African Journal of Pharmacy and Pharmacology

Volume 11 Number 4, 29 January, 2017
ISSN 1996-0816

Academic Journals

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African Journal of Pharmacy and Pharmacology

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Vol. 11(3), pp. 53-61, 29 January, 2017
DOI: 10.5897/AJPP2016.4687
Article Number: ADBBF4D62663
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Impact of liraglutide versus atorvastatin on cardiovascular changes in rat model of adenine induced chronic renal failure

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Received 18 October, 2016; Accepted 18 January, 2017

The prevalence of cardiovascular changes markedly increases with deterioration of patient's renal function and can stack up 65 to 70% in end-stage renal disease. A rapid fall in renal function is often associated with uncontrolled congestive heart failure. Beyond their lipid-lowering effect, statins have been shown to protect the heart in different diseases. Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue, used to control diabetes. It improves cardiac dysfunction in non-diabetics, but underlying mechanisms remain to some extent, unclear. Fifty two male Sprague-Dawley rats weighing 200 to 250 g were grouped into negative control, positive control, liraglutide treated group (0.3 mg/kg), atorvastatin treated group (10 mg/kg), liraglutide and atorvastatin treated group (0.3 and 10 mg/kg, respectively), liraglutide and atorvastatin treated group (0.15 and 5 mg/kg, respectively). Combination of both drugs significantly reduce creatine phosphokinase isoenzyme (CK-MB) in both doses ($p<0.008$, $p<0.002$) and lactate dehydrognase (LDH) ($p<0.04$, $p<0.01$). Liraglutide alone or in combination with atorvastatin in both doses ($p<0.02$, $p<0.01$ and $p<0.01$) significantly increased superoxide dismutase (SOD). Atorvastatin alone ($p<0.02$) or in combination with liraglutide in both doses ($p<0.001$, $p<0.001$) induced a significant decrease of malondialdehyde (MDA). Atorvastatin alone ($p<0.01$) or in combination with liraglutide in both doses induced a significant amelioration of nitric oxide (NO) and cholesterol ($p<0.01$ and $p<0.02$). Significant improvements in blood urea nitrogen (BUN) and glucose profile were seen with all tested drugs either single or in combination. Combined implementation of both drugs improves histopathological changes of cardiac muscle fibres. Liraglutide has promising effects on cardiovascular changes in adenine induced chronic nephropathy through modulation of LDH, CK-MB and improvement of NO and SOD. Also, it can mitigate fibrosis and cardiac tissue changes. Its effects markedly increase in conjunction with atorvastatin. Combined administration of liraglutide and atorvastatin in a high dose has a reliable effect on improving outcome in biochemical and histopthological cardiac muscle fibers changes.

Key word: Atorvastatin, liraglutide, adenine, renal failure.

INTRODUCTION

Increased incidence of cardiovascular system dysfunction is associated with chronic kidney disease (CKD) (Serizawa et al., 2015). Alterations in the kidneys and heart occur in CKD (Hernández-Reséndiz et al., 2015; Thaung et al., 2015). Studies on these structures in this disease have so far not been addressed. We are confronted by an alarmingly increasing number of patients with progressive renal disease.

Adenine is used for induction of renal failure. Only after 2 days of its administration, it is immediately metabolized to 2,8-dihydroxyadenine, which precipitate as crystals in the microvilli and the apical region of the proximal tubular epithelia (Adachi et al., 1993). The crystals were deposited at these tissues, induced degenerative changes in the cells and caused renal dysfunction. These structural alterations were associated with increased levels of serum creatinine and inorganic phosphate, and decreased levels of serum calcium (Yokozawa et al., 1986).

Statins had antiproliferative, anti-inflammatory, anti-thrombotic and anti-oxidant effects in previous studies (Wang et al., 2008). Statin clinical trials showed a reduction in stroke rate in patients with coronary heart disease (CHD) or atherosclerotic risk factors (John et al., 2005; Kucera et al., 2014). Atorvastatin is one of important statins that cause regression of lipid profile. It acts through inhibition of 3-hydroxy-3-methylglutaryl (HMG) Co-A reductase that is considered as a key enzyme in cholesterol synthesis. It is used as primary and secondary prevention of cardiovascular disease and can protect against nuclear damage in coronary artery diseases (Gundapaneni et al., 2016).

Liraglutide is glucagon-like peptide-1 (GLP-1) analogue and it exerts cardioprotective effects in animals and patients with or without diabetes (Nikolaidis et al., 2005; Sokos et al., 2006 Poornima et al., 2008). A large body of evidence has indicated that GLP-1 may have a beneficial effect on cardiovascular system; however, the mechanism is not fully understood, especially in non-diabetics. So, in this work, the authors evaluated its potential impact on cardiovascular changes occurring in chronic renal failure induced in rats in comparison to atorvastatin.

MATERIALS AND METHODS

The chemicals

Adenine was obtained from Sigma and was prepared freshly every day. Liraglutide (victoza®) 6 mg/ml from Novo Nordisk; Atorvastatin (lipitor 40 mg®) was dissolved in 4 ml methylcellulose (0.05%) to make a concentration of 10 mg/ml.

The animals

Fifty two male Sprague-Dawley rats (Urology and Nephrology Center, Mansoura University, Egypt), weighing 200 to 250 g were housed under conditions of controlled temperature and 12 h lighting cycle and fed with standard diet ad libitum. The study was approved by Institutional Ethics Committee for the use of laboratory animals. The animals were divided into 6 groups of 8 animals each. 4 rats died during induction. Group 1: Negative control received 0.5 ml methylcellulose by gavage feeding for 4 weeks; Group 2, Positive control: adenine was injected i.p. (100 mg/kg for four weeks) (Al Za'abi et al., 2015). Group 3: was given adenine as in above mentioned dose plus liraglutide (0.3 mg/kg subcutaneously) injected twice daily (Zhang et al., 2015) for 4 weeks; Group 4: was given adenine as in the above mentioned dose plus atorvastatin (10 mg/kg orally 6 days/week) for 4 weeks (Mehrzadi et al., 2016); Group 5: was given adenine as in the above mentioned dose plus combination of liraglutide (0.3 mg/kg subcutaneously) injected twice daily for 4 weeks and atorvastatin (10 mg/kg orally) 6 days/week for 4 weeks; Group 6: was given adenine as in the above mentioned dose plus combination of liraglutide (0.15 mg/kg subcutaneously) injected twice daily for 4 weeks and atorvastatin (5 mg/kg orally) 6 days/week for 4 weeks.

Parameters of the study

Endothelial dependent factors; endothelin-1 (ET-1) enzyme measured by immunoassay kits were supplied by R and D systems IncMcKinely place N.E., Minneapolis, MN, USA (Suzuki et al., 1989). Nitric oxide (NO) was determined by Griess reagent (Amano and Noda, 1995).

