**Study on the Temperature, respiratory rate, heart rate and Electrocardiogram of concomitant administration of *Maytenus macrocarpa* “Chuchuhuasi” and Propranolol in escalating doses**

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**ABSTRACT**

**Background:** Previous studies of *Maytenus macrocarpa* “Chuchuhuasi” and linked species have corroborated their biological effects related to cardiovascular, respiratory, and other systems. This research has focused on evaluating the effect in the corporeal temperature, respiratory rate, heart rate and electrocardiogram of concomitant administration of “Chuchuhuasi” and propranolol in escalating doses. **Methods:** Albino rats were divided randomly into four control groups and five experimental groups. Temperature was measured by a digital thermometer, respiratory rate by direct-counting and electrocardiogram and heart rate by a Grass Polygraph. Rhythmic and arrhythmic electrocardiographic patterns were identified by a mathematical modeling of autocorrelation. The outcomes were acquired in periods of time but were analyzed using the average of the whole of the experiment. The result was applied to the following statistical tests: one-way ANOVA, Tuckey, Shapiro-Wilk, Pearson Correlation and Chi square with Yate’s correction test. **Results:** The comparison between control and experimental groups showed a profile of rise in the corporeal temperature, then, for the respiratory rate the bias was to increase, in contrast, it was showed trend to decrease of the heart rate and an increase of voltages of p and r wave, also, an increment of p-r interval and presences of arrhythmias. **Conclusion:** This study revealed effects of concomitant administration of propranolol and *Maytenus macrocarpa* on temperature, respiratory rate, heart rate and electrocardiogram. In addition, it showed abnormalities in the electrocardiogram which were associated with arrhythmia patterns Thus, the usage of propranolol and *Maytenus macrocarpa* may negatively impact several aspects of the health of users of these drugs.

**Key words:** Chuchuhuasi, Propranolol, Heart rate, Respiratory rate, Temperature, Arrhythmia.

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DOI : 10.5530/pc.2016.2.3

**INTRODUCTION**

*Maytenus macrocarpa* is a medicinal plant belonging to genus *Maytenus*. This genus is distributed in tropical and subtropical areas of America, Asia and Africa, particularly Bolivia, Colombia, Ecuador and Peru. In the American countries in which *M* macrocarpa grows, it is important due to its medicinal properties. In Peru, this plant is commonly called “Chuchuhuasi”, and its medicinal properties are used by population of Peruvian Amazon as an anti-rheumatic, analgesic, anti-inflammatory, anti-diarrheal, anti-pyretic, anti-parasitic drug amongst other uses. Its traditional uses are principally reported in native communities such as Cocama, Quechua, Shipibo-Konibo and Bora-Bora. In these communities, an infusion of the bark, root and leaves of “Chuchuhuasi” are one of the main forms of use for their medicinal needs.

Several in vivo animal studies have shown different effects of *Maytenus* spp. Several species such as *M. forsskaoliana*, *M. krukovii*, *M. ilicifolia*, *M. emarginata*, *M. heterophylla*, *M. senegalensis*, *M. obscura*, *M. rigidia*, *M. undata* etc have demonstrated biological effects on the central nervous system, respiratory rate, heart rate, blood pressure, temperature, diuresis, inflammation, pain, diarrhea, gastric ulcers and affect the development of pathogenic microorganisms. Various studies report the effects of *M. macrocarpa* on nociception, intestinal motility, reproductive system, temperature, respiratory rate, heart rate and decrease of voltage of p wave and an increase of p-r interval of electrocardiogram. Thus, an understanding about this medicinal plant has been growing in recent years. Its phytochemistry has been examined and it is known to contain multiple constituents including flavonoids, tannins, alkaloids, triterpenes and sesquiterpenes. However, some studies have shown fatal outcomes after intake of medicinal plants with drugs. For example, concomitant use of warfarin and plants such as ginkgo biloba and ginseng are contraindicated in order to reduce the number of deaths by bleeding. In addition, a previous study has shown that concomitant administration of propranolol and Allium sativum (garlic) produce a decrease on blood pressure. This result suggests a harmful effect of propranolol in cotreatments with these medicines. Other studies have demonstrated interactive effects between medicinal plants and drugs. In this context, people who consume “Chuchuhuasi” and common drugs may ignore potential risks in reduction of therapeutic effectiveness, adverse reactions or even death.

