Ritonavir boosting dose reduction from 100 to 50 mg does not change the atazanavir steady-state exposure in healthy volunteers

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Received 25 January 2012; returned 8 March 2012; revised 25 March 2012; accepted 2 April 2012

Objectives: To evaluate the pharmacokinetics, tolerability and safety of 300 mg of atazanavir boosted with 100 or 50 mg of ritonavir, both once daily, at steady state.

Methods: This was a single-blind, multiple-dose, crossover, sequence-randomized trial. Thirteen healthy HIV-1-negative men received witnessed once-daily doses of atazanavir (300 mg) and 100 or 50 mg of ritonavir for 10 days (15 day washout). Atazanavir and ritonavir plasma concentrations were determined for 24 h on day 10. Log-transformed individual pharmacokinetic parameters were compared between treatments (analysis of variance); the difference between treatments on the log scale and 95% CIs were calculated. Fasting cholesterol, triglycerides, glucose and bilirubin plasma levels were measured at the beginning and end of each period and compared (Wilcoxon signed rank test). Gastrointestinal symptoms and other events were recorded.

Results: Ritonavir $C_{\text{max}}$ and the $AUC_{0-24}$ were lower after the 50 mg booster dose than after 100 mg [geometric mean ratio (GMR) (95% CI), 0.40 (0.31–0.51) and 0.35 (0.29–0.42), respectively]. No differences were observed in atazanavir exposure with 50 or 100 mg of ritonavir [GMR $C_{\text{max}}$ (95% CI), 1.00 (0.79–1.28); GMR $AUC_{0-24}$ (95% CI), 0.98 (0.79–1.21)]. Atazanavir trough concentration was >0.15 mg/L in all volunteers. Total and low-density lipoprotein cholesterol increased 0.40 mM ($P = 0.01$) and 0.37 mM ($P = 0.003$) from their corresponding baseline value during the 100 mg dosing period; there were no significant changes on 50 mg. Mild increases in bilirubin were detected on day 10 after both treatments without differences between treatments.

Conclusions: In spite of higher exposure to ritonavir with 100 mg, atazanavir exposure was equivalent; the lipid profile was better under the lower booster dose (50 mg).

Keywords: pharmacokinetics, dose-optimization, antiretrovirals, HIV

Introduction

As HIV infection has become a potentially chronic and manageable condition1 in recent years, protease inhibitors (PIs) are still considered one of the pillars of highly antiretroviral activity because of their recognized antiviral potency and high genetic barrier to antiretroviral resistance.2 However, PI treatment regimens are not free of short- and long-term adverse effects.3 The fact that almost all PIs have limited oral bioavailability due to a first-pass effect makes it necessary to administer these drugs with a potent inhibitor of cytochrome P450 (CYP) 3A4.4 Currently, ritonavir is the only marketed drug with this indication. The co-administration of PIs with ritonavir results in higher and more sustained plasma concentrations of the PIs.5 In spite of the low doses of ritonavir used to boost atazanavir, ritonavir can lead to lipid disturbances, glucose intolerance, insulin
resistance, liver enzyme elevations, gastrointestinal symptoms and body fat abnormalities. These effects potentially compromise treatment adherence, putting patients at higher risk of therapeutic failure and subsequent resistance selection.

Two approaches are currently being explored in the effort to overcome the limitations on using ritonavir to boost PIs. On the one hand, two new drugs capable of inhibiting CYP 3A4 currently under development are cobicistat (GS-9350) and SPI-452.9 In a Phase 2 study, cobicistat had a safety profile comparable to that of ritonavir, as both drugs proved to have similar numbers of treatment discontinuations, levels of hyperbilirubinaemia and emergent adverse events. On the other hand, the feasibility of reducing the ritonavir boosting dose without compromising PI plasma concentrations is also being studied.11–13

Among the PIs, atazanavir presents the best safety profile in the absence of ritonavir and is the only PI that can be administered without ritonavir.14–20 However, atazanavir trough concentrations in plasma are lower and more variable when the PI is taken alone than when ritonavir is also administered.21 Currently approved atazanavir doses in HIV-1-infected patients in Europe are 300 mg if boosted with 100 mg of ritonavir, but with the addition of the booster problems arise in the form of more gastrointestinal adverse events, a less favourable lipid profile, higher hyperbilirubinaemia, and a higher rate of jaundice.22,23

