Cardiovascular Repercussion of Lodenafil Carbonate, a New PDE5 Inhibitor, with and without Alcohol Consumption

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Summary

Background: Millions of men around the world suffer from erectile dysfunction, for which phosphodiesterase 5 inhibitors (PDE-5 inhibitors) are currently the first treatment option. Sexual activity and alcohol consumption are closely related, and the simultaneous use of alcohol and PDE-5 inhibitors can happen. Lodenafil carbonate is a new PDE-5 inhibitor, developed by a Brazilian pharmaceutical company.

Objective: This work aimed at evaluating the cardiovascular safety of lodenafil carbonate, with and without simultaneous alcohol consumption.

Method: Fifteen male volunteers received 160 mg lodenafil carbonate (LC), in three different moments. Participants were assigned to three groups, treated with LC in fasting condition, with alcohol or receiving only placebo. The volunteers were continuously monitored during 24 hours for physical impairment, blood pressure, heart rate, QT interval and lodenafil's pharmacokinetic parameters.

Results: Lodenafil carbonate alone or with alcohol did not induce clinically relevant modifications in arterial blood pressure or heart rate. A statistically significant decrease in blood pressure was seen four hours after LC and alcohol intake, and an increase in heart rate six hours after intake of lodenafil carbonate alone. The QTc interval was not significantly modified. Lodenafil carbonate bioavailability was increased in 74% when drug intake was associated with alcohol.

Conclusion: These results show that the use of lodenafil carbonate did not have clinically relevant effects on blood pressure or heart rate, and was not associated with QT interval prolongation. The association of lodenafil carbonate and alcohol affected its pharmacokinetic properties, increasing the bioavailability of the drug. (Arq Bras Cardiol 2010;94(2): 150-156)

Key Words: Erectile dysfunction; attributable risk; alcohol drinking; phosphodiesterase inhibitors; cardiovascular system.

Introduction

Erectile dysfunction (ED) has multifactorial causes[1] which are related to psychological, organic[2] and drug factors[3]. Around 39% to 67% men between 40 and 70 years of age are estimated to present some degree of ED, and 10% of them have complete ED[4]. ED is treated with different approaches, including psychotherapy, the use of several types of local or systemic drugs and surgical implantation of prosthesis. Recent advances have led to the development of inhibitors of phosphodiesterase type-5 (PDE-5), an isozyme highly concentrated in the cavernous body of the penis, with significant increase in the quality of life of these patients.

Although vasodilation induced by PDE-5 inhibitors may cause some hemodynamic effects, the therapeutic doses used result in mild and transitory effects on blood pressure[5,6].

Lodenafil carbonate (LC) is a dimeric protein composed of two lodenafil molecules linked by a carbonate bridge, and behaves as a prodrug which releases lodenafil as the active metabolite. This new PDE-5 inhibitor was entirely developed by a Brazilian company. Preclinical and clinical studies have shown that the drug has low toxicity and is safe and efficient in the treatment of DE[7-16].

Alcoholic drinks are widely used in Brazil. Around 69% of the population has consumed alcohol in some moment of their life[17]. Alcohol consumption has complex hemodynamic effects, resulting in vasodilation[18] due to direct activity on the tonicity of vascular smooth muscles[19] and also through the nitric oxide system[20,21]. Alcohol exerts a biphasic effect on blood pressure, with an initial increase and then a continued decrease[22,23].

Social alcohol consumption, independent of the use of PDE-5 inhibitors, is strongly related to sexual activity[24]. Alcohol is frequently seen as a "facilitator" of the relationship between two persons, since its moderate ingestion may cause euphoria. When used acutely and in increased amounts, however, alcoholic drinks present a sedative activity and result in potent depression of the central nervous system. In these cases, men can present a difficulty to reach or maintain erection, due to acute alcohol intoxication. Chronic alcohol consumption in men may lead to a condition of sacral neuropathy, which leads

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to alcohol-related impotence[23].