Up to now, there is no research about the concomitant use of *M. macrocarpa* and propranolol. For this reason, this study has focused on evaluating the effects of concomitant administration of *Maytenus macrocarpa* and propranolol in escalating doses on the corporeal temperature, respiratory rate, heart rate, and electrocardiogram in albino rats.
MATERIALS AND METHODS

Study type

The experimental study was performed at the Research Centre of Traditional Medicine and Pharmacology of Facultad de Medicina Humana de la Universidad San Martin de Porres (FMH-USMP).

Plant material

*M. macrocarpa* plant material was collected in the Department of Ucayali (Pucallpa) by using the criteria of the Cerrate method: 19

1. The vascular plant was collected at 08:00 hrs
2. It was put immediately into a field press
3. It was subsequently dried

Berta Loja, (biologist of The Research Centre of Traditional Medicine and Pharmacology, FMH-USMP) authenticated the identity of the plant by macroscopy and microscopy. The outcome was corroborated by specimens in the herbaria of the Universidad Nacional Mayor de San Marcos (USM) and Missouri Botanical Garden (MO). The identification as *Maytenus macrocarpa* was further verified by reference to Peruvian 43, 44 and South American 45–48 flora references.

Animals

Wistar male albino rats were obtained from the Experimental Animal Centre of Universidad Peruana Cayetano Heredia, Peru. The average weight was 300 g for each animal. Rats were housed 2 per cage and maintained at ambient in the following conditions: temperature 22°C, humidity between 30 and 70%, 12 hrs light/dark cycles and noise levels maintained at ambient in the following conditions: temperature 22°C, humidity between 30 and 70%, 12 hrs light/dark cycles and noise levels less than 70 db. They were provided with balanced food and water *ad libitum*. Animals were deprived of food 12 h before the experiment.

Individual animals were divided randomly between the groups. All rodents were intraperitoneally treated. Six rodents were included for each experimental group; the groups were:

- GC or control group; pentobarbital sodium 30 mg/kg,
- GA or positive control or heart stimulant group; atropine sulphate 0.3 mg/kg,
- GPr or negative control or heart depressor group; propranolol 5 mg/kg,
- GM or *M. macrocarpa* group; ethanolic extract of *M. macrocarpa* 1500 mg/kg.

Experimental groups were:

- G1: *M. macrocarpa* 1500 mg/kg+propranolol 7 mg/kg
- G2: *M. macrocarpa* 1500 mg/kg+propranolol 9 mg/kg
- G3: *M. macrocarpa* 1500 mg/kg+propranolol 11 mg/kg
- G4: *M. macrocarpa* 1500 mg/kg+propranolol 13 mg/kg
- G5: *M. macrocarpa* 1500 mg/kg+propranolol 15 mg/kg

Experimental materials

Atropine sulphate (blister) 1 mg/ml, code ISP-13505/04, expiration 04/2013; propranolol (tablets) 40 mg, code EG-2406, expiration 04/2013; pentobarbital sodium (blister) 6.5%, code F.23.01.N.0042, expiration 07/2013; distilled water (blister), code 82100 613 990.

Preparation of aqueous solution of *Maytenus macrocarpa* ("Chuchuhuasi")

The collected leaves of *M. macrocarpa* were washed and sun dried in the shade for several days. The dried leaves were powdered in an electrical grinder. The powdered leaves were extracted with 70% ethanol at room temperature. The extractions were kept at room temperature and allowed to stand for several 7 days with occasional shaking and stirring. The extract thus obtained was filtered through filter paper (Whatman Fitter Paper No. 1). The filtrate was dried in an oven for 2 days. It was prepared as an aqueous solution (40%) of the filtrate of *Maytenus macrocarpa* by adding the appropriate volume of distilled water. The whole aqueous solution was mixed at 30°C (6 rpm) for half an hour. The resultant solution was divided into two components (solid and fluid). The solid component was filtered and removed. The fluid component was used for this research. 49

