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TITLE

Reducing the Dose of Combined Caffeine and Ephedrine Preserves the Ergogenic Effect

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Reducing the Dose of Combined Caffeine and Ephedrine Preserves the Ergogenic Effect

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BELL DG, JACOBS I, MCLELLAN TM, ZAMECNIK J. *Reducing the dose of combined caffeine and ephedrine preserves the ergogenic effect.* **Aviat Space Environ Med 2000; 71:415–9.**

Background: Ingestion of a combination of 5 mg · kg^{-1} caffeine (C), and 1 mg · kg^{-1} ephedrine (E) was reported to have an ergogenic effect on high intensity aerobic exercise performance, but 25% of the subjects experienced vomiting and nausea while engaging in hard exercise after the treatment. The present study was undertaken to investigate whether reduced levels of C+E would alleviate the problem and maintain the ergogenic effect. ***Methods:*** Twelve healthy untrained male subjects completed four randomized and double-blind, cycle ergometer trials to exhaustion at a power output equivalent to ~85% V_{O_2peak} 1.5–2 hours after ingesting a placebo (P) or a mixture of C+E in the following doses: 5 mg · kg^{-1} of C plus 0.8 mg · kg^{-1} of E (CLE); 4 mg · kg^{-1} of C plus 1 mg · kg^{-1} of E (LCE); or 4 mg · kg^{-1} of C plus 0.8 mg · kg^{-1} of E (LCLE). Trials were separated by 1 wk. Venous blood samples were obtained and analyzed for caffeine and ephedrine levels 1.5 h post-drug ingestion. V_{O_2}, V_{CO_2}, V_E, and RQ were measured every minute throughout the exhaustion ride. Heart rate and perceived exertion (RPE) were also recorded every 5 min and at the end of the exercise session. ***Results:*** Plasma levels of C and E immediately before the exhaustion ride were (mean ± SD). 38.7 ± 5.2 μmol · L^{-1} C, 1.285 ± 0.275 μmol · L^{-1} E in the CLE trial; 33.2 ± 5.8 μmol · L^{-1} C, 1.462 ± 0.283 μmol · L^{-1} E in the LCE trial; 33.0 ± 2.9 μmol · L^{-1} C, 1.229 ± 0.202 μmol · L^{-1} E in the LCLE trial. The times to exhaustion for the treatment trials (CLE = 27.5 ± 12.4 min, LCE = 27.6 ± 10.9 min, LCLE = 28.2 ± 9.3 min) were similar and were significantly greater than placebo ($p = 17.0 \pm 3.0$ min). The drugs did not affect V_{O_2}, V_{CO_2}, or V_E. Heart rates were significantly higher for the drug trials while RPE was lower compared with P. No incidents of nausea or vomiting occurred with the lowest dose of the C+E, LCLE. ***Conclusions:*** A lower dose of C+E resulted in an ergogenic effect similar in magnitude to that reported previously with a higher dose, and with a reduced incidence of negative side effects.

Keywords: ergogenic aids, caffeine, ephedrine, performance.

COMBINED CAFFEINE (C) and ephedrine (E) ingestion enhanced aerobic exercise performance in both a laboratory and field setting, according to three recent studies (1,2,3). Both drugs are known to affect stimulatory receptors in the central nervous system (CNS) as well as metabolic receptors in peripheral tissue including skeletal muscle (6,13,16,17,18). Bell et al. (3) speculated that the performance enhancement effects were probably primarily due to CNS stimulation because of the relatively short duration of exercise (12–20 min) and the lack of changes in variables which would support a peripheral metabolic effect.

The initial study by Bell et al. (3) reported a negative side effect of the combined C+E treatment. Three of 12 subjects stopped exercise because they experienced severe nausea and/or vomited after ingesting the treatment dose of 5 mg · kg^{-1} C and 1 mg · kg^{-1} E. No subjects vomited following the ingestion of either C or E alone. A similar incidence of nausea (3 of 11 subjects) was reported in a subsequent study using the same dose of C+E (2).