In this context, we decided to investigate a possible interaction between alcohol consumption and lodenafil carbonate *in vivo*, to determine whether any association between alcohol and that PDE-5 inhibitor could exist. This study aimed at analyzing, in healthy volunteers, a potential effect of lodenafil carbonate in inducing hemodynamic alterations and arrhythmias, when used alone or in combination with alcohol. The presence or absence of pharmacokinetic interactions between the two types of substances was also considered.

Methods

Study design

This open, cross-over, randomized, placebo-controlled study was conducted in accordance with the Helsinki Declaration, Good Clinical Practice and ANVISA legislation. The protocol was approved by the Research Ethics Committee of Universidade Federal de São Paulo (UNIFESP). All participants volunteered and signed an informed consent form before being enrolled in the study.

Inclusion criteria: age between 18 and 45 years; body weight > 50 kg and Body Mass Index (BMI) between 19 and 28 kg/m^2; capacity to understand and agreement with signing the informed consent form; presenting normal results for medical history and laboratory tests performed during the past 90 days before beginning of the study; negative serological results for HIV 1 and 2, hepatitis B and C; normal results for hemoglobin count, and differential and total leukocyte counts; normal results for biochemical tests (creatinin, urea, TGO, TGP, Gamma GT, total protein, uric acid, alkaline phosphatase, direct and indirect bilirubin, fast glucose levels, total and fractioned cholesterol and triglycerides) and normal urine results.

Exclusion criteria: history of allergy to lodenafil carbonate and related drugs; clinical and laboratory results evidencing organic dysfunction or any significant clinical abnormality; history of gastrointestinal, hepatic, renal, cardiovascular, lung, neurologic or hematologic disease, diabetes or glaucoma; history of psychiatric disease interfering with the ability to sign the informed consent form; regular smoking or having smoked until less than one year before beginning of the study; history of use of psychotropic drug, excessive alcohol consumption (over two units of alcohol per day, where one unit was equivalent to one glass of beer or wine or one dose of distilled drinks), or difficulty to abstain from drinking during the study; use of substances modulating hepatic microsomal activity during 30 days before beginning of the study; participation of clinical trials of blood donation (>500 mL) in the three months before beginning of the study; lack of adequate venous access (right or left arm) for collection of 68 (sixty-eight) blood samples.

Treatments

After at least 10 hours fasting, each participant received the following treatments, in a cross-over random design, with intervals of three days between treatments:

- Treatment A (trt A): one oral dose of 160 mg (two 80-mg pills) of lodenafil carbonate. After 30 minutes, participants received 200 mL of the dilutant used for alcohol.
- Treatment B (trt B): one oral dose of 160 mg (two 80-mg pills) of lodenafil carbonate. After 30 minutes, participants received 0.5 mg/kg alcohol diluted to a final volume of 200 mL.
- Treatment C (trt C): two placebo pills. After 30 minutes, participants received 200 mL of the dilutant used for alcohol.

Lodenafil carbonate and placebo pills were taken with 200 mL water at room temperature. The amount of alcohol, adjusted by weight, was diluted with commercial strawberry juice, without sugar, to a final volume of 200 mL. Alcohol administration was planned so that peak plasma concentrations of lodenafil and alcohol coincided, to favor maximum interaction between them. Volunteers remained sitting during four hours, received standardized meals at four, seven, 11, 13 and 23 hours after treatment, and were discharged 24 hours post-treatment, after a clinical examination. Clinical parameters and any complaints recorded by the patients were recorded during the 24-hour period after treatment. One week later, new analyses were performed for safety reasons.

For cardiovascular assessment, continuous electrocardiogram (Holter) was recorded for 24 hours, commencing 30 minutes before administration of treatment or placebo. Heart rate and the occurrence of arrhythmias were evaluated in the 15 participants. QT interval dynamics was assessed for 13 of the participants, with determination of corrected QT interval (QTc). Blood pressure was recorded at every two hours, through manual measurement with mercury column devices.

