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The herbal drug Catuama reverts and prevents ventricular fibrillation in the isolated rabbit heart☆

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Abstract

Introduction: Catuama, an herbal drug very popular in Brazil, was tested on the reversion and prevention of ventricular fibrillation (VF) in the isolated rabbit heart.

Materials and Methods: Catuama (a mixture of *Trichilia catigua*, *Paullinia cupana*, *Ptychopetalum olacoides*, and *Zinziber officinalis*) was perfused in the isolated perfused rabbit heart. Its effects on intraventricular conduction, heart rate, and monophasic action potential (MAP) duration were evaluated, and sustained VF was induced. The effects on reversion and reinduction of arrhythmia were observed, and new measures were taken in the hearts that reverted.

Results: Catuama and *T catigua* reverted VF in all hearts, prevented reinduction, and prolonged intraventricular conduction. Catuama prolonged MAP phase 2. On the other hand, *P cupana* reverted VF in 3 of 5 hearts, but depressed automatism, prolonged MAP phase 3, and did not prevent reinduction.

Discussion: Catuama reverted and prevented VF in this model. *T catigua* extract is probably the main agent responsible for the beneficial actions observed. Further studies are now in progress to clarify these actions.

Keywords: Fibrillation; Pharmacology; Resuscitation; Antiarrhythmia agents

Introduction

The herbal drug Catuama has been widely used in Brazil since 1980 for physical and mental fatigue, neuromuscular asthenia, and weakness disorders. It can be orally administered long term with no reported important toxic side effects.

The Catuama preparation consists of hydroalcoholic extracts from 4 well-known medicinal plants, namely, *Trichilia catigua* (Meliaceae), *Paullinia cupana* (Sapindaceae), *Ptychopetalum olacoides* (Olacaceae), and *Zinziber officinalis* (Zingiberaceae). The dried extract of Catuama contains 40.31% *P cupana*, 28.23% *T catigua*, 28.23% *P olacoides*, and 3.26% *Z officinalis*.

Although most of the plants that constitute part of the herbal extract have been studied to some degree, either chemically or pharmacologically, the therapeutic actions of the herbal extract Catuama itself have not yet been studied. It has a potent relaxant effect on vessels from different animal species, largely dependent on the release of nitric oxide or nitric oxide–derived substances,[1] a relaxant effect on the isolated rabbit corpus cavernosum,[2] and an antidepressant-like action.[3] Recently, it has been reported that *T catigua* extract alone showed potent inhibition of phospholipase A_2 activity in human platelets.[4]

Our group was interested in evaluating the cardiovascular actions of the herbal Catuama on rabbit cardiac contractility. We have found that during these experiments, some of the hearts showed spontaneous ventricular fibrillation (VF) before Catuama infusion. In these hearts, we were surprised by the fact that starting Catuama completely reverted the arrhythmia in all of them.

The objectives of this study were to investigate the effects of Catuama and each herbal component on (1) VF reversion and prevention and (2) ventricular repolarization in the isolated perfused rabbit heart.

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Materials and methods

The present study was approved by the Medical School of University of São Paulo Board of Ethics and conducted according to National Institutes of Health *Guidelines for the Care and Use of Laboratory Animals*.[5]

Drug dilution

The dried extracts of Catuama, *T catigua*, *P cupana*, *P olacoides*, and *Z officinalis* were dissolved in 10% polyoxyethylene sorbitan monolaurate (Tween 80) and filtered in Millipore ester cellulose membrane filter (1.2 μm).

Animal instrumentation

Adult male white New Zealand rabbits weighing 2 to 3 kg were used in the experiments. Each animal received heparin intravenously (200 UI/kg) and was euthanized by a strike to the back of the head.[6] The heart was quickly excised and connected to the classical Langendorff system with retrograde perfusion with modified Krebs-Henseleit solution (NaCl, 120 mmol/L; KCl, 4.7 mmol/L; $CaCl_2$, 1.8 mmol/L; $NaHCO_3$, 25 mmol/L; $MgSO_4$, 1.2 mmol/L; NaH_2PO_4, 1.2 mmol/L; and glucose, 5.5 mmol/L; pH 7.2) oxygenated with 95% oxygen/5% carbon dioxide at 16 mL/min and temperature between 37°C and 38°C. A catheter was inserted into the apex of the heart to drain the thebesian effluent. A detailed procedure for the setup of this preparation has been described previously.[7]

Studies on VF reversion and prevention

In 37 rabbit hearts, 2 pairs (proximal [P] and distal [D]) of wire electrodes (Monicrom 2-0) were sutured to the epicardial surface of the left ventricle to estimate changes in intraventricular conduction times (CTs; P-D time interval).

