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A comparison of the central nervous system effects of caffeine and theophylline in elderly subjects

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1 The effects of oral administration of 250 mg caffeine or theophylline and placebo on subjective ratings and psychological test performance were studied in a double-blind crossover experiment in 20 healthy elderly subjects.
2 Performance on the continuous attention task showed a significant improvement compared with placebo with both active treatments. Performance with caffeine was significantly better than with theophylline. Mean error index scores (normalised AUCs) were: placebo − 0.130; caffeine − 0.083; theophylline − 0.093. No other objective measure shows significant treatment effects.
3 Subjective ratings showed that subjects felt significantly more alert on caffeine than on either theophylline or placebo. Subjects also rated themselves as more energetic and interested on caffeine than on placebo.
4 Plasma concentrations of caffeine were lower than those of theophylline (mean 5.76 and 8.72 mg l^{-1} respectively at 2 h post-drug.
5 These results suggest that caffeine is a more potent CNS stimulant than theophylline.

Keywords caffeine theophylline attention visual analogue scales psychomotor performance

Introduction

Theophylline, widely used as a bronchodilator, has undesirable central nevous system effects, such as restlessness, tremor, insomnia, and convulsions at high doses, which are consistent with known pharmacological properties of methylxanthine compounds (Rall, 1985). Caffeine, another methylxanthine, is a central stimulant found in coffee, tea, cocoa, as well as in some soft drinks and a number of over-the-counter medications. At low levels, caffeine improves alertness and attention in adults while inducing insomnia and tremor at higher levels (Bruce & Lader, 1986). A recent study suggests that healthy elderly subjects may be more sensitive than the young to the effects of caffeine on psychological test performance, but that the reverse is true for subjective assessments such as alertness (Swift & Tiplady, 1988).

Although theophylline is widely used in the elderly, there have been no studies investigating the effects of theophylline on performance tests in this age group. Theophylline has been shown to antagonise diazepam-induced impairment of psychomotor performance in young healthy volunteers (Henaauer *et al.*, 1983), and to improve performance on a prolonged auditory vigilance task (Tiplady *et al.*, 1990).

Caffeine and theophylline are generally supposed to be approximately equipotent in their CNS effects (Rall, 1985). However no direct comparison of their stimulant effects has been made in human subjects. Caffeine appears to be an effective bronchodilator, but to be somewhat less potent than theophylline (Becker *et al.*, 1984; Simons *et al.*, 1984).

The present study is a comparison of the CNS effects of the two xanthines in the elderly using performance and subjective measures which have previously been shown to be sensitive to the effects of caffeine in older adults, *viz* the continuous attention task, choice reaction time, and a visual analogue rating of alertness (Swift & Tiplady, 1988). Other standard performance tasks were included, as it is desirable to assess a broad range of abilities in studies of this type. The dose chosen was 250 mg, which is in the range where stimulant effects of caffeine can be demonstrated without the likelihood of toxic symptoms such as tremor or headache, which might interfere with test performance (American Psychiatric Association, 1980). Performance was assessed over a 3 h period. Both drugs attain peak plasma concentrations within 1–2 h after an oral dose, and have half-lives in excess of 5 h (Becker *et al.*, 1984; Blanchard *et al.*, 1983; Bruce *et al.*, 1986).

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Methods

Twenty elderly volunteers were recruited for the study. One subject was unable to attend the third session for reasons unrelated to the study, and data have been analysed for the 19 complete subjects. They were aged 60–77 years (mean 67) and weighed 45–84 kg (mean 64.5). Subjects were free of serious illness, were non-smokers, and consumed no more than seven cups of tea or coffee per day, and 10 units per week of alcohol. No subject was on any psychotropic medication. One subject was taking allopurinol and another ranitidine. Subjects gave written informed consent, and the study was approved by the Camberwell Ethics Committee.

The study used a three-period crossover design in which subjects received single oral doses of caffeine, theophylline or placebo in a randomised sequence. The study was carried out double-blind. At least 7 days elapsed between sessions. The following measures of performance were used:

Continuous attention task

In this measure of concentrated attention, a series of geometric patterns was flashed on a screen, each pattern being shown for 0.1 s, the interval between patterns being 1.5–2.5 s. The task was to respond whenever two consecutive patterns were the same. A total of 240 presentations with 40 repetitions was used at each time-point (Tiplady, 1985, 1988). The total number of correct (NC) and incorrect (NI) response was recorded, and the error index (EI) calculated as EI = (1-NC/40) + NI/100 (Pigache, 1976).

