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Original Article

Effect of oral antihypertensive drugs on biochemical dosages in the elderly

Efeito dos anti-hipertensivos orais sobre dosagens bioquímicas em idosos

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Objective: to compare serum levels of uric acid, glucose, potassium and sodium in elderly users and non-users of oral antihypertensive drugs. **Methods**: observational, case-control study, including 232 elderly people with mean age 68.9 ± 7.4 years, of which 116 use and 116 do not use oral antihypertensive drugs, of both genders, non-diabetic and with no renal disease. After venous blood collection, glucose and uric acid were measured by colorimetric method; and sodium and potassium by the ion-selective electrode method. **Results**: there was an association between use of antihypertensive drugs and elevations in serum uric acid levels (p=0.040). And, among the classes, diuretic drugs demonstrated in this study relation with changes in uric acid levels (p=0.02) when compared to the other classes. **Conclusion**: the use of antihypertensive drugs, especially diuretics, has been associated with an increase in serum uric acid levels in hypertensive users of oral antihypertensive drugs.
Descriptors: Aged; Antihypertensive Agents; Drug-Related Side Effects and Adverse Reactions.

Objetivo: comparar os níveis séricos de ácido úrico, glicose, potássio e sódio em idosos usuários e não usuários de anti-hipertensivo oral. **Métodos**: estudo observacional analítico do tipo caso-controle, incluindo 232 idosos com média de idade 68,9 ± 7,4 anos, sendo 116 usuários e 116 não usuários de anti-hipertensivo oral, de ambos os sexos, não diabéticos e nem portadores de doença renal. Após coleta do sangue venoso, foram dosados glicose e ácido úrico, por método colorimétrico; e sódio e potássio pelo método de eletrodo íon seletivo. **Resultados**: houve associação entre o uso de anti-hipertensivo e elevações nos níveis séricos de ácido úrico (p=0,040). E, entre as classes, os diuréticos demonstraram, neste estudo, que estão relacionados a alterações nos níveis de ácido úrico (p=0,02), quando comparadas às demais classes. **Conclusão**: o uso de anti-hipertensivo, em especial os diuréticos, mostrou-se associado com aumento nos níveis séricos de ácido úrico em hipertensos usuários de anti-hipertensivo oral.
Descritores: Idoso; Anti-Hipertensivos; Efeitos Colaterais e Reações Adversas Relacionados a Medicamentos.

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Introduction

Systemic arterial hypertension is a multifactorial clinical condition characterized by elevated and sustained blood pressure levels. It is defined as systolic blood pressure equal to or greater than 140 mmHg (millimeters of mercury) and/or diastolic blood pressure equal to or greater than 90 mmHg in adult subjects who do not take any type of antihypertensive medication[1].

In Brazil, cardiovascular diseases account for more than 250,000 deaths per year, and systemic arterial hypertension accounts for almost half of them. A recent study shows that among the elderly, the prevalence ranges from 52.0% to 63.0%, which allows identifying arterial hypertension as a public health problem, which brings to the patient a high cardiovascular risk[2].

Aging is a dynamic and progressive process that causes various changes in the body, either morphological, psychological, functional and biological, leading to a decrease in functional capacity and also a greater risk of developing non-communicable chronic diseases. Among the risk factors for the development of chronic non-communicable diseases, systemic arterial hypertension is the most prevalent[3]. The control of this morbidity requires both non-pharmacological treatment, represented by the adoption of a healthy lifestyle, as well as the pharmacological treatment, through the use of medications, or even the association of both. It is worth noting that the use of drugs to control and maintain blood pressure levels in normal values is indicated in more than 70.0% of the cases[4].

In Brazil, there are seven commercially available classes of oral antihypertensive drugs: diuretics, adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin type 1 receptor blockers, direct renin inhibitors, direct vasodilators and calcium channel blockers[1].