Atazanavir therapy may therefore benefit if the ritonavir dose is reduced provided the incidence of adverse events decreases without jeopardizing the pharmacokinetic profile of atazanavir. Thus, the main objective of the present study was to evaluate the steady-state pharmacokinetics of atazanavir once-daily doses of 300 mg boosted with 100 or 50 mg of ritonavir. Treatment tolerability and safety were also evaluated. In order to avoid eventual consequences such as treatment failure or resistance development in HIV-1-infected patients as a consequence of a ritonavir dose reduction, the study was performed in healthy volunteers.

Methods

Subjects

Healthy HIV-1-negative adult men between 18 and 50 years of age were eligible. Subjects were judged healthy at screening 2 weeks before the first dose based on medical history, physical examination, vital signs, electrocardiogram, laboratory assessments, negative urine drug screens, and negative hepatitis B and C, and HIV serologies. The volunteers were excluded if they had used any prescription or over-the-counter medications in the 14 days before screening, if they had participated in any other clinical trial in the last 3 months, if they had a medical history of alcohol and/or drug abuse or had donated blood in the last 6 months.

The study was approved by the Ethics Committee of Hospital de la Santa Creu i Sant Pau and the Spanish Medicines and Medical Devices Agency. The study was carried out in accordance with the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines. All volunteers gave their written informed consent to participation prior to any procedure.

We assumed that the AUC for atazanavir could only be reduced by decreasing the ritonavir boosting dose, also assuming a 40% interindividual variability of atazanavir.24 We estimated that 11 subjects would be sufficient to detect a decrease of <40% in the AUC on reducing the ritonavir dose, assuming a 0.05 alpha error with 80% power.

Study design

In this single-blind, multiple-dose, crossover, sequence-randomized clinical trial each volunteer participated in two experimental periods, each lasting 10 days and spaced at least 15 days apart. The volunteers received the following two treatments: 300 mg of atazanavir (two capsules of 150 mg) plus 100 mg of ritonavir (solution) in one period and 300 mg of atazanavir (two capsules of 150 mg) plus 50 mg of ritonavir (solution) in the other period.

Experimental procedures

Each period lasted 10 days, as follows:

On day 1 the volunteers were received at 7:00 a.m. after an overnight fast. Again they were asked to report possible adverse events of any nature in the last 24 h and fill in a questionnaire regarding gastrointestinal symptoms in the previous 24 h. The questionnaire included the following gastrointestinal symptoms: (i) nausea; (ii) vomiting; (iii) diarrhoea; (iv) gastrointestinal pain; and (v) flatulence. The number of episodes was recorded for vomiting and diarrhoea if present; if gastrointestinal pain was present, severity was scored on a scale from 1 to 10, with 1 indicating mild pain and 10 unbearable pain. After filling in the questionnaire, the volunteers received a supervised dose of atazanavir with 240 mL of tap water, ritonavir with 240 mL of peach juice and a standard breakfast. They remained at the unit under supervision for at least 30 min after drug intake.

On day 10 the volunteers were received at 7:00 a.m. after an overnight fast. Again they were asked to report possible adverse events of any nature in the last 24 h and to fill in the questionnaire on gastrointestinal symptoms. A cannula was inserted in the cubital vein with interchangeable heparinized mandrels to draw repeated blood samples. Medication was administered between 8:00 and 9:00 a.m. (the same time and under the conditions as in the previous 9 days). In addition to breakfast on taking the medication, at 6, 10 and 13 h after administration the volunteers had a standard lunch, a light snack and a standard dinner, respectively. The subjects remained in the centre 24 h after receiving the medication. Before they left they filled in the questionnaire on gastrointestinal symptoms, samples for haematology and biochemical analysis were taken, and a 12-lead electrocardiogram was performed.

At the end of the study, at least 1 week after the last drug intake, another physical examination was performed; blood samples were again collected for analysis.