Serum creatinine was determined by the method described by Henry (1974). Blood urea nitrogen was measured according to Patton and Crouch (1977); using urea kits (Diamond diagnostics company, Egypt).

Serum indices of cardiotoxicity

Lactate dehydrogenase (LDH) and creatine phosphokinase isoenzyme (CK-MB) were determined kinetically at 340 nm using commercially available kits (Stanbio laboratory, INC. USA).

Preparation of cardiac tissue

The heart samples were dried, weighed, homogenized in 50 mM ice cold phosphate-buffered saline (pH 7.4) and centrifuged for 5 min at 5000 g. The samples were stored at -80°C for biochemical estimations.

Cardiac oxidative stress; MDA, SOD, glutathione

The superoxide dismutase (SOD) activity was determined spectrophotometrically according to the method of Lowry et al. (1955). Malondialdehyde (MDA) was measured using the

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Table 1. Effect of liraglutide and atorvastatin on serum levels of cardiotoxicity indices in adenine induced renal failure in rats (Mean±SEM).

	CK-MB (U/L)	LDH (U/L)
Gp1 (Negative control)	350.5±3.97	303.25±3.35
Gp2 (Positive control)	399.5±3.27^{p}	330.875±3.41^{p}
Gp3 (Liraglutide treated group)	387.8±8.6^{p}	319.63±4.06
Gp4 (Atorvastatin treated group)	388.6±6.3^{p}	316.5±4.21
Gp5 (Liraglutide 0.3 mg/kg plus atorvastatin 10 mg/kg)	383.3±7.3^{p1}	311.375±5.51^{p1}
Gp6 (Liraglutide 0.15 mg/kg plus atorvastatin 5 mg/kg)	381.1±8.6^{p1}	309±4.88^{p1}

P = significant difference when compared with negative control group, P1 = significant difference when compared with positive control.

Table 2. Effect of liraglutide and atorvastatin on levels of cardiac oxidative stress parameters in adenine induced renal failure in rats (mean ± SEM).

	SOD (U/ mg protein)	MDA (nmol/mg protein)	GSH (µ mol/gm tissue)
Gp1 (Negative control)	35.9±1.6	116.38±4.45	4.36±0.25
Gp2 (Positive control)	23±1.52^{p}	179.63±7.84^{p}	2.8±0.34^{p}
Gp3 (Liraglutide treated group)	30.9±1.5^{p1}	156.25±5.51^{p}	3.3±0.23
Gp4 (Atorvastatin treated group)	29.6±1.97	151.87±6.35^{p,p1}	3.09±0.16^{p}
Gp5 (Liraglutide 0.3 mg/kg plus atorvastatin 10 mg/kg)	31.4±2.02^{p1}	134.75±5.64^{p1}	3.63±0.27
Gp6 (Liraglutide 0.15 mg/kg plus atorvastatin 5 mg/kg)	34.13±1.03^{p1}	137.625±5.28^{p1}	3.47±0.22

P = significant difference when compared with negative control group, P1 = significant difference when compared with positive control.

thiobarbituric acid (TBA) (Bernheim et al., 1948). The level of glutathione (GSH) was determined according to Beutler et al. (1963). Blood glucose was determined by enzymatic method according to Trinder (1969) (Bio Med-Glucose, Germany).

Cholesterol and TG

Serum TG was estimated according to the method of Fossati and Principe (1982) while enzymatic determination of serum total cholesterol was determined according to the method of Tietz (1976). They were measured spectrophotometrically with the use of Spinreact kits.

Histological study

Paraffin sections of cardiac tissues (5 µm thickness) were prepared, and then stained with haematoxylin and eosin (H&E) (Kiernan, 1999; Bancroft and Gamble, 2002).

Statistical analysis

All data are expressed as means ± SEM. Comparisons between different groups were analyzed by one-way ANOVA followed by bonfernnie multiple comparison tests. In all cases, a probability error of 0.05 was selected as the criterion for statistical significance. Graphs were drawn using SPSS (version 21 for Windows).

RESULTS

In Table 1, liraglutide insignificantly reduce CK-MB as well as atorvastatin as compared to adenine induced nephropathy group. Abrogating effect of combination of both drugs on CK-MB in both doses (liraglutide 0.3 mg/kg plus atorvastatin 10 mg/kg or liraglutide 0.15 mg/kg plus atorvastatin 5 mg/kg) were significant when compared with positive control group ($p<0.008$ and $p <0.002$, respectively).

As regard LDH, only combination of both drugs can exert a significant reduction in its levels when compared with positive control group ($p<0.04$ and $p<0.01$, respectively).

In Table 2, there were significant changes in SOD as regard tested drugs either liraglutide alone ($p<0.02$) or in combination with atorvastatin in both doses ($p<0.01$ and $p<0.01$, respectively). On the other hand, atorvastatin alone ($p<0.02$) or in combination with liraglutide in both doses induced a significant decrease of MDA as compared to positive control group ($p<0.001$ and $p<0.001$, respectively).

In Table 3, there were insignificant changes in endothelin as regard tested drugs either single or in combination. On the other hand, atorvastatin alone ($p<0.01$) or in combination with liraglutide in both doses induced a significant amelioration of NO as compared to the positive control group ($p<0.01$ and $p<0.02$, respectively).

In Figures 1 and 2, there were insignificant changes in creatinine and TG as regard tested drugs either single or

Table 3. Effect of liraglutide and atorvastatin on levels of endothelial dependant factors; endothelin-1 (ET-1) and nitric oxide (NO) (mean ± SEM).

	Endothelin-1 (ET-1) (pg/ml)	Nitric oxide (NO) (umol/ul)
Gp1 (Negative control)	1.57±0.11	125.5±4.8
Gp2 (Positive control)	3.38±0.27 ^{p}	90.44±2.89^{p}
Gp3 (Liraglutide treated group)	3.26±0.25 ^{p}	105.11±3.5^{p}
Gp4 (Atorvastatin treated group)	3.07±0.21 ^{p}	107.37±3.08^{p,p1}
Gp5 (Liraglutide 0.3 mg/kg plus atorvastatin 10 mg/kg)	293±0.18 ^{p}	107.33±2.62^{p,p1}
Gp6 (Liraglutide 0.15 mg/kg plus atorvastatin 5 mg/kg)	3.09±0.11 ^{p}	106.19±2.7$^{p, p1}$

P = significant difference when compared with negative control group, P1 = significant difference when compared with positive control.

