



Caffeine but not acetaminophen increases 4-km cycling time-trial performance

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ABSTRACT

Acetaminophen has been combined with caffeine for therapeutic purpose, but the effect of co-ingestion of acetaminophen and caffeine on exercise performance has not been investigated. To determine the effect of isolated and combined ingestion of caffeine and acetaminophen on performance during a 4-km cycling time-trial (4TT). Eleven men, completed a 4TT one hour after the ingestion of cellulose (PLA), acetaminophen (20 mg kg⁻¹ body mass, ACT), caffeine (5 mg kg⁻¹ body mass, CAF) or combined acetaminophen and caffeine (20 and 5 mg kg⁻¹ body mass, respectively, ACTCAF). The perception of pain, rating of perceived exertion, electromyography, oxygen uptake were recorded. Plasma lactate concentration was measured before and immediately after the trial. The time and mean power during the 4TT was significantly improved ($P < 0.05$) in CAF (407.9 ± 24.5 s, 241.4 ± 16.1 W) compared to PLA (416.1 ± 34.1 s, 234.1 ± 19.2 W) and ACT (416.2 ± 26.6 s, 235.8 ± 19.7 W). However, there was no difference between ACTCAF (411.6 ± 27.7 s, 238.7 ± 18.7 W) and the other conditions ($P > 0.05$). All other measures were similar under the conditions ($P > 0.05$). Caffeine but not acetaminophen increases power output ultimately increasing performance during a 4TT.

1. Introduction

During a self-paced, high-intensity cycling time-trial (e.g., 4-km cycling TT), the exercise intensity must be strictly regulated to avoid an exacerbated early accumulation of metabolites that can lead to premature fatigue [1,2]. A disturbance in the intramuscular metabolic milieu (i.e., accumulation of the H⁺, ADP, AMP and Pi) at the beginning of a high-intensity cycling TT, provoked by increased muscle recruitment (as inferred from electromyography signals, EMG) ultimately increasing power output (PO) [1,2], will activate peripheral sensory nerve terminal [3]. These increased afferent signals might result in increased perception of pain [4], leading to a reduction in PO [1,2].

Acetaminophen (commonly known as paracetamol) has recently been introduced as a potential pharmacological agent to increase exercise performance due to its analgesic properties [5–7]. The

mechanism by which acetaminophen relieves pain feelings in humans is not fully known, but it has been attributed to the inhibition of the cyclooxygenase enzymes [8,9], potentiation of descending serotonergic pathways [10], and modulation of opioid and cannabinoid CB₁ receptors [9]. Although there is not a consensus [11,12], several studies have reported improved performance during high-intensity exercises after a single clinical dose (1–1.5 g or 20 mg kg⁻¹) of acetaminophen [5,6,13].

It is interesting to note that acetaminophen has been combined with caffeine for therapeutic purpose [14,15], but the effect of co-ingestion of acetaminophen and caffeine on exercise performance has not been investigated. The precise mechanism by which caffeine assists acetaminophen in reduction of pain is not fully known, but caffeine might act as an adenosine antagonist at the A₂ adenosine receptors of the peripheral sensorial nerves, blocking adenosine-induced pain

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transmission [16]. The analgesic effect of caffeine may also involve inhibition of presynaptic adenosine receptors on cholinergic nerve terminals in supraspinal sites [17] and increased release of β -endorphin [18]. Although caffeine has other central and peripheral mechanisms of action [19–21] potentially more prominent to exercise performance than analgesia, it would be interesting to explore whether a combination of acetaminophen with caffeine would improve exercise performance to a larger extent than when they are ingested in isolation.

Therefore, the aim of the present study was to investigate the effect of isolated and combined ingestion of acetaminophen and caffeine on performance during a 4-km cycling TT. We hypothesized that exercise performance might improve to a larger extent when acetaminophen and caffeine are combined, when compared to acetaminophen or caffeine alone.

