CHARACTERISTICS OF PHARMACEUTICAL DRUGS' PROFILE USED BY DIABETIC 2 PATIENTS FROM BAURU'S DIABETICS ASSOCIATION (BDA), REGARDING TO CLASS, FREQUENCY OF USE, ASSOCIATIONS AND INTERACTIONS

Características do perfil dos medicamentos usados por pacientes com diabetes 2 da Associação dos diabéticos de Bauru (BDA), em relação à classe, freqüência de uso, associações e interações

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a chronic disease caused by genetic, metabolic and/or acquired factors that cause insulin deficiency or resistance that result in hyperglycemia. **Objective**:

to characterizing pharmaceutical drugs profile in that concerns the frequency of use, pharmacological classes and possible associations and interactions **Method**: This prospective study was done by applying a questionnaire to 62 individuals with diabetes mellitus 2 (DM2) that have been watched by educational activities at Bauru's Diabetics Association (BDA. ATC classification (Anatomical Therapeutic Classification/2008) was used for pharmaceutic drug classification. **Results**: The group A (alimentary tract and metabolism) showed to be the most used (54%), followed by group C (cardiovascular) (33%). Metformin (52%) and glyburide (25%) were the most used oral hypoglycemic agents (OHA), with only 10% being in use of insulin, alone or associated with other drugs. Metformin was the most used in multiple therapies. **Discussion**: Although the assessment of pharmacotherapeutic follow-up of patients were observed 23 potential drug interactions between combinations of drugs used.The need of different therapies for DM2 is justified by the occurrence of other comorbidities such as hypertension, obesity and dyslipidemia. However, in many cases, the use of all these drugs together can lead to drugs interactions deteriorating patient's quality of life. **Conclusion**: the multidisciplinary team approach is to be aware of the prescribed drugs to DM2 and teach them the correct use these drugs in such a way that patient's quality of life not be endangered or worsened.

Key words: Drug Interactions. Drug Therapy. Diabetes Mellitus

RESUMO

Introdução: *Diabetes mellitus (DM) é uma doença crônica causada por fatores genéticos, metabólicos e / ou adquiridas que causam deficiência de insulina ou resistência que resultam em hiperglicemia.* **Objetivo**: *caracterizar o perfil de drogas farmacêuticas, no que diz respeito à freqüência de uso, classes farmacológicas e possíveis associações e interações.* **Metodologia**: *este estudo prospectivo foi realizado com a aplicação de um questionário a 62 indivíduos com diabetes 2 (DM2) que compareceram às atividades educativas da Associação de Diabéticos de Bauru (ADB). A Classificação ATC (Anatomical Therapeutic Chemical/2008) foi utilizada para a classificação das drogas farmacêuticas.* **Resultados**: *drogas do grupo A (trato digestivo e metabolismo) mostrou ser a mais utilizada (54%), seguidos pelos do grupo C (cardiovascular) (33%). Metformina (52%) e glibenclamida (25%) foram os hipoglicemiantes orais mais utilizados, com apenas 10% em uso de insu-*

lina, isoladamente ou associados a outras drogas. A metformina foi a mais utilizada em terapias múltiplas. **Discussão**: na avaliação do seguimento farmacoterapêutico dos pacientes foram observadas 23 interações medicamentosas potenciais entre as combinações de medicamentos utilizados. A necessidade de diferentes terapias de DM2 é justificada pela ocorrência de outras co-morbidades como hipertensão, obesidade e dislipidemia. No entanto, em muitos casos, a utilização de todas estas drogas em conjunto, podem levar a interações de drogas que deterioram a qualidade de vida do paciente. **Conclusão**: a abordagem da equipe multidisciplinar consiste em estar consciente dos medicamentos prescritos para DM2 e ensinar o uso correto deles de tal forma que a qualidade de vida do paciente não tenha riscos ou piora.