Choice reaction time

Psychomotor speed was determined using the six-choice reaction time test from the Leeds Psychomotor Tester. For each reaction, latency (the time before movement is initiated) and total reaction time are obtained (Frewer & Hindmarch, 1988).

Critical flicker fusion threshold

The critical frequency at which a flickering visual stimulus just appeared to be steady, and below which it appeared to flicker, was determined using the critical flicker fusion apparatus of the Leeds Tester (Hindmarch, 1975; Turner, 1968). This measure of central processing speed is widely used as an indicator of arousal level.

Digit-symbol substitution test

In this pencil-and-paper test of psychomotor speed, there was a key which matched nine symbols to the digits 1–9. A series of random numbers was printed in a grid on the sheet, and the subject wrote the corresponding symbol under each digit, as fast as possible. The number of correct and incorrect symbols written in 90 s was recorded (Wechsler, 1958).

Symbol-digit substitution test

In this automated version of the previous test, the subject observed a key on the screen which associated nine symbols with the digits 1–9. A series of symbols appeared, and the subject responded by pressing the appropriate number key on the computer keyboard as quickly as possible. The number of correct and incorrect responses over 90 s was taken.

Visual vigilance task

In this measure of vigilance, subjects observed a constantly changing random pattern of dots resembling a snowstorm on a monitor screen. At intervals a dark square gradually appeared in one quarter of the screen. The subject pressed a button to indicate the location of the square as soon as possible. The total number of correct and incorrect responses over 5 min was recorded.

Paired-word association test

In this test of verbal memory, the subject was presented with three word pairs of a high degree of association on the screen. The first word of each pair was then shown three times in random order. On each occasion the subject attempted to recall the second word of the pair. The test was repeated with three word pairs of moderate association, and finally with three pairs of low association, giving a total of 27 trials. The numbers of correct responses and errors were recorded (Isaacs & Walkey, 1964; Tiplady, 1985).

Visual analogue scales

Subjective changes were recorded using a series of 10 cm lines, the ends of which were marked: Alert–Drowsy; Interested–Bored; Lethargic–Energetic; Tense–Relaxed. The subject made a mark across the line to indicate how she/he felt at the time. The position of each mark was measured in mm from the left extreme, corresponding to the first adjective of the pair.

Procedures

Each subject first took part in a familiarisation session to minimise any practice effects on the tests. For each test day, subjects were instructed to abstain from alcohol and caffeine for 24 h before the tests until the end of all procedures.

Testing commenced at about 09.00 h. The full battery of tests was given, followed by an oral dose of either 250 mg caffeine, 250 mg theophylline, or placebo, in matching capsules. The continuous attention task and visual analogue scales were administered at 30, 60, 90, 120 and 180 min post-drug. The full battery of tests was repeated between 60 and 120 min post-drug.

Venous blood (5 ml) was taken before drug administration and at 3 and 4 h post-drug for determination of theophylline and caffeine concentrations. The samples were placed in heparinised tubes, centrifuged at 1600 *g* for 10 min, and the plasma taken off and stored at −20° C until analysis. All samples were assayed for caffeine and theophylline using a high-performance

liquid chromatographic method within 4 months of collection.

Statistical analysis

All measures were analysed with Friedman ANOVA. A nonparametric analysis was considered appropriate since data from psychometric tests are in general not normally distributed. A preliminary examination of the data indicated that no significant effect of treatment order was occurring, and it was therefore not considered necessary to include this in the analysis. Where a significant effect among treatments was obtained the ANOVA was followed by pairwise comparisons as described by Conover (1980). The critical level of significance used was 0.05.

Where tests were only administered once post-drug, the Friedman was applied to this post-drug score. In the case of the continuous attention task and visual analogue scales, repeated assessment was carried out, and testing was applied to the area under the dose response curve (AUC 0, 3). For convenience the AUCs were divided by the time (180 min) to give normalised value that could be compared directly to the pre-drug scores (Matthews, 1990). No baseline correction was applied to the data (Fleiss, 1986).

Results

Data from the pre- and post-drug assessments are shown in Table 1. There was a significant effect on both drugs on performance on the continuous attention task ($P < 0.01$). Pairwise comparisons showed that both drug conditions gave lower error scores than placebo, and that caffeine produced a greater reduction than theophylline. Results from choice reaction time were not significant, though there was a trend towards faster responses in the two active conditions. No other objective

Table 1 Results from performance measures and visual analogue scales before and after oral administration of placebo (P), 250 mg caffeine (C) or 250 mg theophylline (T). Data are shown as mean (s.d.)