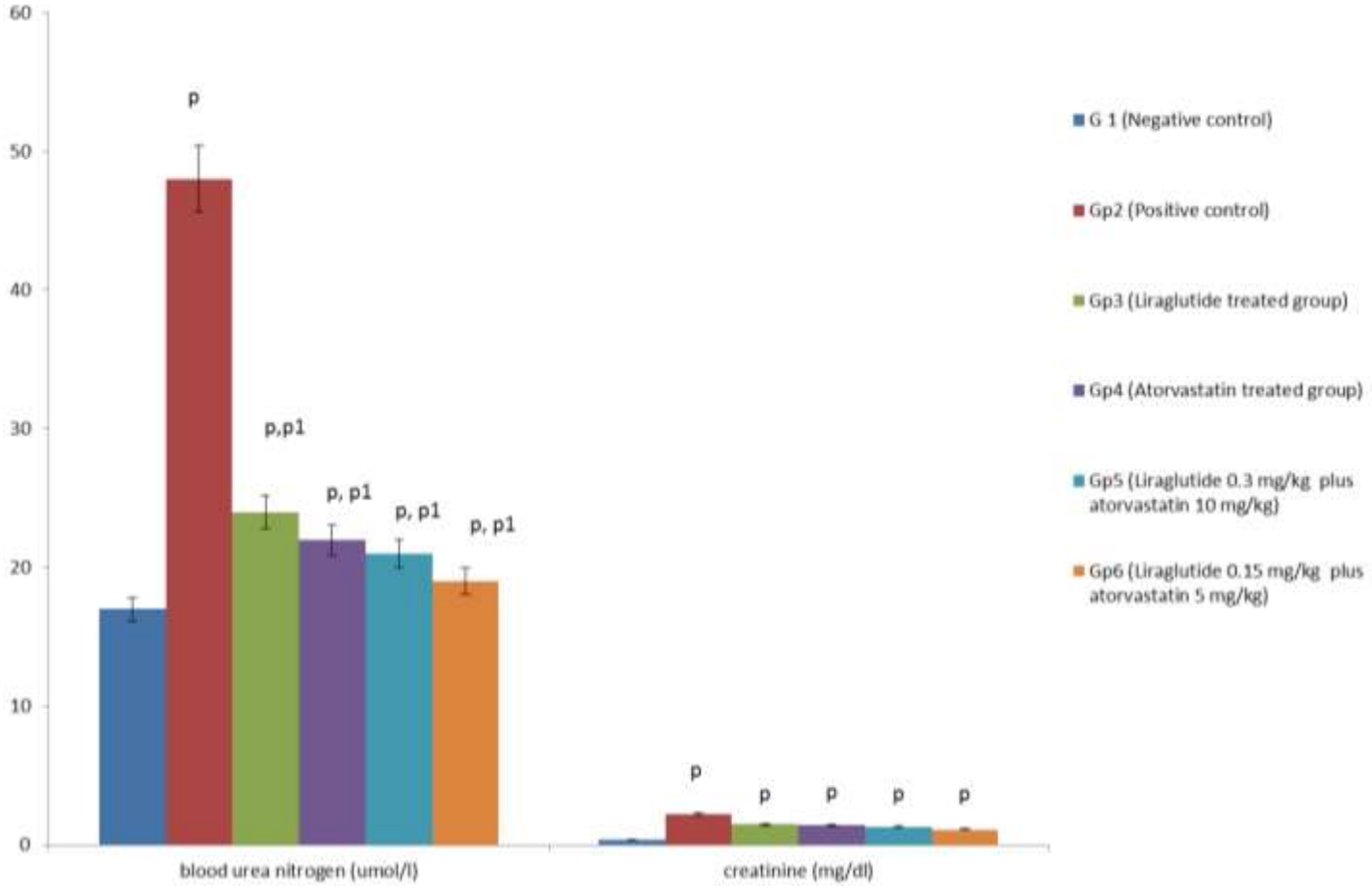

Figure 1. Effect of liraglutide and atorvastatin on creatine (mg/dl), blood urea nitrogen (µmol/L). P = significant difference when compared with negative control group, P1 = significant difference when compared with positive control.

in combination. On the other hand, there were significant improvements in BUN with all tested drugs either single or in combination ($p<0.001$). Also, there were significant changes in glucose profile with all tested drugs when compared with positive control group ($p<0.05$). As regard cholesterol, there were significant changes attributed to atorvastatin alone ($p<0.01$) or in combination with liraglutide ($p<0.006$ and $p<0.004$, respectively).

Histological examination of cardiac tissues

In the negative control group (Figure 3), normal striated cardiac muscle fibers was observed between fine collagen fibres with single centrally located oval nuclei and intercalated discs by light microscope. In semithin section, a clear zone surround central vesicular nuclei with visible cross striations were present.