Palavras-chave: *Fármacos/interação. Diabetes/tratamento. Diabetes melitus.*

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease caused by genetic, metabolic and/or acquired factors that cause insulin deficiency or resistance that result in hyperglycemia. DM is characterized by alterations in carbohydrates, lipids and proteins metabolism. To normalize these alterations, generally there is the need of lifestyle changes, like starting or increasing the frequency of physical activity, changes in diet pattern, generally associated with the use of drugs (ADA, 2005; ADA, 2010).

Diabetes is today an epidemic all over the world. Its incidence is rising so fast and in some countries even in an exponential mode, being one of the most important public health issues nowadays. Currently, these diseases no longer occur preferentially in developed countries, posing a serious health concern for people living in developing countries. In Brazil, there are factors that aggravate and complicate the implementation of programs to prevent and combat these diseases, such as social inequality, combined with the continental dimensions of the country (MALFATTI and ASSUNÇÃO, 2011).

In Brazil, according to a census done from 1986 to 1988, in nine cities, 7,6% of the adult population between 30 and 69 years old were diabetics (MALERBI; FRANCO, 1992). In 2003 a new census, using the same criteria used by the preceding one, was done in Ribeirão Preto, São Paulo State, and 12,2% of the population

comprised between 30 to 69 years old were diabetics (TORQUATO et al., 2003). The diagnostic criteria for diabetes is well established by many national and international scientific societies, like Brazilian Diabetes Society, American Diabetes Association, International Diabetes Federation and World Health Organization. After the diagnosis is done, the treatment must be started. Generally lifestyle and diet changes are needed to reach a good metabolic control, and if these procedures are not enough to reach this target, drug therapy is indicated (ADA, 2003; ASSUNÇÃO; SANTOS; COSTA, 2002).

The treatment of Diabetes mellitus 2 (DM2) must be adapted for each patient individually. Many important prospective studies like the United Kingdom Prospective Diabetes Study (UKPDS) have shown that DM is a progressive disease what means that as time goes by the pancreas tend to produce less insulin and the patients must start using any kind of drug to obtain and maintain a good metabolic control. This study has also showed that those patients that were in the strict control branch developed much less microvascular complications than those patients that were in the conventional treatment branch (ALAD, 2008).

Currently, there are several classes of drugs for treatment of DM2 available in Brazil. Biguanides, sulfonylureas, alpha-glucosidase inhibitor, tiazolinediones, metiglinides and several types of insulins are the most frequently used. Recently new classes of drugs have also been introduced for DM2 diabetes treatment such as incretin mimetics and dipeptidyl peptidase-IV inhibitors (ARAUJO; BRITO; CRUZ, 2000; DAVIDSON; PARENTE; GROSS, 2008, PRATLEY; GILBERT, 2008). Each one of these classes of drugs has its/yours own particularities concerning pharmacological and therapeutical aspects, and each individual patient receives single or multiple drug therapy according to his metabolic profile (COSTA; ALMEIDA, 2004; PRATLEY; GILBERT, 2008).

Some patients reach a good metabolic control with diet alone, but the great majority of them need to use one or more class of oral hypoglycemic agents (OHA) (IRONS et al., 2012), or the association of these with insulin. When taking the decision of what class of OHA to use, it is necessary to take in account if the patient presents insulin resistance or insulin deficiency, and then the doctor makes the best choice of OHA to prescribe alone or in combination, and also if the insulin is required or not. It is also necessary to know if the patient has any other kind of complication like liver or renal failure that will limit the use of some classes of drugs (COSTA; ALMEIDA, 2004).

The drugs combinations most frequently used are: sulfonylureas and biguanides; sulfonylureas and alpha-glucosidase inhibitor;

sulfonylureas and biguanides and alpha-glucosidase inhibitor; sulfonylureas and glitazones; glynides and glitazones; biguanides and alpha-glucosidase inhibitor; biguanides and glitazones; biguanides and glitazones and alpha-glucosidase inhibitor; biguanides and glynides and biguanides and glynides and alpha-glucosidase inhibitor (COSTA; ALMEIDA, 2004).

