✧ RESEARCH PAPER ✧

Drug interactions in Brazilian type 2 diabetes patients

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Drug interactions in Brazilian type 2 diabetes patients

The aim of this paper is to identify the prevalence of the most frequent drug interactions in patients using oral antidiabéticos and their association with capillary glucose and medication adherence. In total, 579 type 2 diabetes mellitus patients from 12 health institutions in Fortaleza, Brazil were interviewed in 2009. A form was applied, including questions on medication use, comorbidities, lifestyle, body mass index and random capillary glucose. Results revealed that 26.7% used five or more different drugs simultaneously and daily. Statistically significant drug interactions occurred between antidiabéticos and diuretics, angiotensin-converting enzyme inhibitors, anti-lipidaemics and corticoids. No significant association was found between polypharmacy, medication adherence and glucose. It is important for nurses, in consensus with other health professionals, to consider the possibility of other drugs that mean less risk for diabetes patients' glucose control or of increased antidiabetics doses.

Key words: antihypertensives, drug interactions, glucose, hypoglycaemics.

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INTRODUCTION

Patients might concomitantly use mutually interacting drugs without any evidence of adverse effects. That is so because many potentially dangerous interactions only occur in a small proportion of patients. In any case, polypharmacy patients are more vulnerable to these problems than subjects in a monopharmacy regimen.¹

Most of the patient population suffering from type 2 diabetes mellitus (DM 2) suffers from overweight, high blood pressure and/or dyslipidaemias. This situation, in combination with the chronic nature of the illness, generally imposes difficulties to prevent acute and chronic complications without the adoption of drugs like oral antidiabetics (OADs), antihypertensives and anti-lipidaemics, among others.²⁻⁴ As a result, patients might be confronted with polypharmacy situations, when five or more drugs are continuously used, which represents a public health problem. Polypharmacy is associated with increased risk and severity of adverse drug reactions, with precipitating pharmacological interactions, causing cumulative toxicity, bringing about drug intake errors and reducing treatment adherence.⁵

It is difficult to establish a causal relation, but one can predict some interactions between OADs and other drugs. Among medication interactions that increase the toxicity of OADs, associations with cloramphenicol (50%), cimetidine (34%), propranolol (34%), non-steroidal anti-inflammatory drugs (34%) and monoamine oxidase inhibitors (34%) stand out. Among drugs that decrease the efficacy of OADs, the most frequent associations involve corticosteroids (83%), diuretics (83%), oral contraceptives (83%) and phenothiazines (67%). Care is recommended when combining sulfonylureas with clofibrate, salicylates, non-steroidal analgesics and sulfonamides, due to increased chances of hypoglycaemia. When using metformin, a biguanide, care is due as the inhibition of vitamin B12 absorption can trigger anaemia. The effect of alpha-glucosidase inhibitors can be reduced if used concomitantly with bile acid sequestrants. The use of this OAD class also negatively affects digoxin absorption and produces toxic liver metabolites when combined with acetaminophen and alcohol. Women who simultaneously use thiazolidinediones and oral contraceptives should adopt another form of contraception for the sake of precaution, as these OAD can reduce the effectiveness of this contraceptive method by 30%.^{6,7}

Thus, polypharmacy can interfere in therapeutic efficacy and, consequently, in adequate glucose control when associating certain drugs with OAD.^{6,7}

Due to the high simultaneous incidence of DM 2 and other chronic conditions like hypertension (70%) and depression (30%), patients who combine other drugs with OAD are common.⁷⁻¹⁰ This polypharmacy demands increased knowledge on these drugs classes, particularly regarding drug interactions. Besides, the complexity of these illnesses and very narrow therapeutic spectrum of the drugs can negatively affect DM control.^{9,11}

Hence, one of the main challenges health professionals face in care delivery to DM 2 patients, mainly when elderly, is to know about the interaction between OAD and other drugs or about the interference of certain drugs in glucose control. Establishing these associations can contribute to enhance the rational use of these drugs without aggravating the metabolic control of the disease, through strict orientations for monitoring glucose, body weight and the first signs of micro- and macro-vascular complications. Thus, the goal of this paper was to identify the prevalence of the most frequent drug interactions among patients using oral antidiabetics and associate them with medication adherence and capillary glucose.