2. Materials and methods

2.1. Participants

Assuming that isolated acetaminophen and caffeine could have a moderate effect size on time trial performance [6,22], and using an alpha of 0.05 and a desired power of 0.80, the total effective sample size necessary to achieve statistical significance was estimated to be 10 participants. Taking in account potential drop outs, eleven men (age: 24.5 ± 6.9 years, body mass: 74.8 ± 6.5 kg, height: 176.4 ± 7.7 cm, $\dot{V}O_{2\max}$ 39.0 ± 6.5 ml·kg⁻¹·min⁻¹), who were accustomed to cycling recreationally, were recruited. Participants were free of acute/chronic pain and were not using acetaminophen or any other analgesic medications. Participants received a verbal and written explanation of the possible risk, discomfort and benefits associated with the study, and signed a consent form agreeing to participate in the study. The present study was conducted according to the principles of the Declaration of Helsinki and was approved (CAAE: 44457215.20000.5208; Approval: 1.097.620) by the Human Ethics Committee of the Federal University of Pernambuco.

2.2. Experimental design

Participants visited the laboratory on seven different occasions. At the first visit, participants answered an acetaminophen risk assessment questionnaire [23] and a caffeine consumption questionnaire [24]. No participant presented any risk associated with acetaminophen ingestion. The participant's habitual consumption of caffeine was 93.3 ± 118.1 mg·day⁻¹. Anthropometric measurements and an incremental exercise test were then performed on a road bike (Giant®, Aluxx 6061, Taichung, Taiwan) coupled to a pre-calibrated CompuTrainer (CompuTrainer® Pro, RacerMate®, Seattle, WA, USA). The seat height was recorded and reproduced for all subsequent sessions. On the second and third visits, at least 72-h apart, participants performed two 4-km cycling TT in each visit for familiarization (separated by 30 min); therefore, participants had the opportunity to practice the 4-km cycling TT four times. The coefficient of variation for exercise time between the two “fresh” trials (first trial of visit 1 and 3) was 1.7 ± 1.3 %.

Experimental trials were performed from the fourth to the seventh visits using a randomized, counterbalanced and double-blind design. A 7-day period between the four experimental trials was adopted for

washout. One hour before each trial, participants ingested gelatin capsule containing either cellulose (PLA), or acetaminophen (20 mg kg⁻¹ body mass, ACT), or caffeine (5 mg kg⁻¹ body mass, CAF), or acetaminophen combined with caffeine (20 and 5 mg kg⁻¹ body mass, respectively, ACTCAF). The substances were encapsulated in capsules of the same colour and shape (Pharmapele®, Recife, PE, Brazil). Participants were instructed to cover the 4-km cycling TT as fast as possible during the trials and received visual feedback for distance completed, but not for exercise time, power output, pedal frequency or physiological parameters. Participants were asked to refrain from consuming caffeine-containing substances and from taking any analgesic medications as well as to restrain from doing exercise during the 24 h before each experimental trial. Participants were also asked to complete a 24-h food recall before the first experimental trial and to replicate it in the following trials. Participants were inquired before trial whether they had adhered to dietary intake and abstaining from caffeine and analgesic medications. All tests were performed at the same time of day to avoid the circadian variation on TT performance [25].

2.3. Incremental test

After a 5-min warm-up at 50 W, PO was increased 25 W every minute until exhaustion. Participants were required to maintain cadence at 70 rpm throughout the test. Oxygen consumption ($\dot{V}O_2$), di-oxide carbon production ($\dot{V}CO_2$), and ventilation ($\dot{V}E$) were measured breath-by-breath during the test through an automatic gas exchange analyser (Cortex, Metalyzer® 3B, Leipzig, Germany). The calibration of the equipment was performed according to the manufacturer's recommendations using gases of known concentration (12 % O_2 and 5 % CO_2) and a 3-L syringe for the volume. Heart rate (HR) was measured via an HR transmitter coupled to the gas analyser (Polar®, T 31/34, Kempele, Finland).

The $\dot{V}O_{2\max}$ was determined as the highest 20-s average $\dot{V}O_2$ during the test. Aerobic peak power was determined as the PO achieved during the last completed stage. When the participants were not able to maintain the PO during an entire stage (i.e., < 1 min), the aerobic peak power was calculated using the fractional time completed in the last stage completed, multiplied by the increment rate [26].

