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Effects of a μ-opioid receptor agonist (codeine phosphate) on visuo-motor coordination and dynamic visual acuity in man

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1 Effects of codeine (30, 60 and 90 mg) on visuo-motor coordination and dynamic visual acuity, together with critical flicker fusion, digit symbol substitution, complex reaction time and subjective assessments of mood, were studied from 0.75–2.0 h after ingestion by six healthy female adults. The study was double-blind and placebo controlled, and triprolidine (10 mg) was used as the active control.

2 The effect on visuo-motor coordination was limited and was dose related and linear, and performance was altered on visuo-motor coordination with 60 and 90 mg codeine, and on dynamic visual acuity with 90 mg codeine ($P < 0.05$). No other effect of codeine was detected.

3 Modulated neuromuscular function is likely to be the common denominator of the changes in performance with codeine, though nausea, but not sedation, may be a contributory factor. It is possible that altered performance with codeine may involve interactions with different receptors than those which lead to sedation.

Keywords codeine performance sedation nausea

Introduction

Opioid drugs often possess analgesic activity and this is believed to involve μ, κ or possibly δ receptors within the brain or spinal cord. However, there are also effects of these drugs on respiration, body temperature, pupil diameter, arousal and mood, and these may also involve opioid receptors, though the precise nature of the interactions has not been established. It is in the context of altered neuromuscular activity, in particular that of the oculomotor system as reported by Griffiths *et al.* (1984) and Rothenberg *et al.* (1980a), that we have studied the effects of codeine, a μ-receptor agonist, on visuo-motor coordination and dynamic visual acuity in man.

Methods

Subjects

Six healthy females with ages from 19 to 30 (mean 23.8) years, and weighing from 51.0 to 72.0 (mean 61.3) kg were used. Subjects were not involved with any other drug therapy except possibly the use of oral contraceptives. Subjects were non-smokers, and no alcohol, or beverages containing stimulants, were taken from 18.00 h on the evening preceding the day of experiment. Subjects retired to bed at their normal times the night before, and on the day of the experiment had a light breakfast at least 1 h before ingestion of tablets.

Performance

Several measures of performance were used, and subjects were trained on the tasks until they had reached steady performance to reduce, as far as possible, any subsequent learning effect.

Visuo-motor coordination (VMC) Subjects were required to position a spot inside a randomly moving circle displayed on an oscilloscope, and the movement of the spot was controlled by a

hand-held stick. An error signal proportional to the distance between the spot and the centre of the circle controlled the difficulty of the task by modulating the mean amplitude of the movement of the circle. The position of the circle and spot, and so the radial error, were recorded. Each tracking run lasted 10 min, a plateau performance was reached within 100 s after the beginning of each run, and the mean amplitude of the task over the final 500 s of each run was the performance score (Borland & Nicholson, 1974).

Dynamic visual acuity (DVA) Acuity was measured using Landolt ring targets with critical detail ranging from 1–10 min of arc projected on to a curved screen by a mirror galvanometer placed at its centre of curvature. The images swept from right to left at a constant velocity of 0.75 or 1.19 rad s^{-1}. An experimental run consisted of eight trials, each of 10 target sizes, at each of the two angular velocities (160 presentations in all). Targets were viewed with the preferred eye. A buzzer warned of each presentation and the subject had to indicate, within 1 s after completion of the target sweep, the position of the gap in the ring. Subjects were required to respond only if certain of the orientation. The number of correct responses and the response time for correct responses for each target size were recorded. The total number of correct responses for all target sizes, and the mean response time for correct responses for the five largest target sizes were calculated (Nicholson *et al.*, 1982).

Complex reaction time (CRT) Reaction time was recorded using a console with 10 buttons arranged in a line. The buttons were illuminated in a random order and, using the preferred hand, subjects were required to cancel each presentation. A test consisted of 30 presentations, and mean reaction time for the last 20 were recorded.

Critical flicker fusion (CFF) Subjects were adapted to the lighting intensity of the room for 3 min, and the flicker fusion threshold was assessed using a central flickering field superimposed on a concentric background. Both fields were generated by green light-emitting diodes, and were in Maxwellian view and appeared at optical infinity. They were viewed monocularly, with the preferred eye, through an artificial pupil which ensured a constant retinal illumination. Fixation cross-wires kept the retinal location of the stimulus constant. The flickering light was presented for 2 s at 16 Hz (lower than the possible fusion point) and the frequency was altered stepwise according to the pattern of response. Fusion threshold was defined as the lowest frequency at which 50% or more of the last 25 responses were considered to be fused (Simonson & Brozek, 1952; Nicholson & Stone, 1983).