Studies have reported several side effects produced by oral antihypertensive drugs, and among them there are reports of metabolic and electrolyte abnormalities, mainly related to the use of some specific classes of antihypertensive drugs[1,5]. The changes addressed in these studies refer mainly to the blood concentrations of potassium, sodium, glucose and uric acid in patients.

The effects of oral antihypertensive drugs on the circulating levels of the elements in question are diverse. Diuretics, for example, have been one of the top-ranked drug classes in the treatment of hypertension, both as monotherapy and in combination; and its use may be associated with hypopotassemia (sometimes accompanied by hypomagnesemia), hyperuricemia, and an increase in fasting blood glucose[1,5-6]. First and second generation beta-blockers may also act to raise blood glucose, especially when combined with diuretics[5]. However, some data appear in a conflicting manner in the scientific literature and it is likely that the number of correlations between the use of antihypertensive drugs and biochemical dosages will increase as additional studies are performed.

The monitoring of patients on antihypertensive therapy is of great importance in order to detect changes related to adverse reactions, either metabolic and/or electrolytic, that can be caused by these drugs, as well as to avoid that these reactions cause serious or permanent effects on users. However, this recommended monitoring is deficient in the Family Health Strategy teams, making it necessary to deepen the knowledge about the reactions produced by the chronic use of these medications. Therefore, the present study aimed to compare serum levels of uric acid, glucose, potassium and sodium in elderly users and non-users of oral antihypertensive drugs.

Methods

This is an observational, analytical, case-control study. In this study, participants were 232 elderly individuals with mean age 68.9 ± 7.4 years old, attended in a private network laboratory with ambulatory care located in the city of Teresina, Piaui, Brazil, from June to October, 2014.

Below is the formula used to calculate the size of independent and bilateral samples.

$$m_1 = \frac{(r_1^2 + r_2^2/k) \cdot (Z_{\alpha/2} + Z_{1-\beta})^2}{(\mu_2 - \mu_1)^2}$$

$$m_2 = \frac{(kr_1^2 + r_2^2) \cdot (Z_{\alpha/2} + Z_{1-\beta})^2}{(\mu_2 - \mu_1)^2}$$

Where: m_1- number of sample 1 - control sample; m_2 - number of sample 2 - experimental sample or case; r_1^2 - glucose variance in the control group; r_2^2- glucose variance in the experimental or case group; $Z_{\alpha/2}$ - normal curve score for the pre-established significance level 5% for bilateral test; $Z_{1-\beta}$ - score for the power of the established β test 80%; μ_2 - mean glucose in the experimental/case group (estimated at 101mg/dL); μ_1 - mean glucose in the control group (estimated at 97.6 mg/dL); k - proportion between the groups, 1 in the case.

However, to simplify the data of the formula, they were entered in the BioEstat 2.0 program, considering two independent samples for bilateral tests, thus obtaining samples of 116 participants in each group.

The study included 232 elderly people, of whom 116 were hypertensive and used oral antihypertensive drugs and constituted the case group; the control group was formed by 116 elderly people, non-hypertensive and non-users of antihypertensive drugs. Diabetic elderly and/or suffering from renal disease, as well as those using other medications mentioned in studies, which interfered in the blood levels of glucose, uric acid, sodium and potassium, were excluded.

Several medications may interfere with serum concentrations of electrolytes and metabolites, increasing or decreasing their values. Thus, each drug cited by the participants was recorded, and it was then verified if there was a possible relationship with changes in the concentrations of the analyzed analytes. If so, the participant was excluded from the survey.

The sample was selected by convenience and the technique used to produce data consisted of the application, prior to the exams, of a questionnaire containing information on age, gender, origin, monthly income, marital status and schooling in order to trace the socioeconomic profile of participants. The questionnaire was supplemented with information on the use of oral antihypertensive medication, time of use of the antihypertensive drugs, name of the antihypertensive drug (to identify the class) and use of other medications.

