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DEFENCE AND CIVIL INSTITUTE OF ENVIRONMENTAL MEDICINE

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CAFFEINE, EPHEDRINE AND THEIR COMBINATION: EFFECTS ON BLOOD PRESSURE AND HEART RATE

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EXECUTIVE SUMMARY

The ability to maintain or acutely enhance the performance of military personnel could be crucial to a mission in scenarios such as extended search and rescue and sustained operations. In this regard, DCIEM has been investigating the effects of various pharmacological and nutritional treatments to determine their effect on physical performance. Two such substances ingested in combination, caffeine and ephedrine, have been shown to enhance physical performance. Before these substances can be recommended for use it is imperative that potential health risks are clarified. Therefore, it was the purpose of this study to determine the effects of acute ingestion of caffeine, ephedrine and their combination on heart rate (HR) and blood pressure variables. The results indicated that in non-users of caffeine resting systolic blood pressure (SBP) surpassed hypertensive levels (140 mm Hg) and remained at this level for 3 hours after ingesting the combination treatment. SBP levels gradually returned to placebo levels 8 hours after ingestion of the combined caffeine and ephedrine. Although diastolic blood pressure and HR also increased after the combined treatment ingestion, the magnitude was minimal and dissipated within 24 hours. It appears that in a healthy young individual acute ingestion of a preparation of caffeine, ephedrine or the two in combination would not have long lasting adverse effects on resting blood pressure or heart rate.

Key words: caffeine, ephedrine, heart rate, blood pressure

ABSTRACT

The ingestion of a combination of caffeine and ephedrine has an ergogenic effect on physical performance. Before recommending tactical applications of such a treatment the health risks must be determined. Therefore, it was the purpose of this study to clarify the effects of an acute ingestion of caffeine, ephedrine and their combination on heart rate and blood pressure variables. Twenty male and female subjects had their resting blood pressure and heart rate measured before and throughout 48 hours after ingesting either caffeine (c) (375 mg), ephedrine (E) (75 mg), c+e, or a placebo (p). Treatments were randomized and double blind. Systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were measured pre ingestion, 1, 3, 5, 8, 24, and 48 hours post ingestion. Venous blood samples were also obtained at these times and analyzed for caffeine and ephedrine level. All measured variables were significantly increased by the treatments. SBP increased the most after the c+e treatment, approached hypertensive values at the 1 hour mark (138 mm Hg), decreased thereafter, and was similar to p levels by 8 hours. DBP increased the most within the first hour in the c and c+e treatment, decreased thereafter, and was similar to p levels by 8 hours. DBP levels remained below the 90 mm Hg level. HR was significantly increased by the c+e and e treatments, reached peak levels at 5 hours (75 b/min) and was similar to placebo levels by 24 hours. Caffeine and ephedrine plasma levels peaked between 2 and 4 hours and by 48 hours they returned to placebo levels. It was concluded that in normo-tensive healthy young individuals acute ingestion of a preparation of caffeine, ephedrine or the two in combination would not have long lasting adverse effects on blood pressure or heart rate.

Key words: ergogenic, diastolic, systolic, heart rate, caffeine, ephedrine

INTRODUCTION

Recent investigations demonstrated that a mixture of caffeine (c) and ephedrine (e) ingested 1.5-2 hours before exercise causes rapid and significant improvements in high intensity aerobic work capacity (Bell and Jacobs, 1999; Bell et al. 1998, 1996). The mechanisms behind the enhanced performances were suggested to be primarily related to the stimulation of receptors in the central nervous system (CNS) although stimulation of metabolic receptors in skeletal muscle undoubtedly also occurs (Dodd et al. 1993; Hoffman and Lefkowitz, 1990; Lefkowitz et al., 1990; Nehlig and Debry, 1994; Rall, 1990). These findings would suggest that c+e may be an effective ergogenic aid, i.e., performance enhancing substance, that could have important tactical applications for Canadian Forces (CF) personnel engaged in operations where a rapid enhancement of high intensity physical work capacity would be beneficial.

Both c and e are considered relatively benign drugs by Health Canada regulatory authorities and are currently uncontrolled. Although the drugs are considered to be benign, adverse effects have been noted (Reynolds, 1989). Further recent reports from the US FDA suggested that ephedrine has caused heart problems and its use should be restricted.