Digit symbol substitution (DSS) and subjective assessments of performance and mood were also used (Nicholson & Stone, 1982). Comments on side effects were recorded using a standardised interview.

Experimental procedure

Three doses of codeine phosphate (30, 60 and 90 mg) were studied as well as an antihistamine, triprolidine hydrochloride (10 mg) in a sustained release form, as an active control. Each subject received, on four separate occasions, an active tablet and a placebo for the other drug, and on two further occasions, matching placebos for the two drugs. The order of administration was chosen to achieve a linear balance for both placebo and the four individual drug doses, and the trial was double-blind. Performance studies within two days of the onset of menstruation were avoided or repeated. Placebo or drug was ingested with water, between 08.30 and 09.00 h. Performance on DVA was measured at 0.75 h (time 1) and 2.00 h (time 2) after each ingestion, and was followed on each occasion by the remaining tests in the order VMC, mood assessments, DSS, CFF and CRT. The total time taken to complete the tests at each session was approximately 35 min.

Data were analysed by a three factor repeated measures analysis of variance (ANOVA), with treatment (four drugs and two placebos) and time as fixed factors, and subject as a random factor. Prior to analysis, the assumptions of ANOVA, i.e. homogeneity of variance, normality and additivity, were studied by considering transformation of the raw measures by the method of Box & Cox (1964), and by examination of residuals (Anscombe, 1961). As a result, for DVA, a logarithmic transformation [ln (x-500)] was applied to the data for response times for each of the five largest target sizes and a variance stabilizing transformation for binomially distributed variables (arc sine square root) was applied to the proportions of correct scores. Principal component analysis was used to investigate the 12 subjective assessments of mood and well-being. Subsequent analysis was confined to the two largest components which were rotated according to the varimax criterion (Kaiser, 1958).

The possibility of a learning or adaptation effect from week to week was examined by covariance analysis. If the effect was present, either as a main effect or as a linear trend, the

treatment means were corrected and their standard errors were adjusted according to Finney (1946). Similarly, if a subject by linear order interaction was identified, it was used to form a composite error term with the residual drug by subject interaction to obtain the necessary standard errors.

Comparisons between treatment means were made by treating the three doses of codeine and triprolidine as two separate families. All comparisons were made against the mean of the two placebos, once it had been established that there was no difference between them. Differences from placebo at individual times were tested using Dunn's multiple comparison method (Dunn, 1961). Individual doses of codeine, meaned over time 1 and time 2, were compared with placebo using Dunnett's multiple comparison method (Dunnett, 1964). This method was similarly applied to test differences from time 1 to time 2 of individual doses of drugs with placebo. The degrees of freedom for the error terms (drug by subject, and drug by time by subject) were split according to the comparisons of interest, and separate error terms were used for individual comparisons where this was unavoidable.

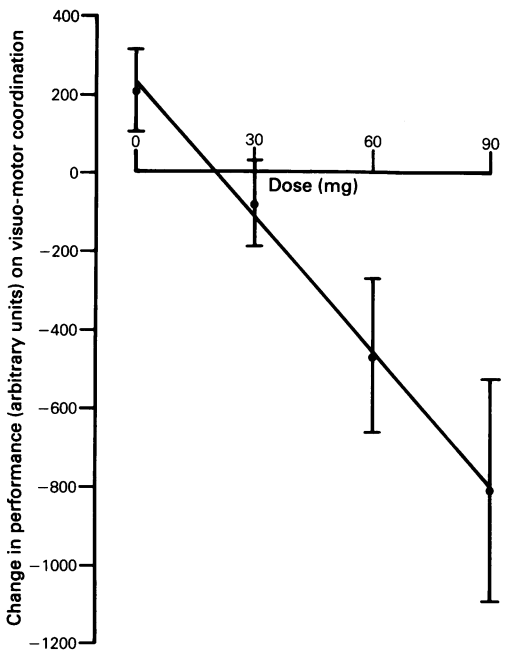

Figure 1 Change in performance (± s.e. mean) on visuo-motor coordination from time 1 (55 min after ingestion) to time 2 (130 min after ingestion) after placebo and after 30, 60 and 90 mg codeine.

Results

Visuo-motor coordination

Performance was not impaired by any dose of codeine at time 1 or time 2, compared with placebo, but when the difference in performance from time 1 to time 2 with codeine was compared with that after placebo, there was a reduction in performance with 60 and 90 mg ($P < 0.05$). The deterioration in performance over time with codeine was dose related and a linear function (Figure 1).