The relations between these drugs are complex and it is important that health professionals have knowledge on how these drugs act and they must also be aware that they are dealing with multiple diseases in one patient (BALESTRE et al., 2007). The aim of this study was to characterize the profile, concerning the class, frequency of use and associations of drugs used for diabetic 2 patients that are watched in educational activities at Bauru's Diabetics Association (BDA).

METHODS

BDA is a philanthropic institution with 775 associates with diabetic types 1 and 2, children and adults. This association offers monittoring multidisciplinary health care. Among these, 62 type 2 diabetic adults patients were enrolled in this study. This study had a random sampling, individuals of both sex, representative and statistically established (68 volunteers would be representative), but 6 patients were excluded from the study because they didn't inform correctly the name and drugs'dosage in using during avaliation.

The study received approval of Ethics Committee in Research from Sagrado Coração University under the protocol nº 07/07. A consent letter was presented and firmed by all the participants of the research.

BDA promotes monthly educative meetings, with experts in specific areas concerning diabetes. Data collection was done with patients that attend these meetings. A questionnaire was applied containing questions relative to identifications of patients, medical and family history of chronic metabolic diseases, physical activities frequency, anthropometric measures and informations about drugs in current use, to this information was used the segment pharmacotherapeutic protocol (Method Dader) (MACHUCA et al., 2003).

The evaluation and classification of potential drug interactions was conducted using a database of scientific articles and books specific to the area.

Drugs classification was standardized in agreement with the international classification system (Anatomical Therapeutic Chemical/ATC) of the World Health Organization (WHO, 2011).

RESULTS

Baseline characteristics of subjects are described in Table 1.

Table 1: Baseline characteristics of diabetics associated to Bauru Diabetic Association (BDA).

Variables	Results
Hypertension (%)	72,05
SBP (mm Hg)	132,54±17,95
DBP (mmHg)	80,39±11,35
Dyslipidemia (%)	42,64
Vascular diseases (%)	17,64
Kidney diseases (%)	14,7
Overweight/Obesity (%)	80,88
Normal range (%)	19,11
Overweight (%)	26,47
Obesity level I (%)	33,82
Obesity level II (%)	17,64
Obesity level III (%)	2,94
BMI (kg/m^2)	30,34±5,8
AC (cm)	101,32±16,98
AC women > 88 cm (%)	85,71
AC men > 102 cm (%)	57,69
Glycemia (mg/dl)	149,20±60,37
Glycated hemoglobin (%)	7,72±1,4

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, AC: abdominal circumference; dates showed in x ± SD

The population this study was of the 68 pacients with clinical diagnostic of the DM 2, registred in BDA, 61.76% were women and 38.23% men, with mean age of the 62.93±9.64 years-old. The white race had prevalence of the 69.11%, black of the 25% and Asiatic of the 5.88%. The time of the diabetes diagnostic had a variation of the one to 34 years (10.74±7.52).

To life habits, 33.82% of the population were tobacco consumers, 29.41% ex consumers and 36.76% no-consumers tobacco. Alcohol drinking practices were frequent in 14.70%. The physical activity practice was observed in 51.47% realized in 1.75±1.91 time for week and 83.32% had adherence to hypoglycemic dietary.

Among all drugs used, category "A" showed the highest prevalence (54%), followed by category "C" (33%) (Figure 1). The most utilized drugs in category "A" were biguanides and sulfonylureas. Among OHA, metformin (51.2%) and glyburide (25%) were the most used, however only 9.5% were using insulin (Figure 2).

Among cardiovascular category (Category C), the most used drugs were enalapril (34.5%), sinvastatin (16.4%), losartan (9.1%) and captopril (7.3%) respectively (Figure 3).

Of the 62 studied patients, 19% did not use OHA, 32% were in monotherapy and 43% were using combined therapy, with two drugs and only 6% with three or more drugs (Figure 4). In cases of monotherapy, metformin represented 50%, followed by insulin and glyburide, both of them with a prevalence of the 20%. In the combined therapy with 2 drugs, the association of metformin and glyburide was the most used (53.8%). In the combined therapy with three drugs, metformin, glyburide and insulin association was the most frequently found (75%). Thus, the most frequent association of drugs in combined therapy was between the biguanides and sulfonylureas (Table 2).