	Before treatment			*After treatment*		
	P	*C*	*T*	*P*	*C*	*T*
Continuous attention task						
Error index	0.129 (0.011)	0.118 (0.098)	0.129 (0.140)	0.130 (0.092)	0.083 (0.053)	0.093 (0.057)[a]
Critical flicker fusion						
Frequency (Hz)	27.7 (3.1)	28.0 (4.2)	27.3 (3.6)	26.4 (3.4)	27.1 (3.6)	26.9 (3.1)
Choice reaction time (ms)						
Latency	0.538 (0.194)	0.549 (0.174)	0.551 (0.200)	0.587 (0.241)	0.552 (0.166)	0.545 (0.148)
Motor time	0.297 (0.094)	0.282 (0.057)	0.311 (0.104)	0.293 (0.087)	0.270 (0.078)	0.279 (0.062)
Total time	0.836 (0.220)	0.831 (0.191)	0.863 (0.291)	0.880 (0.270)	0.822 (0.195)	0.824 (0.165)
Paired word association						
Number correct	25.3 (2.2)	25.1 (2.6)	25.1 (2.0)	23.9 (2.2)	24.7 (2.4)	24.4 (2.3)
Digit-symbol substitution						
Number correct	48.1 (8.6)	48.1 (7.9)	47.9 (7.0)	49.7 (8.9)	51.1 (8.6)	51.1 (6.3)
Symbol-digit substitution						
Number correct	40.9 (5.2)	40.1 (5.9)	39.6 (5.7)	39.7 (4.5)	40.8 (5.7)	39.6 (4.7)
Visual vigilance						
Number correct	18.9 (3.5)	18.6 (2.6)	18.2 (2.5)	19.0 (3.0)	18.7 (3.4)	18.5 (2.8)
Visual analogue scales (mm)						
Alert–Drowsy	32.8 (27.5)	44.8 (28.9)	38.7 (26.8)	48.2 (25.0)	31.5 (20.9)	38.1 (18.3)[b]
Interested–Bored	26.6 (26.2)	27.1 (25.4)	26.9 (26.6)	36.8 (23.9)	28.7 (19.9)	31.1 (20.8)[c]
Lethargic–Energetic	71.6 (23.8)	64.7 (24.7)	61.1 (28.6)	54.7 (20.1)	68.7 (17.8)	65.9 (17.1)[d]
Tense–Relaxed	68.1 (27.9)	72.8 (26.4)	69.8 (27.4)	73.8 (20.6)	71.3 (20.1)	68.6 (18.8)

[a] Friedman ANOVA showed statistical significance between treatments ($P < 0.01$) and pairwise comparisons showed significant differences between P *vs* T; P *vs* C; and T *vs* C.

[b] Friedman ANOVA showed statistical significance between treatments ($P < 0.01$) and pairwise comparisons showed significant differences between P *vs* C; T *vs* C; but not between P *vs* T.

[c] Friedman ANOVA showed statistical significance between treatments ($P < 0.01$) and pairwise comparisons showed significant differences between P *vs* C; but not between P *vs* T or T *vs* C.

[d] Friedman ANOVA showed statistical significance between treatments ($P < 0.05$) and pairwise comparisons showed significant differences between P *vs* C; but not between P *vs* T or T *vs* C.

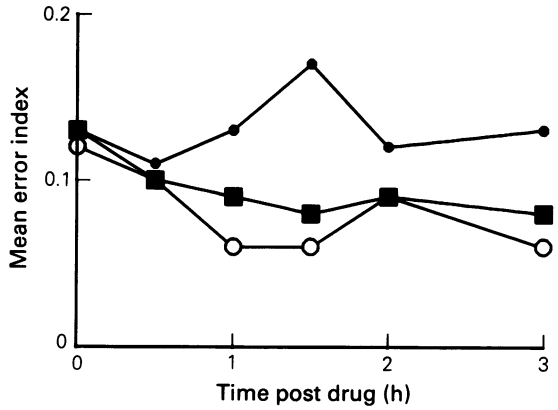

Figure 1 Effects of caffeine (○) and theophylline (■) compared with placebo (●) on performance on the continuous attention task. Data are expressed as mean error index for each time-point.