In light of this increased focus on ephedrine, it is important to clarify the potential health risks caused by ingesting c+e. In the previous studies of Bell and Jacobs (1999) and Bell et al. (1998, 1996) although acute increases in heart rate (HR) were noted when either e or c+e were ingested, measurements were not made after exercise, nor was blood pressure (BP) measured. Others (Weller and Nevola, personal communications) who have used the c+e at similar dose levels found that it elevated both HR and BP at rest and during exercise, but the changes were not followed to determine when levels returned to normal values. Thus the effect of ingesting c+e on resting HR and BP has not been systematically investigated.

Therefore, the purpose of this study was to evaluate the effects of c, e and c+e on HR and BP for a period of 48 hours after ingestion.

Additionally, we could find no published information about the elimination of c and e when administered simultaneously other than in our pilot studies which suggested that the elimination from the circulation for both c and e were prolonged when ingested together as compared to when they are ingested alone. Thus a second purpose was to determine elimination rates of c, e and c+e by measuring their plasma concentration at regular intervals.

METHODS

Subjects

Informed consent was obtained from 20 subjects (16 males and 4 females) with age ranging between 19 and 51 and weight between 60 and 90 kilograms. Each subject

was given a medical examination to ensure that no medical restrictions would preclude their participation in the study. They were also provided with a copy of the experimental protocol listing the various steps involved as well as the associated risks and discomfort associated with the procedure.

Procedures

All subjects performed three drug and one placebo trials in a double blind random order separated by at least 72 hours. A research assistant prepared the treatment capsules and a technician, not associated with the execution of the trials, generated the randomization scheme and coded the treatment capsules.

All subjects were asked to refrain from ingesting caffeine and ephedrine for at least 12 hours prior the beginning of a trial and up to the final blood sample which was taken at the 48th hour post drug ingestion. During the 48 hours post drug ingestion the subjects resumed their normal daily working activities.

At the beginning of each treatment session, each subject was asked to answer a few questions concerning his/her disposition for that day. Measurements of BP and HR were obtained using a sphygmomanometer, stethoscope and radial pulse. Then a venous catheter (Insyte, Deseret) was inserted in an antecubital vein and the first blood sample was taken followed by an injection of heparinized normal saline solution to ensure patency of the catheter and easy access through the heparin lock. Once completed, the subject was given a treatment to ingest.

The blood sampling, BP and HR as well as a subjective symptom evaluation questionnaire were measured and administered pre ingestion and 1, 3, 5, 8, 24 and 48 hours post ingestion. After the sample at the 8 hour period, the catheter was removed and usual intravenous termination care was administered to the insertion site. The 24 and 48 hour blood samples were drawn via a venipuncture of an antecubital vein. After the 24 hour sample, the subjects were again reminded that they should avoid any caffeine product as well as ephedrine until the final blood sample was taken at 48 hours.

Eight mL of blood were drawn at each sample period. The blood was immediately expelled into a tube treated with ethylenebis (oxonitril)-tetraacetate (EGTA, 90 $mg \cdot mL^{-1}$) and glutathione (60 $mg \cdot mL^{-1}$). Plasma was obtained from aliquots of each blood sample and was assayed for the caffeine and ephedrine concentration by means of mass spectrometry (GS-MS) electron-impact, selective-ion monitoring.

Drug and Placebo Administration

All treatments were ingested in opaque gelatin capsules. The subjects consumed either 375 mg of c, 75 mg of e, a combined 375 mg of c + 75 mg of ephedrine, or a placebo. The placebo (p), which contained a dietary fiber (Metamucil ®), consisted of the same numbers of capsules as used for the other treatment trials.

Data Analyses

Data were analyzed using SuperANOVA ® software (Gagnon et al., 1989). A two-factor (treatment x time) repeated-measures deign (ANOVA) was used to compare the changes in HR, BP, and plasma levels of caffeine and ephedrine. When a post-hoc comparison was required a means-comparison contrast technique was employed (Gagnon

et al., 1989) and the Huyn-Feldt-epsilon factors were used to adjust degrees of freedom for multiple comparisons. Statistical significance was accepted at the $P \leq 0.05$ level.

