The Effect of Oral Contraceptives on Caffeine Metabolism and Cycling Performance

Authors: Annette M. Lemanski, Nicholas D. Luden, Michael J. Saunders, Christopher J. Womack, David L. Wenos

Institution: James Madison University, Harrisonburg VA, 22807

Contacts: Annette Lemanski, lemansam@dukes.jmu.edu

Michael Saunders, saundemj@jmu.edu

Christopher Womack, womackcx@jmu.edu

Address of Correspondence:

Nicholas D. Luden, Ph.D.
Department of Kinesiology
James Madison University
Harrisonburg VA, 22807
Phone: (540) 568-4069
Fax: (540) 568-3338
Email: ludennd@jmu.edu

ABSTRACT

PURPOSE: The objectives were to determine the effects of oral contraceptives and the menstrual cycle on the benefits of caffeine supplementation for cycling performance. METHODS: Seventeen recreationally trained female cyclists, oral contraceptive users (n=9) and non-users (n=8), completed four trials consisting of 3-km time trials (TT). Subjects ingested either 6mg/kg of caffeine or a placebo one hour prior to each trial. Magnitude based inferences were used to evaluate treatment differences. RESULTS: ***TBD. CONCLUSIONS:*** TBD.

INTRODUCTION

Caffeine is often consumed for its stimulating effects and ability to improve physical performance (5). There is good evidence that caffeine supplementation can enhance physical performance ranging from peak strength to endurance performance (3–5, 10, 15, 20, 22, 49, 51, 55, 56). The optimal caffeine dose for performance benefits is between 3 and 6 mg of caffeine per kilogram of body mass (13, 20, 22, 51).

The pharmokinetics of caffeine is predominantly regulated by hepatic cytochrome P450 (CYP1A2), the enzyme responsible for metabolizing the majority of caffeine (17, 37, 40, 41, 52, 59). Therefore, different concentration/activity levels of CYP1A2 represents a major source of variability in the pharmacokinetics of caffeine (58). Demethylation is the first step to caffeine metabolism, and is mostly metabolized to form paraxanthine (29). Less is known about paraxanthine kinetics and its potential role in facilitating beneficial effects of caffeine on exercise performance (10), however, caffeine metabolites have an even higher affinity for the adenosine receptors, which stimulate the central nervous system (11, 18), thereby plausibly having an even greater effect on performance than caffeine itself.

The rate of caffeine metabolism is not only sensitive to genetic variations of the enzyme, but also biological sex (5, 29); specifically, female sex hormones, estrogen and estradiol (1, 2, 17, 23, 42). There is an evident trend for higher plasma caffeine and lower plasma paraxanthine concentrations in women compared to men, suggesting that women metabolize caffeine slower than men (6). Women with higher estrogen levels, [such as oral contraceptive steroid (OCS) users, females in the luteal phase, or pregnant], have been found to have decreased CYP1A2 activity and decreased caffeine clearance (2, 32,

42). Despite the varying clearance rates across the menstrual cycle, currently nothing is known about whether or not this impacts the performance response to caffeine intake. Therefore, one of the primary aims of this study was to test the hypothesis that there will be a magnified effect of caffeine on performance in the follicular phase compared to the luteal phase.

The use of hormonal contraceptives is another condition when estrogen levels are elevated, (50), possibly effecting the ergogenic effect of caffeine through dampening the rate of caffeine metabolism. Chronic OCS use has been previously associated with impaired metabolism of caffeine (1, 2, 40, 43, 47, 53). It is commonly reported that OCS's inhibit CYP1A2 activity (1, 2, 25, 43, 44, 53). OCS's appear to modify the metabolism of caffeine by reducing the formation of paraxanthine, which is the primary pathway of caffeine metabolism, possibly limiting its physiological effects (44). There is no current evidence of the interactive effect OCS use has on the ergogenic effect of caffeine. Therefore, the second aim of this project is to test the influence of OCS use on the performance response to caffeine supplementation compared to non-OCS users.