2.4. Experimental trials

Participants arrived at the laboratory, after a 3-h fasting, and a double Ag/AgCl electrode was attached over the *vastus lateralis* belly for further EMG record [27]. To further normalize the EMG signal during the trials, participants performed three maximal voluntary contractions (MVC) with a 1-min passive rest between the contractions on a custom-made bench. The hip and knees angles were set at 120° and 90°, respectively. A non-compliant cuff attached to a calibrated linear strain gauge was fixed to the right ankle just superior to the malleoli for force measurement. The EMG and force signals were acquired with a sample rate of 2000 Hz EMG System, EMG 830 C, São Jose dos Campos, SP, Brazil. The EMG signal during the MVC was further used to normalize the EMG signal during the 4-km cycling TT.

After MVCs recording, participants ingested capsules containing PLA, ACT, CAF, or ACTCAF and rested for 45 min (Fig. 1). Then,

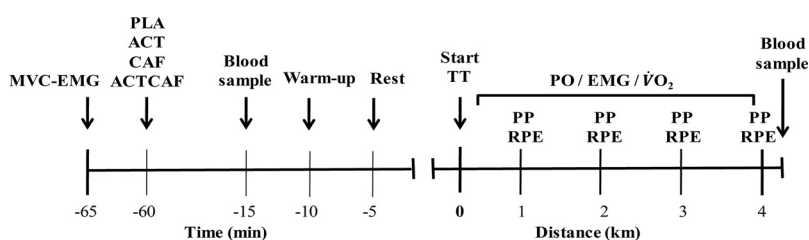


Fig. 1. Timeline of the experimental trial. Maximal voluntary contraction (MVC), electromyographic activity (EMG), placebo (PLA), acetaminophen (ACT), caffeine (CAF) or acetaminophen combined with caffeine (ACTCAF), time trial (TT), power output (PO), oxygen uptake ($\dot{V}O_2$), perception of pain (PP), and rating of perceived exertion (RPE).

participants were questioned about which substances they thought they had ingested, and then performed a 5-min warm-up at 50 % of aerobic peak power, followed by a 5-min rest and a 4-km cycling TT. Participants were instructed to cover the 4-km cycling TT as fast as possible. The trials were performed in an ambient temperature of 21 ± 1 °C and a relative humidity of 38 ± 5 %.

The PO was recorded every second during the entire trial (RacerMate Software, version 4.0.2, Seattle, WA, USA). The $\dot{V} O_2$ and EMG were continually recorded. The RPE and pain perception were recorded every 1-km using the 15-point Borg's scale [28] and the 12-point pain intensity scale [29], respectively. Capillary blood samples (50 μ L) were collected from the earlobe in a sodium-heparinized capillary tube before and immediately after the trial.

2.5. Data analyses

The raw EMG signal was filtered with a fourth-order Butterworth band-pass filter with cut-off frequencies set at 10 and 400 Hz. Signal was full-wave rectified and root mean square (RMS) calculated for a 500-ms window around peak torque during MVC. The RMS of each burst during the 4-km cycling TT was also calculated, averaged for every 1-km epoch and normalized by RMS of MVC. The PO and $\dot{V} O_2$ data were also averaged every 1-km interval. Blood samples were centrifuged at 4000 rpm (4 °C) during 15 min for plasma separation, and plasma lactate concentration ([La]) was determined with commercial kits (Labtest, Lagoa Santa, MG, Brazil) with the reaction reading in a spectrophotometer (Thermo Scientific, Genesis 10S UV-vis, Waltham, MA, USA).

2.6. Statistical analyses

The assumption of normality was checked with the Shapiro-Wilk test. The performance time was compared between the conditions via ANOVA of repeated-measures. The dependent variables measured during the TT were compared between conditions using a 2-way ANOVA of repeated-measures (condition \times distance). Duncan's *post hoc* test was conducted when a significant main effect or interaction was detected. The level of significance adopted was $\alpha < 0.05$. Data were analysed using the statistical package Statistica (StaSoft®, Inc. version 10, Tulsa, OK, USA).

3. Results

3.1. Blinding

From 44 trials, participants guessed 16, 14, 7 and 5 % the ingestion of PLA, ACT, CAF and ACTCAF, respectively, indicating a success in the blinding process.