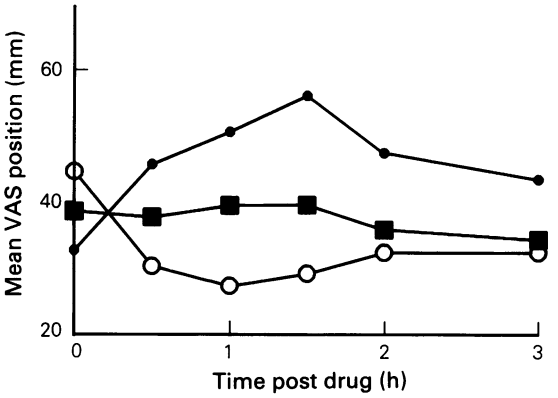

Figure 2 Subjective effects of caffeine (○) and theophylline (■) as compared with placebo (●). Data from the alert–drowsy visual analogue scale are expressed as mean position along the line in mm. Increases in value represent changes in the direction of drowsiness.

measure showed any evidence of treatment effect. The alert-drowsy visual analogue scale showed a significant treatment effect ($P < 0.01$). Pairwise comparisons in this case showed caffeine to lead to greater alertness than either placebo or theophylline – no significant difference was found between theophylline and placebo although there was a trend in the expected direction. Caffeine was also associated with greater interest ($P < 0.01$) and energy ($P < 0.05$) than placebo. In both cases the pairwise comparisons showed a significant difference between placebo and caffeine, but neither the placebo-theophylline nor theophylline-caffeine differences proved significant. No significant effects were observed for the calm–tense scale.

The time course of the effects on the continuous attention task and the alert–drowsy visual analogue scale are shown in Figures 1 and 2. These are broadly as expected from the pharmacokinetics of the drugs, with maximum placebo-drug differences being seen at 1–1.5 h. Data for the placebo session were not constant, but showed increasing drowsiness and a fall-off in performance during the morning, with a peak at 1.5 h post-drug.

Plasma drug concentrations are shown in Figure 3. The concentrations of theophylline were rather higher than for caffeine. Values at 4 h were only slightly lower

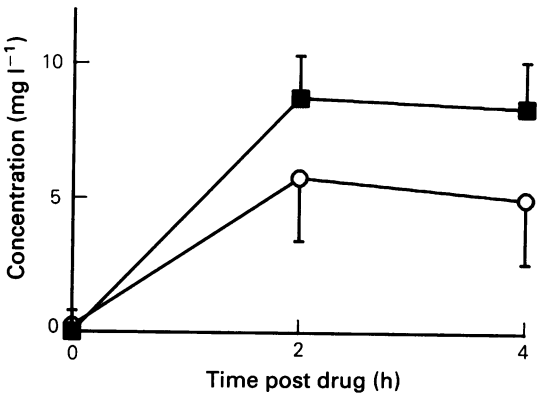

Figure 3 Plasma concentrations of caffeine (○) and theophylline (■) after oral administration of 250 mg. Data are plotted as means with error bars indicating standard deviations.

than at 2 h, as would be expected with a half-life of more than 5 h.

Discussion

These results show that the CNS effects of caffeine and theophylline can be demonstrated in elderly subjects. The three measures previously shown to be capable of detecting the effects of caffeine in the elderly showed trends in the expected direction, and these were significant for both caffeine and theophylline on the attention task and for caffeine on alertness. The attention task would be expected to be more sensitive in this context, since it was carried out five times over the test period, while the choice reaction time was assessed only once.

The observed drug effects do not occur against a constant baseline. The placebo curve shows a marked deterioration of attention at about the mid-point of the period. This may relate to a decline in interest during the session. Thus part of the effect of the stimulant will be reversal of a decline in performance that would otherwise occur. In young subjects, virtually all of the effects of caffeine may be accounted for in this way (Fagan *et al.*, 1988).

Taken together, these results suggest that caffeine is a more potent CNS stimulant on a dose-for-dose basis than theophylline. For both the continuous attention task and the alert–drowsy scale, caffeine produced significantly greater effects, and the trend was similar on the other subjective measures.

The plasma drug concentrations obtained for caffeine were lower than those for theophylline, suggesting that the greater stimulant effect of caffeine cannot be explained by pharmacokinetic factors. The mean concentration of theophylline obtained (8.72 mg l^{-1} at 2 h) was in the range for effective bronchodilatation, but slightly less than the normally accepted therapeutic range. (10–20 mg l^{-1}; Rall, 1985).

Theophylline and caffeine are very similar in their pharmacological profiles. The stimulant effects of both drugs are believed to be related to adenosine receptor inhibition (Spealman, 1988), and both are effective bronchodilators (Becker *et al.*, 1984; Simons *et al.*,

1984). In the latter study, comparable bronchodilator effects were shown in children with caffeine and theophylline, while the plasma concentration of caffeine was about 50% higher. Although dose-response curves would be desirable to obtain an accurate estimation of the relative potencies of the two drugs, the available data suggest a dissociation of the two effects, with caffeine the more potent stimulant, and theophylline the more potent bronchodilator. Although the studies were carried out in different age groups, the relative potencies of agents with essentially similar actions is unlikely to be affected.