RESULTS

Systolic Blood Pressure

Figure 1 depicts the effect of the treatments on systolic blood pressure (SBP). There was a drug by time interaction. At one hour post treatment ingestion, SBP had peaked in all treatments trials, with c+e>e>c>p. SBP at peak ranged from 117.6 ± 8.3 mm Hg (mean ± SD) for placebo to 138.3 ± 10.6 mm Hg for c+e. At 3 hours SBP had decreased but all treatments were still greater than p (c+e=e>c>p). By five hours SBP for the treatments were further reduced, but still significantly greater than p (c+e=e=c>p). At 8 hours only e was significantly greater than p. By 24 hours all levels were similar and equal to pre ingestion levels.

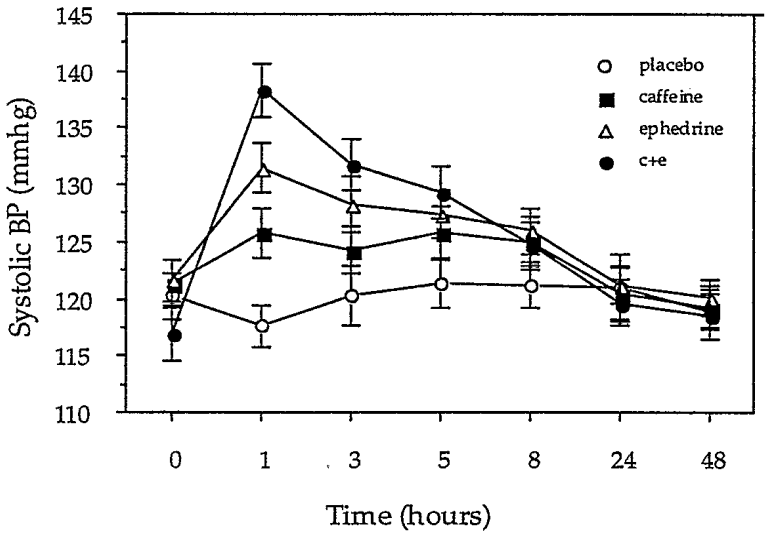

Figure 1: Effect of c, e and c+e ingestion on systolic blood pressure.
Values are mean (SEM).

Diastolic Blood Pressure

Figure 2 depicts the effect of the treatments on diastolic blood pressure (DBP). Again there was a drug by time interaction. At one hour post treatment ingestion, DBP had peaked in all treatments trials, with c+e=e=c>p. DBP at peak ranged from 77.6 ± 6.9 mm Hg for placebo to 83.7 ± 7.0 mm Hg for c+e. At 3 hours DBP had decreased and only C was greater than p. At 8 hours all levels were similar. The magnitudeof the changes in DBP were considerably less than those for SBP.

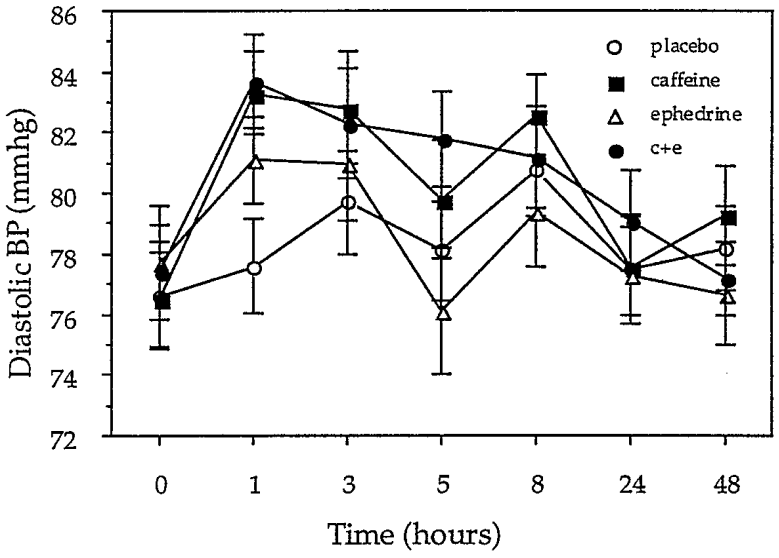

Figure 2: Effect of c, e and c+e ingestion on diastolic blood pressure.
Values are mean (SEM).

Heart Rate

Figure 3 depicts the effect of the treatments on HR. There was a drug by time interaction. The e and the c+e treatment were similar and significantly increased HR over p and c levels, which were similar, and this effect was maintained until 24 hours post ingestion.

