDIA Program in Coronel Fabriciano, 316 of whom were from the 1,082 patients registered in the Caladinho health unit and 347 from the 769 patients in the Centro health unit on the day of the data collection.

Data were collected on the patients' age, gender, and antihypertensive and glucose lowering medication in January 2007. In Coronel Fabriciano, data on health unit users are decentralized, i.e., each program (HIPERDIA, Psychoactive Drug Dispensing System) records the data on the medicines dispensed for that purpose. Data conversion to electronic format began in 2007, but the amount of data available in the system is still low.

Information on patients in the HIPERDIA Program (name, age, gender, current medication, dose) is recorded manually in a notebook known as the "records ledger", containing only the information concerning the medicines. This study included patients registered in the HIPERDIA Program since December 2003 and attending the primary care units in the Caladinho and Centro neighborhoods.

Information on antidepressant use by selected patients was obtained by consulting the Psychoactive Drug Dispensing System in the Coronel Fabriciano stockroom (electronic system) and a data survey during the research conducted by the two authors (A. F. Valadão and K. F. Firmino; unpublished data) that lists the users and the antidepressants dispensed in Coronel Fabricia-

no, including for patients treated at the primary care units analyzed in the current study.

For purposes of simplification, this study uses "record" to refer to the data collection site for patients in the HIPERDIA Program and in the Psychoactive Drug Dispensing System.

The drug-drug interactions were classified as *pharmacokinetic*, when one of the drugs potentially interfered in the absorption, distribution, metabolism, and excretion of another, or *pharmacodynamic*, as when drugs with similar or opposite effects are administered jointly [10,11].

The data were presented as proportions, means, standard deviations (SD), and confidence intervals. Data analysis used Microsoft Office Excel, version 2007 (Microsoft Corp., USA).

Results and discussion

Of the 663 records that were analyzed, 66.37% were from women and 33.63% from men, with a median age of 60 years (range: 18 to 101).

The sample consisted of 523 individuals (78.9%) with hypertension, 32 (4.8%) with diabetes, and 108 (16.3%) with both diabetes and hypertension. These data suggest a relatively low rate for diabetes alone, compared to that of patients with both diabetes and hypertension, confirming the tendency for diabetics to develop cardiovascular disorders. According to the 2002 consensus of the Brazilian Society of Diabetes, arterial hypertension is present in 50% of patients with type 2 diabetes mellitus and appears in late form in patients with type 1 diabetes, as renal function decreases [12].

In all, 1,483 drugs were prescribed for treatment of hypertension, diabetes, and depression on 663 patient records, resulting in a mean of 2.24 (SD = 1.13) drugs per individual, ranging from 1 to 6 medicines per patient. This figure is lower than the national mean, which is 5 drugs by one-third of individuals older than 60 years [13,14], and can be identified as one of the reasons for the relatively low drug-drug interaction rate found in this study. The patients were taking a mean of 3.7 (SD = 2.27) pills per day.

Analysis of the medicines used according to therapeutic class showed: 75.46% antihypertensive drugs, 11.19% glucose lowering drugs, and 2.23% antidepressants. Figure 1 summarizes the data.

Table 1 lists the drugs identified and shows the diuretic hydrochlorothiazide as the most

Figure 1

Relative frequency of therapeutic classes found in patient records in the HIPERDIA Program.

