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POTENTIAL DRUG INTERACTIONS IN PRESCRIPTION OF HEART FAILURE PATIENTS ASSISTED IN A PRIMARY PUBLIC HEALTH UNIT IN MARINGÁ, PARANÁ, BRAZIL

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ABSTRACT
Purpose: The aim of this study was to detect probable drug interactions from elderly patients with heart failure in a primary health care. **Methods:** A cross-sectional study involving standardized of Electronic Health Records by the health department from patients with heart failure. The sample was screened using as criterion the use of digoxin to evaluate drug interactions it was used the Micromedex database 2.0, whose focus was only the interaction among digoxin with other medications. To define probably inappropriate medications the Beers criteria was used. **Results:** Heart Failure patients currently use polytherapy. From the analyzed patient records, we found that 62 (95.38%) contained important drug interactions, such as High Risk or Moderate Risk with higher prevalence in males (71.43%) and (71.05%) of women with High Risk interactions. When standardized conduct was considered by each type of drug interaction with digoxin and the electronic records analysis was observed a non-compliance with pre-established protocol treatment. **Conclusion:** Drug interactions were due to errors in medication prescribing, errors in dose management and others factors. It is well known that there is computerized physician order entry able to help the physician in his therapeutic approach in a multidisciplinary health patient assistance.

KEYWORDS: Heart Failure, Drug Interaction, Prescribers, Unit Health Care.

INTRODUCTION
Drug interactions occur when both the effects of a drug as their toxicities are altered by another drug, generally unexpected and undesirable in pharmacotherapy. This severity depends on the amount of drugs used, age and condition presented by the patient.[1] This leads several adverse drug reactions (ADRs) frequently in elderly or in patients suffering from chronic diseases or by using of polytherapy in most comorbidities.[2]

Heart failure (HF) is a prevalent chronic disease in elderly[3] that uses polytherapy. The prevalence of heart failure in North America is almost 5.7 million whose incidence reaches approximately 660,000 per year and probably, will increase by 3 million people.[4] The mortality of heart failure remains quite high, with about 277,000 deaths per year. Approximately 20% of patients die within 1 year after diagnosis; the 5-year mortality is 59% in men and 45% in women.[5]

In Maringá, in 2008, there were 762 hospital admissions for hypertension whose spending represented 21% of total spending of admissions. In addition, 10% of deaths recorded during this period were caused by ischemic heart disease. In Paraná, in 2007, 1.157,509 hospitalizations were recorded by cardiovascular disease (CD) by SUS. Regarding costs, in November 2009, there were 91,970 hospitalizations for CD at national level, resulting in a cost of R$ 165.461.644,33.[6] The HF is a serious public health problem and associated with disabling symptoms, is the only CD whose prevalence has increased in recent years and cause a huge burden to the healthcare system due to frequent and prolonged hospitalizations.[7]

An estimated 23 million people worldwide have IC and two million new cases are diagnosed annually.[8] The increased incidence of HF is related to therapeutic advances that have led to a greater survival the elderly population and thus increase in hospital admissions for this disease, raising health care costs. According to DATASUS (2010), in Brazil there are about two million patients with HF and every year are diagnosed 240,000 new cases.

The main drugs used in the treatment of the HF are: angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, diuretics, angiotensin receptor blockers (ARBs), calcium antagonists channels and digoxin[3] and are used often combined leading to a wide range of important interactions. Digoxin is a digitalis glycoside extensively used in HF and has close therapeutic range. Its use can commonly induce various adverse effects and drug interactions.[9] Indeed, today the digoxin remains the glycoside most prescribed in the world.[10,11]

The aim of this study was to detect probable drug interactions in patients associated with heart failure in a public primary health care unit.

METHODOLOGY

A descriptive retrospective study involving standardized electronic health records (EHRs) by the health department for patients with heart failure treated in a basic health unit Ney Braga in Maringá, Paraná, Brazil.