The third study (1) was a field trial that examined the efficacy of 375 mg of caffeine and 75 mg of ephedrine. This study confirmed in a field setting, involving a standard cross-country run wearing light fighting order, that performance was enhanced following C+E ingestion. Further, although some dizziness and mild hand tremors were noted, no vomiting occurred during the trials for the nine subjects tested. We retrospectively attributed part of this reduced side effect to the fact that the subjects were somewhat heavier than originally anticipated, i.e., mean body mass of 82 kg. Thus the 375 mg of caffeine and 75 mg of ephedrine corresponded to 4.6 mg · kg^{-1} C and 0.9 mg · kg^{-1} E. The heaviest individual in this study weighed 104.5 kg and he showed a similar performance enhancement to the other subjects even though the dose relative to body weight was only 3.6 mg · kg^{-1} C and 0.7 mg · kg^{-1} E. It is this reduction in the incidence of nausea, and the maintenance of the ergogenic effect with a lower relative dose of C+E than used previously, which suggests that the C+E dose could be reduced and optimized. Thus, it was the purpose of this study to investigate the effects on performance of lower doses of C+E than used previously. It was hypothesized that a lower dose of both C and E would result in an ergogenic effect similar in magnitude to that reported previously. In addition, it was hypothesized that the lower dose would be associated with a reduced incidence of nausea than previously reported.

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This manuscript was received for review in July 1999. It was revised in October 1999. It was accepted for publication in October 1999.

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METHODS

Subjects

Informed consent was obtained from 12 subjects with a mean age of 32 yr (±9), weight of 80.6 kg (±10.5), height of 1.77 m (±0.07), and $V_{O_{2peak}}$ of 45.6 ml · kg^{-1} · min^{-1} (±3.2). The subjects were not trained competitive athletes, but most had participated previously in experiments involving exercise to exhaustion. Seven subjects consumed caffeinated beverages and foods regularly, i.e., the equivalent of drinking 2–6 cups per day; while five were non-caffeine consumers, i.e., < 1 cup per day.

Procedures

During the study, the subjects visited the laboratory on seven separate occasions. On visit 1, subjects were medically screened and then had their $\dot{V}_{O_{2peak}}$ determined on an electrically braked cycle ergometer (Ergomed 920/930, Siemems-Elema, Sweden) using a 3-min stepwise incremental protocol. Subjects began pedaling at a power output of 90 W and this was increased 30 W every 3 min until exhaustion. Subjects pedaled at 60–80 revolutions per minute (rpm). The linear regression of oxygen uptake on power output was calculated from the submaximal power output during this test. The highest oxygen uptake recorded was considered the $V_{O_{2peak}}$.

During visit 2, the subjects were familiarized with the exercise test that was to be used during the experimental treatment trials, i.e., the exhaustion ride (ER). This consisted of exercising on an electrically braked cycle ergometer for 5 min at a power output equivalent to approximately 50% $\dot{V}_{O_{2peak}}$, followed by a step increment to a power output of approximately 85% $V_{O_{2peak}}$. The ride ceased when the subject's pedal frequency dropped below 50 rpm. The 85% $\dot{V}_{O_{2peak}}$ power output was estimated from the regression equation described previously. Pre- and postexercise the subject was given a questionnaire to assess his well-being. He was to check off various symptoms if present and state any other side effects of the treatment. The list of symptoms included dizziness, nausea, headache, itchy scalp, hand tremor, cramping, nervousness, anxiousness, and vomiting.

During visit 3, the control trial, the subjects were familiarized with the blood sampling procedures. A blood sample was taken just prior to exercise and then the subject again performed the ER.

Visits 4 to 7 were the treatment trials. These were separated by a minimum of 1 wk and the subjects always exercised at the same time of day. The subjects reported to the laboratory in a fasted (12 h) and rested state. There they ingested gelatin capsules containing the treatment prescribed. At 30 min after capsule ingestion, a light meal (toast, muffin and fruit juice) was eaten. The subject then waited a further 1–1.25 h, after which a 10-mL blood sample was taken. This was followed by the ER protocol.

Drug and Placebo Administration

All treatments were ingested in opaque gelatin capsules. The subjects consumed a placebo (P) or three different mixtures of C and E, 90–105 min before exercise. The mixtures of C+E were as follows: 5 mg · kg^{-1} body weight of C + 0.8 mg · kg^{-1} body weight of E (CLE); 4 mg · kg^{-1} body weight of C + 1 mg · kg^{-1} body weight of E (LCE); 4 mg · kg^{-1} body weight of C + 0.8 mg · kg^{-1} body weight of E (LCLE). The placebo consisted of the same number of capsules, but contained Metamucil®, a dietary fiber. The order of treatments was randomized among subjects and double blind.

Measurements

Oxygen consumption ($\dot{V}_{O_2}$), carbon dioxide production ($\dot{V}_{CO_2}$), and ventilation ($\dot{V}_E$) were analyzed every minute via a metabolic cart (AMETEK, model OCM-2, Pittsburgh, PA) during the measurement of $V_{O_{2peak}}$ and during the ER. Heart rate was monitored during all exercise sessions (Polar, model Vantage XL, Port Washington, NY). Also every five minutes during the ER, the subject rated how hard he thought he was working using the Borg scale of perceived exertion (RPE) (4). Plasma blood samples were assayed for both C and E by gas chromatograph-mass spectrometry electron impact single ion monitoring (Hewlett Packard, model MSD 5970a, USA).