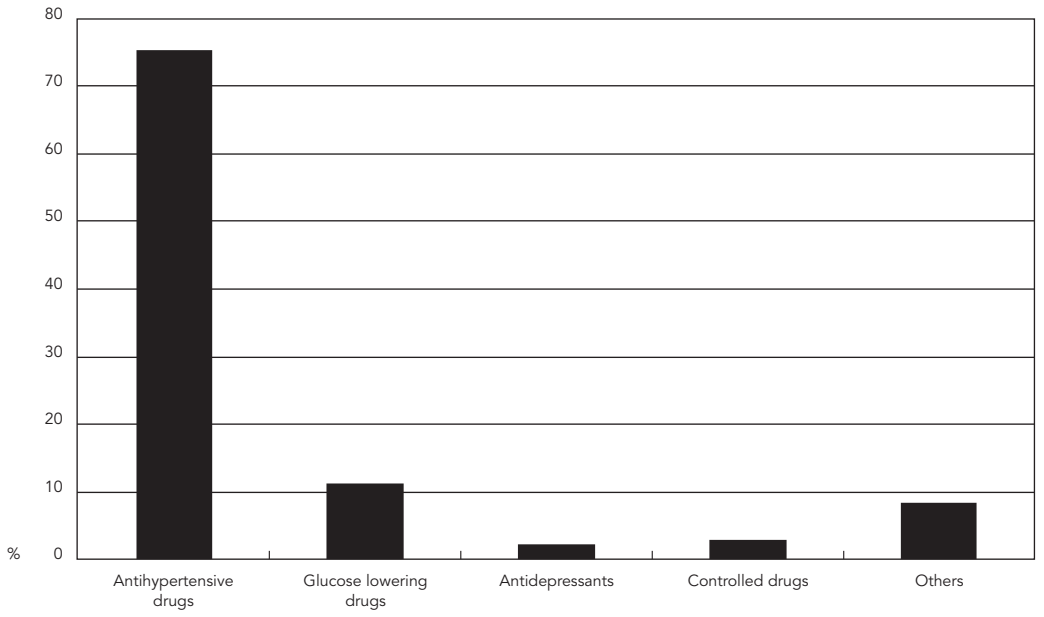

Table 1

Relative frequency of prescribed medications.

Drugs	Absolute frequency	Relative frequency (%)
Antihypertensive drugs		
Hydrochlorothiazide	339	22.86
Captopril	334	22.52
Propranolol	146	9.84
Nifedipine	107	7.22
Furosemide	63	4.25
Methyldopa	45	3.03
Digoxin	35	2.36
Enalapril	11	0.74
Atenolol	9	0.61
Propatylnitrate	7	0.47
Amlodipine	6	0.40
Chlorthalidone	6	0.40
Amiodarone	3	0.20
Verapamil	3	0.20
Spironolactone	2	0.13
Amiloride	1	0.07
Carvelidol	1	0.07
Isosorbide	1	0.07
Subtotal	1,119	75.46
Glucose lowering drugs		
Glibenclamide	52	3.51
Insulin	52	3.51
Metformin	51	3.44
Gliclazide	4	0.27
Chlorpropamide	3	0.20
Glimepiride	3	0.20
Rosiglitazone	1	0.07
Subtotal	166	11.19
Antidepressants		
Fluoxetine	13	0.88
Amitriptyline	9	0.61
Imipramine	6	0.40
Nortriptyline	3	0.20
Mirtazapine	1	0.07
Paroxetine	1	0.07
Subtotal	33	2.23

(continues)

frequently prescribed antihypertensive, corresponding to 22.86% of all the drugs prescribed, followed by captopril (22.52%) and propranolol (9.84%). These data are not entirely consistent with the 3rd Brazilian Consensus on Arterial Hypertension [15], which establishes the drugs of choice for initial treatment of arterial hypertension as diuretics in monotherapy, follow by beta-blockers, calcium channel antagonists, angiotensin-converting enzyme inhibitors, and angiotensin II antagonists. Despite the guidelines, the treatment choice should be based on the patient's predominant physiopathogenic conditions, individual conditions, associated diseases, socioeconomic conditions, and the capacity of the medication to interfere in cardiovascular morbidity and mortality [15].