Measurement of the physiological parameters

The measurement of physiological parameters was by standard techniques as described by Huaccho et al. Briefly:

- Each rodent was anesthetized with 30 mg/kg of pentobarbital sodium then placed in an incubator at an average temperature of 20°C.
- The Grass Polygraph (model 98k 04826) was used to capture the electrical heart signals (lead II); these were processed by an application in Matlab with the following filters: Notch with a cut-off frequency of 60 Hz, a high pass with a cut-off of 0.2 Hz and a low-pass with a cut-off of 40 Hz. The results were applied to the mathematical modelling of autocorrelation which was considered as digital processing of periodicity. We obtained two types of electrocardiographic patterns: rhythmic and arrhythmic. Rhythmic electrocardiography patterns were used to determine the heart rate, electrocardiographic waves and p-r interval (Figure 1).

- We followed periods such as pre-dose (baseline), at 0, 5, 10, 15, 20, 25, 30, 45, and 60 min. For each period of time, the following tests were performed:
  - Three measurements of corporeal temperature by a digital medical thermometer (non-contact) NC 100.
  - Respiratory rate was measured by counting the number of respiratory movements for one minute.
  - Captured heart electrical signals by the Grass Polygraph.

Ethics and research

This study was approved by the Institute of Research of FMH-USMP, which followed strictly the principles of research with laboratory animals: International Guiding Principles for Biomedical Research Involving Animal (1985). 46

Statistical analysis

Quantitative variables were analyzed using one-way ANOVA, Tuckey, Shapiro-Wilk and Pearson Correlation. Qualitative variables were analyzed using chi square with Yate’s correction test. Significance was defined as p<0.05, with a 95% confidence interval using the statistical package GraphPad Prism 5.01.

RESULTS

Effects on temperature

All experimental groups showed variation on temperature. The Shapiro-Wilk test determined a Gaussian distribution. ANOVA and Tukey test showed statistical differences, particularly, between the next groups: GC compared to G 1 and 5; GA compared to G 1, 2, 4 and 5; GPr compared to G 3, 4 and 5; GM compared to G 3, 4 and 5 (Table 1). With respect to G5, it showed the greatest increase on temperature and G4 showed the greatest decrease on temperature.

Effects on respiratory rate

With reference to data from respiratory rate, the Shapiro-Wilk test determined a Gaussian distribution. ANOVA and Tukey test showed p<0.05,
Figure 1: Digital processing of periodicity. Rhythmic electrocardiography patterns (A) and arrhythmic electrocardiography patterns (B)

Figure 2: Comparison of heart rate in 8 sec. Control group, pentobarbital sodium 30 mg/kg (GC); propranolol group, propranolol 5 mg/kg (GPr); atropine group, atropine sulphate 0.3 mg/kg (GA); *Maytenus macrocarpa* group, ethanolic extract of *Maytenus macrocarpa* 1500 mg/kg (GM) and *Maytenus macrocarpa* + propranolol V group, ethanolic extract of *Maytenus macrocarpa* 1500 mg/kg and propranolol 15 mg/kg (GS)
specially, between the following groups: GC compared to G 1, 3, 4 and 5; GPr compared to G 1, 2, 3, 4 and 5 (Table 1). G1 showed the largest increase in respiratory rate.

**Effects on heart rate**

The Shapiro-Wilk test showed a Gaussian distribution for groups G 3 and 4. ANOVA and Tukey test showed p<0.05, particularly, the following groups: G5 compared to GC, GPr, GA and GM (Table 1). G5 particularly, showed the greatest decrease on heart rate. (Figure 2)

**Effects on electrocardiographic patterns**

From thirty minutes to the end of the experiment, arrhythmic patterns were registered in the electrocardiogram (Figure 1); Chi-square with Yates correction test showed p<0.05 between GA compared to G1 (Table 2). These results suggest that this concomitant administration could cause arrhythmia on rats.