Data Analyses

Data were initially analyzed using repeated measures analysis of variance (ANOVA). While data were being analyzed, it was decided to evaluate the effects of history of caffeine consumption on the results. For this purpose the subjects were allocated into two groups according to their caffeine consumption: regular users and nonusers. A one "within" and one "between" factor repeated-measures ANOVA was used to compare the time to reach exhaustion for the treatment trials, the final HR and final RPEs in the caffeine user and nonuser groups. A two "within" (treatment × time) and one "between" (caffeine users) factor repeated-measures ANOVA was used to compare the changes in heart rate, gas exchange, RPE at similar times during the ER. When a significant effect was found ($p < 0.05$), a means comparison contrast technique was employed to isolate differences among treatment means (9).

RESULTS

Treatment Trials

Mean ± SD plasma concentrations for C and E 90 min after drug ingestion were: caffeine (38.7 ± 5.2 μmol · L^{-1}), ephedrine (1.285 ± 0.275 μmol · L^{-1}) for CLE; caffeine (33.2 ± 5.8 μmol · L^{-1}), ephedrine (1.462 ± 0.283 μmol · L^{-1}) for LCE; caffeine (33.0 ± 2.9 μmol · L^{-1}), ephedrine (1.229 ± 0.202 μmol · L^{-1}) for LCLE. No ephedrine was detectable in the placebo trial, however, some caffeine was measured (0.5 ± 1.3 μmol · L^{-1}). Consistent with the higher dose of C administered during the CLE trial, the C concentration was significantly higher when compared with all other trials. The LCE and LCLE resulted in similar plasma C Levels. Similarly the LCE plasma E levels were significantly greater than both the CLE and LCLE trial values.

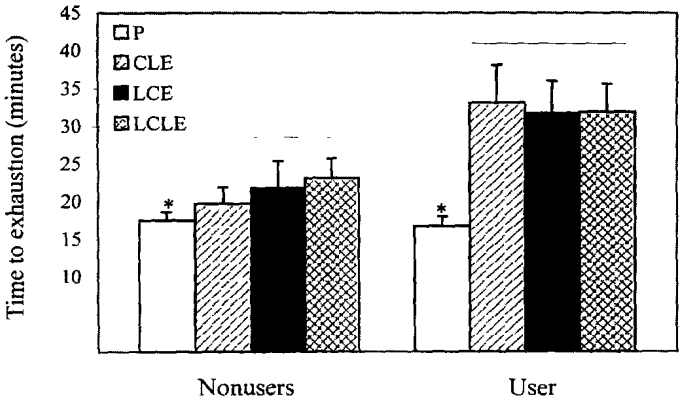

Fig. 1. Time to exhaustion (mean ± SEM) in caffeine users and nonusers after ingesting different doses of caffeine plus ephedrine. p = placebo; CLE = 5 mg · kg^{-1} C + 0 8 mg · kg^{-1} E, LCE = 4 mg · kg^{-1} C + 1 mg · kg^{-1} E, LCLE = 4 mg · kg^{-1} C + 0.8 mg · kg^{-1} E *P similar in users and nonusers and significantly different from C+E trials. Lines represent similar means Users significantly different from nonusers for the C+E treatment trials.

Endurance Ride

ER times to exhaustion with all C+E treatments were similar and significantly greater then P times (CLE = 27.5 ± 12.4 min, LCE = 27.6 ± 10.9 min, LCLE = 28.2 ± 9.3, p = 17.0 ± 3.0 min). **Fig. 1**, represents times to exhaustion for users and nonusers of caffeine. ER time to exhaustion when C+E was consumed for users (32.3 ± 11.0 min) was significantly longer than for nonusers (21.5 ± 6.1 min). Placebo ER time for users and nonusers was similar and approximated 17 min.

Respiratory Gas Exchange

During ER the different C+E levels did not effect $\dot{V}O_2$, $\dot{V}CO_2$, or $\dot{V}E$, **Table I.** There was no difference between caffeine users and nonusers for any of the respiratory values.

Heart Rate

The 5-, 10-, and final-minute HRs for P were significantly lower than all C+E treatment trials. There was no difference in HR response between users and nonusers, Table I.

