EFFECTS OF CAFFEINE AND CYCLIZINE ALONE AND IN COMBINATION ON HUMAN PERFORMANCE, SUBJECTIVE EFFECTS AND EEG ACTIVITY

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1 The effects of caffeine and cyclizine alone and in combination, on performance tests and subjective ratings have been examined in two groups of twelve volunteer subjects using a balanced design for order of administration of treatments, a lactose control and with double-blind conditions. In the second study the electroencephalograph (EEG) was recorded after subjective ratings. Results were analysed by analysis of variance and values of $P < 0.05$ taken as significant.

2 Caffeine in doses of 75 to 300 mg increased auditory vigilance compared with lactose dummy. Auditory reaction times were shortened, tapping rates increased and subjects felt more alert. No changes occurred in short term memory, arithmetic or digit symbol substitutions. An increase in energy in the delta band (2.3–4 Hz) occurred after caffeine 100 mg.

3 Cyclizine by contrast, produced few changes. Subjects were more alert after 25 mg and more sedated after 100 mg than after dummy. One test only showed impairment: arithmetic, after the 100 mg dose, which also increased energy in the delta frequency band.

4 Combinations of caffeine 100 mg with cyclizine 50 and 100 mg did not produce any subjective changes, or changes in performance tests, differing from lactose. At no time on any test did the performances after combinations of drugs differ from caffeine 100 mg.

5 Performance after both combinations of caffeine and cyclizine differed from that after cyclizine 100 mg on the following tests: vigilance, arithmetic and reaction time, thus showing a tendency for the caffeine effect to predominate. Subjective ratings of sedation after combination of the drugs were intermediate between the ratings following caffeine and cyclizine administered alone.

Introduction

Cyclizine is used as an anti-emetic agent and being chemically related to histamine (H_1) receptor blocking drugs may produce drowsiness (Lederer & Putnam, 1958). However, Brand, Colquhoun & Perry (1968) found that doses up to 100 mg cyclizine failed to impair mental performance or vigilance.

Cyclizine is also combined with caffeine and ergotamine in the treatment of migraine in order to alleviate nausea. The possible drowsiness produced by cyclizine may be prevented by caffeine. Caffeine alone has been extensively studied but the results are inconsistent (Weiss & Laties, 1962). No information is available on the effects of combinations of cyclizine and caffeine given simultaneously. In view of this we have completed two controlled studies on the effects of cyclizine and caffeine alone and in combination on human performance and subjective arousal, and these are presented in this paper.

Methods

Subjects

Two trials were each conducted on twelve healthy volunteers. In trial 1 there were nine women and three men, aged 21–43 years, while five women and seven men, aged 21–32 years, participated in Trial 2. One subject only was common to both trials. They were transported to and from the laboratory by car one day a week for 6 weeks. No caffeine containing beverages were allowed during the pre-trial day. On experimental days they were allowed a light standardised breakfast at home before 08.00 h but no caffeine containing beverages, alcohol or cigarettes until the end of testing.

Procedure and tests

The procedure and tests were the same for both trials. Subjects were studied in the same groups of four on

Tuesdays, Wednesdays or Thursdays at weekly intervals for 6 consecutive weeks. They arrived in the laboratory at 08.45 h and completed a set of visual analogue lines for subjective ratings. At 09.00 h treatments were administered and electrodes placed for heart rate and EEG recording. At 09.45 h subjects entered a soundproof room held at 21°C and divided into four cubicles. They then began a session slightly exceeding 2 h in duration consisting of the following tests in the order given:-