METHOD

Study design

This study used a cross-sectional research, developed between March and July 2009, at 12 public primary care institutions located in Fortaleza, Brazil. The city of Fortaleza is divided into six administrative regions. In the city, 173 000 diabetes patients are registered in the *Hiperdia* programme (specific for hypertension and/or diabetes patient treatment). To obtain representative data about drug interactions among DM 2 patients in this city, two diabetes mellitus care programmes were chosen from each region, organized at different institutions.

Sample

A cluster sample was developed and, for calculation purposes, a formula for infinite populations was used. Sixty percent was adopted as the prevalence rate of OAD use. Statistical significance and sample error were set at $\alpha = 0.05$ and 5%, respectively.¹² The sample size was established as 369 subjects. Ten percent was added for data losses related to refusals, hospitalizations, dropouts and wrong and/or unavailable information.

Subjects

Health institutions were chosen through the analysis of clinical files. Then, non-probabilistic selection of the research subjects was applied inside each health institution. The following inclusion criteria were adopted: having a registered and confirmed DM 2 diagnosis; being attended at the institutions selected for the study; living in Fortaleza, Brazil and having a fixed or mobile telephone number; and being under OAD treatment for at least 6 months. The exclusion criteria were: undergoing combined OAD and insulin treatment, being hospitalized during data collection and being incapable of answering the interview questions. After applying these criteria, a sample of 579 DM 2 patients resulted.

Instruments

Sociodemographic, clinical and medication intake-related variables were collected with the help of a form. The researchers responsible for data collection participated in a 16-hour training to guarantee data reliability. After obtaining Institutional Review Board approval from Universidade Federal do Ceará (protocol 44/07), the researchers returned to one of the selected health institutions for a pilot test, involving 39 patients. The information collected in that phase was not considered in this research.

Data collection

Data were collected between March and July 2009 through home visits. After applying the eligibility criteria and after the patient had accepted to participate in the research, sociodemographic and clinical and medication treatment data were collected. Next, the body mass index (BMI), random capillary glucose and medication treatment adherence were measured. The information collected in this phase was confronted with the clinical files as a veracity check.

The following levels were used for capillary glucose analysis: fasting patients: 70–110 mg/dL (good), 111–140 mg/dL (acceptable) and > 140 mg/dL (unsatisfactory). In subjects who had eaten, the classification was as follows: 70–140 mg/dL (good), 141–160 mg/dL (acceptable) and > 160 mg/dL (unsatisfactory). For statistical purposes, however, levels classified as *good* were called normal, and those considered as *acceptable* or *unsatisfactory* were called high.¹³ The BMI was interpreted based on World Health Organization recommendations.¹⁴

The Treatment Adherence Measure test was used to assess pharmacological treatment adherence. This tool has been adapted and validated in Portuguese, with good internal consistency based on Cronbach's alpha (0.66). The subjects were asked to answer yes or no to the following questions: (i) have you ever forgotten to take your medication for DM2?; (ii) have you ever been careless about the time when you take your medication for DM2?; (iii) have you ever stopped taking medication for DM2 because you felt better?; (iv) have you ever stopped taking medication for DM2, on your own initiative, because you felt worse?; (v) have you ever taken more than one or many pills for DM2, on your own initiative, because you felt worse?; and (vi) have you ever interrupted your treatment with pills because you ran out of medication? 'No' answers to all questions were considered as compliance.¹⁵

Patients who took five or more drugs from different pharmacological classes were classified as polypharmacy cases.¹⁶ Daily and simultaneous use of oral diabetics and other drugs was investigated. In these cases, drug interactions known in literature were calculated. Patients were also asked whether they understood nurses' medication intake orientations or not.

Data analysis

Data were entered in triple and stored in an Excel database. Statistical Package for the Social Sciences (SPSS, SPSS Inc., Chicago, IL, USA) software version 17.0 was used for information processing. The Kolmogorov–Smirnov test was applied to test for data normality and Levene's test for homoscedasticity. The non-parametric χ^2 test was used to associate daily and simultaneous use of OAD and other drugs described as drug interactions in literature, as well as OAD use and the presence of polypharmacy. Statistical analysis also included the calculation of central trend and dispersion measures, with a 95% confidence interval. Significance was set as $P < 0.05$.