RPE

At 5 min, RPE for P was significantly greater than all C+E treatment trials, and CLE was lower than LCE. At 10 min, RPEs for P were still higher than all C+E treatment trials and CLE was significantly lower than both LCE and LCLE, Table I. Final RPEs were similar for all conditions. There was no difference in RPE response between users and nonusers.

Nausea and Sickness

Of the 12 subjects, 3 reported single incidents of nausea during the trials. Two were nonusers and one was a user of caffeine. One nonuser was nauseous and vomited after completing his third treatment trial (CLE). The other nonuser vomited during his 4th treatment trial (LCE) and stopped exercising because of this. The one user was nauseous after his 4th treatment trial (LCE). No symptoms of nausea were reported for the LCLE, the trial employing the lowest dose of both C and E.

DISCUSSION

The results support the hypothesis that reduced levels of C+E would decrease the incidences of nausea yet still sustain a marked ergogenic effect. When all C+E combinations in the present study are grouped, time to exhaustion for ER was 27.8 min. Compared with P (17.0 min), this represents an approximate 64% improvement which was significantly higher than previously reported (38%) for a higher dose of C+E (3). However, caution must be used when making this comparison

TABLE I. RESPIRATORY PARAMETERS, HEART RATE AND RPE DURING EXERCISE AT 85% Vo_2 PEAK AFTER INGESTING A PLACEBO (P) OR DIFFERENT DOSAGES OF CAFFEINE AND EPHEDRINE.†

		P	CLE	LCE	LCLE
		Time (min)			
Vo_2 (L · min^{-1})	5	2.96 (0.37)	3.02 (0 54)	2 99 (0.43)	3 04 (0.37)
	10	3.17 (0.42)	3 25 (0.44)	3.18 (0 38)	3.25 (0 42)
	final	3.28 (0.37)	3.40 (0.40)	3.31 (0.40)	3.36 (0.37)
Vco_2 (L · min^{-1})	5	3 32 (0.36)	3.34 (0.47)	3 43 (0.50)	3.39 (0.48)
	10	3.34 (0.37)	3.37 (0.42)	3.33 (0.43)	3.42 (0 42)
	final	3.37 (0.36)	3.43 (0.46)	3.61 (0.50)	3.39 (0.48)
VE (L · min^{-1})	5	82 (10)	84 (14)	85 (12)	88 (12)
	10	91 (12)	95 (19)	95 (17)	100 (17)
	final	104 (17)	109 (17)	108 (14)	110 (17)
HR (bpm)	5	158 (14)*	167 (13)	166 (13)	168 (14)
	10	166 (13)*	172 (13)	173 (12)	174 (13)
	final	172 (13)*	182 (14)	183 (15)	182 (14)
RPE	5	5.3 (1.8)*	4.0 (1.7)‡	4.7 (1.4)	4.5 (1.6)
	10	7.7 (1.8)*	5.1 (2.3)‡§	5.9 (1.7)	6.0 (2.2)
	final	9.0 (1.5)	7 4 (2.4)	7.8 (2.3)	8.7 (1.5)

† CLE = 5 mg · kg^{-1} C + 0 8 mg · kg^{-1} E; LCE = 4 mg · kg^{-1} C + 1 mg · kg^{-1} E, LCLE = 4 mg · kg^{-1} C + 0.8 mg · kg^{-1} E.
* P significantly different from all other treatments a same time interval
‡ CLE significantly different from LCE at the same time interval.
§ CLE significantly different from LCLE at the same time interval

between the two studies as placebo times were different, 17.0 min in the present study vs. 12.6 previously (3). This suggests that in the previous study the subjects either worked at a higher relative intensity or were less fit. The fitness level of the subjects in the present and the previous study was similar at 46 and 47 ml · kg^{-1} · min^{-1}, respectively. In both studies, subjects worked at a power output level calculated to be 85% $V_{O_{2peak}}$. However, if the actual %$\dot{V}_{O_{2peak}}$ for the placebo trials is compared at the 5-min mark of ER, the subjects worked at intensities of 80% and 84% in the present and previous study, respectively. Although this difference in work intensity was not statistically significant, the slight change in effort at this work level may account for the difference in time to exhaustion. Thus the 64% improvement in ER with the C+E treatment trials in this study also must come under this scrutiny. Further, to support this observation, it has been reported that the effect of the combination of C+E is reduced at higher relative intensities (1,14). In the former study (1) where work intensities were greater than 90% $V_{O_{2peak}}$, C+E ingestion produced a significant 5% improvement in run times. In the latter study (14) where work intensities were 125% $\dot{V}_{O_{2peak}}$, C+E ingestion produced no improvement in time to exhaustion.