- (1) An auditory vigilance test, lasting 1 h, in which subjects were presented via headphones with tape recorded short tones 0.5 s in duration occurring every 2 s and set in white noise. The signals to be detected were 40 tones 0.4 s in duration with 10 randomly scattered in each 0.25 h of the test. Subjects recorded their detections by pressing buttons (Wilkinson, 1968).
- (2) An arithmetic test consisting of simple additions of five pairs of digits for 0.25 h. The number of sums completed and the number of errors made were counted.
- (3) An auditory reaction time test lasting 0.25 h in which the subject pressed a microswitch as rapidly as possible in response to tones presented via headphones; these occurred with a mean interval of 7 s and varied from 5 to 9 s.
- (4) A short term memory test (STM) lasting 0.25 h in which 90 series of 8 digits are recorded by the subject. The number of individual errors and the number of lines containing an error were counted.
- (5) A digit symbol substitution test (DSST) lasting 90 s (Wechsler, 1955).
- (6) A tapping test lasting 60 s using a microswitch.
- (7) Subjective effects were measured using visual analogue lines (Lader & Norris, 1969) in which the subject records his mental state by marking a series of 100 mm lines indicating dimensions of mental and physical state.
- (8) The EEG was recorded from midline positions Fz and Pz according to the Jasper (1958) notation with an indifferent electrode on the mastoid area. Silver cup electrodes were used and fixed using Grass electrode cream. The EEG was monitored using a Grass polygraph with subjects relaxed and with their eyes closed. A series of tuned filters was used to measure the energy in 10 s epochs, in the following four frequency bands: 2.3–4.0 Hz; 4.0–7.5 Hz; 7.5–13.5 Hz; and 13.5–26 Hz. These correspond approximately to the clinically described frequency bands delta, theta, alpha and beta respectively.

At the same time heart rates were monitored using silver stick-on electrodes to record classical limb lead I.

After the first test session subjects were given a standardized meal followed by a second test session beginning 4 h after treatment.

Drugs

Drugs were prepared in identical gelatin capsules. Each subject received all six treatments given at weekly intervals according to a balanced latin square design and with double-blind conditions. In Trial 1 the following preparations were used: caffeine 75, 150 and 300 mg; cyclizine 25 and 50 mg and lactose dummy. In Trial 2 each subject received: caffeine 100 mg; cyclizine 50 and 100 mg; caffeine 100 mg + cyclizine 50 mg (C100+CY50); caffeine 100 mg + cyclizine 100 mg (C100+CY100) and lactose dummy. Caffeine was in the anhydrous form and cyclizine as its hydrochloride.

Analysis of results

All measured variables were analysed by analysis of variance. The visual analogue line scores were analysed by analysis of variance after arc-sine transformation. The average energy in each frequency band for a series of ten epochs for each subject under different treatment conditions was also submitted to analysis of variance. Means differing by $P < 0.05$ were accepted as significantly different.

Results

Performance tests

Mean values after different treatments together with the significance of differences are summarized in Table 1.

Trial 1

All doses of caffeine significantly increased the number of signals detected over 1 h in the auditory vigilance test compared with lactose except for the 300 mg dose 0.75–1.75 h post treatment. Auditory reaction time tested over 15 min was also significantly shortened by caffeine 75 and 150 mg 2–2.25 h post treatment. Tapping rates increased after caffeine 150 and 300 mg. Values after cyclizine 25 and 50 mg did not differ from those after lactose in these three tests. There were no changes ascribable to treatments in arithmetic, STM or DSST.

Trial 2

In Trial 2 no treatment produced changes in auditory vigilance significantly different from those following lactose. Mean correct detections, however, were higher 0.75–1.75 h and 4–5 h after caffeine than after cyclizine 50 or 100 mg. Neither combination differed significantly from caffeine or lactose but the number

Table 1 Mean values are shown for twelve subjects in each trial after each of six treatments.