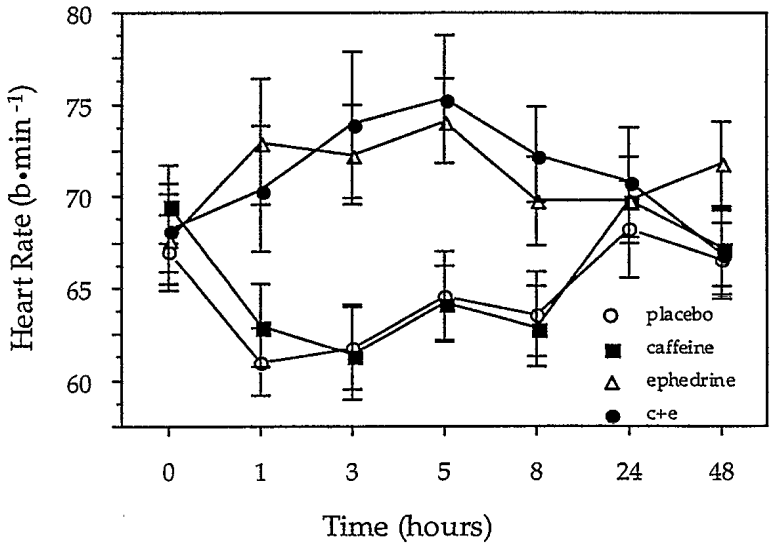

Figure 3: Effect of c, e and c+e ingestion on heart rate. Values are mean (SEM).

Caffeine and Ephedrine Concentrations

Figure 4 shows the level of ephedrine in the plasma during the e and c+e treatment trials. There was no difference between the clearance rates. Peak levels occurred between 2 and 4 hours after drug ingestion.

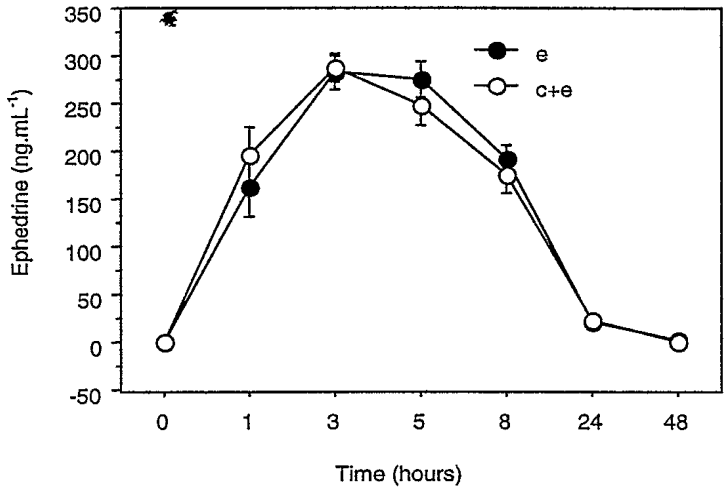

Figure 4: Plasma ephedrine levels post e and c+e ingestion. Values are mean (SEM).

Figure 5 shows the level of caffeine in the plasma during the c and c+e treatment trials. There was no difference between the clearance rates. Peak levels occurred between 2 and 4 hours.

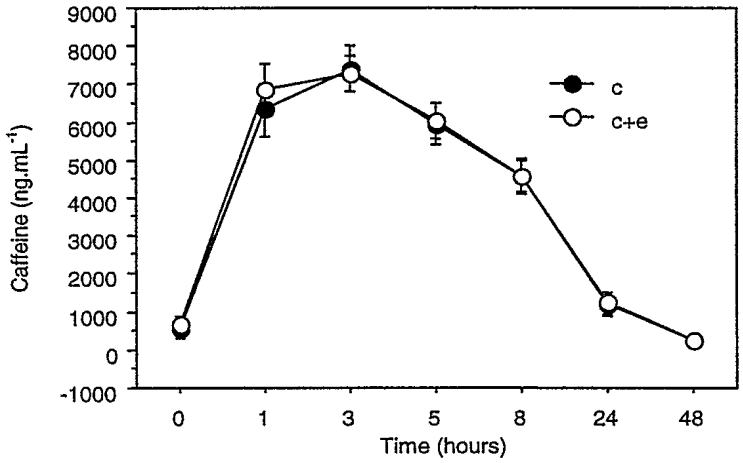

Figure 5: Plasma caffeine levels post c and c+e ingestion. Values are mean (SEM).