Study methods

Blood samples at the end of each treatment (day 10) were drawn into 5 mL tubes containing EDTA at baseline (0–1 h prior to drug administration) and at 1, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h after the patient took the medication for analysis of atazanavir and ritonavir concentrations in plasma. Samples were centrifuged at 3000 rpm for 10 min at 4°C and plasma was separated and immediately frozen at −80°C until analysis. Both drugs were quantified at the retrovirology laboratory at Hospital Universitari Germans Trias y Pujol by means of HPLC with a photodiode array detector (HPLC-PDA 2996; Waters, Barcelona, Spain) following a validated method. The method involved liquid–liquid extraction of drug from plasma with tert-butyl methyl ether after basification and a second wash with hexane. The mobile phase consisted of a gradient elution with phosphate buffer: acetonitrile (pH 6.70). The method was linear over the range of 0.044–17.5 mg/L for atazanavir and 0.05–20 mg/L for ritonavir. The intra- and interday coefficients of variation were <10% for both drugs. The assay was externally validated by
Safety assessments included physical examinations, electrocardiograms, vital sign measurements and laboratory evaluations (biochemistry, haematology and urinalysis) prior to the study, during the trial and at study completion. The assessments during the trial consisted of laboratory parameters (biochemistry, haematology) and an electrocardiogram 24 h after the last dose of each study period. Fasting lipid profile (total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides), glucose, insulin and bilirubin were determined at the beginning and at the end (24 h after the last dose intake) of each study period. Gastrointestinal symptoms were closely followed throughout the study, as explained above. Adverse event monitoring was also ongoing.

**Statistics**

**Pharmacokinetics**

After quantification of atazanavir and ritonavir plasma concentrations, the following pharmacokinetic parameters were calculated for each drug using a non-compartmental approach with WinNonlin software (Professional Edition, Version 2.1, Scientific Consulting, Pharsight, Mountain View, CA, USA): $C_{max}$, time taken to reach the $C_{max}$ ($t_{max}$), concentration at 24 h post-dose ($C_{min}$), the AUC$_{0–24}$ calculated by means of the log-linear trapezoidal rule and average plasma concentration ($C_{ave}$) calculated as AUC$_{0–24}$/24. Terminal elimination half-life ($t_{1/2}$) was obtained by linear regression analysis of the terminal log-linear portion of the plasma concentration curve. The AUC was extrapolated to infinity (AUC$_{0–∞}$) by addition of the residual area calculated by the last plasma concentration/terminal elimination rate constant; apparent total plasma clearance at steady state (CL$_{ss}$/F) was then calculated as dose/AUC$_{0–∞}$. Apparent volume of distribution at steady state (V$_{ss}$/F) was calculated as dose/$C_{ave}$. Concentrations below the limit of quantification were set to zero to calculate AUC$_{0–24}$.

Log-transformed values of the parameters were compared using an analysis of variance model appropriate for a two-period crossover design containing factors for period, sequence, subject within sequence, and treatment. The difference between treatments was estimated on the log scale; 95% CIs were calculated. These estimates were back-transformed, and the resulting ratios [geometric mean ratios (GMRs)] and 95% CIs are provided.

Although it was not the intention of the study to prove bioequivalence between treatments, the 90% CIs of AUC$_{0–24}$ were compared with the normative range of 0.80–1.25 in order to evaluate the total exposure to the drug.

Pharmacokinetic parameters are expressed as geometric mean (range).

**Safety and tolerability**

To determine the effect of each treatment on the studied variables, non-transformed values at baseline and at the end of each treatment period were compared using the Wilcoxon signed rank test.

Total, LDL and HDL cholesterol, triglycerides, glucose, insulin and bilirubin plasma levels were transformed to the difference from pre-administration values and compared between treatments by means of the Wilcoxon signed rank test.

Data regarding safety and tolerability are expressed as median (range) except for gastrointestinal effects and adverse events, which are summarized as frequencies.

**Results**

**Subjects**

Of the 13 healthy male volunteers who received treatment in at least one period and who were therefore included in the safety analysis, 12 completed the study and their samples were analysed for plasma concentrations and included in the pharmacokinetic analysis. The characteristics of the study population at screening are given in Table 1.
Pharmacokinetic characteristics

Ritonavir plasma concentrations were higher after 100 mg doses than after 50 mg doses (Figure 1). At 24 h, ritonavir concentrations were above the limit of quantification in only three volunteers (after administration of 100 mg of ritonavir in all cases); thus, the 24 h ritonavir concentration was not calculated. As was expected, the $C_{\text{max}}$, $C_{\text{ave}}$ and $AUC_{0–24}$ indicated that exposure to ritonavir was significantly reduced after the 50 mg dose. Total apparent plasma clearance and $V_{ss}/F$ were significantly higher during the 50 mg ritonavir dosing period than during the 100 mg period. No other parameters, such as $T_{\text{max}}$ or $t_{1/2\lambda_2}$, differed statistically between doses (Table 2).