Test	Time after treatment (h)	Trial 1												Time after treatment (h)	Trial 2											
Vigilance (Detections/h)	0.75-1.75	21.3 CY50	22.4 L	22.7 CY25	26.6 C300	27.4 C150	28.8 C75						4-5	19.2 L	20.5 CY25	20.8 CY50	24.7 C75	25.7 C150	29.9 C300							
Arithmetic (Sums/15 min)	1.75-2	68.1 CY25	69.8 CY50	70.6 C75	71.6 L	75.4 C300	77.3 C150						5-5.25	69.2 CY25	72.9 L	75.1 CY50	75.1 C75	78.1 C300	79.8 C150							
Reaction time (ms)	2-2.25	235.4 C150	237.0 C75	238.8 C300	257.3 CY50	257.4 CY25	257.9 L						5.25-5.5	242.8 C150	245.1 C300	248.9 C75	253.5 CY25	257.8 CY50	281.1 L							
Short term memory (No. of errors)	2.25-2.5	42.3 C150	47.5 CY50	47.9 L	48.2 C300	51.0 C75	53.2 CY25						5.5-5.75	39.0 C150	41.0 C300	41.9 L	44.9 CY50	53 CY25	53.9 C75							
DSST (Substitutions/90s)	2.55	77.8 L	78.0 C75	79.4 CY50	79.9 CY25	80.3 C150	80.5 C300						5.8	80.9 L	81.0 C75	81.7 CY25	82.2 C150	82.9 C300	83.4 CY50							
Tapping (Taps/min)	2.6	338.5 CY25	340.4 L	341.1 CY50	350.7 C75	352.3 C150	352.5 C300						5.85	338.1 CY50	340.6 CY25	350.2 L	350.4 C75	357.1 C300	362.4 CY50							
Vigilance (Detections/h)	0.75-1.75	14.2 CY100	16.4 CY50	16.7 L	17.5 C100+	18.0 C100+	19.7 C100						4-5	11.5 CY100	13.1 CY50	14.7 C100+	14.8 CY50	14.9 L	16.8 C100							
Arithmetic (Sums/15 min)	1.75-2.0	63.1 CY100	65.7 CY0500	66.3 L	68.5 C100+	71.4 C100	71.6 C100+						5-5.25	62.4 CY100	64.8 CY50	67.6 L	71.0 C100	71.3 C100+	72.3 CY50							
Reaction time (ms)	2-2.25	249.7 C100+	250.3 C100+	258.8 C1001	259.6 L	272.9 CY50	280.8 CY100						5.25-5.5	246.9 C100+	259.8 C100+	272.2 C100	284.4 C100	296.9 CY50	299.4 CY50							
Short term memory (No. of errors)	2.25-2.5	43.8 C100	51.6 C100+	54.8 CY50	55.8 L	62.1 CY50	68.7 CY100						5.5-5.75	48.2 C100	50.3 C100	57.3 L	57.7 CY100	58.7 CY50	65.4 C100+							
DSST (Substitutions/90s)	2.55	80.7 CY100	81.3 C100+	82.0 CY50	82.6 L	84.0 C100	85.3 C100+						5.8	82.4 CY50	83.1 L	83.9 CY100	84.3 C100+	86.1 C100+	86.6 CY50							
Tapping (Taps/min)	2.6	354.3 CY100	357.0 CY50	357.3 L	358.4 C100+	373.2 C100	373.8 CY50						5.85	358.9 L	365.1 CY50	371.3 CY100	373.2 C100	374.2 C100+	375.2 CY50							

L, lactose dummy; cyclizine hydrochloride 25, 50 and 100 mg, CY25, 50 and 100 respectively; caffeine (anhydrous) 75, 100, 150 and 300 mg, C75, 100, 150 and 300 respectively; caffeine 100 mg with cyclizine 50 mg or 100 mg, C100+CY50 and C100+CY100 respectively. Means not significantly different ($P > 0.05$) are underlined by a common bar. Means not underlined by a common bar are significantly different ($P < 0.05$).

of detections was higher 0.75–1.75 h after both combinations than after cyclizine 100 mg.

No differences occurred in reaction time between active drugs and lactose. Mean values were longer after cyclizine 50 and 100 mg than lactose, but they differed significantly only from the lowest values obtained after treatment with the two combinations. The effects of both combinations were similar to caffeine alone such that reaction times did not differ from caffeine or lactose but were significantly shorter than after cyclizine 100 mg 2–2.25 h post treatment. By 5.25–5.50 h after treatment reaction times were shorter following C100 + CY50 compared with cyclizine 50 and 100 mg and following C100 + CY100 compared with cyclizine 50 mg.

No significant treatment effects occurred in the first session of the arithmetic tests, but 5–5.25 h after cyclizine 100 mg the number of sums completed was reduced compared with lactose, caffeine and both combinations. This was the only performance test in which cyclizine differed significantly from lactose. There were also less sums completed after cyclizine 50 mg than after caffeine 100 mg or the combinations.

Tapping rates were lower 2.6 h after cyclizine 100 mg compared with caffeine 100 mg and C100 + CY50. The same pattern was true for STM. In addition the number of errors made in STM was higher 2.25–2.5 h after both doses of cyclizine than after caffeine 100 mg.

