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Article

Possible pharmacological interactions in hypertensive and/or diabetic elderly in family health units at Blumenau (SC)

Vicente Codagnone Neto[1], Victor Pundek Garcia[1], Ernani Tiaraju de Santa Helena[2,*]

[1]School of Medicine, Regional University of Blumenau, [2]Department of Medicine, Regional University of Blumenau

The aim of this study was to examine the possible adverse drug-drug interactions in the elderly population (≥60 years) diagnosed either with diabetes, arterial hypertension or both, at a Family Health Unit (FHU) clinic in Blumenau, state of Santa Catarina, Brazil. For this purpose 318 subjects were interviewed using a pretested form with social and demographic aspects regarding their disease and its complications. All drugs used by this population were grouped, and the drug-drug interactions were detected by using the "Drug Interaction Checker" software, and classified for frequency and severity. The average age of patients was 70.6 years, with a higher number of female patients (216; 67.9%). Most subjects were being treated for both diseases (149; 46.86%). Out of a total of 1,541 medications prescribed, the most prevalent were: hydrochlorothiazide (131; 8.4%) and enalapril maleate (130; 8.4%). A total of 295 possible drug-drug interactions were detected in 152 patients (1.9 interactions per subject), 275 (93.2%) moderate and 20 (6.8%) severe or highly severe. The possible interaction prevalence was 0.93 (0.55 to 1.40 depending on health unit). The most frequent possible interaction was that between acetylsalicylic acid and enalapril maleate (37; 12.5%). Patients had an average consumption of 6.6 drugs and 9.8% of subjects reported physical discomfort when using medicines. Elderly patients use many medications that could cause adverse reactions and possible drug-drug interactions, where this issue warrants closer attention of prescribers and health providers.

Uniterms: Drug-drug interaction. Systemic arterial hypertension/use of medications. Diabetes Mellitus/use of medications. Elderly/use of medications. Family health program.

Buscou-se identificar possíveis interações medicamentosas em pessoas idosas com diabetes melito (DM) e/ou hipertensão arterial sistêmica (HAS) sendo atendidas em unidades de Saúde da Família, em Blumenau (SC). Entrevistaram-se 318 pessoas com 60 e mais anos, portadoras de DM e/ou HAS, mediante questionário estruturado pré-testado, com variáveis sócio-demográficas da doença e do tratamento. As interações medicamentosas foram verificadas através do aplicativo *"Drug Interaction Checker"* e classificadas quanto a freqüência e severidade. A maioria dos pacientes era do sexo feminino (216; 67,9%), com média de idade de 70,6 anos (DP = 6,9), recebendo tratamento por ambas as doenças (149; 46,86%). Dentre 1.541 medicamentos prescritos, os mais prevalentes foram: hidroclorotiazida (131; 8,4%) e maleato de enalapril (130; 8,4%). Foram detectadas 295 possíveis interações medicamentosas em 152 idosos (média 1,9 interações), das quais (275; 93,2%) foram moderadas e (20; 6,8%) severas ou muito severas. A prevalência de possíveis interações foi de 0,93 (0,55 a 1,40, dependendo da unidade de saúde). A possível interação mais freqüente foi entre ácido acetilsalicílico e maleato de enalapril (37; 12,5%). Cada paciente fazia uso de 6,6 medicamentos em média e 9,8% relataram algum desconforto físico com o uso de medicamentos. Idosos utilizam grande quantidade de medicamentos que resultam em reações adversas e possíveis interações medicamentosas, merecendo maior atenção dos prescritores e gestores.

Unitermos: Interação medicamentosa. Hipertensão arterial sistêmica/uso de medicamentos. Diabetes melito/uso de medicamentos. Idosos/uso de medicamentos. Saúde da família.

Correpondence: E. T. S. Helena. Universidade Regional de Blumenau, Centro de Ciências da Saúde, Departamento de Medicina. Rua Antônio da Veiga, 140 – Victor Konder - 89012-900 - Blumenau - SC, Brasil. E-mail: erntsh@furb.br

INTRODUCTION

Weight gain in the Western population as a whole, together with inadequate feeding habits, physical inactivity, and the use of tobacco and alcohol, have contributed to an increase in the prevalence of health problems such as arterial hypertension and diabetes (Ogden *et al.*., 2006).