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References

American Psychiatric Association (1980). *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition).

Becker, A. B., Simons, K. J., Gillespie, C. A. & Simons, F. E. R. (1984). The bronchodilator effects and pharmacokinetics of caffeine in asthma. *New Engl. J. Med.*, **310**, 743–746.

Blanchard, J. & Sawers, J. A. (1983). Comparative pharmacokinetics of caffeine in young and elderly men. *J. Pharmacokin. Biopharm.*, **11**, 109–126.

Bruce, M., Scott, N., Lader, M. & Marks, V. (1986). The psychopharmacological and electrophysiological effects of single doses of caffeine in healthy human subjects. *Br. J. clin. Pharmac.*, **22**, 81–87.

Bruce, M. S. & Lader, M. H. (1986). Caffeine: clinical and experimental effects in humans. *Human Psychopharmacology*, **1**, 63–82.

Conover, W. J. (1980). *Practical nonparametric statistics*, 2nd edition, p. 304. New York: Wiley.

Fagan, D., Swift, C. G. & Tiplady, B. (1988). Effects of caffeine on vigilance and other performance tests in normal subjects. *J. Psychopharmacology*, **2**, 19–25.

Fleiss, J. L. (1986). *The design and analysis of clinical experiments*, p. 271. New York: Wiley.

Frewer, L. J. & Hindmarch, I. (1988). The effects of time of day, age, and anxiety on a choice reaction task. In *Psychopharmacology and reaction time*, eds Hindmarch, I., Aufdembrinke, B. & Ott, H. pp. 103–114. Chichester: Wiley.

Henaauer, S. A., Hollister, L. E., Gillespie, H. K. & Moore, F. (1983). Theophylline antagonises diazepam-induced psychomotor impairment. *Br. J. clin. Pharmac.*, **25**, 743–747.

Hindmarch, I. (1975). A 1,4-benzodiazepine, temazepam (K3917), its effect on some psychological parameters of sleep and behaviour. *Arzneimittel-Forschung (Drug Research)*, **25**, 1836–1839.

Isaacs, B. & Walkey, F. A. (1964). A simplified paired-associate test for elderly hospital patients. *Br. J. Psychiat.*, **110**, 80–83.

Matthews, J. N. S., Altman, D. G., Campbell, M. J. & Royston, P. (1990). Analysis of serial measurements in medical research. *Br. med. J.*, **300**, 230–235.

Pigache, R. M. (1976). Comparison of scoring methods for tests of attention, including an error index for use with schizophrenic patients. *Perceptual and Motor Skills*, **42**, 243–253.

Rall, T. W. (1985). Central nervous system stimulants. The methylxanthines. In *The pharmacological basis of therapeutics*, 7th Edn, eds Gilman, A. G., Goodman, L. S., Rall, T. W. & Murad, F. pp 589–603. New York: MacMillan.

Simons, F. E. R., Simons, K. J. & Becker, A. B. (1984). The bronchodilator effects and pharmacokinetics of caffeine, theobromine and theophylline in asthma. In *Sustained release theophylline in the treatment of CRAO*, eds Jonkman, J. H. G. *et al.* Amsterdam: Excerpta Medica.

Spealman, R. D. (1988). Psychomotor stimulant effects of methylxanthines in squirrel monkeys: relationship to adenosine antagonism. *Psychopharmacology*, **95**, 19–24.

Swift, C. G. & Tiplady, B. (1988). The effects of age on the response to caffeine. *Psychopharmacology*, **94**, 29–31.

Tiplady, B. (1985). An automated test battery for the detection of changes in mental function and psychomotor performance. *Br. J. clin. Pharmac.*, **20**, 305P.

Tiplady, B. (1988). A continuous attention test for the assessment of the acute behavioural effects of drugs. *Psychopharmacology Bulletin*, **24**, 213–216.

Tiplady, B., Fagan, D., Lamont, M., Brockway, M. & Scott, D. B. (1990). A comparison of the CNS effects of enproffyline and theophylline in healthy subjects assessed by performance testing and subjective measures. *Br. J. clin. Pharmac.*, **30**, 55–61.

Turner, P. (1968). Critical flicker frequency and centrally acting drugs. *Br. J. Ophthalmol.*, **52**, 245–250.

Wechsler, D. (1958). *The measurement and appraisal of human intelligence*, 4th edition. Baltimore: Williams and Wilkins.

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