There were no treatment effects in DSST.

Subjective effects

These are shown in Table 2.

In Trial 1 subjects were significantly more alert, using the mental sedation score, 2.7 h after all doses of caffeine and also after cyclizine 25 mg. Ratings of increased alertness were still present at 6 h after caffeine 150 and 300 mg. Ratings of physical sedation were similar after caffeine.

In Trial 2 subjects were significantly more alert and had lower ratings for physical sedation 2.7 h after caffeine 100 mg than after lactose. Six hours after treatment only the rating of physical sedation remained significant. The only significant effect after cyclizine was increased mental sedation at 6 h after the 100 mg dose. Ratings following combinations of caffeine and cyclizine were usually intermediate between values obtained for the individual drugs. At no time on either rating did values after combination differ from those obtained after lactose.

Heart rate

There were no treatment effects on heart rate in either trial.

EEG effects

These are shown in Table 2.

Due to an undetected fault in a tape recorder, many of the EEG readings of Trial 1 were lost.

In Trial 2 the energy in the delta frequency band was greater 2.8 h after cyclizine 100 mg and caffeine 100 mg than after lactose, cyclizine 50 mg and both caffeine/cyclizine combinations 2.8 h after treatment. By 6.1 h the energy in the delta band was still significantly higher after cyclizine 100 mg compared with cyclizine 50 mg and the combinations but not lactose. In the theta band energy was lower after the combinations compared with both lactose and cyclizine 100 mg 2.8 h after treatment and also after caffeine 100 mg compared with cyclizine 100 mg at this time. There were no treatment differences 6.1 h after treatment in the theta bands or at any time in the alpha and beta bands.

Discussion

These results show that caffeine improved auditory vigilance, reaction time and tapping rates. The results of early investigations on caffeine effects on performance are conflicting. Payne & Hauty (1954) found the onset of fatigue slower after caffeine 20 mg (salt not stated) in a vigilance test. As early as 1912 Hollingworth reported that caffeine 300 mg (base) reduced reaction times. Gilliland & Nelson (1939) also found reaction times were reduced after one to two cups of coffee. Later, in more controlled studies, Knowles (1963) and Franks, Hagendorn, Hensley, Hensley & Starmer (1975) recorded reaction times after caffeine 250 and 300 mg (base)/70 kg, which were shortened but not significantly different from placebo. In Trial 1 we obtained significant decrements in reaction time after caffeine 75–300 mg but in Trial 2 the observed decrement after caffeine 100 mg did not differ significantly from that following lactose. Since only the subjects varied between the two trials these results are probably indicative of considerable subject variation in sensitivity to caffeine, an observation previously made by Goldstein, Warren & Kaiser (1965). Alternatively, subjects in Trial 1 received three caffeine doses and may have come to expect to feel alert whereas in Trial 2 they did not note alertness on most occasions and may have been less reactive to the single caffeine 100 mg dose.

Increased tapping rates after caffeine have been reported by Gilliland & Nelson, (1939), Holck & Smith (1939), Lehman & Csank (1957) but Flory & Gilbert (1943) found no effect after 324 mg caffeine citrate. In the present study tapping rates were increased by caffeine 150 and 300 mg, but not 75 or 100 mg. Tapping requires muscular work and since caffeine is known to strengthen and prolong the

Table 2 Values for mental and physical sedation were derived from visual analogue scales 100 mm long. Mental sedation was derived by summation of alert-drowsy, clear headed-muzzy, attentive-drowsy, quick witted-mentally slow; physical sedation by summation of strong-feeble, lethargic-energetic, proficient-incompetent and well co-ordinated-clumsy. Scores were transformed using arc sine transformation. Values are given in radians and ranked in order of increasing sedation. The EEG energy in the different frequency ranges shown for Trial 2 are given as means for twelve subjects and over 20, 10 s epochs for each subject. The energy in each frequency band is expressed using an arbitrary scale which can range between 0 and 255. The frequency bands were: delta 2.3–4 Hz, theta 4–7.5 Hz, alpha 7.5–13.5 Hz and beta 13.5–26 Hz.