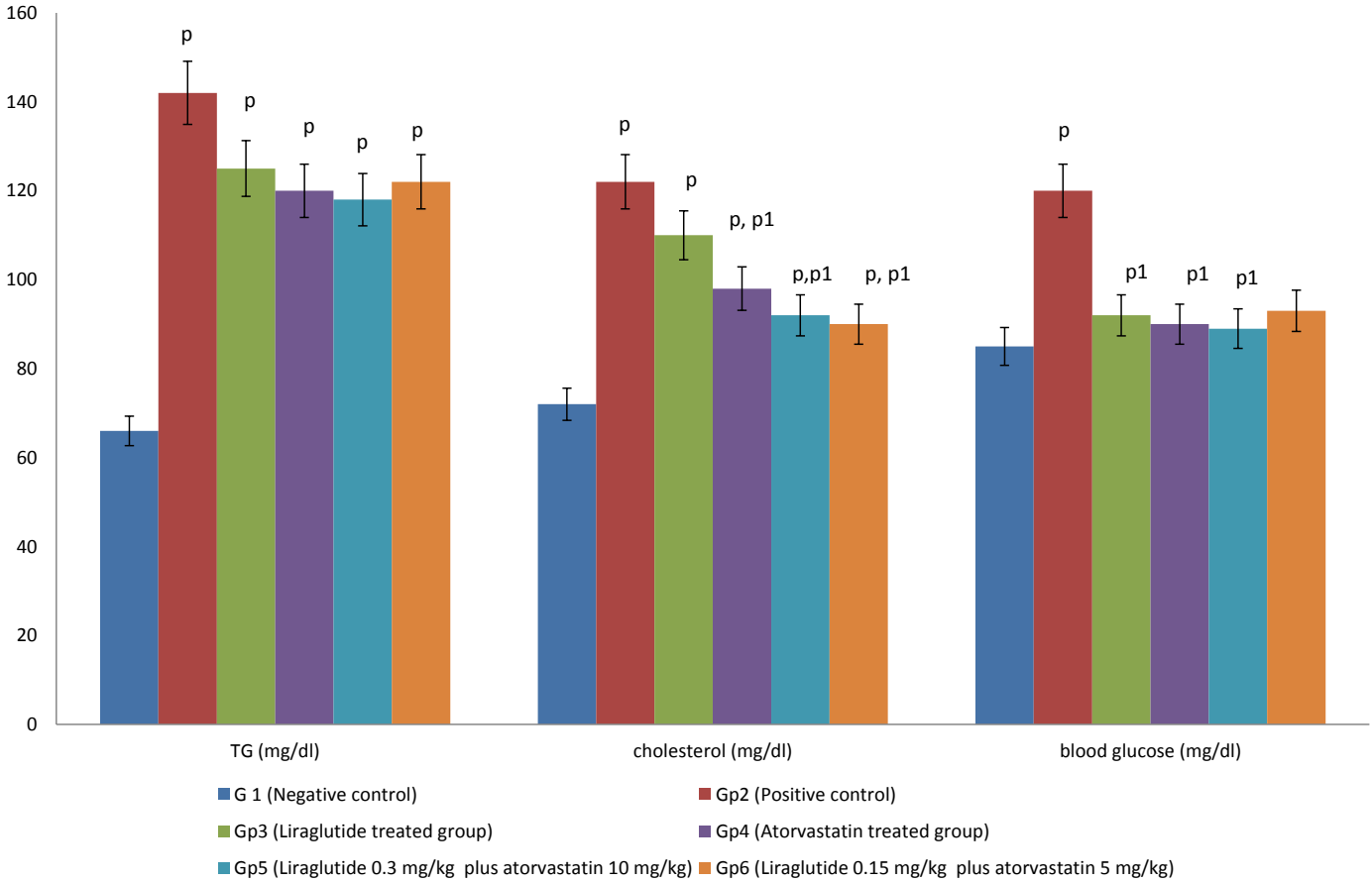

Figure 2. Effect of liraglutide and atorvastatin on blood glucose (mg/dl), cholesterol (mg/dl) and triglyceride (mg/dl P = significant difference when compared with negative control group, P_1 = significant difference when compared with positive control.

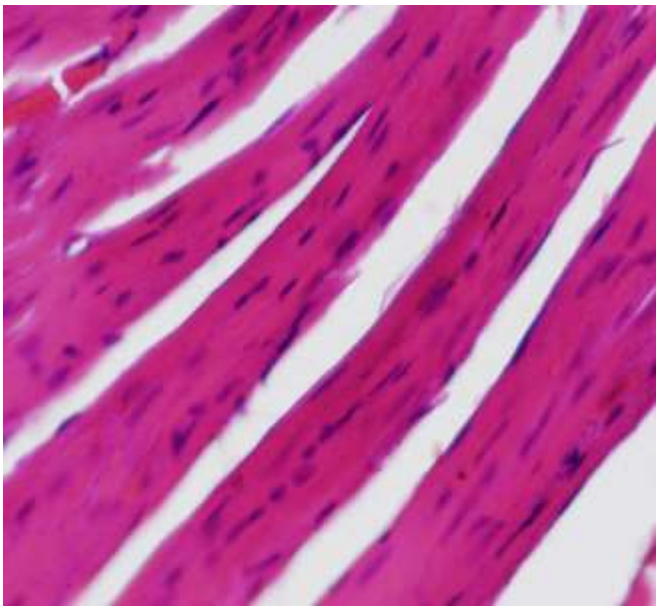

Figure 3. Group (1): cardiac muscle fibres showing striated muscle fibres with single centrally located oval nuclei and intercalated located oval nuclei (H & E, 400x).

Positive control group is shown in Figure 4. LM showed distorted striation of separated muscle fibres with vesicular nuclei and myofibroblast. Collagen fibers moderately and significantly increase in the cardiac muscle as compared to the negative control group (P< 0.05). Loss of muscle fibers striation and some nuclei, congested blood vessels and presence of myofibroblasts were seen in semithin sections.

With regards to the liraglutide treated group (Figure 5), LM illustrated splitted muscle fibres with patchy loss of striation, some nuclei become pyknotic with chromatin margination, congested blood vessels and lymphocytic infiltration. Focal areas of collagen fibres deposition were also seen in the cardiac muscle but significantly less in comparison with positive control group.

Atorvastatin treated group (Figure 6). LM demonstrated restorated striation of cardiac muscle fibers together with pyknotic nuclei, plenty of myofibroblasts and lymphocytic infiltration. Mild significant decrease in collagen fibres in cardiac muscle were observed in comparison with positive control. Semithin sections revealed myofibroblast and lymphocytic infiltration. Combined high dose group (Figure 7) (LM) revealed significant restoration of near

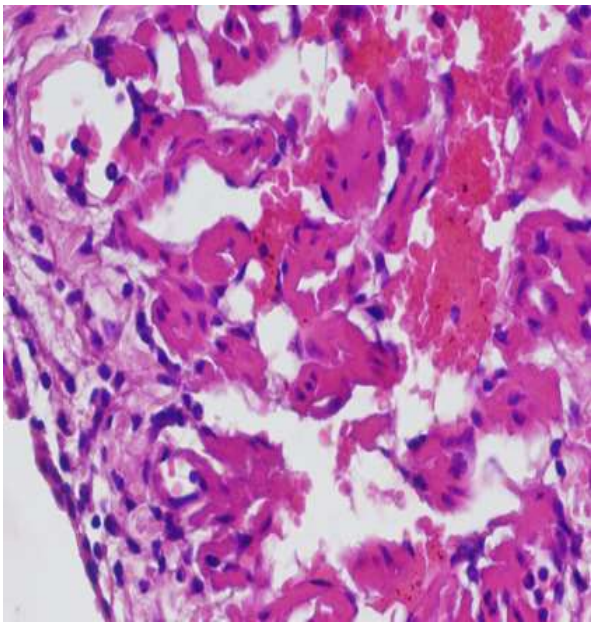

Figure 4. Group (2) cardiac muscle fibres showing distorted fibres striation, muscle fibres separation with vesicular nuclei and myofibroblas (H & E, 400x).

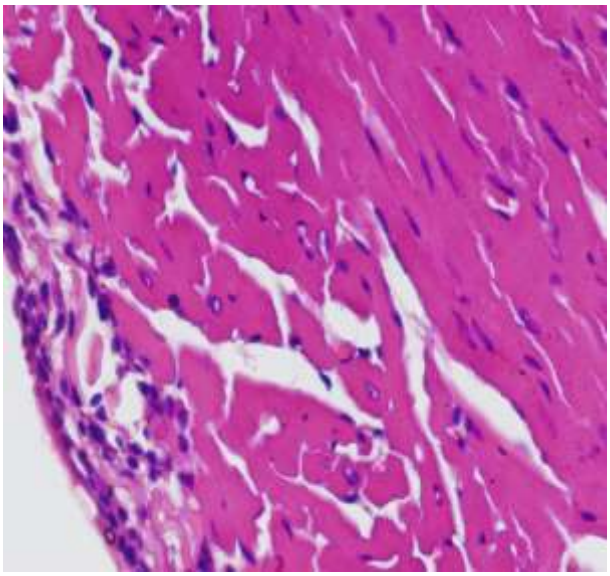

Figure 6. Group 4: Cardiac muscle fibres showing restored striation, pyknotic nuclei, lymphocytic infiltration and increased myofibrobasts (H& E, 400x).