Blood collection and lodenafil dosage

For determination of plasma concentrations of lodenafil and alcohol, blood samples were collected in K_3EDTA-containing vials, 30 minutes before treatment and 0.33; 0.67; 1; 1.33; 1.67; 2; 2.33; 2.67; 3; 3,33; 3,67; 4; 6; 8; 10; 12; 16 and 24 hours after treatment. After at most 1 hour of collection, samples were centrifuged for 10 minutes at 4°C, plasma was separated and stored in polypropylene tubes at -20°C. Lodenafil concentrations were determined following a method developed and validated in our laboratory, using HPLC associated to a mass spectrometer (triple quadruple, Micro Mass). The method is linear between 1 and 2,000 ng/mL, and the inter and intra-day coefficient of variation was smaller than 7%. Plasma concentration of alcohol was determined by GC-SM (gas cromathography – mass spectrometry)

Statistical analysis of results

Data were analyzed by single-factor ANOVA, using the Tukey-Kramer method or the paired Student's t-test (Excel; Microsoft Corp, Redmond, Wash) when necessary. Differences were considered significant when $P<0.05$.

Results

Sample population

The sample included 15 men, with the following characteristics: mean age 29.7 years (range 21 to 41 years);

mean weight 70.1 kg (range 60.7 to 79.8 kg); mean height 1.73 m (range 1.65 to 1.80); mean BMI 23.5 kg.m^{-2} (range 21.8 to 26.1 kg.m^{-2}).

Pharmacodynamics results

Blood pressure

Baseline results [mean±standard deviation (SD) in mmHg] were not significantly different from those observed in groups trt A (114.3±10.2), trt B (113.6±8.5) and trt C (113.2±7.5) (ANOVA, $p>0.05$) (Table 1). Blood pressure (BP) was assessed in each group during 24 hours after treatment with lodenafil carbonate (Figure 1). The ANOVA analysis showed modification of BP at 4 hours after treatment ($p<0.05$; Table 2), whereas according to the Tukey-Kramer test, BP was lower in group trt B (lodenafil carbonate + alcohol) (106.7±8.2) than in groups receiving treatment A (lodenafil carbonate) (117.3±10.5) and C (placebo) (118.9±10.7), which were not different between themselves.

Heart rate

Heart rate (HR) was monitored in each group during 24 hours after treatment with lodenafil carbonate (Figure 2). Baseline results [mean±SD in beats/minute (bpm)] were: for trt A, 61.7±7.8; for trt B, 63.2±7.2; and for trt C, 67.8±7.7. A significant difference between the groups was observed only 6 hours after treatment (ANOVA, $p<0.05$). The Tukey-Kramer test showed that mean heart rate in groups receiving treatment A (71.1±9.4) and B (78.1±13.2) were similar, and significantly higher than in the placebo group (61.9±5.9) (Table 2).

The QT interval dynamics was analyzed in 13 participants. The maximum QTc interval (mean±SD) was 451±19 msec, 453±20 msec and 458±23 msec for treatments C (placebo), A (lodenafil carbonate) and B (lodenafil carbonate + alcohol), respectively. Variance analysis did not show statistically significant differences among groups ($p=0.6332$). Figure 3 presents the block diagram relative to the maximum QTc interval of the groups, and Figure 4 shows the correlation between maximum QTc and serum concentration of lodenafil.

Pharmacokynetics results

The peak concentration (Cmax) of alcohol in blood [1.1±0.2 mg/mL; coefficient of variation (CV) 20%] was reached 30 minutes after ingestion. Alcohol administration 30 minutes after treatment with lodenafil carbonate resulted in Cmax for both substances at nearly the same time (1 hour), allowing the assessment of results in peak concentrations of alcohol and lodenafil. The comparison of treatments A and B showed that alcohol ingestion (trt B) increased not only lodenafil Cmax (mean±SD) – trt A 158±108 ng/mL vs trt B, 210±123 ng/mL, $p=0.0138$ –, but also the area under the curve (AUC_{tq}) (mean±SD) – trt A, 528±380 vs trt B, 922±758 ng-h/mL, $p=0.0082$. Figure 5 presents the pharmacokynetics profile for lodenafil in 24 hours, when ingested without alcohol (trt A), with alcohol (trt B) and also of alcohol analyzed separately after the first 4 hours.