In the presence of this unbalanced way of life, physicians are facing a great challenge: providing adequate therapeutic support to patients with interrelated and even synergistic diseases. These resultant drug combinations can decrease the overall treatment efficacy and/or favor adverse reactions of varying degrees of severity. The strategy to treat coexisting pathologies results in polypharmacy (use of five or more drugs), a situation that could be exacerbated by the consumption of over-the-counter (OTC) remedies (Junius-Walker *et al.*, 2007).

With the increased life expectancy in Brazil, the at-risk population for development of diverse age-related diseases has grown. As a result, clinicians are faced with a growing number of patients who are evidently fragile to deal with invasive treatments and interventions. Thus, polypharmacy appears to be a problem in this sub-population. In a review, Rozenfeld (2003) pointed out that Brazilian epidemiological studies show that medicine use increases with age, and around 80% of aged people consume at least one medicine regularly while 30% of elderly consume over-the-counter (OTC) medicines. Medical prescriptions in this group commonly evidence inadequate doses and indications, unexpected pharmacological interactions and unsuitable medication associations, besides the use of therapeutically ineffective medications.

The treatment of patients with arterial hypertension and/or diabetes is no exception regarding polypharmacy. When patients are diagnosed with arterial hypertension and/or diabetes, many different medications could be appropriate for their treatment, including drugs for dyslipidemia, hypertension, antiplatelet therapy and glycemic control (Triplitt, 2006).

The identification of drug-drug interactions in patients with hypertension and/or diabetes could be very important, because these diseases are highly prevalent in Brazil. The treatment of these diseases includes highly complex therapeutics, which are undergoing rapid development and employ substances that are relatively new in the market, whose interactions are not yet fully clarified, or documented. A significant proportion of these new drugs are available on the Brazilian public health system (Brasil, 2009).

The extent of suffering and deaths caused directly by pharmacological interactions is not clear, but current evidence shows that this problem deserves serious attention on the part of both the medical community and the population who self-medicate and disregard the risks involved (Lima, 2004). Currently, an increasing number of people have access to a host of medications (thanks to large number of medication providers, such as physicians, pharmacists, friends and relatives), and their utilization can become abusive, particularly with regard to the risk for undesirable pharmacological interactions among chronically diseased patients (Lima, 2004; Rozenfeld, 2003).

Results from different studies on adverse drug reactions (ADRs) have been pooled in some meta-analyses, showing that the proportion of drug-related hospitalization is between 2.4 and 6.2% where many such cases were preventable (Cresweel *et al.*, 2007). Another prospective observational study in England found that adverse drug reactions cost £466 million annually, resulting in the deaths of around 5700 patients (Pirmohamed *et al.*, 2004).

The aim of the present study was to verify the possible pharmacological interactions in elderly arterial hypertension and/or diabetes patients attended at Family Health Strategy units of Blumenau, in the state of Santa Catarina, Brazil.

MATERIAL AND METHODS

This is a cross-sectional epidemiologic study on a sample population composed of elderly people with arterial hypertension and/or diabetes, living and registered in the area covered by the Family Health Strategy (FHS), in the city of Blumenau, state of Santa Catarina (SC), Brazil.

Elderly persons were considered individuals, aged 60 or older, as proposed by WHO for developing countries (Brasil, 2006).

Individuals with at least six months of clinical follow-up, and living in areas covered by FHS units in place for at least 1 year before the field work started in 2006 April, were included in the study.

Two-stage random sampling took place. In the first stage, a simple random sampling of 10 Family Health units was carried out (of the 34 existing units that had been in operation for more than 1 year). In the second sampling stage, those people living in the area covered by the units and registered as arterial hypertensive and/or diabetic were identified. Subsequently, stratified random sampling was done, distributing the sample size proportionally for people with arterial hypertension and/or diabetes registered in every unit. Thus, the people aged 60 years or more were identified and included in this study.