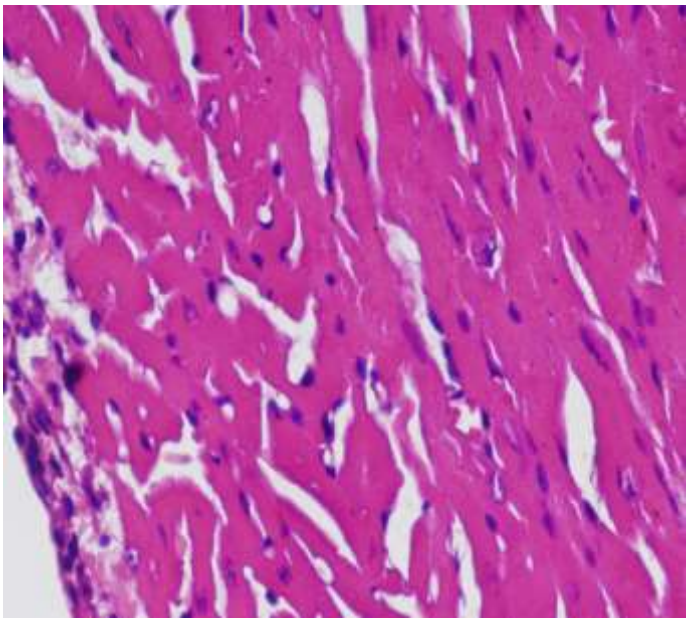

Figure 5. Group 3: Cardiac muscle fibres showing splitted muscle fibres, congested blood vessels lymphocytic infiltration and pyknotic nuclei (H & E, 400x).

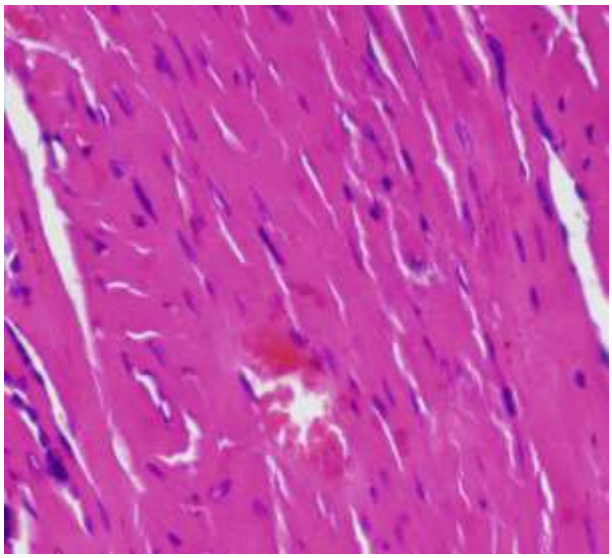

Figure 7. Group 5: Cardiac muscle fibres showing near normal striation with few collagen fibres (H&E, 400x).

normal cardiac striation with decreased collagen fibres in comparison with positive control, liraglutide treated, atorvastatin group and combined low dose treated group. With regards to combined low dose group (Figure 8), LM showed that cardiac muscle fibres restored their normal striation and scattered myofibroblasts and collagen fibres in the cardiac muscle were observed but significantly less in comparison with positive control group, liraglutide treated and atorvastatin groups.

DISCUSSION

GLP-1 receptor agonist may have potential multiple effects in patients with cardiovascular disease beyond their effect in managing diabetes. Little studies shows

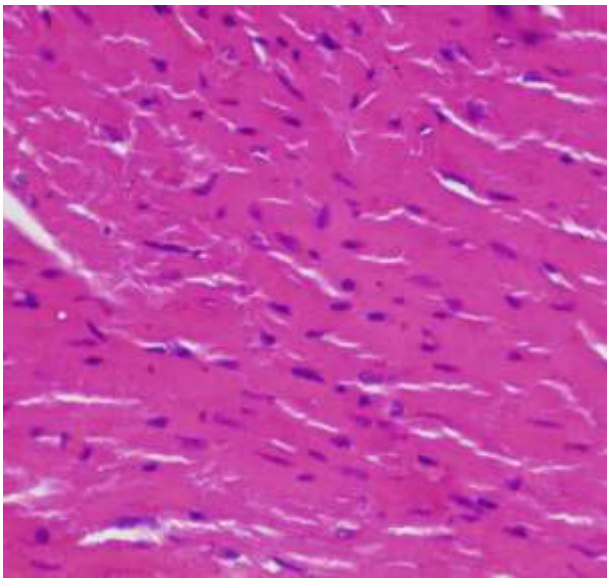

Figure 8. Group 6: Cardiac muscle fibres showing myofibroblast with scattared collagen fibres (H&E 400x).

that GLP-1 receptor agonist may be effective for cardiac disorders in patients without diabetes mellitus.

In this study, combination of both drugs in both doses had significant effects on CK-MB and LDH. These findings were collaborated by Liu et al. (2016) who stated that pre-treatment with liraglutide in human neuroblastoma cell line exposed to beta-amyloid Aβ decrease LDH leakage and cellular apoptosis. In the same direction, Sharma et al. (2014) illustrated that liraglutide reduce LDH and apoptosis. It was found that liraglutide suppressed NADPH oxidase and pro-inflammatory signals, and reduced collagen deposition in ischemia reperfusion model and obesity (Inoue et al., 2015; Wang and Yang, 2015).

In the present study, liraglutide alone or in combination with atorvastatin in both doses enhance SOD. Atorvastatin alone or in combination with liraglutide in both doses induced a significant decrease of MDA. In other studies on myocardial ischemia, atorvastatin exerts significant cardioprotective effects through increase of SOD and decreased MDA content (Sun et al., 2015). In the same direction, Mehrzadi et al. (2016) stated that atorvastatin enhance the renal SOD activity however, not reduce MDA. Rats pretreated with atorvastatin 2 or 5 mg/kg/day challenged with acetaminophen, showed higher hepatic SOD activities, lower MDA levels (Farag et al., 2015). Additionally, atorvastatin increase intrarenal activities of SOD and decrease MDA content (Zhou et al., 2014). Gao et al. (2015) show that liraglutide significantly increased SOD levels in non-alcoholic fatty liver disease. Also, it prevented brain edema, suppressed neuro-inflammation following intracerebral hemorrhage (Hou et al., 2012).

In the present study, atorvastatin alone or in combination with liraglutide in both doses induced a significant amelioration of NO and no effect on endothelin was reported. This work is supported by Nakata et al. (2007) who show that atorvastatin upregulates vascular nNOS through NF-kappa B pathway. However, other studies like Cetinkaya et al. (2013) mentioned that atorvastatin significantly decreased the levels of endothelin-1 in aged ovariectomized rats. Also, it was found that atorvastatin pretreatment attenuated endothelin 1 alterations and diminished histological injury scores (Chang et al., 2010; Cámara-Lemarroy et al., 2014). Contrary to this work, studies of Dai et al. (2013) showed that liraglutide inhibit nuclear factor kappa B (NF-κB) phosphorylation that culminates in suppression of ET-1 expression. However, it was found that liraglutide (30 µg/kg twice daily) reversed insulin resistance, obesity-induced perturbations in cardiac endothelial nitric oxide synthase in high fat diet mice (Noyan-Ashraf et al., 2013).

