Effects of Propafenone Associated with Propofol on Myocardial Contractility, Heart Rate, Coronary Flow, and the Incidence of Arrhythmia in Isolated Hearts of Rats

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Objective - To study the influence of propafenone associated with propofol on myocardial contractility (dP/dt and heart rate), coronary flow, and the incidence of arrhythmia in isolated rat hearts.

Methods - Forty albino rats were anesthetized with sulfuric ether, a modified Langendorff method was performed, and the rats were fed with Krebs-Henseleit (K-H) solution, (95% O₂, 5% CO₂, pH 7.4±0.1, perfusion pressure between 90 and 100 cm of water, and temperature 37±0.5°C). Control records were obtained after a stabilization period and rats were distributed into the following 4 groups: I (control), II (100 mcg propafenone), III (25 mcg propofol), and IV (propafenone-propofol).

Results - A decrease (P<0.05) in the heart rate in groups II and IV was observed, with a greater decrease in group II. A decrease was noted in the dP/dt ratio (P<0.05) in groups II and IV, during all periods. Group III experienced depression from the 1st to the 3rd minute. Coronary flow had a decrease (P<0.05) in all groups, compared with the control group, especially in group IV with a decrease from 14 mL/min to 11 mL/min. Arrhythmogenic effects of propafenone (pro-arrhythmia) were verified in 50% of group II. In the association with propofol (group IV), no significant difference occurred, and arrhythmias (pro-arrhythmic effect) were observed in 40% of the hearts.

Conclusion - The association propafenone-propofol was not harmful to the use of propafenone solely, regarding the effects observed in myocardial contractility, coronary flow, and in the incidence of arrhythmias.

Keywords: myocardial contractility, propafenone, propofol

Cardiac rhythm disturbances are a frequent finding in patients with heart diseases; and are responsible for the development of increasing clinical and experimental research. To recognize and treat arrhythmias correctly is of utmost importance because they are risk factors for sudden cardiac death. Since the study by Wenckeback 1, at the beginning of the 20th century, about the efficiency of antiarrhythmic therapy, several studies have been conducted demonstrating that the control of rhythm disturbances is essential in the prevention of sudden cardiac death and in the reduction of mortality because of acute myocardial infarction 2-5.

Maintenance of arrhythmia control usually demands additional care, and chronic treatment is still a challenge, especially in light of evidence of the arrhythmogenic effects of most known medications 6-9. The clinical decision to treat patients with cardiac arrhythmias involves careful analysis and knowledge of the elected antiarrhythmic medication.

Among the most commonly used antiarrhythmic medications in our country for the treatment of ventricular and supraventricular arrhythmias, propafenone stands out, classified as an IC drug according to Vaughan Williams 10,11. 2,3-dihydrochloride (hydroxy-2 propylamine) 3 propoxy phenyl (propafenone) was synthesized in 1970 and has been widely used in the suppression of supraventricular and ventricular arrhythmias. The medication contributes to the reduction of the permeability of the cellular membrane to sodium and to a lesser extent to calcium, disrupting the action potential of myocardial fibers 12,13. It also has an antiadrenergic effect to block nonselective beta-adrenergic receptors. These mechanisms suggest negative inotropic and chronotropic effects especially if the dose exceeds that predicted.

Because of specific studies 14-17 that demonstrated the antiarrhythmic efficiency of propafenone, it has been used in patients with heart diseases that can be surgically treated.

Regarding anesthesia in cardiovascular surgery, the severity of heart diseases leads to concern about the level of myocardial depression caused by most anesthetic medications.

Propofol (2,6-diisopropylphenol) is an intravenous
anesthetic agent for use in the induction and maintenance of an anesthetized state with rapid action and elimination and is widely used in cardiovascular surgeries. Intravenous injection of a therapeutic dose produces hypnosis rapidly with minimal excitement. Propofol binds to plasma proteins above 95% with elimination through hepatic metabolism, forming inactive compounds that are eliminated in the urine. Studies of propofol have demonstrated decreases in heart rate, coronary flow, and incidence of arrhythmias.