Regarding the p wave, ANOVA and Tukey test showed p<0.05 for the following groups: GC compared to G 1, 2, and 5 (Table 2). All experimental groups showed an increase of voltage of p wave. With regard to r wave, the Shapiro-Wilk test showed non-Gaussian distribution for the following groups: G 3, 5 and GC. ANOVA, Kruskal-Wallis, and Tukey tests showed p<0.05, particularly in the following groups: G4 compared to GC, GA, GPr and GM. According to this outcome, G4 showed the greatest increase of voltage of r wave (Table 2). In relation to p-r interval, the Shapiro-Wilk test showed Gaussian distribution. The increase of p-r interval was correlated with doses of experimental groups, this was proved by Pearson correlation test; r=0.1210. All experimental groups showed the largest increase of p-r interval.

**DISCUSSION**

"Chuchuhuasi", a traditional medicine plant that is well known in the Peruvian Amazon, is used for its reported effects on pain, rheumatism, ulcers, etc.6-14 Previous studies of “Chuchuhuasi” have shown outcomes such as anti-nociception,28 stimulating intestinal motility,27 bradycardia25
and several others biological effects.\textsuperscript{30,31} 
In recent years, there has been an increasing amount of literature on the interaction between some drugs and medicinal plants and its adverse reactions\textsuperscript{35–38}. However, there is no evidence that \textit{Maytenus macrocarpa} could have effects with concomitant administration of drugs such as propranolol. Studies have reported a dual effect of propranolol on temperature.\textsuperscript{37–49} In contrast, “Chuchuhuasi” and other Maytenus spp. have shown a decrease of corporeal temperature.\textsuperscript{15,31} In the present study, G4 showed a decrease of temperature, possibly due to a hypothermic effect carried out by propranolol and its effect on the thermogenesis of rats.\textsuperscript{30} In contrast, G5 induced an increase of temperature. This result may partly be explained by a decrease in tail blood flow by propranolol, which could decrease an effective mechanism in heat loss of rats.\textsuperscript{50} In both outcomes, the effect of propranolol could be influenced by “Chuchuhuasi”. It has been reported that “Chuchuhuasi” and propranolol reduce respiratory rate.\textsuperscript{31,51,52} In contrast, the result of G1 presented the largest increase of respiratory rate. This result is likely to be related to an increase of temperature of propranolol and “Chuchuhuasi”. Both mechanisms could increase respiratory rate in order to maintain normal temperature range in rats.\textsuperscript{50} The negative chronotropic effects of propranolol on the heart are well known.\textsuperscript{30} According to several studies, M. krukovii, \textit{M. macrocarpa} and M. forsskaoiana have similar effects.\textsuperscript{25,36,31} In contrast, individual this study has demonstrated an opposite effect. Nonetheless, all experimental groups showed a decrease in heart rate in our study. The observed decrease in heart rate could be attributed to sympatholytic effect of propranolol, which may be influenced by “Chuchuhuasi”. A possible explanation for this might be the regulation of some potassium channels in heart by some terpenoids which may be present in this medicinal plant.\textsuperscript{12,34,33,52}

The results obtained from the electrocardiogram were noteworthy because they could present a possible deleterious effect. An increase of voltage of p wave was observed in all experimental groups. This increase in p wave voltage indicates an intensification of the auricular pressure systole,\textsuperscript{33} which could be a consequence of a negative chronotropic and inotropic effect produced by propranolol, and possibly also by “Chuchuhuasi”.\textsuperscript{31,50,51} If we compared the human intake, it could mean that the concomitant administration could increase the cardiac output and could be harmful to the people who suffer a heart disease. Propranolol and “Chuchuhuasi” decrease the voltage of r wave.\textsuperscript{31} In our research, G4 showed the largest increase of r wave, suggesting a possible positive inotropic action. This hypothesis might be explained by the activation of baroreflex and secretion of catecholamines carried out by propranolol, and also by “Chuchuhuasi”, on peripheral vascular resistance.\textsuperscript{12,16,31,52}

Another outcome was an increase of p-r interval for G4 and G5. This finding was unexpected and suggests a decrease of electrical conduction induced by propranolol on the heart.\textsuperscript{52} For “Chuchuhuasi”, a similar effect may have been produced by sesquiterpenes.\textsuperscript{12,14,33,54} This observation may support the hypothesis that the concomitant administration of propranolol and “Chuchuhuasi” could have deleterious effect on heart because an increase of p-r interval which is typical in heart block\textsuperscript{56} could produce arrhythmias.\textsuperscript{37} Moreover, the electrocardiogram revealed readings compatible with arrhythmia in G1 (Table 2). These have not been analysed further.