The side effect of nausea with C+E ingestion was an important issue in this study. The results support the fact that the lowest level of C+E (LCLE) reduced and in fact alleviated the nausea associated with the high levels of caffeine and ephedrine in both the user and nonuser groups. With the high dose of either C or E, sickness still occurred in both groups. High levels of E affected both one user and nonuser, while high levels of C affected one nonuser. Thus the dosage of E may be more critical for users where nausea is concerned, while the dosage of both C+E are important for nonusers.

The different response during the C+E trials between users and nonusers of caffeine is another important issue that must be addressed. A significant and important finding from the present study is that caffeine users, although less sensitive to caffeine than nonusers, produced better results than the nonusers. This finding is contrary to some of the literature that suggested that non-caffeine users respond better to acute doses of caffeine than users (5,7). However, the present results do agree with the work of Graham and Spriet (10) who showed that a higher dose of caffeine appeared to attenuate the ergogenic effect, especially in nonusers. They suggested that the higher dose might have stimulated the central nervous system to the point at which the usually positive ergogenic responses were overridden. They also stated that the lightest caffeine users had the poorest response and that they complained of mental confusion. Similarly, in the current study the user group showed the best response with the high level caffeine combination (CLE) while the nonusers showed the worst response (see Fig. 1). Further, the nonusers showed an improved response with the lowest dose (LCLE).

It appears for the users that the LCLE combination is very close to being optimal with regards to performance enhancement with the least amount of side effects. Although the nonusers produced their best performance with the lowest drug dose, this performance was not comparable to the users. These findings suggest that the dose level is not optimal for the nonusers. Further, by looking at the trend in performance for the nonuser in Fig. 1, it appears that the dosage of both C and E could be reduced even further.

How much further the dose could be reduced may be related to subjective feelings arising in the CNS. Kaplan et al. (15) showed that a lower 250 mg dose of caffeine produced better performance enhancement during psychomotor tests compared with a 500-mg dose. Further, the lower dose was associated with subjective feelings of calmness, peacefulness, pleasantness and elation; whereas, the higher dose produced feelings of being more anxious, excited and irritable. In the present study 8 of 12 subjects reported feelings of being anxious, excited or more irritable when on the lowest dose of C+E (LCLE). Five of these were the nonusers, i.e., the whole group; while only 3 of 7 from the user group reported the same symptoms perhaps indicating over stimulation.

Further, to lend credence to the CNS connection, the oral dose of C+E was reduced by 20% from our initial study (3). This produced a 19.0 and 17.1% reduction in ephedrine and caffeine, respectively, in the plasma for the LCLE treatment. What is noteworthy is that the subjects could tell the difference between treatments and guessed correctly when they were on the LCLE combination. Perhaps the different subjective feelings reported by the individuals in Kaplan et al. (15) and the present study may point to a key for finding optimum dosage levels for C and E. Subjective feeling of anxiety, irritability and excitement may reflect over stimulation of the CNS, as suggested by Graham and Spriet (10), and may indicate the likelihood of a less than optimal ergogenic effect.

Support for a centrally mediated mechanism for enhanced performance is again suggested from the RPE data. In general, RPEs for the C+E treatment trials in the present study were significantly lower at similar ER times. These results were similar to our previous study (3). There is also the suggestion that caffeine may be playing the more crucial role in the central sensation as the CLE treatment produced lower RPEs than the other two treatments. However, when exhaustion was reached RPEs were similar, although the trend was for the CLE RPEs to be the lower.

The sensitivity of individuals to arousal from caffeine ingestion can vary greatly. There is ample evidence that the same amount of caffeine ingested in one individual may be associated with positive subjective effects (11,12,15,19) while in another individual it can produce negative effects (10,15). This same phenomenon probably occurs with C+E ingestion in the present study and likely follows the Yerkes-Dodson law that postulates the relationship between arousal and performance follows an inverted U-shape curve (8). Thus in the case of the user it may be optimal; whereas, in the case of the nonusers the level is too high and not optimal.

In conclusion, the reduced dose levels of C+E used in this study preserved the ergogenic effect previously

observed when a higher dose was used. Further, the most reduced treatment (LCLE) was also the most effective in reducing the nauseous side effects of C+E ingestion.

ACKNOWLEDGMENTS

The authors thank Sandoz Canada for providing the caffeine, and Roberts Pharmaceutical Canada for providing the ephedrine for these trials We acknowledge the skillful technical assistance of Mrs. Ingrid Smith, Ms. Kelly Beaudreau, Mr. Jan Pope and Mr. Gary Seabrook

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513548