The study participants were visited at home and a pretested questionnaire was applied by trained and qualified interviewers. Data on the following variables were obtained: sex, age (average value and age ranges), marital status (if married, single, widow, or separated), race/color (as reported by the interviewee), religion practiced, educational level (collected as completed years of study and categorized as 1st to 4th elementary school, 5th - 8th middle school, and complete high school or graduated), current consumption of tobacco and alcohol (type and quantity), time of diagnosis (in months), time of treatment (in months), other associated diseases, name and amount of consumed medications, use of natural homemade remedies, presence of any physical discomfort when using medication.

In order to estimate the presence of drug-drug interactions, the medications consumed by every person in the last 7 days were identified. These medications were entered into an on-line software program (Drug Interaction Checker), which performed a bibliographical search of three (3) databases: the U.S. Food and Drug Administration (FDA), American Hospital Formulary Service (AHFS Drug Information) and First DataBank, generating a report containing the following information: *1) Presence of interaction:* whether any type of interaction is occurring or not; *2) Severity:* any interaction being classified as 'very severe' (drug combination is contraindicated and should not be dispensed or administered to patient); 'severe' action is required to decrease the interaction risk); and 'moderate' (interaction risk should be evaluated and action measures are also necessary); *3)Symptoms and clinical signs* and; *4) Mechanism of action*.

Consumed medications were organized according to the Brazilian Common Denomination, which assigns the name of active principles utilized by pharmaceutical industry through the Ordinance # 1179, dated June 17th, 1996.

The data were descriptively presented in tables by frequencies with a confidence interval of 95%. For the continuous variables, the central trend (mean and median) and dispersion (standard deviation) measures were calculated. The prevalence (number of events divided by persons at risk) of possible interactions was also calculated.

This present study was developed with data collected by the Project "Adherence to pharmacological treatment of patients with hypertension and/or diabetes mellitus in the family health units in Blumenau (SC)", previously approved by the Institutional Review Board/Independent Ethics Committee of the Regional University of Blumenau (040/2004).

RESULTS

Three hundred and eighteen individuals aged 60 years or older with arterial hypertension and/or diabetes, were interviewed.

These people were predominantly female (216; 67.9%), had a mean age of 70.6 years (standard deviation of 6.9 years) and median age of 69.9 years. The majority of these people had studied only up to 1st – 4th years of elementary school (210; 66.2%) or were illiterate (75; 23.7%) (Table1).

With respect to lifestyle, 29 people affirmed to be smokers (9.1%, 95% CI 6.2 – 12.8) and 264 reported not to be in use of any type of alcoholic beverage (83.0%, 95% CI 78.4 – 87.0). The most consumed type of beverage (by 32 persons) was beer (10.1%, 95% CI 7.0 – 13.9).

Table 2 shows information on diseases and medications.

The average treatment time of patients with arterial hypertension was 162.3 months (SD = 144.7) and median was 120 months. The average time for treatment of diabetes was 115.3 months (SD = 96.6) and the median was 84 months.

Out of a total of 1541 prescribed medications, the four most frequent medications were: hydrochlorothiazide (131; 8.4%), enalapril maleate (130; 8.4%), lovastatin (100; 6.5%) and metformin (97; 6.3%) (Table 3). Patients were in use of, on average, 4.8 medications.

The presence of 295 possible drug-drug interactions in 152 elderly people (47.8%; n= 318) was detected. Out of these possible interactions, 275 were of moderate severity (93.2%), 19 were severe (6.5%) and 1 was very severe (0.3%). The prevalence of possible interactions was 0.93, (0.55 to 1.40 depending on the family health unit).

The most frequent medications in the interactions were acetylsalicylic acid (85; 14.3%), enalapril maleate (75; 12.6%), glibenclamide (71; 12.0%) and digoxin (51; 8.6%).

As shown in Table 5, the most frequent potential drug-drug interactions were between: acetylsalicylic acid and enalapril maleate (37; 12.5%) glibenclamide and hydrochlorothiazide (33; 11.1%), acetylsalicylic acid and glibenclamide (22; 7.4%) and enalapril maleate and furosemide (21; 7.1%).

Twenty possible interactions were detected with a higher grade of severity. One of these was considered very severe and occurred with nortriptyline hydrochloride and selegiline. This drug-drug interaction can lead to a severe reaction, including the symptoms: hyperpyrexia, convulsions, excitability, muscle stiffness, fluctuations in blood pressure, epilepsy, coma, and death.