The variables of the study were: gender, age, marital status, monthly income, use of antihypertensive drugs or not, time of use of antihypertensive drugs, antihypertensive drugs class, serum concentrations of glucose, sodium, potassium and uric acid.

After 12-hour fasting, a venous blood collection was performed in the laboratory between 6:45 a.m. and 8 a.m. for further biochemical analysis. The samples were conditioned in vacuum tubes with separator gel and without anticoagulant. After the collection procedures, the blood was centrifuged for 10 minutes at 3000 rpm to separate the serum from the other components, and the serum was used for the analysis. Serum uric acid and glucose concentrations were determined by using a colorimetric enzyme kit, processed in the automated random access analyzer for biochemical and turbidimetric dosages, A15 (BioSystems). Serum sodium and potassium were determined by using a selective ion electrode, using the electrolyte analyzer (MAX ION*).*

After being collected, the data were analyzed by using statistical software Statistical Package Social Sciences version 18.0. Initially, the Kolmogorov-Smirnov test was applied to evaluate the normal distribution of the data for the quantitative variables, and since they did not follow a standard of normality, a non-parametric Mann-Whitney test was applied for independent samples for comparison between the groups case and control. Absolute and relative trends were obtained.

To verify the association between the qualitative variables, according to the use of antihypertensive

medication, the Pearson's chi-square test was applied. The level of statistical significance established for all study trials was 5%.

The study complied with the formal requirements contained in the national and international regulatory standards for research involving human beings.

Results

The mean age of the individuals studied was 68.9 ± 7.4 years, in which 59.9% were in the age group of 60 to 69 years of age. It was observed that 52.2% of the elderly were female, and 62.9% of the participants were married or lived in a stable union, and 72.0% had monthly income of up to one minimum wage. In summary, the sociodemographic profile of the study participants showed that 83.2% were from other Brazilian states. Overall, about 56.0% reported not using other types of medications.

There was an association between use of antihypertensive drugs and female gender (p=0.049), which shows that women are more adherent to treatment than men; and also between use of drugs to treat hypertension with monthly income (p=0.001).

The most commonly used antihypertensive drug class in monotherapy was angiotensin-converting enzyme inhibitors (29 patients), followed by AT1 receptor blockers (22 patients); the most commonly active substances used in monotherapy were captopril and losartan, respectively, for each class of drugs indicated.

As for the therapeutic regimen, it was possible to detect that 59.4% of the elderly in the case group were treated in monotherapy, while 27.5% used two drugs and 10.3% were treated with more than two antihypertensive drugs.

Table 1 shows the classes of antihypertensive most used by the participants of this study, but other classes were also found less frequently, such as beta-blockers (19), calcium channel blocker (14) and renin inhibitor (1).

Table 1 - Antihypertensive drugs used by the elderly participants of this study that used antihypertensive drugs, according to the pharmacological class (n=116)

Antihypertensive class	n(%)
Angiotensin I receptor blocker	47(40.50)
Diuretic	40(34.48)
Conversion Enzyme Inhibitor	43(37.06)

*Value greater than 116 because some patients made use more than one type of oral antihypertensive drug

When comparing the results of the biochemical measurements between the control and the case groups, it was found significantly higher serum levels (p=0.040) for serum uric acid concentrations among users (Table 2). No statistically significant differences were found for sodium, potassium and glucose concentrations.