Symptoms

The occurrence of the surveyed symptoms reported by the 20 subjects after ingesting the various treatments is shown in Table 1. The onset of symptoms occurred within one to three hours and usually dissipated by 5 hours. C+E treatment was associated with the highest incidence of side effects.

Table 1. Symptoms reported by subjects

	Placebo	Caffeine	Ephedrine	C+E
Anxiety	0	3	2	5
Nervousness	0	3	0	5
Insomnia	2	0	0	3
Wakefulness	2	3	2	7
Hand Tremor	0	1	1	2
Nausea	0	2	1	4
Headache	1	1	1	2

DISCUSSION

The generally accepted threshold for hypertension from a medical point of view is 140 mm Hg for resting systolic and 90 mm Hg for resting diastolic pressure. With regards to the former, some systolic pressure readings exceeded this threshold specifically when the subjects were exposed to the c+e combination. It appears from Figure 1 that this increased hypertension occurred approximately one hour after ingestion and that by three hours it had decreased below the hypertension threshold. We were aware, however, from previous works (Bell et al., 1998; Graham and Spriet 1995) that caffeine users and non users respond differently to similar treatments. Therefore, we split our group into users and non users groups and reinvestigated the systolic response.

Figure 6 shows the results. Numerous deductions can be drawn from this figure, specifically from the top panel which shows SBP after ingesting the combination of c+e. First, the systolic response in non caffeine users appears to be greater than in users. Second, the SBP in non users surpasses the hypertension threshold and remains elevated until after the 3 hour mark. Third, although the SBP had dropped below hypertensive levels by five hours, levels did not approach placebo values until 24 hours later. These data suggest that non caffeine users are at greater risk with regards to elevated SBP when ingesting c+e.

Is the 2-hour elevation in SBP dangerous for normo-tensive subjects? Young healthy individuals performing moderate exercise, akin to doing a forced march, raise their SBP to values in excess of 160 mm Hg (Astrand and Rodahl, 1970). Further, in work using the arms, SBP can exceed 175 mm HG (Astrand and Rodahl, 1970). Thus the recorded variations in the systolic BP over the course of the c+e trial should be easily tolerated by a normo-tensive individual. Nevertheless, a warning is necessary because, as

with any drug, some individuals may be extraordinarily sensitive. In a subsequent experiment we have measured systolic and diastolic pressure in excess of 214/112 in a young, healthy male, after ingestion of c+e (Pasternak, H. Jacobs, I. and Bell, D. Personal communication). He was a non caffeine user.

Further, it is possible that our data collection points did not capture the highest SBP sustained by each subject. Peaks might have occurred between 1 and 3 hours if SBP pressures correlates with plasma levels of c and e. We can see by Figures 4 and 5 that peak plasma levels of e and c appeared to crest by 3 hour. At this time SBP were lower.