TABLE I - Socio-demographic variables

Variables		Frequency (N)	Relative Freq. (95% CI)	
Sex	Female	216	67.9 (62.5 – 73.0)	
	Male	102	32.1 (27.0 – 37.5)	
Age range				
	60-70	160	50.3	44.7 – 55.9
	70-80	126	39.6	34.2 – 45.2
	80 or older	32	10.1	7.0 – 13.9
Marital Status				
	Married/Stable Union	153	48.2	42.5 – 53.8
	Single	12	3.7	2.0 – 6.5
	Separated	29	9.2	6.2 – 12.8
	Widow	124	38.9	33.6 – 44.6
Color				
	White	270	84.9	80.5 – 88.7
	Brown	34	10.7	7.5 – 14.6
	Black	12	3.7	2.0 – 6.5
	Other	2	0.7	0.0 – 2.2
Religion*				
	Roman Catholic	243	76.8	71.9 – 81.4
	Protestant/Evangelic	57	18.1	14.0 – 22.7
	Spiritist	1	0.3	0.0 – 1.8
	Other	13	4.1	2.2 – 6.9
	None	2	0.7	0.0 – 2.2
Educational level*				
	Illiterate	75	23.7	19.1 – 28.7
	1st – 4th years – elementary	210	66.2	60.7 – 71.4
	5th – 8th years – middle	25	7.9	5.2 – 11.4
	Complete High School or graduated	7	2.2	0.9 – 4.5

(*) Excluding unknown cases.

Out of 19 pharmacological interactions considered severe, the most frequent were: bromazepam and fluoxetine hydrochloride (3; 1.0%), amiodarone hydrochloride and digoxin (3; 1.0%), metformin and norfloxacin (2; 0.7%), amiodarone hydrochloride and sodium warfarin (2; 0.7%) and glibenclamide and norfloxacin (2; 0.7%).

The clinical manifestations and mechanism of action of more severe pharmacological interactions are shown in Table VI.

It is noteworthy that in one individual, 11 possible drug-drug interactions were detected, 3 being severe and 8 moderate. The severe interactions comprised: amiodarone hydrochloride and digoxin; amiodarone hydrochloride and sodium warfarin; sulfasalazine and sodium warfarin.

Out of 318 interviewees, 60 (18.9%) reported spontaneously physical discomfort when utilizing some type of medication. Given that a person could complain about more than one discomfort, there was a total of 75 complaints for the 60 patients. Out of these, 17(22.6%) complaints were of stomach pain, 9 (12.0%) nauseas, 7 (9.3%) dizziness, 4 (5.4%) weakness, 4 (5.4%) shortness of breath, 3 (4.0%) diarrhea. The other symptoms amounted to a total of 31 complaints (41.3%).

TABLE II - Treatment

Variables	Frequency (N)	Relative Freq.	95% Confidence Interval
Disease undergoing Treatment			
Hypertension	146	45.9	40.3 – 51.6
Diabetes mellitus	23	7.2	4.6 – 10.7
Both	149	46.9	41.3 – 52.5
Time of Treatment Hypertension*			
< 1 year	15	5.2	2.9 – 8.4
1 - 5 years	74	25.4	20.5 – 30.8
5 - 10 years	68	23.4	18.6 – 28.7
10 - 20 years	88	30.2	25.0 – 35.9
> 20 years	46	15.8	11.8 – 20.5
Time of Treatment Diabetes Mellitus			
< 1 year	15	8.9	5.1 – 14.3
1 - 5 years	50	29.8	23.0 – 37.3
5 - 10 years	50	29.8	23.0 – 37.3
10 - 20 years	37	22.0	16.0 – 29.1
> 20 years	16	9.5	5.5 – 15.0
Number of Medications*			
0	7	2.3	0.9 – 4.6
1 to 4	164	53.4	47.7 – 59.1
5 to 8	119	38.8	33.3 – 44.5
9 to 13	16	5.2	3.0 – 8.3
21	1	0.3	0.0 – 1.8
Use of Natural Homemade Remedies*			
Yes	144	46.0	40.4 – 51.7
No	168	53.7	48.0 – 59.3
Not Informed	1	0.3	0.0 – 1.8

(*) Excluding unknown cases.