The most frequent glucose lowering drugs were glibenclamide and insulin, each representing 3.51% of all the drugs prescribed, followed

Table 1 (continued)

Drugs	Absolute frequency	Relative frequency (%)
Antidepressants		
Fluoxetine	13	0.88
Amitriptyline	9	0.61
Imipramine	6	0.40
Nortriptyline	3	0.20
Mirtazapine	1	0.07
Paroxetine	1	0.07
Subtotal	33	2.23
Controlled drugs		
Diazepam	12	0.81
Clonazepam	10	0.67
Bromazepam	4	0.27
Haloperidol	3	0.20
Biperidene	2	0.13
Carbamazepine	2	0.13
Phenobarbital	2	0.13
Thioridazine	2	0.13
Chlorpromazine	1	0.07
Diltiazem	1	0.07
Phenytoín	1	0.07
Levodopa	1	0.07
Levomepromazine	1	0.07
Subtotal	42	2.83
Other		
Acetyl salicylic acid (ASA)	70	4.72
Other	53	3.57
Subtotal	123	8.29

by metformin, with 3.44%. The similarity in the prescription rates for these drugs may suggest equal preference in medical prescription. A study by Pereira et al. [16] in 2005 showed a preference for monotherapy with glibenclamide.

Fluoxetine was the most widely prescribed antidepressant (40.63% of the antidepressant prescriptions, followed by amitriptyline (28.13%), imipramine (21.88%), nortriptyline (6.25%), and paroxetine (3.11%) respectively.

The group of "controlled" medications included those covered by Ministry of Health Ruling 344/98 [17], excluding the antidepressants that were used by the patients in the sample.

The most widely described drug in the "others" group was acetylsalicylic acid 100mg (ASA). This group also included other drug classes like anticoagulants, antacids, anti-inflammatory drugs, herbal drugs, and lipid lowering drugs.

Table 1 provides the drugs in each group, indicating their absolute and relative frequencies.

Antidepressants had been prescribed in combination with antihypertensive and glucose lowering drugs in 29 of the 663 records (4.37%). This does not necessarily mean that the 29 patients had a diagnosis of clinical depression, since the record does not provide the patients' clinical diagnosis for other diseases, but the proportion is similar to that found in the SHEP study (Systolic Hypertension in the Elderly), which found associated clinical depression in 4.8% of 4,508 elderly patients with systolic hypertension [18].

Nineteen of the 29 records showed a total of 47 potential drug interactions. Not all of the records showed potential interactions, but those that did had a mean of 2.37 interactions (ranging from 1 to 5). This can be explained by the capacity of antidepressants to interact with other drugs through pharmacokinetic and pharmacodynamic mechanisms. Although relatively few patients were exposed to interactions, this figure is worrisome, since the interactions that were identified mostly occur through synergy and can increase the hypotensive and glucose lowering effects. In addition, the mean number of interactions is problematic, since such interactions can trigger severe side effects in patients.

Table 2 lists the most frequent interactions between antidepressants and the drugs in the HIPERDIA Program. Other drug associations

Table 2

Relative frequency of prescribed medications.

Antidepressant	Drug class, HIPERDIA Program	Absolute frequency	Relative frequency (%)	Description of interaction
Fluoxetine	Diuretics (Furosemide Hydrochlorothiazide)	9	19.15	Increased risk of hyponatremia [22]
Imipramine	β-blockers (Propranolol. Atenolol)	5	10.64	Increased hypotensive effects due to desensitization of β-adrenergic receptors [22]
Fluoxetine	Angiotensin-converting enzyme inhibitors (Captopril. Enalapril)	5	10.64	Risk of development of hyponatremia and precipitation of adverse effects from ACE inhibitors (dry cough) [22]
Fluoxetine	β-blockers (Propranolol. Atenolol)	4	8.51	Decreased metabolism of β-adrenergic blockers with increases in their adverse effects [22]
Fluoxetine	Sulfonylureas (Glibenclamide)	3	6.38	Increase in hypoglycemia [22]

with potential interactions were also found, but were not described, since their frequencies were not significant; however, they are important and require attention by health staff, especially pharmacists.

The classification of interactions between antidepressants and antihypertensive and glucose lowering drugs according to mechanism of action indicated that 23.4% could occur through pharmacokinetic mechanisms and the majority (61.7%) through pharmacodynamic mechanisms, all of which involving drug-drug synergies, which could cause serious side effects such as severe hypotension or hypoglycemic attack. In 14.9% of cases, the interactions could occur through the two mechanisms simultaneously.