Adverse events

During the period of hospital stay for the three groups, in which the participants received lodenafil carbonate (160 mg) in fasting or lodenafil carbonate (160 mg) with alcohol, or placebo, three cases of adverse events were reported, with different individuals. One of them was related to mild cephalea, after treatment with placebo. The other two cases were also of mild cephalea, in individuals receiving treatment B (LC and alcohol). Analgesia was not necessary in any of the cases, and recovery was complete.

Table 1 - Baseline values of heart rate and systolic and diastolic blood pressures

Parameter	trt A	trt B	trt C	ANOVA (*p*)
	160 mg LC	160 mg CL + 0.5 g/kg alcohol	placebo	
Basal systolic BP				
(mmHg)				
mean±SD (CV)	114.3±10.2 (10.2)	113.6±8.5 (7.4)	113.2±7.5 (6.6)	0.9380
(median) (range)	(114) (101-132)	(113) (102-129)	(113) (100-127)	
Basal diastolic BP				
(mmHg)				
mean ±SD (CV)	72.1±7.8 (10.8)	70.9±7.3 (10.3)	73.3±8.1 (11.1)	0.6991
(median) (range)	(69) (62-83)	(70) (59-83)	(71) (62-90)	
Basal heart rate				
(bpm)				
mean±SD (CV)	61.7±7.8 (12.6)	63.2±7.2 (11.5)	67.8±7.7 (11.4)	0.0823
(median) (range)	(62) (51-78)	(63) (52-77)	(67) (57-81)	

LC - lodenafil carbonate, CV - coefficient of variation.

Discussion

Phosphodiesterase 5 (PDE-5) inhibitors are vasodilators, but when used in therapeutic doses for treatment of ED do not, generally, result in clinically significant hypotension[25-27] .

Alcohol and PDE-5 inhibitors may be simultaneously used and, since both have cardiovascular activity, the combination may have additive effects. In a study about the effects of alcohol and sildenafil, this drug was shown to induce mild hypotension when used alone, with no significant clinical consequences. Alcohol, on the other hand, had a biphasic effect, inducing an increase in heart rate and moderate initial increase in blood pressure, followed by a more sustained decrease in BP. Sildenafil and alcohol, however, did not interact in a way that resulted in an increase of the hypotensive effect individually presented by them[28]. Similar results have been observed in studies with vardenafil and alcohol[29] or tadalafil and alcohol[30], with no clinically significant modifications of BP.

The present study, which included healthy participants, did not show additive effects between lodenafil carbonate and alcohol which might result in clinical consequences, as observed for other types of PDE-5 inhibitors. The only statistically significant result involved a decrease in blood pressure observed 4 hours after treatment in group B, treated with alcohol 30 minutes before ingestion of lodenafil carbonate. At that moment, lodenafil concentration was 74% of Cmax, showing that the largest reduction of BP did not coincide with Cmax itself. The concentration of lodenafil at that moment (4 hours after treatment) was also lower than the maximum concentration observed for trt A (lodenafil carbonate without alcohol). These results suggest that alcohol may be involved with a decrease in BP when associated to lodenafil, since the blood pressure of individuals treated only