TABLE III - Medications consumed (n= 1541)

Variables	Frequency (N)	Relative Freq.	95% Confidence Interval
Hydrochlorothiazide	131	8.4	7.2 – 10.0
Enalapril Maleate	130	8.4	7.2 – 10.0
Lovastatin	100	6.5	5.3 – 7.8
Metformin	97	6.3	5.1 – 7.6
Acetylsalicylic Acid	87	5.6	4.5 – 6.9
Glibenclamide	87	5.6	4.5 – 6.9
Atenolol	59	3.8	2.9 – 4.9
Captopril	51	3.3	2.5 – 4.3
Omeprazole	42	2.7	2.0 – 3.7
Propranolol Hydrochloride	33	2.1	1.5 – 3.0
Furosemide	33	2.1	1.5 – 3.0

TABLE IV - Most frequent medications in interactions (n=590)

Variables	Frequency (N)	Relative Freq.	95% Confidence Interval
Acetylsalicylic Acid	85	14.3	11.7 – 17.5
Enalapril Maleate	75	12.6	10.1 – 15.7
Glibenclamide	71	12.0	9.5 – 14.9
Digoxin	51	8.6	6.5 – 11.2
Furosemide	46	7.8	5.8 – 10.3
Hydrochlorothiazide	46	7.8	5.8 – 10.3
Captopril	28	4.7	3.2 – 6.9
Spironolactone	27	4.5	3.0 – 6.6
Lovastatin	21	3.5	2.2 – 5.4
Sodium Warfarin	12	2.0	1.1 – 3.5

TABLE V - Most frequent potential drug-drug interactions and their clinical effects

Variable	N (%)	95%Confidence Interval	Clinical effect
Acetylsalicylic Acid + Enalapril Maleate	37 (12.5)	8.9 – 16.9	Decreased Antihypertensive effect
Glibenclamide + Hydrochlorothiazide	33 (11.1)	7.8 – 15.4	Decreased Antihypertensive effect; Worse Glucose tolerance
Acetylsalicylic Acid + Glibenclamide	22 (7.4)	4.7 – 11.1	Reinforced Hypoglycemic effect
Enalapril Maleate + Furosemide	21 (7.1)	4.5 – 10.7	Postural hypotension
Acetylsalicylic Acid + Captopril	15 (5.1)	2.9 – 8.2	Decreased Antihypertensive effect
Spironolactone + Enalapril Maleate	11 (3.7)	1.9 – 6.6	Hyperkalemia
Digoxin + Spironolactone	10 (3.4)	1.6 – 6.1	Digoxin toxicity symptoms (anorexia, nauseas, vomits, headache, fatigue, disorientation, hallucination and arrhythmia)
Digoxin + Hydrochlorothiazide	10 (3.4)	1.6 – 6.1	Digoxin toxicity symptoms (anorexia, nauseas, vomits, headache, fatigue, disorientation, hallucination and arrhythmia)
Digoxin + Lovastatin	9 (3.0)	1.4 – 5.7	Increased rhabdomyolysis risk
Captopril + Furosemide	7 (2.4)	1.0 – 4.8	Postural hypotension
Propranolol Hydrochloride + Glibenclamide	7 (2.4)	1.0 – 4.8	Decreased responses to insulin and sulphonylureas; Potentially increased frequency and severity of hypoglycemia episodes

DISCUSSION

The sample studied has shown similarities with the populations studied in other national (Marin *et al.*, 2008; Meireles *et al.*,2007; Paniz *et al.*, 2008; Zaitune *et al.*, 2007; Silva *et al.*, 2006) and international (Lawson *et al.*, 2006; Dubova *et al.*, 2007; Bjorkman *et al.*, 2002) investigations involving elderly attended in the primary care system.