METHODOLOGY

Subjects

Twenty-eight healthy, recreationally trained female cyclists (15 OCS users, 13 non-users) from James Madison University and the greater Harrisonburg/ Rockingham County area volunteered for the study. However, seven OCS users and four non-users withdrew from the study due to injuries, Lyme disease diagnosis, switching birth control prescription, seasonal flu, vasovagal syncope, or scheduling difficulties. Inclusion criteria included: female, 18-35 years of age, non-smokers, cycle $\geq$ 30 minutes at least two days a

week, and $VO_{2max} \geq 40$ ml/kg/min. Further, subjects were required to be eumenhorreic with menstrual cycle length between 21-35 days over the past 6 months. Descriptive data are shown in *Table 1.0.* Subjects who are not on any form of contraception will be assigned to the control group (n=15), and the subjects on monophasic or tri-phasic oral contraceptives will be assigned to the OCS user group (n=15). In the OCS user group, subjects were limited to monophasic oral contraceptives or tri-phasic oral contraceptives containing ethinyl estradiol and levonorgesterel for at least 6 months (8). Subjects were fully informed about the experimental procedures and possible risks before given written informed consent. Informed consent included information of the experimental procedures and risks prior to participation. James Madison University Institutional Review Board approved this study.

Experimental Design

Subjects reported to the laboratory for two familiarization trials and four experimental trials. Two experimental trials (1 placebo and 1 caffeine) were conducted during the luteal phase and two experimental trials (1 placebo and 1 caffeine) were performed in the follicular phase of the menstrual cycle. The luteal phase trials were performed from days 7 to 13 of the menstrual cycle, and the follicular phase trials were performed from days 18 to 24. Each treatment trial was performed in the morning between 6:00am and 10:00am. Trials were separated by at least 48 hours.

Preliminary Testing

Following height and body mass measurements, VO_{2max} was assessed during an incremental test on a bicycle ergometer (Velotron™ cycle ergometer, Racermate, Inc. Seattle, WA, USA). Workload started at 50 W and was increased in 25 W increments

every minute until volitional fatigue, or pedaling rate dropped below 50 rpm for >10 seconds. Breath samples were collected and oxygen consumption was analyzed with a Moxus® Modular Metabolic System (AEI Technologies, Pittsburgh, PA, USA). VO_{2max} was determined as the highest 30 second mean oxygen uptake value.

Supplementation

In a crossover, double-blind design, subjects were provided caffeine treatment or placebo. Anhydrous caffeine at 6mg/kg body weight was measured into opaque gelatin capsules. For placebo pills, gluten-free rice flour was put into opaque gelatin capsules. Supplementation was ingested with water, 60 minutes prior to the performance trial.

Familiarization Trials

Two familiarization trials were completed on a Velotron™ cycle ergometer before each subject began experimental trials. A 5-min self-selected warm-up was performed before all 3-km time-trials. Subjects were instructed to approach the time trial as a competition, emphasizing the importance to perform each trial as a race and put forth 100% effort. All trials were completed without verbal feedback and only elapsed distance was displayed. The familiarization trial protocol was identical to the performance trials with the exception of caffeine/placebo supplementation.

Performance Trials

Two venous blood samples were obtained; one upon arrival to the laboratory for baseline caffeine measures and another 60 minutes post treatment, just prior to the exercise trial. Following the second blood draw, subjects warmed-up on a treadmill for 5 minutes at 3.5 mph, followed by the 3k-time trial on a Velotron cycle ergometer. Subjects were aware of the distance traveled and distance remaining during the trial, but were

blinded to time and wattage output. Performance was recorded in time to complete and average watts for the 3-km time trial.

Blood Analysis

Approximately 3 ml of whole blood was obtained from an antecubital vein for measures of caffeine and estrogen concentrations. Samples sat for 30 minutes to coagulate, and then spun in a refrigerated centrifuge (AccuSpin™) at 2500 rpm for 15 minutes. Samples were subsequently decanted and plasma samples were stored in an -80ºC freezer for analysis of serum caffeine levels.

Dietary and Exercise Control

Subjects completed 24-hour food logs and were instructed to replicate their diet for 24 hours prior to each subsequent trial. Subjects were asked to refrain from any food or drink (besides water) for four hours before and from caffeine and alcohol for 12 hours before each trial. The OCS user group was required to authenticate intake of their respective oral contraceptive within the past 24 hours. In addition, 48-hour physical activity logs were completed prior to each trial, and were instructed to maintain consistent exercise habits between trials. Subjects were asked to refrain from any vigorous physical activity 12 hours prior to each trial.