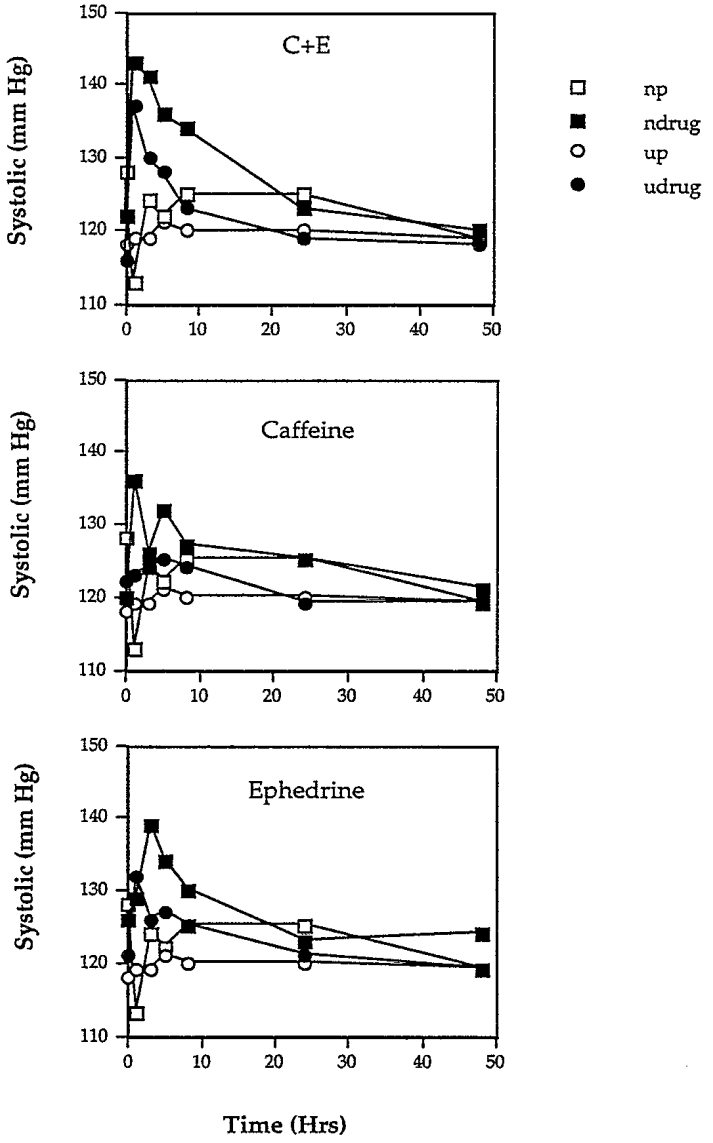

Figure 6. Effect of caffeine, ephedrine and c+e on S BP in caffeine users = u = circles, and non users = n = squares. Open symbols represent placebo trials, closed symbols drug trials.

than at one hour. Thus it is possible that higher SBP may have occurred before 3 hours and after 1 hour. Regardless of the peak, the other results remain the same

The difference between the users and non users could be questioned as the starting systolic pressures were different. Upon examination of the changes in blood pressure, expressed as the difference from the pre-ingestion values, Figure 7, the difference disappears. However, one must be cautious in disregarding the sensitivity of non caffeine users. As previously mentioned we have recorded systolic BP over 200 after c+e ingestion and before exercise commenced.

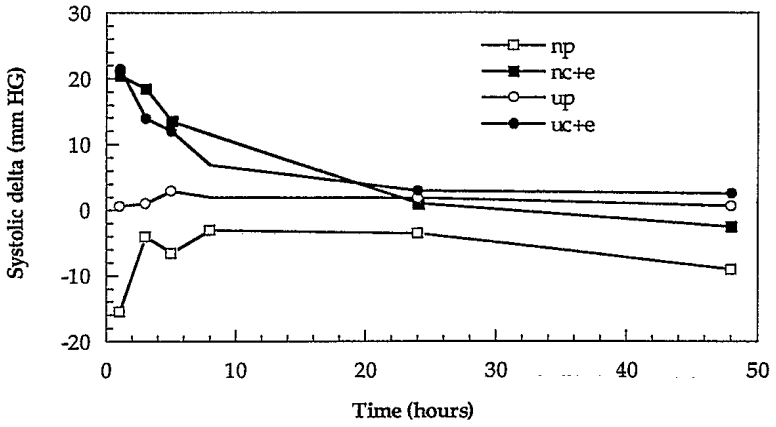

Figure 7. Effect of caffeine use and c+e on the change in systolic BP in caffeine users = u = circles, and non users = n = squares. Open symbols represent placebo trials, closed symbols c+e trials.

The diastolic pressure threshold for hypertension, 90 mm Hg, was not exceeded at any pressure reading (statistical mean) during the trial regardless of the treatment administered or whether the individual was a caffeine user or non user (Figure 8). It is, however, noteworthy to mention that non caffeine users consistently obtained higher reading in DBP than the users group when c or c+e was ingested. The increase in blood pressure noted in the present experiment in conjunction with caffeine consumption is in agreement with others (Daniels et al., 1998; Sung et al., 1990; Robertson et al., 1978).

Although HR's were within normal limits for an average adult population, the striking feature of Figure 3 cannot be dismissed. Ephedrine, whether taken alone or in combination with caffeine, appears to drive the increased HR response. The response was also similar in caffeine users and non users. This we have noted in other studies (Bell et al., 1998; Bell and Jacobs, 1999) and this increase was not abolished by exercise (Bell and Jacobs, 1999).

It was anticipated that the plasma clearance rate of the combination of c and e would be longer than when either drug was ingested alone, as suggested in a preliminary study (Bell et al. 1998). Our findings did not confirm this speculation. Clearance rates of c, taken separately or in combination with e were similar. The same results were noted with e when taken alone or in combination.