Potential drug-drug interactions were detected in 152 out of the 318 elderly interviewed (47.7%). This frequency is lower than the figure reported in a Mexican study, where almost 80% of patients presented potential pharmacologic interactions. This difference could be associated to the Mexican study's inclusion criteria, namely, patients older than 50 years, with non-malignant algic syndrome. It is noteworthy that the prevalence of hyperten-

TABLE VI - Clinical manifestations and mechanism of action of most severe potential drug-drug interactions

Severe interactions	Clinical manifestation	Mechanism of action
Bromazepam Fluoxetine Hydrochloride	Increased BZD levels; Clinical effect increased BZD.	Certain SSRIs (Selective Serotonin Reuptake Inhibitors) could decrease the Phase I metabolism of BZD through the competitive inhibition of CYP-450.
Amiodarone Hydrochloride Digoxin	Digoxin toxicity symptoms (anorexia, nauseas, vomits, headache, fatigue, disorientation, hallucination and arrhythmia)	Multiple mechanisms appear to be involved. Amiodarone decreases the renal and non-renal clearance of digitalis glycosides (DG), decreases the volume of distribution and increases the bioequivalence of DG. Also, DG depressed the sinus node, producing bradycardia.
Metformin Norfloxacin	Deep Hypoglycemia	Unknown
Amiodarone Hydrochloride Sodium Warfarin	Bleeding risk.	The amiodarone has been shown to inhibit the metabolism of R and S enantiomers of Warfarin by CYP-450. It could also inhibit the metabolism of acenocoumarol and other anticoagulants.
Glibenclamide Norfloxacin/Cinofloxacin	Deep Hypoglycemia.	Unknown
Phenprocoumon Sodium Levothyroxine	Hypothyroidism could increase oral anticoagulant requirement. The administration of thyroid hormones or hyperthyroidism could decrease the oral anticoagulant requirement.	Unknown
Atenolol Clonidine Hydrochloride	Severe Hypertension.	β-Blockers inhibit the vasodilatation mediated by β2-receptor, decreasing the opposition to vasoconstriction mediated by α2-receptor.
Sodium Warfarin Sulfasalazine	Bleeding risk; Decreased Prothrombin activity.	Unknown
Sodium Warfarin Sodium Levothyroxine	Hypothyroidism could increase the oral anticoagulant requirement. The administration of thyroid hormones or hyperthyroidism could decrease the oral anticoagulant requirement.	Unknown
Diazepam Fluoxetine Hydrochloride	Increased BZD levels; Clinical effect increase of BZD.	Certain SSRIs (Selective Serotonin Reuptake Inhibitors) could decrease the Phase I metabolism of BZD through competitive inhibition of CYP-450.

sive and diabetic patients was higher in the present study (67.3% and 29.5%, respectively), as were the predominant interactions, generally associated to medications used to treat these pathologies (Dubova *et al.*, 2007).

In addition, another European multicenter study conducted in 5 countries involving individuals aged 65 years or older in use of 4 medications or more, detected some type of possible interaction in 46% of the sample (Bjorkman *et al.*, 2002).

With respect to tobacco use, the vast majority, 90.9% of those interviewed, stated they were non-smokers. Studies have shown that the percentage of smokers declines proportionally with age (Paniz *et al.*., 2008; Sawatzky *et al.*., 2007; Dubova *et al.*, 2007). In a comparative study of

smoking prevalence, a higher decline in total percentage of smoking elderly individuals was evident from 1989 until 2003 where in 2003 a percentage of 14% of elderly smokers was found in the sample (Monteiro *et al.*, 2007).

In this study, 60 persons (18.9%) reported physical discomfort with the use of some medication, with stomach pain (12%) and nausea (9.3%) being the predominant complaints. The inadequate use of medications in elderly has been high in many studies, with some symptoms being connected with specific drugs. In the study of Gurwitz *et al.*. (2003) there was association of dry mouth with the use of antidepressive medications and nauseas with digoxin and NSAIDs. According to Dubova *et al.*. (2007), cardiovascular disease allied to polypharmacy (>5 drugs) and advanced age (>60 years), are risk factors for drug-drug interactions.

The most consumed medication was hydrochlorothiazide (8.4%) followed by enalapril maleate (8.4%), lovastatin (6.5%), metformin (6.3%), acetylsalicylic acid (5.6%), glibenclamide (5.6%) and atenolol (3.8%). Given this, with the exception of metformin and omeprazole, the 10 most-prescribed medications were associated with 58% of cases of possible interactions. The predominance of drugs affecting the cardiovascular system, pancreas and endocrine system and drugs utilized in homeostasis and thrombosis was also evidenced in a Brazilian study with elderly individuals, irrespective of the disease (Marin *et al.*, 2008).