A special concern is that patients with heart diseases who use propafenone may undergo cardiac surgery and receive propofol, because both medications are myocardial depressors with the possibility of an enhancing effect concerning myocardial contractility. As studies in the literature about the possible enhancing effect of interaction of these medications were not found, the present experimental investigation was conducted aiming at studying the heart’s performance, assessing the variables: myocardial contractility, heart rate, coronary flow, and incidence of arrhythmias.

**Methods**

Forty adult albino Wistar rats housed in the vivarium at the Medical School of Barbacena – UNIPAC, were studied without regard to sex, with weights ranging from 210 to 350g (mean, 280g). All animals were treated according to the “Ethical Principles in Animal Research” adopted by the Brazilian College of Animal Experimentation (COBEA) and by the “Guide for the Care and Use of Laboratory Animals” published by the National Institutes of Health - USA.

After anesthesia with inhalation of sulfuric ether, the animals underwent a wide thoracotomy. The anterior thoracic wall was reflected, and the heart and the great vessels were exposed. After that, 500 U of sodium heparin were administered in the posterior vena cava to prevent thrombosis. The animal’s aorta was isolated and repaired with a 2.0 cotton thread; and cannulated with a 20G-caliber plastic catheter, making sure that the integrity of the aortic valve was maintained during introduction of the catheter. The catheter was then fixed to the aorta with another 2.0 cotton thread. Next, the left ventricle was drained with the introduction of redistilled water recovering and stabilizing cardiac activity, an empty plastic balloon was introduced into the left ventricle through a hole in the left atrium. The mitral valve was preserved, and the balloon was connected to a monitor (model DH073, BESE-Bioengenharia, Belo Horizonte, MG) with the help of a metal cannula. Systolic and diastolic pressure, heart rate, and an electrocardiogram were recorded (printer Epson LX-810).

Diastolic pressure was adjusted to 5±2 mmHg, through movements of introduction and withdrawal of redistilled water in the latex balloon in all periods of group I; in groups II, III, and IV, the diastolic pressure was not adjusted except in the period (fig. 1). Coronary flow was determined by the assessment of the drained volume of the right and left cavities in 1 minute, collected in a graduated glass bottle. The incidence of arrhythmia was assessed by observing cardiac rhythm, recorded on the electrocardiogram in D2 derivation by 2 electrodes placed on the heart.

The 40 hearts were distributed into 4 groups and prepared according to the method described. The groups were perfused with a Krebs-Henseleit solution at 37°C temperature for 30 minutes, and the parameters were recorded in the control (t0), after the 1st (t1), 3rd (t2), 5th (t3), 10th (t4), and 15th (t5) minute. The groups can be characterized as follows: group I - control: 10 hearts without medication; group II - propafenone: 10 hearts differing from the control group because of the administration of 0.1 mL of the K-H solution via a proper lateral route above the bulb of the cannula inserted into the aorta; 10 hearts differing from the control group because of the administration of 100 mcg of propafenone diluted in 0.1 mL of the K-H solution via a proper lateral route above the bulb of the cannula inserted into the aorta; group IV - propafenone: 10 hearts differing from the previous groups by the administration of 0.1 mL of the K-H solution containing 100 mcg of propafenone in an appropriate lateral vein above the cannula bulb inserted in the aorta followed by 0.1 mL of the solution containing 25 mcg of propofol by the same route.

The variations of heart rate in bpm, of the velocity of circumferential cardiac fiber shortening (dP/dt in mmHg.s^-1), of coronary flow (mL/min), and the incidence of arrhythmias were studied. For statistical analysis, we used the Student t test for paired data (significance level: P<0.05) and single-factor analysis of variance with the same significance level.