Atazanavir concentration–time profiles were almost identical with the two booster doses (Figure 2). No differences were observed in total systemic atazanavir exposure between treatments. The 90% CI of the ratio of the log-transformed $AUC_{0–24}$ (82.50–116.38) was within the acceptable range of 0.8–1.25, indicating the bioequivalence of co-administration of atazanavir with 50 and 100 mg of ritonavir, given that the ritonavir dose did not affect total exposure to atazanavir. No statistically significant differences between ritonavir doses were observed in the other atazanavir pharmacokinetic parameters, except for a slight but significant reduction in $t_{1/2\lambda_2}$ (Table 3).

Safety and tolerability

There were no serious adverse events during the study and medication was generally well tolerated. Only one subject was excluded and replaced due to a non-drug-related adverse event (local hand inflammation). No effect was observed on the electrocardiogram-derived variables (data not shown).

Among the adverse events classified as possibly related to drug intake, flatulence was the most frequently reported but was unrelated to the ritonavir boosting dose. Other adverse events included gastrointestinal disturbances (reported by two subjects after intake of 100 mg of ritonavir), diarrhoea (only present in two subjects, one in the 100 mg period and the other in the 50 mg period) and headache (three episodes reported by two different subjects after the 50 mg period).

When atazanavir was boosted with 100 mg of ritonavir, significant increases in total cholesterol, LDL cholesterol and bilirubin levels were detected, whereas only the plasma level of bilirubin was significantly elevated when atazanavir was boosted with 50 mg of ritonavir. There were no significant differences in bilirubin levels between treatments, and normal values were achieved within a week of stopping treatment in all participants (Table 4).

Discussion

There is a growing interest in whether lower ritonavir boosting doses could help maintain plasma concentrations of PIs while possibly improving the profile of adverse events and the cost of antiretroviral therapy for HIV-1-infected patients. In our study atazanavir was boosted with 100 or 50 mg of ritonavir for 10 days, and although a clear reduction in ritonavir plasma concentrations was observed with the lower dose, atazanavir

### Table 2. Ritonavir steady-state pharmacokinetic parameters after single daily doses of 300 mg of atazanavir (ATV) with 100 mg of ritonavir (RTV100) and ATV with 50 mg of ritonavir (RTV50)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RTV100</th>
<th>RTV50</th>
<th>GMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (mg/L)</td>
<td>1.75 (1.02–2.83)</td>
<td>0.69 (0.37–1.32)</td>
<td>0.40 (0.31–0.51)</td>
</tr>
<tr>
<td>$AUC_{0–24}$ (mg·h/L)</td>
<td>11.82 (5.99–22.34)</td>
<td>4.17 (2.15–9.00)</td>
<td>0.35 (0.29–0.42)</td>
</tr>
<tr>
<td>$C_{\text{ave}}$ (mg/L)</td>
<td>0.49 (0.25–0.93)</td>
<td>0.17 (0.09–0.38)</td>
<td>0.35 (0.29–0.42)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.76 (1.00–6.00)</td>
<td>1.76 (1.00–6.00)</td>
<td>1.00 (0.68–1.48)</td>
</tr>
<tr>
<td>$V_{ss}/F$ (L)</td>
<td>40.20 (26.23–108.62)</td>
<td>60.15 (27.57–548.01)</td>
<td>1.49 (1.05–2.14)</td>
</tr>
<tr>
<td>$CL_{ss}/F$ (L/h)</td>
<td>8.46 (4.48–16.70)</td>
<td>12.00 (5.56–23.30)</td>
<td>1.42 (1.19–1.69)</td>
</tr>
<tr>
<td>$t_{1/2\lambda_2}$ (h)</td>
<td>3.29 (2.38–5.36)</td>
<td>3.48 (1.96–19.45)</td>
<td>1.05 (0.75–1.48)</td>
</tr>
</tbody>
</table>

Values are geometric means (ranges). GMR = RTV50/RTV100.
plasma concentrations showed little decrease and a slightly better safety and tolerability profile with this dose.