In the present study with all tested drugs either single or in combination, they improve significantly BUN and glucose profile; also, they improve creatinine. Zhou et al. (2014) reported that liraglutide decreased total cholesterol, blood urea nitrogen, serum creatinine in streptozotocin-induced diabetic rats. Atorvastatin effectively reduced creatinine and may carry a good approach as potential antidiabetic effect and serve as the therapeutic drug for diabetic kidney disease management in streptozotocin-induced diabetic rats (Liao et al., 2016). On other hand, Mehrzadi et al. (2016) mentioned that atorvastatin could not reduce elevated serum creatinine concentration, kidney weight, renal ROS and MDA levels.

Little studies are available on liraglutide and atorvastatin effects on structure of the cardiac muscle fibres. The obtained results in the present study revealed indistinct and distorted striation in the cardiac muscle fibers with separation, congested and dilated blood vessels, vesicular nuclei and loss of some nuclei, and presence of myofibroblast in positive control group. These results are in agreements with El Rabey et al. (2013). In our work, liraglutide partially improved histology of cardiac tissue and combined treatment of liraglutide and atorvastatin in both doses improved cardiac tissue as reflected by restoration of the striation and myofibroblast and scattered collagen fibres in the cardiac muscle. The evaluated data in this study declared a significant difference between all groups in collagen fibres. These results are in agreements with Deshmukh et al. (2012) who reported similar results. Also, Liu et al. (2013) reported that liraglutide significantly enhance cardiac structure and decreased the parameters of LV posterior wall and its end-diastolic diameter. However, in other studies, only minor cardiovascular effects of GLP-1 despite increased insulin levels and reduced plasma glucose concentration in compensated diabetic heart failure was reported (Halbirk et al., 2010). Atorvastatin

significantly reduced hyperplasia of fibrotic tissue in the model of heart failure and significantly reduced expression of type I and III collagen (An et al., 2013). Similarly, atorvastatin improve radiation-induced cardiac fibrosis and significantly reduced the expression of TGF-β1, Smad3/P-Smad3 in rats (Zhang et al., 2015).

Conclusion

This study show promising effects of liraglutide and atorvastatin on cardiac muscle fibres. They not only depend on their role in modulating glucose and lipid profile. Combined administration of liraglutide and atorvastatin in a high dose has a reliable effect on improving outcome in biochemical and histopthological cardiac muscle fibers changes.

Conflict of interest

The authors declare that there is no conflict of interest.

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academicJournals

Vol. 11(4), pp. 62-67, 29 January, 2017
DOI: 10.5897/AJPP2016.4701
Article Number: 815E93B62665
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Use of phytoterapics and medicines without professional prescription in a municipality Potiguar, Brazil

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Received 13 November, 2016; Accepted 6 December, 2016

The use of herbal medicines or drugs without professional prescription is a recurrent practice in several regions of Brazil. This action generates risks to the user, such as intoxication, masking of disease symptoms and important pharmacological interactions. The objective of this study was to analyze the profile of phytotherapeutic and drug use, without professional prescription, among residents of the municipality of Santa Cruz, Rio Grande do Norte, Brazil. Thus, a field survey was carried out through the application of a semi-structured questionnaire in the Likert scale model to 180 residents. The majority were women (80%), the predominant marital status were married (56%) and 44% were 49 years of age or older. It was observed that the target population has a low level of knowledge about self-medication, besides a constant consumption of Non-steroidal anti-inflammatory drugs NSAIDs without prescription. In addition, respondents do not have the habit of questioning health professionals, increasing of the self-medication. Therefore, health education actions are necessary in order to clarify the population, the change of habits in this practice, in search of a better quality of life.

Key words: Self-medication, medicinal plants, plant-drug interactions.

INTRODUCTION

Drugs and phytotherapics are frequently used as professional prescription in several Brazilian cities, justifying itself for several reasons, among them, easy access to products, public health service and influence of the media or people close to users. In this context, therapeutic resources are used on their own, and this

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practice is called self-medication (Yadav and Rawal, 2015; Jaramillo et al., 2003; Luras et al., 2016; Luras et al., 2016; Albatti et al., 2016).

For many of the socially underprivileged regions, going to the pharmacy is the main way to solve health problems, where a large proportion of the drugs consumed are over-the-counter, without the prescription. Among the most consumed classes are analgesics, antipyretics and anti-inflammatory drugs (Non-steroidal anti-inflammatory drugs - NSAIDs) (Jain, 2011).

The main risks of this practice are, for example, incorrect choice of therapy, masking of symptoms, possible pharmacological interactions, increase of bacterial resistance, more pronounced adverse reactions and potential intoxications (Silva et al., 2011).

Relative to this, in the search of relief of health problems, the population makes use of medicinal plants. Many of these uses have been oriented through empiricism, that is, in popular knowledge, which in fact may not have the desired therapeutic purpose (Castel-Branco et al., 2015).

Thus, it is inferred that the use of drugs and phytotherapics without professional prescriptions can lead to potential intoxications to the user as well as interactions between the two, which may compromise the therapeutic goal (Castel-Branco et al., 2015; Lessa and Bochner, 2008). Therefore, the study aimed to investigate the profile of users of basic health units in the municipality of Santa Cruz, Rio Grande do Norte, Brazil on the use of medicines and phytotherapics without professional prescription.

METHODS

The study was descriptive and transversal of a qualitative approach, carried out in basic health units of the municipality of Santa Cruz, State of Rio Grande do Norte, Brazil. A total of 180 users of both sexes participated in the study, being considered as inclusion criteria, being over 18 years old and users of BHUS (Basic Health Unit) in the municipality, as well as declaring a voluntary interest in the study participation. The sample was characterized as non-probabilistic and for convenience. The research was carried out, after prior authorization of the FACISA (Faculty of Health Sciences of Trairi) / UFRN (Federal University of Rio Grande do Norte) Ethics Committee (1,206,323), according to the standards that govern Resolution 466/2012. The data were collected through the application of a semi-structured questionnaire in the Likert scale, that is, being analyzed within a type of measurement, elaborated solely to meet the objective of this study (Boone and Boone, 2012).

This instrument was structured as follows: 1. socio-demographic (age, family income, profession, schooling and marital status); 2. Applied (Frequency of use of health unit, source of information about medicine and herbal medicines, frequency of use of medicine and herbal medicine, perception of risk of use of medicine/herbal medicine without professional guidance, types and herbal medicines and medicines used for own account).

These were tabulated and analyzed through the STATISC 10.0 Software, using ANOVA and Cluster Analysis.

RESULTS

Among those interviewed, it was observed that 80% were women, 56% declared married marital status. Regarding the age group, 44%, were 49 years of age or older. The same percentage was observed as a predominance in the educational level, being predominant those with incomplete elementary education. In the family income, the majority was included in up to a minimum wage (73%).