ATC Classification (2009)

A – Alimentary tract and metabolism
B – Blood and blood forming organs
C – Cardiovascular system
H – Genito-urinary system and sex hormones
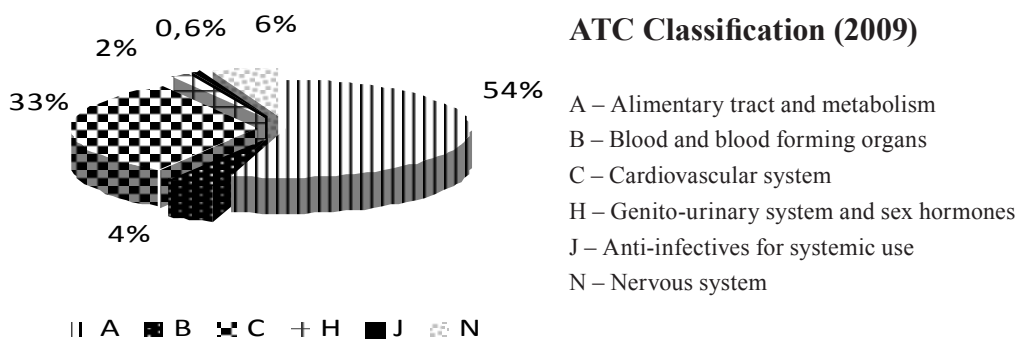J – Anti-infectives for systemic use
N – Nervous system

Figure 1: Drugs categories used by DM2 individuals, according to Anatomical Therapeutic Classification (ATC) (WHO, 2011).
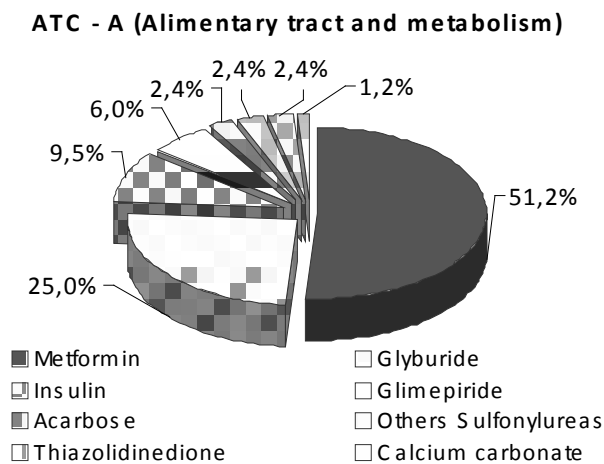
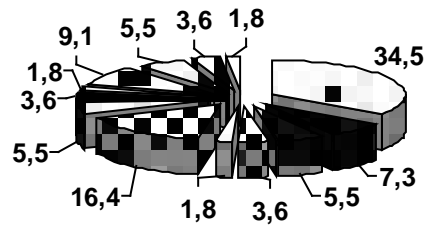Figure 2: Percentage distribution of drugs in group A, according to ATC (Anatomical Therapeutic Chemical)

9,1   5,5   3,6   1,8
1,8
3,6
34,5
5,5
16,4   1,8   3,6   5,5   7,3

☐ **Enalapril**   ■ **Captopril**   ☐ **Atenolol**
☒ **Nifedipine**   ☐ **Labetalol**   ⊟ **Sinvastatin**
☐ **Hydrochlorothiazide**   ■ **Clonidine**   ☐ **Digoxin**
☐ **Losartan**   ☐ **Propranolol**   ☐ **Indapamide**
☐ **Furosemide**