For the screening of patients it was used as criteria the use of digoxin, since the diagnosis of the disease was not included in the EHRs. Data collection was carried out among June-September 2013 of the last 10 years and they were transferred to a database that included sex, age, medicines, dosages, weight, blood pressure and. To evaluate drug interactions it was used the Micromedex 2.0 program, whose focus was only the interaction among digoxin with other medications. To determine inappropriate medications, the Beers criteria was used.[12]

The Beers criteria, also known as Beers list refers a list of drugs considered inappropriate and/or unsafe to be administered in geriatrics. Is a reference for health professionals around the safety of drug administration in the elderly. It is based on the physiological changes in the pathophysiology of age and making these patients more susceptible to the side effects of drugs.

All statistic analyses were performed with the aid of software R version 3.0.1. Results were expressed as means, frequencies and percentages. For parametric analysis, it was used the Tukey test. For the other tests it was used ANOVA and Fisher's test for analysis of different groups. P values <0.05 were considered significant.

The study received ethical approval from the municipal health department of Maringá and the ethics committee of the State University of Maringá. Protocol No. CEP: 303 834/2013.

RESULTS

Our study showed that of the 65 medical records analyzed, 37 (56.92%) were women whose average age was 69.26 ± 13.2. Most patients studied were older than 60 years old (76.93%) and had uncontrolled pressure (60%) and were overweight (76.93%), corroborating literature data where patients with HF have obesity and hypertension[3,13] as shown in Table 1.

Table 1: Patients' characteristics

	Patients	
	N	**%**
Total	65	100
Patient's age (average)	69.3±13.2	
Women	37	56.9
Men	28	43.1
<60	15	23.1
≥60	50	76.9
Normal Pressure	26	40
High Pressure	39	60
BMI		
Normal	15	23.1
Overweight	36	55.4
Obesity I	9	13.8
Obesity II	5	7.7

Normal pressure was considered till 138x89 mmHg. BMI (Body Index Mass): Normal values <25, Overweight have mid values to 25 till 30, Obesity I value mid to 30 till 35 and Obesity II values over 35.

In Table 2 is described the main drugs and pharmacological classes used by patients with probable drug interactions when combined with the drug digoxin. Among the most prescribed medications listed were: captopril (36.92%), carvedilol (44.62%), spironolactone (44.62%), furosemide (43.07%), hydrochlorothiazide (33.85%) and omeprazole (33.85%).

Table 2: Main drugs used by patients

MEDICATIONS	Total	
	N	%
Amiodarone	2	3.1
Atenolol	6	9.2
Captopril	24	36.9
Carvedilol	29	44.6
Enalapril	5	7.7
Spironolactone	29	44.6
Furosemide	28	43.1
Hydroclorothiazide	22	33.9
Nifedipine	5	7.7
Omeprazole	22	33.9
Propranolol	5	7.7
Verapamil	1	1.5
Main Drug Categories		
Diuretics	10	15.4
Beta Blockers	8	12.3
ACEI	4	6.2
Diuretics and Beta Blockers	17	26.2
ACEI and Beta Blockers	4	6.2
ACEI and Diuretics	8	12.4
ACEI, Diuretics and Beta Blockers	11	16.3

Beta Blockers: Atenolol, Carvedilol and Propranolol. ACEI: Captopril and Enalapril. Diuretics: Furosemide, Hydroclorothiazide, Spironolactone.

From the analyzed patient records, we found 62 (95.38%) contained important drug interactions according to Micromedex database 2.0, such as High Risk (HR) or Moderate Risk (MR) with higher prevalence in males 20 (71.43%) and 27 (71.05%) of women with HR interactions (Table 3).

Table 3: Drug interactions

Interactions	N	Portents (%)
MR	16	24.6
HR	4	6.2
RM and HR	43	66.2

HR (High Risk): amiodarone, hydroclorothyazide, spironolactone and verapamil. MR (Moderate Risk): atenolol, captopril, carvedilol, enalapril, furosemide, nifedipine, omeprazole and propranolol.

In Table 4, it was listed the inappropriate uses of medications used by patients, according to Beers criteria (digoxin, spironolactone, nifedipine and verapamil).

Table 4: Frequency of medications avoided according to Beers criteria

Medications	N	Portents (%)
Digoxin (>0,125mg)	65	100
Spironolactone (>25mg)	29	44.2
Nifedipine	7	10.8
Verapamil	1	1.5

Digoxin dose higher than 0.125mg/day and spironolactone dose higher than 25mg/day should be avoided according to Beers criteria.