Table 2 - Distribution of elderly patients with or without the use of antihypertensive drug, according to serum sodium, potassium, uric acid and glucose concentration

Analytes	Cases (n=116)			Controls (n=116)			p*
	Mean	Standard deviation	Median	Mean	Standard deviation	Median	
Sodium (mmol/L)	138.8	6.9	139.5	138.9	7.2	140.0	0.923
Potassium (mol/L)	4.3	0.6	4.2	4.2	0.6	4.1	0.352
Uric acid (mg/dL)	4.9	1.6	4.7	4.4	1.5	4.2	0.040*
Glicose (mg/dL)	96.3	11.7	96.0	97.2	11.5	96.5	0.824

*Mann-Whitney Test

Table 3 shows the mean and standard deviation values of the serum concentrations of the analyzed analytes, grouping the elderly of the case group, users of oral antihypertensive drugs, according to the antihypertensive drug class used, which were compared with the results of the control group, by using the Mann Whitney test. Elderly patients who used diuretics alone or in combination with another antihypertensive agent had a significantly higher uric acid concentration (p = 0.02) than the non-users group. There was no statistically significant difference for the other analytes (glucose, sodium and potassium).

Table 3 - Serum concentrations of analytes in elderly users of antihypertensive drugs, according to the antihypertensive drug class used (n=116)

Antihypertensive class	Mean	Standard deviation	p*
Beta blocker			
Sodium (mmol/L)	138.70	4.98	0.809
Potassium (mol/L)	4.26	0.56	0.574
Uric acid (mg/dL)	4.83	1.69	0.369
Glicose (mg/dL)	96.11	14.02	0.882
Calcium channel blocker			
Sodium (mmol/L)	138.14	5.11	0.698
Potassium (mol/L)	4.43	0.59	0.236
Uric acid (mg/dL)	4.82	9.83	0.223
Glicose (mg/dL)	94.79	1.44	0.489
AT1 receptor blocker			
Sodium (mmol/L)	137.90	7.5	0.561
Potassium (mol/L)	4.22	0.59	0.990
Uric acid (mg/dL)	4.86	1.50	0.082
Glicose (mg/dL)	96.94	13.69	0.898
Diuretic			
Sodium (mmol/L)	139.88	4.77	0.488
Potassium (mol/L)	4.27	0.54	0.476
Uric acid (mg/dL)	5.20	1.45	0.02*
Glicose (mg/dL)	97.60	13.13	0.741
Angiotensin-converting enzyme inhibitors			
Sodium (mmol/L)	138.79	7.70	0.714
Potassium (mol/L)	4.34	0.61	0.276
Uric acid (mg/dL)	4.90	1.74	0.169
Glicose (mg/dL)	96.74	9.37	0.804

*Mann-Whitney Test

Regarding the time of use of antihypertensive drugs, it was verified that within the case group, 38.8% had been using oral antihypertensive drugs for a time interval between 1 and 3 years, and 31.0% had been using the drug for more than 5 years; the time of use also did not show itself as a relevant factor for changes in biochemical dosages, and there was no association between the time of use of antihypertensive drugs and changes in the serum concentrations of glucose, uric acid, sodium and potassium.

Discussion

The elderly population has increased thanks to advances in knowledge and technologies in the field of health, especially those related to investments in public health. With this, the morbidity and mortality profile of the population has changed, increasing the prevalence of chronic diseases, such as hypertension, rheumatism, dementias, cerebrovascular accidents, coronary diseases, diabetes mellitus and others. In the same way that the number of elderly people is increasing, the consumption of medicines accompanies this growth. The elderly are the users responsible for the consumption of 43.0% of all medications given under medical prescription. One of the reasons for representing the most medicalized age group in society is the higher prevalence of chronic diseases that accompany aging[7].

The main non-pharmacological recommendations for the primary prevention of systemic arterial hypertension are: healthy eating, controlled consumption of sodium and alcohol, intake of foods high in potassium, combat to sedentary lifestyle and smoking[1]. In cases of mild hypertension in which there is no response to non-drug treatment, it is necessary to include drug therapy.

In this study, the variables *gender* and monthly income were important when associated with use of antihypertensive drugs. This is because the female gender showed greater association with treatment with these drugs, which corroborates data presented in other studies[8-9]. This finding emphasizes the predominance of women in research on the prevalence of systemic arterial hypertension and adherence to treatment. However, it should be considered that the sample size of women in the study is higher than the number of men.