RESULTS

Among the 579 subjects, female (70.3%), white (48.1%) and mulatto (34.8%) patients predominated. Regarding the age range, subjects were between 18 and 92 years old, distributed as follows: 18–59 years (41.1%), 60–69 years (29.5%), 70–79 years (20.1%) and 80–92 years (9.3%), with a mean age of 63.1 years (standard deviation (SD) ± 11.6). Average education was 4.3 (SD ± 3.7) years. Little more than half (55.8%) of the subjects were married or lived with a fixed partner, whereas a minority

(6.9%) was single. The majority had its own house (84.9%) and 45.8% lived in a family group (partner, children and/or grandchildren).

Most patients were retired (49.4%), and social security benefits were the main income source (48.7%). Low socioeconomic classes predominated, and the mean monthly family income equalled US\$445.9 (SD $\pm$ 327.1).

Tobacco and alcohol consumers together represented 13.8% of the sample. Most patients were sedentary (75.5%). The patients' BMI was distributed as follows: overweight (35.7%), eutrophic (24.7%), class 1 obesity (20.8%), class 2 obesity (6.2%), class 3 obesity (2.3%) and low weight (2.3%).

Polypharmacy was identified in 26.7% of the subjects. On average, polypharmacy patients took 4.5 (SD $\pm$ 1.3) pills per day, whereas the remainder took 2.9 (SD $\pm$ 1.6) pills ($P < 0.001$) (Table 1).

The main OAD used were metformin (22.9%), glibenclamide (21.5%) and associations of both (43.5%), with a mean intake of 3.0 (SD $\pm$ 1.7) OAD per day. A substantial part of the sample (79.8%) suffered from comorbidities associated with DM 2 and took drugs to treat them (71.7%). On average, they took 4.2 (SD $\pm$ 3.6) pills per day for comorbidity treatment. The main comorbidities were arterial hypertension (72.9%) and cardiovascular illness (11.2%). In addition, bone and/or joint problems were identified (6.9%).

Except for OAD, the most used drugs were antihypertensives: angiotensin-converting enzyme inhibitors (ACEIs) (38.1%), diuretics (29.7%), central adrenergic inhibitor (18.1%) and beta-blocker (14.9%). At the same time, DM 2 patients also used acetylsalicylic acid (29.8%), anti-lipidaemics (8.8%) and anti-ulcer medications (6.2%). Fewer patients also used antidepressants (3.6%), non-steroidal analgesics (1.6%) and corticoids (1.4%).

Seventeen percent of subjects used metformin and glibenclamide daily and simultaneously with diuretics ($P < 0.001$). Also, 23.3% of the sample took metformin, glibenclamide and ACEI daily and simultaneously ($P < 0.001$); 3.1% took anti-lipidaemics simultaneously and daily with metformin and 3.4% with glibenclamide ($P < 0.001$). Less than 2% of the subjects took OAD simultaneously with corticoids ($P = 0.019$) (Table 2). No statistically significant association was found when crossing polypharmacy with random capillary glucose ($P = 0.091$), drug treatment adherence ($P = 0.497$) and

Table 1 Association between the scheme and the presence of oral antidiabetic drug polytherapy, Fortaleza, Brazil, 2009

Drug polytherapy	Scheme oral antidiabetic						P^*	
	Glibenclamide	Metformin	Metformin and glibenclamide	Acarbose	Glibenclamide and acarbose	Metformin and acarbose	Metformin, glibenclamide and acarbose	Metformin and gliptina
	n	%	n	%	n	%	n	%
Yes	34	5.7	23	4	95	16.4	03	0.5
No	113	19.6	122	21	181	31.6	01	0.1
Total	147	25.3	145	25	276	48	03	0.5

* chi-square ($\chi^2 = 52.69$).