The suggested causes for explaining the existence of prescriptions with drugs involving potential interactions includes the complexity of these medicines, lack of information in the public healthcare services on their interactions and adverse effects, and lack of effective implementation of a pharmaceutical care model. In addition, the municipality lacks a single, unified patient registry.

Pharmaceutical care encompasses patient follow-up and evaluation of drug usage and therapeutic efficacy [19] and is included in the field of comprehensive treatment measures under the Unified National Health System [20]. Thus, pharmacists play a crucial role in primary care units, since they are responsible for assessing and interpreting prescriptions and should identify any contraindications and potential interactions. In addition, if necessary they should contact the prescribing physician to clarify any problems that have been detected [21].

Patient data are still decentralized in the municipality. Therefore, the prescribing health professional lacks access to patient information, which could otherwise reduce the risk of prescribing drugs that might lead to interaction. One possible solution would be the implementation of an electronic system with the patient's complete record, which could be accessed by attending physicians from their offices or clinics. However, although electronic data systems can contribute to adequate treatment and identification of potential interactions, they do not take individual patient conditions into account and thus do not rule out the need for assessment of patient conditions and participation by pharmacists in public primary healthcare services.

Another factor that can influence the existence of prescriptions with potential drug interactions is physicians' knowledge of such interactions. This study did not investigate whether the simultaneous prescription of drugs with potential for interaction was due to the physician's lack of knowledge. This highlights the need for drug information services in order for health professionals to assess the risk/benefit ratio when prescribing. Such care should be taken in order to prevent adverse reactions to medicines, contribute to treatment adherence, and improve quality of life for patients in the HIPERDIA Program.

Conclusion

In conclusion, 4.37% of the 663 patients in the HIPERDIA Program used antidepressants, of which 19 were exposed to 47 interactions due to pharmacokinetic (23.4%), pharmacodynamic synergy (61.7%), and simultaneous pharmacokinetic/ pharmacodynamic mechanisms (15.9%).

This study thus contributed with pharmacoepidemiological information on the prevalence

of potential drug-drug interactions in patients under the HIPERDIA Program that take antidepressants, since studies are scarce in the literature on prevalence of drug interactions.

The interactions detected in treatment of patients in the HIPERDIA Program that are on antidepressants emphasize the important role of pharmacists in the health team, to conduct an assessment of the prescription before dispensing medicines to patients, as well as to monitor them throughout treatment through pharmaceutical care, in order to prevent adverse reactions and suggest necessary changes, thereby improving patients' quality of life and reducing costs from drug-drug interactions.

Resumo

O objetivo do estudo foi investigar a prevalência e descrever as possíveis interações de medicamentos mais freqüentes entre antidepressivos e anti-hipertensivos/hipoglicemiantes do programa HIPERDIA de duas unidades básicas de saúde do Município de Coronel Fabriciano, Minas Gerais, Brasil. A coleta de dados foi realizada mediante consulta ao caderno de cadastro dos pacientes usuários do programa de HIPERDIA e pela consulta ao sistema de dispensação de psicotrópicos do município. As interações foram classificadas segundo o mecanismo farmacocinético e farmacodinâmico. A prevalência do uso de antidepressivos em pacientes do HIPERDIA foi de 4,37% (29 de 663 cadastros analisados). Dos pacientes do HIPERDIA em tratamento com antidepressivos, 19 estão expostos a 47 interações, 23,4% delas ocorrem por mecanismos farmacocinéticos, 61,7% por mecanismos farmacodinâmicos de sinergismo e 15,9% interagem das duas formas simultaneamente. Complicações podem ser provocadas por interações entre fármacos e os profissionais prescritores podem não estar atentos a tal fato.

Interações de Medicamentos; Anti-Hipertensivos; Hipoglicêmicos; Antidepressivos

Contributors

P. V. Coelho and C. A. Brum participated in the writing, revision, and correction of the article.

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