The study was principally focused on determining the possible effect of concomitant administration of “Chuchuhuasi” and propranolol. The study makes no attempt to specify the component of \textit{Maytenus macrocarpa} that could produce the possible interaction with propranolol, and as a result, the adverse effects on rats. Our hypotheses were based on previous studies of \textit{M. macrocarpa}. Future research should focus on a phytochemical analysis of the \textit{M. macrocarpa} extract.

One of the limitations with this research is that it does not measure blood pressure. Furthermore, it does not analyze others waves and intervals in electrocardiogram. Both measurements would be more useful to understand the effects on cardiovascular system and further studies are needed to address this. In spite of this, our findings enhance understanding of the effects of concomitant administration of medicinal plants and drugs. The most striking result to emerge from the data is the arrhythmic electrocardiography patterns. A work needs to be done to classify it. In summary, these findings are useful for understanding about possible adverse effects of the concomitant administration of “Chuchuhuasi” and propranolol. These effects could be more severe in people with cardiovascular disease. The current findings add to a growing body of literature on risk of the concomitant intake of medicinal plants and drugs.\textsuperscript{35–38} Further experimental investigations are needed to promote the rational use of the herbal medicine.

CONCLUSION

The present research has shown the effects of concomitant administration of propranolol and \textit{Maytenus macrocarpa} on temperature, respiratory rate, heart rate and the electrocardiogram. Also, it revealed abnormalities in the electrocardiogram such as arrhythmias. These interactions may have adverse effects on the health of people who are co-administering propranolol and \textit{Maytenus macrocarpa}. Further research is required to clarify the mechanism of each effect.

AUTHORS’ CONTRIBUTIONS

Author contributions to the study and manuscript preparation are as follows. ZHR, ZHA, MCJ, and SGA conceived and designed the study. ZHR, ZHA, WPJ, GBJ, and ZGD performed the experiments. SGA and MCJ carried out the process of capture of heart electrical signals. WPJ, GBJ, VBT, and ZGD acquired data of data. Statistical analysis: ZHR, ZHA, and SGA. All authors analyzed and contributed to data interpretation. SGA drafted the manuscript. All authors revised and approved the final manuscript.

ACKNOWLEDGMENTS

This research was supported by the authors and FMH-USMP. We would like to express our appreciation and thanks to Dr. Frank Lizarras Caparo (Dean of the FMH-USMP), Dr. Benjamí Castañeda Castañeda (Past Director of the Research Institute of the FMH-USMP), Professor Angel Alvarado Yarasca and Professor Berta Loja Herrera (Research Centre of Traditional Medicine and Pharmacology of FMH-USMP), and technician Carlos Pante Medina (Laboratory of Pharmacology of FMH-USMP) for their collaborations.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ABBREVIATIONS USED

ANOVA: Analysis of variance; GC: Control group; GA: Atropine group; GPr: Propranolol group; GM: Maytenus macrocarpa group; G1: M. macrocarpa 1500 mg/kg+propranolol 7 mg/kg group; G2: M. macrocarpa 1500 mg/kg+propranolol 9 mg/kg group; G3: M. macrocarpa 1500 mg/kg+propranolol 11 mg/kg group; G4: M. macrocarpa 1500 mg/kg+propranolol 13 mg/kg group; G5: M. macrocarpa 1500 mg/kg+propranolol 15 mg/kg group.


SUMMARY

- Concomitant administration of propranolol and Maytenus macrocarpa produced changes on temperature, an increase of respiratory rate, a decrease of heart rate.
- Concomitant administration of propranolol and Maytenus macrocarpa produced changes in electrocardiogram such as an increase of voltages of p and r wave, an increase of p-r interval and arrhythmias.
- This study revealed effects of concomitant administration of propranolol and Maytenus macrocarpa on temperature, respiratory rate, heart rate and electrocardiogram. In addition, it showed abnormalities in electrocardiogram which was associated with arrhythmia patterns.

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