Respondents were initially asked about the types of health services they attended, with the majority (68%) being referred to Basic Health Units (BHUs). These institutions provide free services to the local population. Regarding the frequency of use of these basic health units, most of them go at least once a month (49%). Thus, Figure 1 shows the period of access to these services.

When questioned about the habit of practicing self-medication, the majority (62%) reported being a frequent practice. Already, the sources of information on medicines, the majority 59%, pointed out to perform with health professionals. (Figure 2).

As most of the interviewees do self-medication on a frequent basis, they were asked about the safety of this practice applied to some drug classes (non-steroidal anti-inflammatory drugs (NSAIDs), antihypertensives, hypoglycemic agents and antibiotics) - Table 1. NSAIDs were considered by 63% of the interviewees as a group of medicines with low health risks, if consumed without professional guidance.

Relative recent consumption of herbal medicines, 61% claimed to do so, being the most cited: Horsetail (98%), Carqueja (94%), Boldo-do-chile (93%), Green tea (84%), Mint %), Fennel (68%), Boldo Brasileira (63%), Cidreira (57%) and Camomila (53%). Only 6% of the interviewees claimed to question health professionals about these products.

The self-medication can have its negative effects on the health of the user intensified, if this uses still phytotherapics without professional guidance. Some examples of these effects are listed in Table 2 (Brazil, 2011).

Finally, we performed an Analysis of Variance involving the socio-demographic variables of the study as the frequency and knowledge about the risks of self-medication, through ANOVA. Statistically relevant ($p \leq 0.05$) the level of schooling and income, according to Table 3.

Through the analysis of Cluster it was possible to verify through the analysis of variance between socio-demographic variables and self-medication, it was observed a relationship between Income, Schooling, Frequency with which practice self-medication, With whom doubts about medicines and Level of knowledge about risk of self-medication ($p \leq 0.05$). Figure 3.

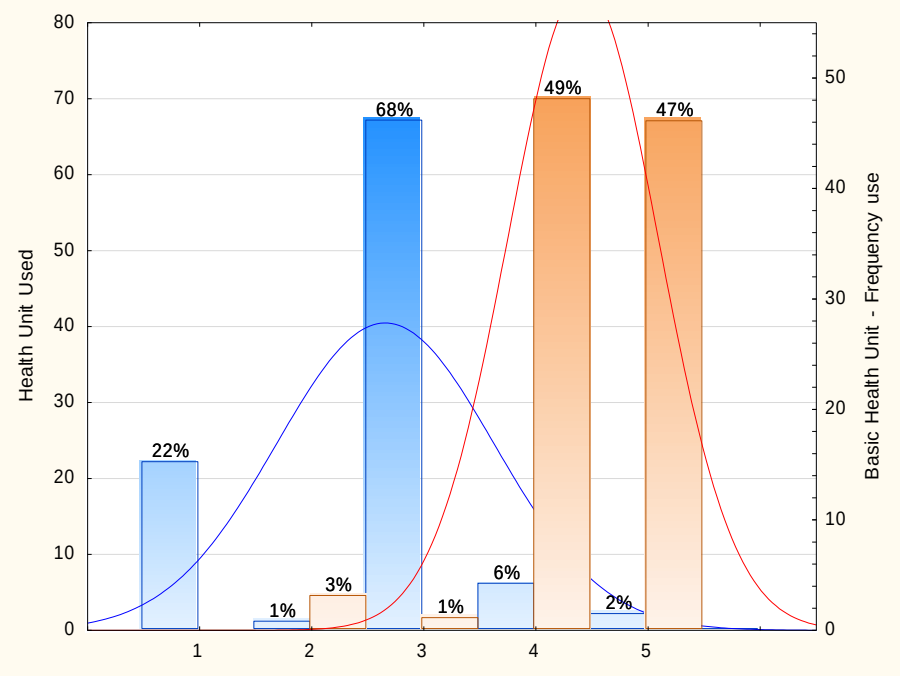

Figure 1. Frequency of use of BHUS (Basic health units) and types of services most used. Health Unit Used (1.Public hospital; 2.Private Hospital; 3. Basic health Unit; 4.Beauty Therapy;5. Health insurance) Basic Health Unit - Frequency use(1- daily; 2.Weekly; 3. fortnightly; 4. Monthly; 5. Semiannually).

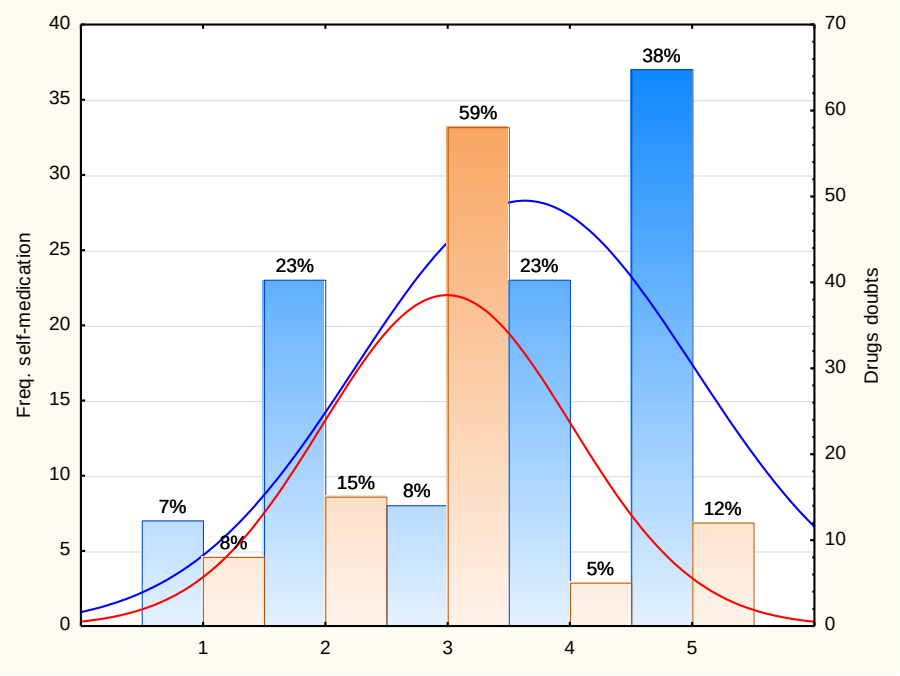

Figure 2. Frequency with which the interviewees practice self-medication and with whom they have doubts about medication. Frequency of self-medication (1. daily; 2.Weekly; 3. fortnightly; 4. Monthly; 5. Semiannually) Drugs doubts (1. Friend, 2. Relative, 3. Health professional, 4. Internet, 5. Tv).

Table 1. Percentage of interviewees who consider the self-medication of some drug classes without danger.