Figure 3: Medicine drug "C" category (cardiovascular) percentage

19%   32%
6%
43%
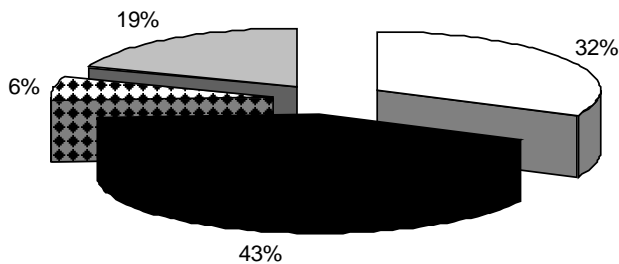
☐ One drug   ■ Two drugs   ☒ Three or more drgus   ☐ Don´t use

Figure 4: Oral anti-diabetes medicine drug therapy used by DM2 individuals. used by DM2 individuals.

Table 2: Oral anti-diabetes medicine drugs used in simple or combined modality therapy by DM2 individuals.

Monotherapy – One drug	%	Combined therapy – Two drugs	%
Metformin	50,0	Metformin + glimepiride	11,5
Glyburide	20,0	Metformin + glyburide	53,8
Insulin	20,0	Metformin + gliclazide	3,8
Clorpropamide	5,0	Metformin + insulin	26,9
Glimepiride	5,0	Glyburide + insulin	3,8
Polytherapy - Three or more drugs		%	
Metformin + blyburide + insulin		75,0	
Metformin + pioglitazone + acarbose + gliclazide		25,0	

It was found 23 possibilities of drugs interactions, which 71% was related with hypoglycemic risk and 29% with antihypertensive lost effect risk (Figure 5). The major class interactions with hypoglycemic risk were between ACE (angiotensin conversion enzyme inhibition) and sulfonylurea drugs, follow by ACE and insulin (Figure 6).
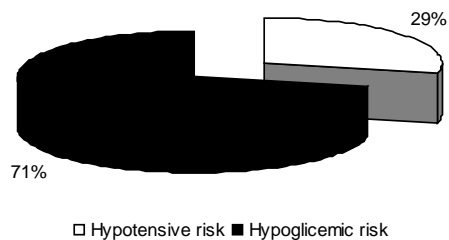

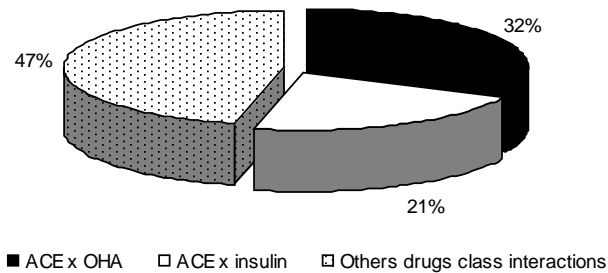Figure 5: Possible drugs interactions effects.

32%

47%

21%

■ ACE x OHA ☐ ACE x insulin ☐ Others drugs class interactions

Figure 6: Possible drugs class interactions

DISCUSSION

This sample was formed by 62 diabetic 2 patients that were mostly using class "A" therapeutical category – ATC drugs. However, its important to notice that the association between diabetes, hypertension and dyslipidemia is very frequent (HERNAEZ et al., 2004; BAZOTTE; SILVA; KOYASHIKI, 2005), and that all these conditions are components of the metabolic syndrome (COSTA et al., 2004; WANG et al., 2004; IDF, 2011), so these components can increase the association of combined drugs therapy (COELHO; BRUM, 2009).

In the present study, the concomitant use of "A" and "C" ATC categories of drugs, was frequently observed, because diabetes and hypertension are very frequently associated and the treatment of both conditions is essential to reduce cardiovascular mortality risks in diabetic patients. Despite ACE-inhibitors and beta-blockers can influence the compensation of diabetics, their use is not contraindicated in these patients, because of their huge benefit in the prevention of cardiovascular events (HENDRYCHOVÁ, VLČEK, 2012). Cardiovascular diseases (CVD), in diabetic 2 patients are responsible for about 80% of the deaths. In diabetic patients, the relative risk of death for CVD, adjusted for the age and sex, is three times higher than the general population (STAMLER et al., 1993). Lifestyle changes can occur if a continuous motivation of the patient is done, and this can help to keep glycemic levels under control (UKPDS, 1998; PEREIRA et al., 2005).