The most frequent potential drug-drug interactions include acetylsalicylic acid with enalapril maleate or glibenclamide, but most patients use acetylsalicylic acid in low doses (80 to 200mg) to prevent major cardiovascular events, thereby lowering the risk of interactions. Out of 295 possible drug-drug interactions, 20 (6.8%) were considered severe or very severe and included the most frequently prescribed medications (metformin, glibenclamide and atenolol). The use of norfloxacin it notable because, when associated to metformin (2 occurrences) or glibenclamide (2 occurrences) norfloxacin can cause deep hypoglycemia by an as yet unknown mechanism. Norfloxacin should also be prescribed with caution in elderly when associated to steroids because of the risk of tendon ruptures. The use of trimethoprim-sulfamethoxazole (in patients utilizing metformin) or cephalexin (in those using glibenclamide) could represent alternatives.

Also, it is important to consider the patient's renal function and manage this risk. The use of atenolol combined with clonidine (1 occurrence) could lead to severe hypertension by blockage of B2 receptors, annulling the balance with vasoconstriction mediated by alpha receptors. An alternative to this prescription could be the combination of atenolol with enalapril maleate (Mion *et al.*, 2002).

Digoxin was the fourth medication in the list of main causers of pharmacological interactions, and was related to 13.8% of pharmacological interactions, despite being present in only 1.6% of prescriptions. Due to its narrow therapeutic window (0.8 to 2.0 ng/mL) and reduced renal function in elderly patients, there is a higher chance of toxicity. Its association with amiodarone represents 1% of interactions and is considered severe, causing effects of digitalis intoxication. It is a drug considered inappropriate, but of low risk by the Beers criterion for elderly, at doses above 0.125mg/dose, even after taking into account the presence of other drugs for cardiac failure (inhibitors of angiotensin conversion enzyme, betablockers and diuretics) and for arrhythmias (amiodarone) (Packer *et al.*, 1993; Fick *et al.*, 2003; Fialová *et al.*, 2005; Chutka *et al.*., 2004).

Many studies are evaluating the use of electronic means to help healthcare professionals in the identification of possible pharmacological interactions in their prescriptions. The possibility of reducing pharmacological interactions using such devices is a current focus of study. However, many difficulties have been pointed out in the use of such systems, including the main issue of the lack of specificity in results, with too many interactions being indicated, few of which are actually relevant. Other problems include the lack of emphasis in warnings for the more severe interactions, leading to many people ignoring or underestimating the warnings issued by these computer programs (Tamblin *et al.*, 2003; Ahearn, Stephen, 2003).

Limitations

This study presents some limitations. There are several definitions of elderly and most of these can be criticized because they are based on age alone. Although the WHO recommends 60 years and older for developing countries, many authors around the world have adopted 55 or 65 years. It is important to bear in mind that being elderly does not only refer to age alone, but to a special phase in life, all of which are related to particular conditions (social, clinical, emotional) that must be taken into account when comparisons are made

There are different software programs supported by a variety of databases which identify possible drug-drug interactions. This array of options could explain the frequency of discrepancies found among studies. In this study, an open web database was used to facilitate access and achieve better comparisons.

It is worth mentioning that cross-sectional studies such as the present investigation, can only detect preva-

lent cases of interactions. In severe cases, it is likely that patients with symptoms complain to their doctors or ask to change medicines. Therefore, some cases can only be detected in longitudinal investigations such as cohort studies.

CONCLUSIONS

Access to medications was broadened following implementation of the Family Health Strategy, particularly to drugs requested for hypertension and diabetes (Paniz *et al.*, 2008). However, the high proportion of possible drug-drug interactions and adverse reactions suggest that measures should be taken in order to improve the quality of care, by means of continued education for prescribers, as well as by improvement of dispensation conditions in these units (usually done by nursing staff). The frequent staff turnover of family health teams, compromising sustained continuity of care, associated to treatment that is sometimes given by different medical specialists, could also contribute to the occurrence of possible interactions. Further investigations should be undertaken to evaluate the consistency of the results obtained and to study their possible determinants.

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