(a) Subjective effects	Time after treatment (h)		Time after treatment (h)	
	2.7	Trial 1	6	
Mental sedation	0.64 0.67 0.72 0.74 0.85 0.91 C300 C150 C75 CY25 LAC CY50		0.68 0.75 0.77 0.83 0.83 0.85 C300 C150 C75 CY25 L CY50	
Physical sedation	0.66 0.67 0.72 0.77 0.81 0.86 C300 C150 C75 CY25 L CY50		0.68 0.73 0.75 0.81 0.81 0.85 C300 C75 C150 L CY25 CY50	
Subjective effects				
	2.7	Trial 2	6	
Mental sedation	0.61 0.74 0.81 0.83 0.85 0.93 C100 C100+ L C100+ CY50 CY100		0.72 0.80 0.83 0.84 0.86 0.95 C100 C100+ L C100+ CY100	
Physical sedation	0.61 0.74 0.79 0.82 0.82 0.90 C100 C100+ L CY50 C100+ CY100		0.72 0.80 0.81 0.82 0.85 0.91 C100 C100+ C100+ CY50 L CY100	
(b) Energy in EEG frequency band				
	2.8	Trial 2	6.1	
Delta	51.9 52.1 54.1 54.7 57.0 60.3 C100+ C100+ L CY50 C100 CY100		51.4 54.8 55.1 56.0 56.7 59.5 C100+ CY50 C100+ C100 L CY100	
Theta	67.6 67.8 70.8 72.8 75.4 76.6 C100+ C100+ C100 CY50 L CY100		68.3 72.0 72.2 73.2 75.0 76.3 C100+ C100+ C100 CY50 CY100 L	
Alpha	102 103 108.7 110 112.8 126.5 C100+ CY100 CY50 C100+ C100 L		100.3 111 114.8 121.1 123.3 125.4 CY100 C100+ CY50 L C100+ C100	
Beta	53.7 57.1 57.2 57.2 57.5 60.6 C100+ C100 C100+ CY100 CY50 L		57.7 58.0 60.0 60.4 60.5 60.6 CY100 C100+ CY50 C100 C100+ L	

Abbreviations indicating treatments are the same as Table 1. Means which are not significantly different ($P > 0.05$) are underlined by a common bar. Means which do differ ($P < 0.05$) are not underlined by a common bar.

contraction of isolated skeletal muscle (Huidobro, 1945; Goffart & Ritchie, 1952) caffeine effects on tapping may be due to a peripheral action. However, since these effects occur with doses also producing subjective arousal, peripheral effects and central stimulation cannot be separated.

Performance was unaffected by cyclizine 25 and 50 mg. Cyclizine 100 mg tended to impair performance but this achieved significance only in the arithmetic test 5 h after treatment. Brand *et al.* (1968) found no impairment in either an audiovisual checking test or a 2 figure addition test following doses of cyclizine between 15 mg and 100 mg.

Combinations of caffeine and cyclizine gave either intermediate values not differing from lactose or values similar to caffeine alone. This finding contrasts with those of Franks *et al.* (1975) who studied the interactions of caffeine with ethanol. In various perceptual and cognitive tests caffeine failed to antagonize the ethanol induced decrement in performance. Only in auditory reaction time did caffeine partially reverse the prolongation produced by ethanol.

Subjective arousal after caffeine 150–300 mg has

been reported (Barmack, 1940; Goldstein, Kaiser & Warren, 1965) although Knowles (1963) claimed no subjective effects occurred after 250 mg caffeine (as the base). Our results showed subjective arousal after all doses of caffeine including Trail 2 where effects on performance tests were not significant.

Lederer & Putnam (1958) reported moderate-severe drowsiness in 14 of 100 volunteers given cyclizine 50 mg, Brand, Colquhoun, Gould & Perry (1967) also found an increase in the proportion of subjects complaining of drowsiness after cyclizine 15–100 mg. Our results indicate that subjective drowsiness is minimal after doses of 50 mg and only important at doses of 100 mg. The pattern of changes in subjective ratings after the combinations was similar to those seen in the performance tests.

In conclusion caffeine improved auditory vigilance, reaction time and tapping, but cyclizine up to 100 mg produced no significant difference from lactose except reduced arithmetic at 5 h. Cyclizine tended to impair performance however, and combinations of the two active drugs gave either intermediate values not differing from lactose, or values similar to caffeine given alone.

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