Table 2 Association between daily use and concomitant use of oral antidiabetics and drugs prescribed, Fortaleza, Brazil, 2009

Drugs used daily	OAD used simultaneously	<i>n</i>	%	<i>P</i> *	Drug interaction described in the literature
Antiplatelet (acetylsalicylic acid)	Metformin	29	5.0	0.053	Increases the action of glibenclamide
	Glibenclamide	42	7.2		
	Arcabose	01	0.1		
	Metformin and glibenclamide	99	17		
	Metformin, glibenclamide and arcabose	03	0.5		
Non-steroidal analgesics (diclofenac)	Metformin	5	0.8	0.998	You can increase the action of OAD
	Metformin and glibenclamide	5	0.8		
Central adrenergic inhibitor (methyldopa)	Metformin	26	4.4	0.251	Decreases the action of glibenclamide
	Glibenclamide	26	4.4		
	Arcabose	01	0.1		
	Metformin and glibenclamide	53	9.1		
	Metformin, glibenclamide e arcabose	01	0.1		
Diuretics (hydrochlorothiazide and furosemide)	Metformin	54	5.0	< 0.001	Decreases the action of glibenclamide
	Glibenclamide	51	7.2		
	Metformin and Glibenclamide	98	17		
	Metformin, glibenclamide and arcabose	0.3	0.5		
Beta-blocker (propranolol and atenolol)	Metformin	28	4.8	0.960	Increases the action of glibenclamide
	Glibenclamide	21	3.6		
	Metformin and glibenclamide	38	6.5		
ACEI (captopril and enalapril)	Metformin	70	1.2	< 0.001	You can increase the action of OAD
	Glibenclamide	76	13.1		
	Metformin and glibenclamide	135	23.3		
	Metformin, glibenclamide and arcabose	03	0.5		
Antidepressants (amitriptyline and fluoxetine)	Metformin	08	1.3	0.580	Increases the action of glibenclamide
	Glibenclamide	07	1.2		
	Metformin and glibenclamide	06	1.1		
Antilipemic (simvastatin)	Metformin	18	3.1	< 0.001	Increases the action of glibenclamide
	Glibenclamide	12	2.0		
	Metformin and glibenclamide	20	3.4		
	Metformin, glibenclamide and arcabose	02	0.3		
Antiulcer (omeprazole and ranitidine)	Metformin	07	1.2	0.953	Increases the action of metformin
	Metformin and glibenclamide	22	3.7		
	Metformin, glibenclamide and arcabose	08	1.3		
Corticoids (prednisone)	Metformin	1	0.1	0.019	Decreases the action of glibenclamide OAD
	Glibenclamide	6	1.1		
	Metformin and glibenclamide	2	0.3		

* Chi-square test.

Table 3 Association between drug polytherapy, random capillary blood glucose, medication compliance and understanding about taking drugs, Fortaleza, Brazil, 2009

Variables	Pharmacological polytherapy				<i>P</i> value*
	Yes		No		
	<i>n</i>	%	<i>n</i>	%	
Random capillary blood glucose					
Normal	41	7	71	12.2	0.091
High	95	16.4	230	39.7	
Compliance with drug treatment					
Yes	21	3.6	67	11.5	0.497
No	134	23.1	356	61.4	
Understood nursing orientations for medication intake					
Yes	131	22.6	370	63.9	0.071
No	24	4.1	53	9.1	

* Fisher's exact test.

understanding of nursing orientations about drug intake ($P = 0.071$) (Table 3).

DISCUSSION

The prevalence of polypharmacy in this study remained far below that of other studies in Brazil and the United States but was similar to studies in Sweden, the Netherlands and Taiwan.^{7,9,11,17–19} This might be related to the fact that most of these patients depended on medication distribution at local public health services in the primary care network, differently from the studies cited, which were mostly conducted at secondary care services.

In this study, most patients in the sample were elderly and took an average 4.5 (SD $\pm$ 1.3) pills per day. Estimated drug interaction risks amount to 13%, 58% and 82% for elderly taking two, five, seven or more drugs, respectively.²⁰ It is important for nurses to take into account the association between the number of drugs taken per day and these elderly diabetes patients' kidney, liver and gastric function, as an alert for the development of drug interactions.²¹ Therefore, during nursing consultations, nurses need to monitor and evaluate urine analysis and liver transaminase test results and dietary habits to prevent and assess complications.