According to the data obtained in this study, it was verified that individuals who receive up to a minimum wage were majority in both groups, case and control (61.2% and 82.8%, respectively). This is a finding that deserves to be highlighted, since the

low economic condition can influence the attitude and adherence to the treatment when associated with other variables[3]. According to other studies[10-11], more than 80.0% of hypertensive patients are found in low-middle income regions. There is a large body of evidence linking socioeconomic status with the conventional risk factor for hypertension. The population with low socioeconomic status is known to have a lifestyle that is harmful to health, which is related to the development of inappropriate eating habits, as well as to smoking and alcohol consumption.

In relation to the biochemical measurements of sodium, potassium, glucose and uric acid, this study showed that uric acid levels were different between cases and controls, that the use of antihypertensive drugs, in general, caused changes in serum uric acid concentrations and that the class of antihypertensive drugs associated with the greatest changes in uric acid levels in the patients studied was the class of diuretics. These data are in line with the results of another study[12], in which diuretics were associated with changes in serum uric acid levels, as well as increased risk of gout.

The association between the use of diuretics and the increase of uric acid (and consequently the risk of uric acid gout) has been evidenced in some studies[12-15]. In this sense, a cohort study conducted with white adults showed a 2.4 times higher risk of gout in women and a 3.4 times higher in men with a history of use of diuretics[14]. Study conducted in Taiwan[13] also found this association, emphasizing that the increased risk of gout from any therapy with the use of diuretics represents an important modifiable risk factor in patients with a history of gout, which may also be applied to the elderly group here studied. And in a large US study involving 5,789 hypertensive individuals, 37.0% of whom were treated with diuretics, an association was found between the use of thiazide diuretics or loop diuretics with the incidence of gout and, in addition, that study showed changes in serum urate levels[12].

The relationship between increased serum urate and the development of gout can be explained by mechanisms that go beyond the effects of hypertension itself. In fact, systemic arterial hypertension decreases renal blood flow, which may increase urate reabsorption and thus lead to insufficient excretion of urate. In addition, diuretics increase diuresis and therefore promote depletion of body fluid volume. Diuretic therapy may affect the transport of ions to the luminal membrane of the proximal tubule cells, and sodium-dependent anion reabsorption increases its concentration in the proximal tubule cells, resulting in urate exchange via URAT1, with increased urate reabsorption by the kidney and hyperuricemia[12,16].

Still in relation to diuretics, some studies have evidenced the role of this class of drugs with the increase of glycemia[5,17-18], which was not observed in the group of elderly participants of this study. In a meta-analysis in which the effects of low doses of thiazide diuretics on glycaemia and kalemia were evaluated, the adverse effects of thiazides on glucose metabolism in diabetic patients have been observed since their introduction into clinical practice[6]. However, the onset of glucose intolerance in non-diabetic patients under chronic thiazide use is controversial.

In a study involving 40 participants using diuretics for an average time of 29 months, it was shown that prolonged duration of treatment is associated with increased fasting glucose and that overall glycemic status is aggravated when thiazide diuretics are combined with beta-blockers[5]. In this study, in elderly hypertensive patients using combination therapy of diuretics and beta-blockers, or in use of another class of antihypertensive drugs, the serum glucose concentrations were not statistically different from those found in non-hypertensive elderly in the control group. There was also no association between serum sodium and potassium concentrations and the use of any class of antihypertensive medication in the study population.

Conclusion

According to the results, the use of antihypertensive drugs, especially diuretics, was associated with an increase in serum uric acid levels in hypertensive users of oral antihypertensive drugs. However, there were no differences for sodium, potassium and glucose concentrations among elderly users and non-users of antihypertensive drugs.

Collaborations

Carvalho MEMM, Alves ELM and Martins MCC contributed to the design and project, analysis and interpretation of data, essay writing or critical review of intellectual content and final approval of the version to be published.

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