3.2. Exercise performance

There was a significant effect of substance ingestion on exercise performance ($P = 0.029$, Fig. 2). The time to complete the 4-km cycling TT was significantly faster in CAF (407.9 ± 24.5 s) than in PLA (416.1 ± 34.1 s, $P = 0.015$) and ACT (416.2 ± 26.6 s, $P = 0.016$), but there was no significant difference between PLA and ACT ($P = 0.976$). There was also no significant difference between ACTCAF (411.6 ± 27.7 s) and the other three conditions ($P > 0.05$).

3.3. Power output distribution, neuromuscular recruitment, and metabolic and perceptual responses

There was a main effect of condition ($P = 0.022$) and distance ($P = 0.008$), but not condition \times distance interaction ($P = 0.795$) for PO (Fig. 3A). The PO was higher throughout the trial in CAF (241.4 ± 16.1 W) compared to PLA (234.1 ± 19.2 W, $P = 0.007$) and ACT

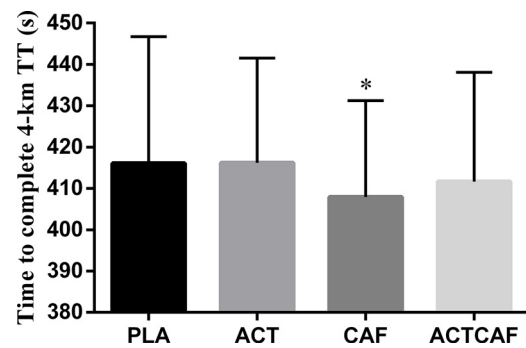


Fig. 2. Performance time during a 4-km cycling TT after placebo (PLA), acetaminophen (ACT), caffeine (CAF) and acetaminophen combined with caffeine (ACTCAF) ingestion. Data are shown as mean \pm SD. *Significantly faster than PLA and ACT ($P < 0.05$).

(235.8 ± 19.7 W, $P = 0.031$), without any other differences (all $P > 0.05$). The PO was higher at the beginning and end of the trial, compared to the middle of the trial ($P = 0.012$ and $P = 0.049$, respectively). There was only a main effect of distance for RMS ($P = 0.027$, Fig. 3B), $\dot{V} O_2$ ($P = 0.001$, Fig. 3C), RPE ($P = 0.001$, Fig. 3D), and pain perception ($P = 0.001$, Fig. 3E), without any condition or condition \times distance interaction ($P > 0.05$). Plasma lactate increased after the trial ($P = 0.001$), but there was no condition ($P = 0.322$) or condition \times distance interaction ($P = 0.336$).

4. Discussion

The present study is the first comparing the effect of isolated and combined caffeine and acetaminophen ingestion on exercise performance. Our findings indicated that the isolated ingestion of caffeine increases power output throughout a 4-km cycling TT, ultimately improving exercise performance, when compared to placebo and acetaminophen alone. However, this effect is lacking when caffeine is combined with acetaminophen. Acetaminophen alone had no effect on exercise performance.

4.1. Acetaminophen alone

In the present study, the ingestion of acetaminophen alone (20 mg kg^{-1}) did not increase 4-km cycling TT performance. Based on previous findings [6,7], the acetaminophen ingestion was expected to improve exercise performance. This non-improvement in exercise performance after acetaminophen ingestion in the present study conflicts with previous observations that acetaminophen ingestion (1.5 g) improves exercise performance during a 16.1-km cycling TT [7], increases total work done during a 3-min all-out test [30], increases time to task failure at 70 % $\dot{V} O_{2\text{max}}$ [6], raises the peak or mean power output during repeated sprints [5,13], and increases mean torque during a 60×3 -s MVC (2-s passive recovery period) protocol [31]. On the other hand, other studies failed to find an effect of acetaminophen ingestion on time to task failure at 70 % $\dot{V} O_{2\text{max}}$ [11] or repeated sprint performance [12]. The reason for these contradictory results is not clear, but it may be related to different exercise protocols and tasks measuring exercise performance. Our findings add to these showing that acetaminophen ingestion (20 mg kg^{-1}) did not improve exercise performance during a self-paced, high-intensity exercise such as a 4-km cycling TT. In view of these conflicting results, it could be argued that the ergogenicity of the acetaminophen might be task-dependent. It is recommended therefore that acetaminophen should be tested in TT of different lengths.