Our study showed a higher probability of interaction ($p \leq 0$) when used lot of medications by the patient (Table 5).

Table 5: Average number of used drugs compared by each drug interaction group.

Association	Difference	p-value
HR-0	3.76	0.0036 *
HR and MR-0	5.34	0.0000 *
MR-0	4.77	0.0000 *

HR and MR-HR	1.42	0.3972
MR and HR	1.27	0.7491
MR-HR and MR	0.89	0.7998

It was used Tukey test to evaluate associations among different types of drug interactions. HR (High Risk), MR (Moderate Risk) and 0 without interaction.

DISCUSSION

HF patients frequently are treated with medicines polytherapy, because it is the final outcome of several pathologies.[3] Diabetes, hypertension and obesity are the most common associated diseases in patients with HF.[13] These diseases aggravate the patient conditions and promote the use of drug combined therapies often complex.[3] In our work 60% of patients presented high pressure (Table 1).

Obesity and advanced age cause decreased metabolism and lead to various types of drug interactions.[1,3,13] In our work, the plenty of associated diseases commonly in growing older patients lead to the use of a large number of medications.

Many medications used are described in the literature on the treatment of HF, including: beta-blockers, angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), diuretics, antiarrhythmics, direct vasodilators, digitalis and calcium channel blockers.[3,13] Due to the wide variety of arrangements for drug therapy and the utilization of complex combined associations seem many times empirical[3] and it may cause drug interactions with undesirable adverse reactions[1,14] (Table 3).

The objective of the Beers criteria[12] is to improve the quality of life of elderly patients by reducing the use of potentially inappropriate medications in this group. In table 4, it was listed the inappropriate uses of medications used by patients. In HF, using a digoxin dose higher than 0.125 mg it has no additional benefit and may increase the risk of toxicity since the renal clearance is slower in the elderly.[12] All EHRs analyzed contained the use of doses from 0.25 mg digoxin and all these patients had more than 65 years old.

Higher doses up to 25 mg of spironolactone per day increase the risk of hyperkalemia in elderly patients with HF and it should be avoided. This problem is also associated with dioxin use further increases the risk of hyperkalemia in these patients.[12,15,16] Nifedipine, a calcium antagonist drug used by 7.7% of the elderly patients should be avoided in the elderly due to the risk of hypotension and myocardial ischemia. Verapamil, a calcium channel antagonist promotes fluid retention and exacerbates the HF. It was contraindicated drug in HF[12] and was used by only one patient.

ACE inhibitors are recommended for all patients with HF, even asymptomatic. Many studies have demonstrated your efficacy and have shown to reduce morbidity and mortality, by the better vasodilator outcome.[3,17] However, when captopril is administered increases the bioavailability of digoxin. For this reason, serum digoxin levels should be determinate before and after the first captopril dose and it should be decreased from 30% to 50% the digoxin dose throughout therapy.[18] In our study 44,6% of patients were treat with ACEI and none dose adjustment was reported for digoxin (Table 2).

Although diuretics drugs do not increase patient survival, they are the drugs of excellence in the treatment of congestive HF symptoms. Hydrochlorothiazide is indicated in cases of mild fluid retention being substituted by furosemide when in case of large retention volume.[3] However, when administering hydrochlorothiazide, depleting potassium with digoxin, 40% of patients develop hypokalemia in less than a week worsening clinical patients state and it may lead to death if none monitoring or supplementation with potassium is introduced in the therapy scheme.[18,19] The use of furosemide associated with digoxin causes the same toxic effects and hypokalemia.[20] Studies also showed that the use of spironolactone (aldosterone antagonist) decreased 30% overall mortality decline to the progression of heart failure and sudden death.[21] Nevertheless, spironolactone increases the bioavailability of digoxin at 30% where a dose adjustment is necessary to avoid toxic effects of glycoside.[18] In our work it was demonstrated that 70.8% of the patients were using of diuretics and any dose adjustment for digoxin was found and any reports of digoxin intoxication.