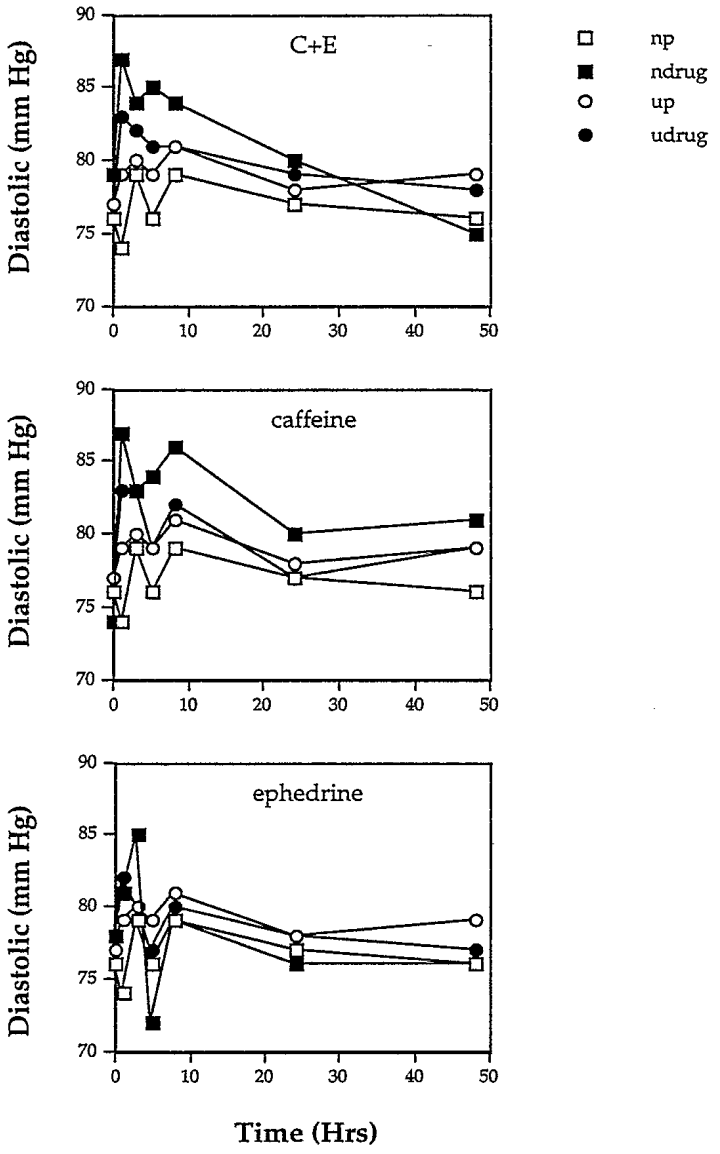

Figure 8. Effect of caffeine, ephedrine and c+e on D BP in caffeine users = u = circles, and non users = n = squares. Open symbols represent placebo trials, closed symbols drug trials.

CONCLUSION

It appears that in a normo-tensive healthy young individuals acute ingestion of a preparation of caffeine, ephedrine or the two in combination would not have long lasting adverse effects on resting blood pressure or heart rate.

ACKNOWLEDGEMENTS

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The ability to maintain or enhance our soldiers' performance could be crucial to a mission in scenarios such as extended search and rescue and sustained operation. In this regard, DCIEM has been investigating the effects of ingesting various substances to determine their effect on physical performance. Two such substances, caffeine (c) and ephedrine (e) ingested in combination have been shown to enhance physical performance. Before these substances can be used by Canadian Forces personnel it is imperative that no long lasting adverse effects result as a consequence of their ingestion. Therefore, it was the purpose of this paper to look at the effects of an acute ingestion of caffeine, ephedrine and their combination on heart rate and blood pressure variables over an extended period. The results indicated that in non-users of caffeine systolic blood pressure (SBP) passed hypertensive levels (140 mm Hg) and remained at this level for 3 hours after ingesting the combination treatment. SBP levels returned to placebo levels after 8 hours. Although diastolic blood pressure and HR also increased after treatment ingestion, their effects were minimal and dissipated by 24 hours. It appears that in a normo-tensive healthy young individual acute ingestion of a preparation of caffeine, ephedrine or the two in combination would not have long lasting adverse effect on BP and HR.

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