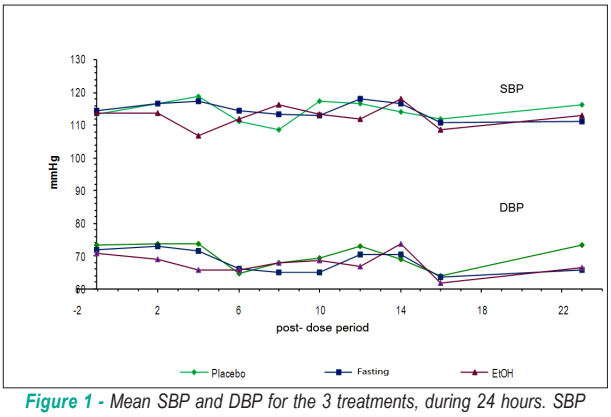

Figure 1 - Mean SBP and DBP for the 3 treatments, during 24 hours. SBP - systolic blood pressure; DBP - diastolic blood pressure

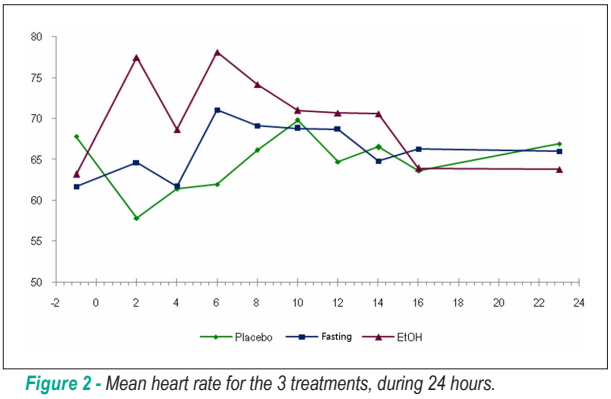

Figure 2 - Mean heart rate for the 3 treatments, during 24 hours.

Table 2 - Results at the moment when statistically significant differences in heart rate and systolic and diastolic blood pressures were observed

Parameter	trt A	trt B	trt C	ANOVA(*p*)
	160 mg LC	160 mg CL + 0.5 g/kg alcohol	placebo	
Systolic BP				
4 hours after treatment				
mean±SD	117.3±10.5 (10.5)	106.7±8.2 (7.7)	118.9±10.7 (9.0)	0.003*
(median) (range)	(120) (94-134)	(105) (93-123)	(119) (95-136)	
Diastolic BP				
4 hours after treatment				
mean±SD	71.5±8.5 (11.9)	65.8±8.7 (13.2)	73.7±9.2 (12.4)	0.0482*
(median) (range)	(70) (60-84)	(54) (51-81)	(74) (59-86)	
Heart rate				
6 hours after treatment				
mean±SD	71.1±9.4 (13.2)	78.1±13.2 (16.8)	61.9±5.9 (9.5)	0.0003†
(median) (range)	(72) (56-86)	(75) (62-98)	(61) (50-72)	

*After variance analysis (ANOVA), the groups were compared in pairs, with the Tukey-Kramer method. LC - lodenafil carbonate, CV - coefficient of variation. * results of treatment B are different from results of treatments A and C; treatments A and C had similar results. † results of treatments A and B are different from results of treatment C, mas similar between themselves.*

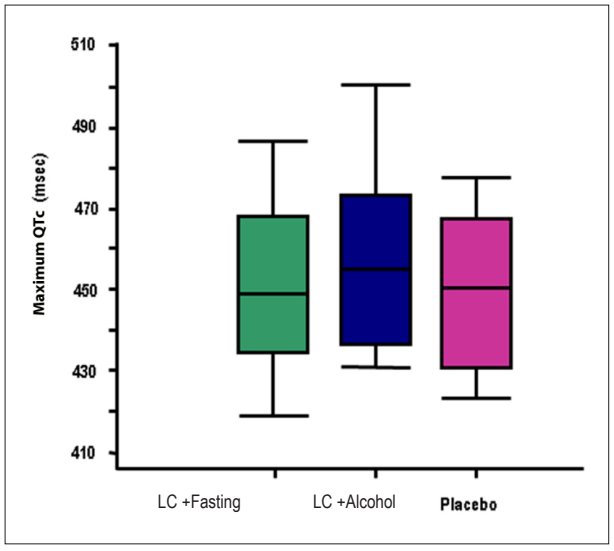

Figure 3 - Mean QTc interval in the 3 groups. ANOVA, p=0.6332 . LC - lodenafil carbonate