Drug class	Percentage of risk
Non-steroidal anti-inflammatory drugs NSAIDs	63
Antihypertensives	11
Antibiotics	19
Hypoglycemic agents	10

Table 2. Phytotherapeutic-drug/phytotherapeutic interaction-pathological conditions.

Medicinal plant	Interaction
Cavalinha (*Equisetum*sp.)	-
Carqueja (*Baccharistrimera*)	Avoid concomitant use with antihypertensives and for diabetes.
Boldo-do-chile (*Peumusboldus* Molina)	Contraindicated for people with gallstones, obstruction of the bile ducts and severe liver diseases.
Alecrim (*Rosmarinusofficinalis* L.)	Do not use in people with gastroenteritis and a history of seizures.
Chá verde (*Camelliasinensis* var *assamica*)	-
Hortelã (*Mentha x piperita* L.)	Do not use in diabetics and people with urinary lithiasis or in cases of treatment with simvastatin and felodipine.
Erva-doce (*Pimpinellaanisum* L.)	In case of allergic reactions, discontinue use immediately.
Boldo-brasileiro (*Plectranthusbarbatus*Andrews)	It should not be used by hypertensive patients with obstruction of the biliary tract. Do not use in the case of treatment with metronidazole or disulfiram, CNS depressants and antihypertensives.
Cidreira (*Cymbopogoncitratus* (DC.) Stapf)	It may potentiate the effect of sedative drugs.
Camomila (*Matricariarecutita* L.)	Occasional allergic reactions.

Adapted from: Pharmacotherapeutic Form of the Brazilian Pharmacopoeia (2011).

Table 3. Analysis of Variance between the statistically relevant variables.

Variable	Between SS	df	Withinss	df	F	Significance P
Schooling	151.3315	1	89.6992	96	161.9616	0.000000
Yield	5.9402	1	78.1925	96	7.2930	0.008183
F Self-medication frequency	6.2661	1	178.9992	96	3.3606	0.039872
Risk of Self-medication	4.1167	1	124.2200	96	3.1815	0.047636
Doubts about drugs	5.1237	1	88.2519	96	3.2476	0.02367

DISCUSSION

Most of the interviewees (68%) said they attend basic health units, being public services for primary health care. However, there is no frequent departure from these services, which could be explained by several factors in the Brazilian reality. Among these, the difficulty of marking the service or access, or even the availability of time (Graden et al., 2015), since these units work in the daytime. This pecularity may make it difficult to guide people about various health issues, such as the correct use of therapeutic devices.

This reality may be aggravated by some social factors, such as low education and income of the population, since access to information could be compromised. The target audience of the study, fits this profile, a fact that can influence the therapeutic use of the device without proper professional guidance. This may lead to incorrect dosage, negative pharmacological interactions and masking of pathological symptoms (Abrahão et al., 2013; Torres et al., 2014).

This was a practice performed by most of the enrolled, although largely claim to consult health professionals about medications. This may be due to difficulty access

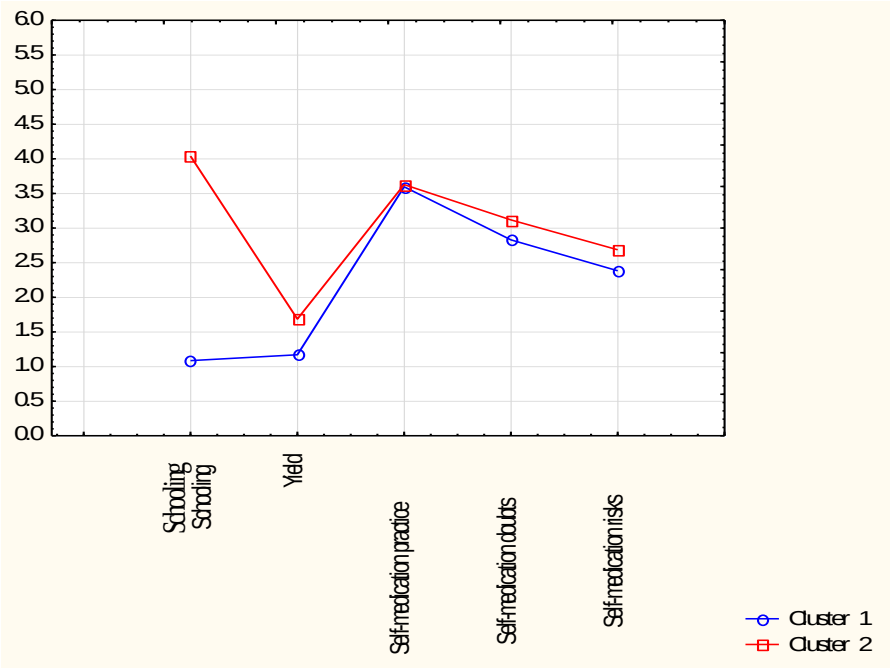

Figure 3. Cluster analysis.

to health care, marketing influence or induction to consumption in drugstores (Wehling, 2014).

This is worrying, since most respondents (74%) say they have little or no knowledge about the risks of self-medication, demonstrating that actions to clarify this public should be carried out.

As for the specific classes of medicines, the majority claimed to take some NSAIDs on their own, since they believe there is no health hazard (Basic Health Unit). These drugs have three main effects: anti-inflammatory, analgesic and antipyretic action, being exerted through the inhibition of cyclooxygenase (COX).

However, they are not risk-free medicinal products, which can trigger a series of adverse effects such as: gastrointestinal bleeding, dyspepsia, peptic ulcer, dysfunction and renal failure due to incorrect use (dose, route of administration, pharmacological interactions) Inhibition of platelet aggregation and increased bleeding time, jaundice and interactions with other drugs (Wehling, 2014; Torres et al., 2014; Silva et al., 2013).

Complementarily, the interviewees were asked about their level of knowledge about phytotherapics / teas and possible interactions with drugs, and how they have questions about this topic. Since 89% of the interviewees do not clarify doubts with health professionals, TV and friends are the main sources of information about herbal medicines and teas. This reinforces the low knowledge that most (87%) claims about the interaction of herbal and medicinal products, proving to be a cause for concern, since innumerable drugs may present interactions with herbal / phytotherapeutic risks to the user's health.

Although there is a variation between different groups of schooling, it is variable and income is not enough to influence the practice of self-medication or knowledge about the risks of this practice, confirming the descriptive analysis that is a common practice in the group analyzed. Especially in developing countries, given the lack of health education and service qualities complicate this reality (Hussain et al., 2011).

Conclusion

The set of results obtained in this research allows us to visualize that the interviewed group performs the use of medicines and phytotherapeutics, mostly without proper guidance from a qualified health professional.

Therefore, they are more exposed to the undesirable effects of this practice, among them, masking disease symptoms and the risk of major intoxication.

In this way, health education actions, quality service provision and professional qualification should be intested to better guide users about the risks of this practice.

Conflict of Interests

The authors have not declared any conflict of interests.

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