Beta-blockers promote important changes in the prognosis of HF. Three beta-blockers have been approved in well-conducted studies showing improvement in heart ejection fraction and reduction in morbidity and mortality: carvedilol, bisoprolol and metoprolol.[3] However, in our study, 16.93% of prescriptions were found digoxin associated with atenolol and propranolol. In our work, 33,9% were treated with this drug and did not have any potassium monitored was reported in EHRs.

Moreover, the concomitant use of digoxin and carvedilol high the effects of bradycardia, whereas is recommended frequently electrocardiogram monitoring after short periods.[22] In our study, we found 44.62% of records with prescriptions carvedilol without accompanying electrocardiogram, because none EHR had this data.

The use of proton pump inhibitor such as omeprazole decreases the secretion of hydrochloric acid in the stomach which inactivates part of digoxin ingested. Therefore, there is an increase in the bioavailability of

digoxin that will result in toxic effect.[23] Continuous use of omeprazole and digoxin should be monitored and reduce the dose to avoid toxicity. In this work, 33.85% of patients used omeprazole and digoxin whose dose was maintained (Table 2).

Calcium channel blockers are also used in HF therapy, however, when it is necessary (hypertensive heart disease and/or ischemic), amlodipine can be considered, and the use of nifedipine and verapamil associated to digoxin should be avoided.[3] The concomitant use of verapamil and digoxin rise the risks of digoxin toxic effects. Indeed, the bioavailability is increased from 50% to 75%, where digoxin dose has to be reduced to half or one quarter and their monitoring should be continuous.[24] In our study, 15.4% of records contained nifedipine or verapamil associated with digoxin without dose adjustment being, therefore, contraindicated (Table 2).

Ninety percent of HF patients develop some variety of heart arrhythmia. Amiodarone, class III antiarrhythmic agent, is used as a prophylactic in HF and decreased cases of suddenly death.[25] Nevertheless, when amiodarone is administered in patients treated with digoxin, it should consider discontinuing or reducing of digoxin to normal dose half and should be consider monitoring and follow-up. Amiodarone increases the digoxin's bioavailability at 70% and exacerbates the toxic effects.[12] In our work were found two elderly patients being treated with amiodarone associated with digoxin without digoxin dose adjustment.

Considering a standardized clinical conduct by each drug interaction with digoxin and to do the analysis of electronic records, we noticed a non-compliance with the protocol in this work. It was not reported any digoxin dose adjustment and also none potassium supplementation Also, there are no data about follow-up and monitorization of any patient probably drug interactions as the same way none type of intervention was reported.

Electronic health records were incomplete and incorrectly filled causing possible prescription errors and/or therapeutics mistakes causing a plenty of drug interactions and ADRs. These ADRs promote high costs to the public health system by aggravating the quality of life of patients, which justifies the implementation of a computerized physician order entry (CPOE) able to minimize prescription errors and probable drug interactions[14] and join a multidisciplinary staff.

Currently, there are studies reporting the important role of the prescribing professional working commitment together with a multidisciplinary health team in the treatment of HF patients. It is showing significant improvements as well as minimizing a potential drug interaction risk that enhances their clinical condition.[26] Also, there are studies of CPOE being used in hospitals and primary health care showing that their use could reduce: drug interactions, errors in drug prescriptions, health costs for the primary unit care and improve the quality of life of patients.[27,28]

CONCLUSION

Our study showed that drug interactions in a primary health care were due to medication prescribing errors, dose management errors, drug and drug's classes standardization and lack of an effective therapeutic protocol for the treatment of this disease and reducing drug interaction risks. It is well known that there is computerized physician order entry able to assist the physician in his therapeutic prescription. Furthermore, the approach and inserted the health professionals in a multidisciplinary health staff is necessary. The control and monitoring of patients with the improvement of the symptoms of HF lead to an increasing patient survival, decrease in the number of hospitalizations and consequently lower costs in the health system. Preventive measures recommended by the Department of health, in UBS, made by trained professionals, would help and reduce the complications already reported. Medical training may offers strengthening links with the whole multidisciplinary team and can improve treatment compliance by patients with reduction of health problems.

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DECLARATION OF CONFLICTING OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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