**Results**

Heart rate decreased (P<0.05) in groups II and IV (1st to 15th min), and in group III, only in the 3rd and 10th minutes; however, no statistically significant difference existed in group I.
In group II, a decrease was recorded from 100% (control) to 71% (1st min), 68% (3rd min), 71% (5th min), 83% (10th min), and 78% (15th min); in group IV decreases occurred from 100% to 77% (1st min), 69% (3rd min), 70% (5th min), 76% (10th min), and 80% (15th min), on average. In the comparison between groups, groups II and IV demonstrated significant variation compared with the control group; however, they did not have significant variation when compared with each other. Heart rate had a significant variation (P<0.05) only in the first minute in the comparison between groups II and III (fig. 2 and tab. I). The dP/dt decreased in group II (from the 1st to the 15th min), in group III (1st and 3rd min), and in group IV (from the 1st to the 15th min). In percentage values, in group II, a decrease was recorded from 100% (control) to 62% (1st min), 75% (3rd min), 80% (5th min), 78% (10th min), and 76% (15th min). In group III, a percentage decrease occurred from 100% (initial) to 77% (1st min), and 86% (3rd min). In group IV, a percentage decrease occurred from 100% (initial) to 54% (1st min), 62% (3rd min), 68% (5th min), 73% (10th min), and 76% (15th min). All these decreases demonstrated in mean percentile values were statistically significant. In the comparison between groups, the dP/dt ratio was smaller (P<0.05) in group II when compared with that in the control group in all periods. Group III had a significant decrease (P<0.05) only in the first minute regarding the control group. Group IV had a significant decrease (P<0.05) from the first to the fifth minute compared with the control group. In the comparison between groups II and III, the dP/dT ratio did not have a significant decrease. Variations occurred between groups II and IV, and II and IV were not significant (fig. 3 and tab. II).

Coronary flow decreased in groups II and IV (1st to 15th min), and in group III (3rd, 5th, 10th, and 15th min). In terms of percentages, in group II a decrease occurred from 100% (control), to 88% (1st min), 86% (3rd min), 80% (5th min), 75% (10th min), and 72% (15th min) was recorded. In group III, a percentage decrease from 100% (control), to 99% (1st min), 92% (3rd min), 89% (5th min), 84% (10th min), and 77% (15th min) was recorded. In group III, a percentage decrease from 100% (control), to 91% (1st min), 88% (3rd min), 85% (5th min), 79% (10th min), and 74% (15th min) was recorded.
Summary of the content:

Despite the great advances in clinical and experimental electrophysiology in the last 20 years, sudden cardiac death is still a complex physiopathologic event. Patients with cardiac disease as well as those with congestive heart failure are an important risk group for sudden death. Around 75% of sudden deaths are due to episodes of ventricular tachycardia or ventricular fibrillation. Patients with congestive heart failure experience severe ventricular arrhythmias and sudden death in up to 50% of cases. Antiarrhythmic therapeutics are indicated, but the proper treatment of a cardiac arrhythmia is a challenge in clinical practice due to the adverse effects of antiarrhythmic medications and increased mortality.

All these decreases were statistically significant, demonstrated in mean percentage values (P<0.05). In the comparison between groups, coronary flow did not decrease in groups II and IV as compared with that in the control group. A significant decrease occurred (P<0.05) in the 10th and 15th minutes of group III, as compared with the control group. No significant difference occurred (P<0.05) between groups II and IV, between groups II and IV, and when group II was compared with group III (fig. 4 and tab. III).

During the study, arrhythmias were not present in groups I (control) and III (propofol). In group II (propafenone), arrhythmias were observed in 5 of the 10 hearts, and in the propofol-propafenone association (group IV) an increase in the arrhythmias were observed in 4 of the 10 hearts studied.

Discussion

Despite the great advances in clinical and experimental electrophysiology in the last 20 years, sudden cardiac death is still a complex physiopathologic event. Patients with cardiac disease as well as those with congestive heart failure are an important risk group for sudden death.