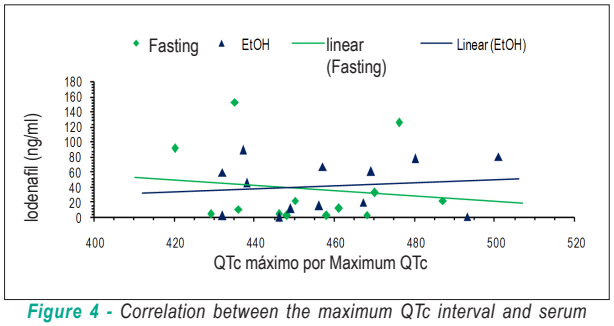

Figure 4 - Correlation between the maximum QTc interval and serum concentration of lodenafil

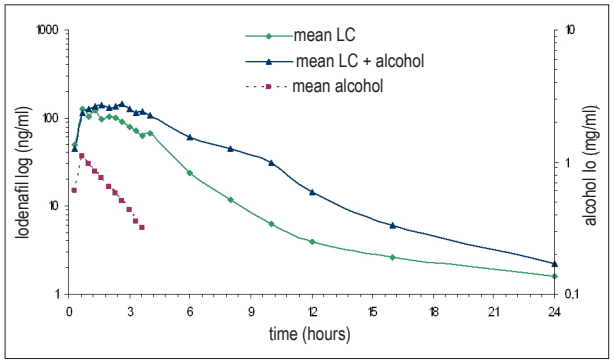

Figure 5 - Pharmacokinetic profile of alcohol alone and lodenafil, after treatment with 160 mg lodenafil in fasting and with alcohol. LC - lodenafil carbonate

with lodenafil carbonate (trt A) was not statistically different from that in individuals treated with placebo.

Studies conducted with PDE-5 inhibitors such as sildenafil, vardenafil and tadalafil showed that they induced small or non-significant increase of heart rate[27,28]. The present study showed no clinical consequences of lodenafil carbonate, ingested in fasting or with alcohol. A statistically significant modification of heart rate was observed only 6 hours after treatment.

Our results show that the mean heart rate was similar among the groups at the first measurements. Between 1 and 2 hours after treatment, when lodenafil concentrations are close to Cmax, treatments A and B induced similar results, which were different from those seen in the placebo group. Only six hours after treatment, however, was this difference statistically significant. The increase in heart rate observed in individuals treated with lodenafil carbonate did not result in clinical consequences. The lodenafil Cmax at 6 hours corresponded, in average, to 15% Cmax in treatment A and 30% in treatment B.

As a whole, and particularly in relation to blood pressure, the analysis of hemodynamic effects of lodenafil carbonate and its association with alcohol showed results similar to previous reports about the interaction of alcohol and sildenafil[28] and vardenafil[29]. In those studies, any effects observed were credited to alcohol alone, and not to its interaction with PDE-5 inhibitors, as also suggested in the present work. Considering heart rate, no clinical consequences of an association between PDE-5 inhibitors and alcohol were observed in the participants. Modifications of heart rate, seen 6 hours after treatment in groups A and B, seem to be related to lodenafil carbonate and not to alcohol, although plasma concentration of the drug had already decreased to 30% of Cmax, at that moment. This effect deserves further investigation.

One of the main concerns related to the use of PDE5 inhibitors is their arrhythmogenic potential, which has motivated the investigation of therapeutic and overdosage of existing PDE-5 inhibitors, as well as the measurement of QTc intervals. These studies have shown a QT interval change below 10 msec, which is considered safe for the methodology used[25]. Among PDE-5 inhibitors, vardenafil showed the greatest effect in increasing the QTc interval, although maintained within the range accepted as maximal variation[25,31].