Statistically significant associations were found between daily and simultaneous use of OAD and other drugs,

described in literature as drug interactions: between OAD and diuretics ($P < 0.001$), ACEI ($P < 0.001$), antilipidaemics ($P < 0.001$) and corticoids ($P = 0.019$). Publications in the United States, Canada, Europe, Asia and Brazil have argued that the number of drug interactions in chronic patients is increasing and that this might entail different effects for glucose control.^{7,9–11,22–27}

The presence of interaction in the combined use of OAD and ACEI was observed in other studies, which also detected increased insulin production in DM 2 patients taking ACEI, a favourable aspect to reach glucose control.^{9,10,28–30} These drugs can also prevent the incidence of new DM 2 cases in 27%, although no plausible explanation exists yet for this preventive mechanism.² Some researchers have established the theory that ACEI is able to help in the maturing of adipocytes, impeding the deviation of fats to the liver, skeletal muscles and pancreas, which seems to influence body weight gain.^{28–30}

Some studies justify the diabetogenic action of diuretics, which seems to be enhanced when combined with first-generation beta-blockers (propranolol and atenolol).^{10,23,26,31,32} In Brazil, any antihypertensive drug, except for direct vasodilators, can be used for blood pressure control in an initial monopharmacy regimen, especially for patients with arterial hypertension stage 1 who did not respond to non-medication measures.³² Therefore, it is important for nurses, in consensus with other health professionals, to consider the possibility of antihypertensives that represent less risk for diabetes patients' glucose control, or to increase the OAD dose or use insulin when they perceive that these drug interactions negatively their DM 2 patients glycaemic control.

The harmful effects of chronic corticoid use on blood pressure, glucose, body weight and sulfonylurea actions are well known in literature.^{1,6} Nevertheless, a study appointed that glucocorticoids seem to exert a positive effect on the pharmacodynamics of drugs used to treat cardiometabolic problems, such as beta-blockers, angiotensin antagonists, psychoactive drugs and some OAD, mainly in elderly patients.³³ Anyway, in these situations, it is important for health professionals to reinforce their activities regarding diet compliance, correct OAD and antihypertensive intake and regular exercising, so as not to impair DM 2 metabolic control.

When associating statins with OAD use, no drug interaction descriptions were found in literature. Fibrates, in

turn, enhance the action of sulfonylureas, which represents a risk for hypoglycaemia.^{1,2} Moreover, the use of these anti-lipidaemics depends on clinical judgment, as well as on their ability to lead DM 2 patients to adequate LDL-cholesterol levels. It should also be highlighted that high statin doses possess a moderate ability to reduce triglycerides, thus decreasing the need for combined therapy.³⁴

In Brazil and Latin America, drug transcription and/or prescription by nurses remains a polemic issue. It is fundamental that these professionals strengthen their health promotion activities, focusing on the lifestyle of DM2 patients using OAD with a view to enhancing glycaemic control. Nevertheless, nurses active in care delivery to DM 2 patients need knowledge on these drug interactions and should orient patients about them.

As data were collected at patients' homes without previous scheduling, fasting and fed patients had to be divided for the analysis of capillary glucose levels. Also, as capillary glucose is less accurate and more variable than venous glucose, the sample had to be stratified into good, acceptable and unsatisfactory to identify statistical differences. The use of a cross-sectional design and random capillary glucose data reduces evidence levels. Therefore, further research on the theme is due, using more precise monitoring and control techniques and resources to clarify the role of certain pharmacological compounds in DM 2 metabolic control.

CONCLUSIONS

In the study sample, 26.7% took five or more different drugs simultaneously and daily ($P < 0.001$). Statistically significant drug interactions were found between oral antidiabetics and diuretics ($P < 0.001$), ACEIs ($P < 0.001$), anti-lipidaemics ($P < 0.001$) and corticoids ($P = 0.019$). No significant association was found between polypharmacy, medication adherence ($P = 0.497$) and glucose ($P = 0.091$).

IMPLICATIONS FOR NURSING PRACTICE

It is important for nurses, in consensus with other health professionals, to consider the possibility of rethinking drug indications as support measures or not to achieve good glycaemic control. Also, these study results highlight the importance of reinforcing orientations towards compliance and metabolic control of DM 2.

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CONTRIBUTIONS

Study design: MFMA, MMCD, PJSA.

Data collection and analysis: VSV, TMA, MFMA, PSSA.

Manuscript preparation: MFMA, MMCD, MLZ.

CONFLICT OF INTERESTS

The author(s) declare that they have no conflict of interests.

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