Table I - Heart rate variation (bpm) in the groups studied

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<tbody>
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<td>I</td>
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<td>204±19</td>
<td>196±34</td>
<td>192±26*</td>
<td>193±27</td>
<td>195±23*</td>
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</tr>
<tr>
<td>IV</td>
<td>236±29</td>
<td>182±57*</td>
<td>162±64*</td>
<td>167±56*</td>
<td>178±52*</td>
<td>188±54*</td>
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</tbody>
</table>

Group I: control; group II: propafenone; group III: propofol; group IV: propofol+propafenone; control(t₀), 1st min (t₁), 3rd min (t₂), 5th min (t₃), 10th min (t₄), 15th min(t₅). *P<0.05 - Student t test.

Table II - ST/Dt variation (mmHg/s) in the groups studied

<table>
<thead>
<tr>
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<td>2218±578</td>
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<tr>
<td>IV</td>
<td>2354±736</td>
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<td>1405±404*</td>
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<td>1666±411*</td>
<td>1687±455*</td>
</tr>
</tbody>
</table>

Group I: control; group II: propafenone; group III: propofol; group IV: propofol+propafenone; control(t₀), 1st min (t₁), 3rd min (t₂), 5th min (t₃), 10th min (t₄), 15th min(t₅). *P<0.05 - Student t test.
Propafenone is a medication that has been used frequently in cardiovascular surgeries with the possibility of interaction with propafenone. However, studies on the add-on effect of the propafenone-propofol association were not found. Taking into account that the 2 medications have a suppressor myocardial effect, a study is necessary.

Salerno et al. reported a decrease in left ventricular function in patients receiving propafenone. Baker et al. reported similar results. Meneghin observed that even in healthy hearts, propafenone has a reversible negative inotropic effect. A similar fact was reported by Santana, Faraj, and Nakamura et al., all of whom studied isolated rat hearts.

In the present investigation, propafenone produced significant myocardial depression. However, associated with propofol it did not have an additive effect.

Rouby et al. studying the effects of propofol in patients with artificial hearts, concluded that cardiovascular depression of propofol is associated with the venous and arterial vasodilation effect rather than with myocardial depression. However, in the present study the significant depressive myocardial effect of propofol was confirmed.

Heart rate significantly decreased in all assessed periods in the propafenone and propofol groups, contrary to the findings of Riou et al. who did not demonstrate significant negative chronotropic effects in the myocardium of rats.

Coronary flow analysis did not demonstrate a significant decrease in groups II and IV in all times assessed, regarding the control groups apart from the 10th and 15th minutes of group II.

The pro-arrhythmic effect of propafenone was reported by Podrid and Zipes. In our investigation, 50% of the hearts studied in group II experienced arrhythmias. However, with the use of propofol, in isolation, arrhythmias were not observed, and an increase in the incidence of arrhythmias associated with the use of propofol and propafenone did not occur.

Based on the results obtained, we conclude that propafenone has negative inotropic and chronotropic effects, with arrhythmogenic effects and decreases in coronary flow. Propafenone-propofol association neither exaggerated the negative inotropic effect of propafenone in isolation nor increased its arrhythmogenic effect.

Table III - Coronary flow variation in the groups studied (mL/min)

<table>
<thead>
<tr>
<th>Groups</th>
<th>t0</th>
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<th>t2</th>
<th>t3</th>
<th>t4</th>
<th>t5</th>
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</thead>
<tbody>
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<tr>
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<td>13±3</td>
<td>12±4</td>
<td>12±4</td>
<td>11±3</td>
</tr>
<tr>
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<td>12±4</td>
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</tr>
</tbody>
</table>

Group I: control, group ± I: propafenone; group III: propofol; group IV: propofol+propafenone; control(t0), 1st min (t1), 3rd min (t2), 5th min (t3), 10th min (t4), 15th min(t5). *P<0.05 - Student t test.

References

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