The electrograms were acquired through the ECG 100B System (Biopac Systems, Inc., Goleta California, USA). Recordings were obtained continuously with AcKnowledge III software for the MP1000WSW analog-digital system connected to a microcomputer with an acquisition sample rate of 2000 samples per second and a bandpass of 50 to 500 Hz.

After 20 minutes of stabilization, baseline measures were performed. The heart rate (HR) was calculated as the temporal distance between 2 subsequent ventricular electrograms, expressed as beats per minute and CT as the temporal distance between the electrograms recorded at P and D in milliseconds. Every value is the mean of 5 consecutive measures.

Ventricular fibrillation was induced by burst electrical stimulation of the right ventricular apex: current, 10 mA; pulse duration, 2 milliseconds; frequency, 50 Hz; voltage, 10 V; duration of stimulation, 5 minutes. If a stable VF was not achieved even after 2 repetitions of this protocol, the heart was rejected. This model has been previously described in detail and allows a stable VF for more than 30 minutes.[7]

After the stabilization period, a test extract solution (200 μg/mL) was added to the perfusion solution and recordings were obtained again, up to reversion of the arrhythmia or for another 20-minute period. A pilot study was performed to determine the best effective concentration of extract for successful VF reversion.

If VF reverted, new measures were obtained: time of reversal, pause after reversion, HR, and CTs. Then, the same protocol of VF was applied to induce a VF again.

Five groups (n = 5-6 each) were constituted according to the extract solution added to the perfusion: Catuama, *T catigua*, *P cupana*, *Z officinalis*, *P olacoides*. Control experiments were performed in parallel to test the effects of the vehicle (Tween 80), and any significant influences were observed. In addition, 2 other groups were studied for comparison of antiarrhythmic drugs classically used in defibrillation: lidocaine (n = 4; 3 μg/mL of lidocaine chloride) and amiodarone (n = 4; 1.5 μg/mL of amiodarone hydrochloride).

Results are expressed as mean ± SD. Statistical analysis was performed by Kruskal-Wallis analysis of variance by ranks complemented with the Tukey test when differences were found. Significance level was set at 5%.

Studies on ventricular repolarization

In 30 rabbit hearts, a pacemaker was implanted on the right atrium to maintain constant HR (160 beats per minute).

Left ventricular epicardial monophasic action potential (MAP) waveforms were acquired with a custom-made, nonpolarizable, unipolar silver–silver chloride electrode. The electrode was connected to the ECG 100B System (Biopac Systems, Inc). Recordings were obtained with an AcKnowledge III for the MP1000WSW analog-digital system connected to a microcomputer with an acquisition sample rate of 2000 samples per second.

The criteria of MAP quality were amplitude not less than 10 mV; fast and clean upstroke not longer than 5 milliseconds; no contamination by QRS or intrinsic deflection; mild plateau with convexity facing upward; and horizontal diastolic baseline without deflections.[8]

After a stabilization period of 20 minutes, 10 to 15 MAP waveforms were recorded 5 minutes before addition of extract solution and 2, 5, 10, 15, 20, 25, and 30 minutes after. Then, hearts were perfused with fresh Krebs solution for drug withdrawal, and new recordings were obtained after 5, 10, 15, and 20 minutes. In the control group, the same measurements with corresponding times were made.

Six groups (n = 5 each) were constituted according to the solution (25 μg/mL of each herbal extract solution) added to the perfusion solution: control, Catuama, *T catigua*, *P olacoides*, *P cupana*, and *Z officinalis*. This dose was determined to be the smallest to cause detectable alterations in MAP measures.

Three parameters were studied: MAP duration at 20% of repolarization (T20), at 50% of repolarization (T50), and at 90% of repolarization (T90). Five MAP curves were selected at each time point to obtain mean values with intermeasurement variation less than 10%. All measurements were made manually to avoid the bias often found in computer-based formulas.

Results are expressed as mean ± SD. Statistical analysis was performed by 1-way repeated-measures analysis of variance complemented with the Holm-Sidak