Consistent with the pharmacokinetic characteristics of ritonavir we observed, the changes in $CL_{ss/F}$ and $V_{ss/F}$ values between the 50 and 100 mg doses are compatible with a non-linear pharmacokinetic profile. The values for both parameters were 0.75 times lower for the higher ritonavir dose, suggesting that the bioavailability of ritonavir is greater with a 100 mg dose. The changes in $CL_{ss/F}$ and $V_{ss/F}$ may have been caused by (i) the higher capacity of the drug to inhibit CYP 3A4 activity at the higher dose, or (ii) an increase in the proportion of ritonavir that is absorbed due to inhibition of the efflux pumps, such as P-glycoprotein, in the intestinal wall. Considering the proportional change in $CL_{ss/F}$ and $V_{ss/F}$, the second possibility is the most plausible explanation for the increase in bioavailability.

In our study atazanavir pharmacokinetic profiles were very similar when 300 mg of the drug was co-administered with 50 or 100 mg of ritonavir in healthy volunteers. Similar results were obtained for saquinavir boosted by two doses in a Thai population; nonetheless, these results should not be extrapolated to other PIs without study since the pharmacokinetics of these drugs may be different in a Thai population. Although in our study atazanavir exposures were bioequivalent in terms of $C_{\text{max}}$ and AUC for the two ritonavir boosting doses, this was not true for $C_{\text{min}}$. The GMR of $C_{\text{min}}$ was slightly inferior to the well accepted interval of bioequivalence [0.79 (0.59 – 1.04)]. This result is not likely to have a clinical impact in naive patients, since all our volunteers in the present study had $C_{\text{min}}$ values above the proposed cut-off of 0.15 mg/L regardless of the ritonavir boosting dose. However, close monitoring of plasma concentrations of atazanavir should be performed in previously experienced patients with partial resistances to PIs.

Overall, the two dosage regimens used in this study were well tolerated. The adverse events reported most often in this trial (flatulence, diarrhoea and gastrointestinal symptoms) were consistent with those previously reported in studies conducted in patients receiving atazanavir/ritonavir therapy. Mild increases in lipid profile (LDL and total cholesterol) from baseline values were observed solely when atazanavir was boosted with 100 mg of ritonavir. This increase was >10 mg/dL in half of the participants, and might have a potential impact on the risk of cardiovascular disease, depending also on other individual factors such as age, sex, blood pressure, diabetes and smoking habit. Even though the length of our crossover trial was relatively short, we observed mild increases in lipid profile (LDL and total cholesterol) from baseline values solely when atazanavir was boosted with 100 mg of ritonavir. Our results for the 100 mg dose of ritonavir are in line with those obtained in the atazanavir arm of the CASTLE study, where patients were treated for 96 weeks. Thus, we might hypothesize that the lack of effect on the lipid profile we observed when lower (50 mg) ritonavir doses were used would probably be maintained in the long term. However, appropriately designed clinical trials in HIV-1-infected patients to corroborate this hypothesis are required.

Considering the pharmacokinetic, safety and tolerability results of our study, one may speculate that co-administration of 50 mg of ritonavir with 300 mg of atazanavir may bring clinical benefit. However, this study was performed in healthy volunteers and not in HIV-1 patients, the duration of the study was only 10 days, the volunteers did not take any other medication during the study, and ritonavir was administered as an oral solution. Thus, we would only recommend a reduced ritonavir dose if therapeutic drug monitoring can be performed. The patient must also be willing to take ritonavir as a solution (unless a new ritonavir formulation is developed). In any case, controlled trials should be conducted in a large number of patients and over longer study periods to evaluate the pharmacokinetics, efficacy and safety of the two booster doses.

In summary, our results in healthy HIV-1-negative volunteers have shown that atazanavir exposure is equivalent when boosted with 100 or 50 mg of ritonavir and that the profile of adverse events is slightly better with the 50 mg booster dose. These results are promising and should be viewed as the basis of further investigation of a possible reduction in ritonavir doses in HIV-1-infected patients in order to minimize adverse ritonavir-related effects. If feasible and safe, a smaller booster dose would benefit both patients by reducing adverse events and the public health service by reducing the cost of treating such adverse events.