Electrocardiographic evaluation performed in the present study, particularly of the maximum QTc interval, did not show significant alterations induced by lodenafil carbonate. Similar results have been found for other commercially available PDE-5 inhibitors, which have also shown reliable safety. However, no studies were found in which alcohol has been added to increase doses of PDE-5 inhibitors.

Acute ingestion of high amounts of alcohol may induce prolongation of the QTc interval, which has been related to ventricular tachyarrhythmia and sudden death[31]. Furthermore, other events, such as atrial fibrillation and re-entry ventricular arrhythmias, with potential risk of death, have also been reported[31].

In the present study, 160 mg lodenafil carbonate, which represents twice the therapeutic dosage, was associated to 0.5 g/kg alcohol. This condition leads to a greater risk of prolongation of the QTc interval, since the methodology established similar moments for alcohol and PDE-5 inhibitors Cmax. The results showed that, even in extreme conditions, lodenafil carbonate did not interfere with the maximum QTc interval. Furthermore, no correlation was observed

between serum concentrations of the lodenafil metabolite and maximum QTc interval measurement, and high concentrations of lodenafil observed at some points did not have corresponding increase in maximum QTc intervals.

It is important to observe that participants had no sexual practice or any other type of physical activity during the study, so that this variable did not interfere with the cardiovascular parameters studied.

In this study, we used twice the therapeutic dosage proposed for lodenafil carbonate, to be able to analyze possible cardiovascular consequences of a larger dosage which may result from overdoses of this drug. The amounts of alcohol used in the present work were similar to those used in the investigation of interactions between alcohol and vardenafil (0.5 g/kg alcohol)[29] and tadalafil (0.6 g/kg alcohol)[30]. The vasodilating effect of PDE-5 inhibitors is a constant source of concern for the physician treating a patient with cardiovascular problems, usual in the clinical practice involving ED. Alcohol is consumed by a significant number of Brazilians, and its cardiovascular consequences, which include hypertension, hypotension and even arrhythmia, are well known. The use of lodenafil carbonate as a new drug in the PDE-5 inhibitors family implies in the need of studies among healthy volunteers as well as among patients, particularly those with heart diseases. To our knowledge, no studies have been conducted for a direct comparison between lodenafil carbonate and other types of PDE-5 inhibitors. Similarly, there are no reports on the evaluation of the QT interval in patients using sildenafil, vardenafil or tadalafil associated to alcohol, as in the present study.

Pharmacokinetic properties of sildenafil and vardenafil are not affected by alcohol[28,29]. The present study showed that pharmacokinetic characteristics of lodenafil were affected by alcohol, with an increase in Cmax and AUC, increasing also the bioavailability of the drug. The linear absorption behavior of lodenafil carbonate - at least until the dosage of 160 mg[14] -, suggests that, in the currently used dosage of 80 mg, a similar bioavailability behavior would be observed.

This study aimed to identify the physiological effect of lodenafil carbonate, and its association with alcohol, in healthy individuals. The results allow the determination of effects in individuals without cardiovascular diseases, so that future studies may be performed with cardiac patients.

Considering that this study used twice the therapeutic dosage of lodenafil carbonate, and that its bioavailability was increased by alcohol, clinical and electrophysiological parameters observed in the population studied suggest that lodenafil carbonate has no negative effects on the cardiovascular system. The drug did not induce any clinical consequences, particularly relative to its arrhythmogenic potential, which could be observed with the methodology used in this study.

Limitations of this study

The sample analyzed in this study was composed of young men with no history of cardiovascular disease. Although they represent adequately the population using PDE-5 inhibitors for recreational purposes, this group cannot be considered an adequate model for the population of patients with erectile dysfunction.

Acknowledgments

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Potential Conflict of Interest

Drs. Luiz Antonio Galvão Lucio and Jorge Barros Afiune are physicians and belong to the staff of Cristália laboratories, where the protocol was developed.

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Study Association

This study is not associated with any post-graduation program.

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