4.2. Caffeine alone

In the present study, caffeine ingestion (5 mg kg^{-1}) improved

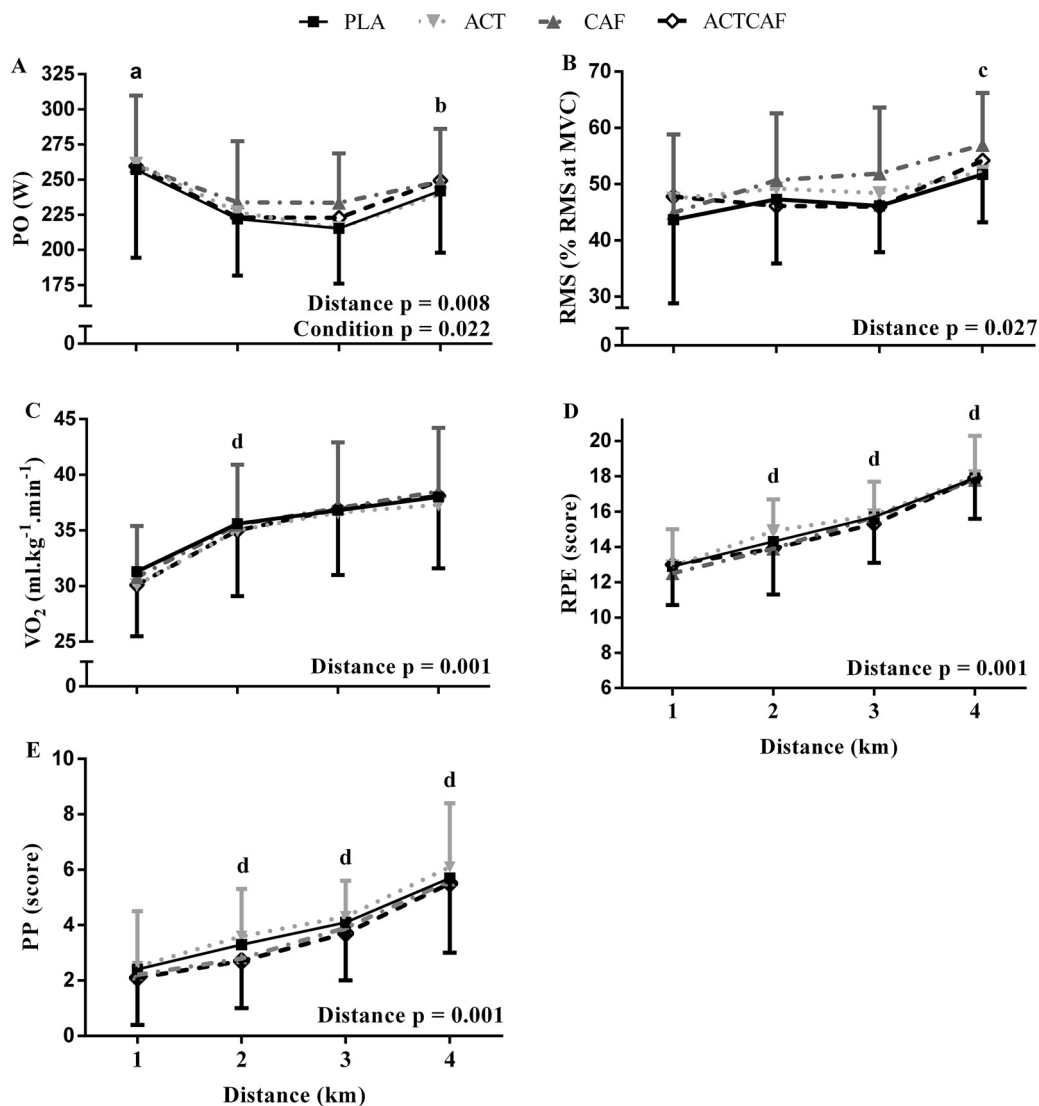


Fig. 3. PO: Power output (A), electromyography (B), oxygen uptake (C), rating of perceived exertion (D), and pain perception (E) during a 4-km cycling time-trial after placebo (PLA), acetaminophen (ACT), caffeine (CAF) or acetaminophen combined with caffeine (ACTCAF) ingestion. Data are shown as mean \pm SD. (A) PO was higher in CAF than in PLA and ACT throughout the trial (main effect of condition). ^aSignificantly higher than in 2 and 3 km ($P < 0.05$), ^bSignificantly higher than in 3-km ($P < 0.05$). (B) ^cSignificantly higher than all previous points ($P < 0.05$). (C, D and E) ^dSignificantly higher than previous one ($P < 0.05$).