The frequent use of metformin, glyburide, insulin, enalapril, captopril and sinvastatin probably occur due to the fact that these drugs can be easily found in pharmacies of the Basic Health Service

as essential drugs to the continuous basic attention of the Basic Medicine Drugs National Relation, besides the low prices available when they are acquired in public pharmacies (BRASIL, 2006).

Pereira et al. (2005) and Bazotte et al. (2005) had evidenced that metformin, glyburide and insulin were used for DM2 individuals as monotherapy or in association. The same datas were found in our study. The use of insulin in diabetic 2 patients generally occurs 10 years after the diagnosis is done. This occurs because there is a reduction in the pancreatic function, with reduction of insulin production and secretion (PEREIRA et al., 2005). The monotherapy with insulin, compared to its association with OHA in diabetics 2, leads to an improvement in glycemic profile, reduction in hypoglycemia incidence, reduction in body weight, reduction in insulin needs, and can be used as a transition to intensified insulin therapy treatment (MALERBI et al., 2006).

The monotherapy with OHA is generally indicated in the initial phases of diabetes. In the present study it was observed that 32% of the individuals were on monotherapy. Pereira et al. (2005) have found different results, with 63.1% of their patients in monotherapy. In a study with diabetic 2 patients, metformin used alone lowered glycemic levels in about 25%, or 60 to 70 mg/dl and the glycosylated hemoglobin levels in 1.5 to 2% (ARAUJO; BRITO; CRUZ, 2000). It was also demonstrated that the effectiveness of glycemic control with metformin was similar to that obtained with sulfonylureas; on the other hand, metformin use is associated with weight loss, that is so important for the majority of patients with DM2 (JOHANSEN, 1999).

In our study most of patients used at least two drugs for antidiabetic therapy. The major drugs association were between sulfonylureas and biguanides, with 53 .8% between metformin and glyburide and 26.9% between metformin and insulin. Pereira et al. (2005) found in the same profile combined therapy, however the values observed were different: metformin with glyburide in 19.2% and insulin with metformin in 5.4%.

Metformin was the most frequent drug used by patients evaluated. The elimination of metformin is dependent on renal function. Thus, drugs impairing renal function can cause accumulation of metformin and increase the risk of lactic acidosis (GRAHAM et al., (2011)

This possibility should be kept in mind, when, for example loop diuretics, angiotensin-converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporine, aminoglycosides or X-ray contrast media are given to metformin-treated patients at risk of decreased renal function, or when renal function is already compromised. In this study 32% of interactions

were observed between OHA and ACE, and the most frequent association was between metformin and the captopril.

The difficulties in analyzing the use of biguanides in elderly patients is the lack of studies, and the few existing feature limitations with small cohorts and inclusion criteria, all non-randomized. In elderly patients, the risk of lactic acidosis increase, been necessary the serum creatinine monitoration (DOUCET, 2005).

Although all the interactions found were characterized as potential interactions, by patients clinical and laboratory monitorization, the Pharmacotherapeutic follow-up based on the methodology Dader recommends continuous monitoring thus promoting early identification of potential problems related to the use of medicines.

CONCLUSION

The combined therapy in diabetics 2 can be justified by the presence of many comorbidities such as hypertension, obesity and dyslipidemia. However, in some cases, the inadequate use of these drugs can lead to the occurrence of drug interactions that can be dangerous and can deteriorate patients' quality of life.

Based on the premise that patients served by the Outreach Program "Diabetes" in the ADB are evaluated by the group of health care professionals such as physical therapy, pharmacy, nutrition, nursing and psychology, the characterization of these pharmacoterapheutic profile favors the identification of potential problems in therapy in different areas, resulting in promotion, protection and recovery of patients, in order to achieve improvements in quality of life.

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