### Table 3. Atazanavir steady-state pharmacokinetic parameters after single daily doses of 300 mg of atazanavir (ATV) with 100 mg of ritonavir (RTV100) and ATV with 50 mg of ritonavir (RTV50)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RTV100</th>
<th>RTV50</th>
<th>GMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/L)</td>
<td>4.90 (1.77 – 7.35)</td>
<td>4.92 (2.93 – 7.35)</td>
<td>1.00 (0.79 – 1.28)</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (µg/L)</td>
<td>0.66 (0.23 – 1.82)</td>
<td>0.52 (0.24 – 1.29)</td>
<td>0.79 (0.59 – 1.04)</td>
</tr>
<tr>
<td>$AUC_{0–24}$ (µg. h/L)</td>
<td>46.72 (16.34 – 85.16)</td>
<td>45.78 (31.50 – 73.45)</td>
<td>0.98 (0.79 – 1.21)</td>
</tr>
<tr>
<td>$C_{\text{ave}}$ (µg/L)</td>
<td>1.94 (0.68 – 3.55)</td>
<td>0.49 (0.25 – 0.93)</td>
<td>0.98 (0.79 – 1.21)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>1.80 (1.00 – 4.00)</td>
<td>1.93 (1.00 – 6.00)</td>
<td>1.07 (0.86 – 1.33)</td>
</tr>
<tr>
<td>$V_{ss/F}$ (L)</td>
<td>81.28 (51.51 – 214.10)</td>
<td>69.23 (45.26 – 117.86)</td>
<td>0.85 (0.66 – 1.10)</td>
</tr>
<tr>
<td>$CL_{ss/F}$ (L/h)</td>
<td>6.42 (4.08 – 9.52)</td>
<td>6.55 (4.48 – 16.70)</td>
<td>1.02 (0.83 – 1.26)</td>
</tr>
<tr>
<td>$t_{1/2\alpha}$ (h)</td>
<td>7.87 (5.83 – 22.39)</td>
<td>7.32 (5.07 – 12.60)</td>
<td>0.83 (0.71 – 0.98)</td>
</tr>
</tbody>
</table>

Values are geometric means (ranges).

GMR = RTV50/RTV100.
Acknowledgements

We would like to thank Mary Ellen Kerans for reviewing the English of the last version of the manuscript.

Funding

This study and J. A. E. were supported by a grant from the Spanish Ministry of Health, Project TRA-076. J. A. E. was also partially supported by the Albán Program, the European Union Program of High Level Scholarships for Latin America (scholarship no. E06D101499CU). M. V. was supported by FIS through a grant (CP04/00121) from the Spanish Health Ministry in collaboration with Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Barcelona. M. V., R. M. A. and M. J. B. are members of CIBERSAM (funded by the Spanish Health Ministry, Instituto de Salud Carlos III).

Transparency declarations

None to declare.

Author contributions

J. A. E., PhD student, participated in the experimental sessions, analysis of the data and article writing and editing. J. M. participated in the study design, discussion of the results and article writing and editing. L. T. participated in the preparation of the medication and article writing. S. C. participated in the quantification of drug plasma levels. R. M. A. was the physician responsible for the experimental sessions and participated in the preparation of the manuscript. M. A. M. supervised the preparation of the medication and participated in the preparation of the manuscript. B. C. and P. D. participated in the discussion of the results and article writing. M. P. participated as physician in the experimental sessions and contributed to the preparation of the manuscript. M. J. B. participated in the study design and experimental sessions. M. V., principal investigator of the study, participated in the study design, supervised the experimental sessions and contributed to the preparation of the manuscript. M. J. B. participated in the study design and experimental sessions. M. V., principal investigator of the study, participated in the study design, supervised the experimental sessions and contributed to the preparation of the manuscript. M. J. B. participated in the study design and experimental sessions. M. V., principal investigator of the study, participated in the study design, supervised the experimental sessions and contributed to the preparation of the manuscript. M. J. B. participated in the study design and experimental sessions. M. V., principal investigator of the study, participated in the study design, supervised the experimental sessions and contributed to the preparation of the manuscript. M. J. B. participated in the study design and experimental sessions.

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