exercise performance by $\sim 2\%$, when compared to both placebo and acetaminophen. These findings are consistent with several other studies showing a positive effect of caffeine compared to placebo (2–2.4%) on performance in a 4-km cycling TT [20,22]. However, the comparison between the ergogenicity of caffeine and acetaminophen had not been investigated; therefore, our findings suggest that caffeine has a greater ergogenic potential than acetaminophen, at least during a high-intensity cycling TT as used in the present study.

Different mechanisms have been proposed to explain the ergogenicity of caffeine [21,22]. One of them is that caffeine might have analgesic properties due to its peripheral effect on A₂ adenosine receptors [16] and/or on central β -endorphin release [18]. In the present study, caffeine alone led to greater mean cycling power output, with the same level of perceived pain and effort. This finding agrees with previous studies showing an increased power output with caffeine during high-intensity exercise, without changes in muscle pain [32,33] or RPE [20,22].

It should be highlighted that caffeine has other physiological effects not directly related to pain relief, which might be more important to improve exercise performance. In the present study, an increased power

output with caffeine supplementation was not accompanied by an increased muscle recruitment, as inferred from results of EMG. Caffeine is expected to have a central effect due to its action as an antagonist of the A₁ adenosine receptors in the central nervous system [33]. It is predictable therefore that caffeine ought to increase muscle recruitment. However, data from the literature are contradictory, with some studies showing an increased muscle recruitment with caffeine during a 4-km cycling TT [20] and lower reduction in voluntary activation of the *vastus lateralis* during intermittent isometric knee extension contractions [34], while others failed to find any effect of caffeine on motor unit recruitment [22,35]. These contradictory findings may be because caffeine can also influence spinal excitability and the muscle contractile apparatus. Caffeine increases spinal excitability [36], which would demand less central neural drive to maintain muscle activation. Caffeine in a physiological concentration in plasma ($\sim 40 \mu\text{mol L}^{-1}$) also improves calcium release from the sarcoplasmic reticulum, which increases muscle force for a given level of muscle recruitment [37,38].

4.3. Combined acetaminophen and caffeine ingestion

Clinical trials have demonstrated that the combination of acetaminophen (500–2000 mg) and caffeine (65–260 mg) reduces the time of onset of analgesic action and increase analgesic effectiveness, compared to acetaminophen alone [14,15]. We found a non-significant effect of the combination of acetaminophen and caffeine on exercise performance, when compared to placebo or to isolated ingestion of ACT or CAF. However, although not significant, time to cover the 4-km was slightly faster in ACTCAF compared to PLA (~1 %), but slightly slower compared to CAF (~1 %). The mechanism by which acetaminophen would negatively influence caffeine-induced improvement in exercise performance cannot be provided from our data. Further studies should test different combinations of caffeine and acetaminophen doses to determine if there is a dose combination most able to improve exercise performance. At the time of our study, however, the combination of acetaminophen with caffeine is not recommended.

4.4. Limitations

The present study has some limitations that should be mentioned. We recruited participants who did cycling recreationally, whose day-by-day variation may be greater than in trained cyclists. However, participants performed four familiarization trials, which helped to reduce the potential effect of learning. This assumption is supported by the low coefficient of variation between the two “fresh” familiarization trials (~1.7 %), which is very close to that reported for trained cyclists (~1.9 %) [39].

5. Conclusions

Acute caffeine ingestion but not acetaminophen increases cycling power output, improving performance of a 4-km cycling TT. The acetaminophen seems, however, to negatively affect the ergogenicity of caffeine. Therefore, the combined use of caffeine and acetaminophen should be avoided.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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