Performance was impaired by triprolidine at time 2 ($P < 0.01$), but not at time 1, though it was impaired when the mean of the two values were analysed ($P < 0.05$). The reduction in performance from time 1 to time 2 with triprolidine was similar to that observed with 90 mg codeine, though it was not different from placebo as the variability in the data at individual times required a separate error term when compared with placebo (Table 1).

Subjects did not report impaired performance.

Dynamic visual acuity

There were no effects on response times at either target velocity, or on the number of correct responses at the higher target velocity (1.19 rad s^{-1}), each compared with placebo. Results for the percentage of correct responses over all target sizes, at the lower target velocity (0.75 rad s^{-1}), are given in Table 2. The number of correct responses was not decreased by any dose of codeine at time 1 or time 2, but when the difference in performance from time 1 to time 2 was compared with that after placebo, there was a reduction with 90 mg codeine ($P < 0.05$). The number of correct responses was decreased at time 2 ($P < 0.01$), but not at time 1, with triprolidine, and when the difference in performance from time 1 to time 2 after triprolidine was compared with that after placebo, there was a decrease in the number of correct responses ($P < 0.05$).

Complex reaction time

There were no effects of codeine or triprolidine.

Digit symbol substitution

There were no effects of codeine, and the change in the mean (time 1 and time 2) number of sub-

Table 1 Performance on visuo-motor coordination (arbitrary units) after drugs (means for six subjects)

Time (min) after ingestion	*Placebo*	*Codeine (mg)*			*Triprolidine (mg)*
		30	*60*	*90*	*10*
Time 1 (55)	5369	5233	5690	5571	4482
Time 2 (130)	5581	5154	5223	4763	3767
					**
Mean	5475	5193	5456	5167	4124
					*
Difference	212	−79	−467	−808	−715
			**	*	

Differences from placebo: $*P < 0.05$; $**P < 0.01$.

Table 2 Percentage of correct responses on dynamic visual acuity at a target velocity of 0.75 rad s^{-1} after drugs (means for six subjects)

Time (min) after ingestion	*Placebo*	*Codeine (mg)*			*Triprolidine (mg)*
		30	*60*	*90*	*10*
Time 1 (45)	94.0	95.4	95.6	96.9	91.9
Time 2 (120)	95.9	94.4	95.4	93.8	89.8
					**
Mean	94.9	94.9	95.5	95.3	90.8
Difference	1.9	−1.0	−0.2	−3.1	−2.1
				*	*

Differences from placebo: $*P < 0.05$; $**P < 0.01$; transformed data used for analysis.

stitutions with triprolidine just failed to reach significance ($P < 0.07$).

Critical flicker fusion

The values were corrected for a differential linear order effect ($P < 0.05$) in which, irrespective of treatment, the fusion threshold was higher at time 1 than at time 2 ($P < 0.05$). No effects of codeine were observed, but triprolidine lowered fusion threshold at both times ($P < 0.01$) and the mean of time 1 and time 2 was also lower ($P < 0.001$).

Mood assessments

Two components of the mood assessments accounted for 78% of the total variance. The first component was highly weighted on assessments of relaxation, calmness, irritability, passiveness and carefreeness, and showed no differences between treatments, but there was an overall reduction from time 1 to time 2 ($P < 0.05$). The second component was highly weighted on assessments of wakefulness, energy, alertness, ability to concentrate and efficiency. There were no effects with codeine, but it was reduced by triprolidine ($P < 0.05$).

Side effects

There were few side effects with placebo and 30 mg codeine, but triprolidine led to drowsiness in three subjects. Nearly all subjects experienced side effects with 60 and 90 mg codeine, and the most frequent were headache, drowsiness, nausea, thirst and a feeling of strangeness. Lightheadedness, dizziness and confusion were also reported.

Discussion

Clearly, the present study has shown that the central effects of codeine are limited, and that, if they are present, neuromuscular activity may be

involved. This latter effect of codeine would appear to be dose related and linear, and the time course, like its analgesic activity (Kantor *et al.*, 1966, 1984), follows closely its known plasma concentrations (Waife *et al.*, 1975). The minimal effects of codeine in the present study are consistent with previous observations (Redpath & Pleuvry, 1982; Liljequist, 1981). Effects of triprolidine confirm previous findings (Nicholson, 1979; Nicholson & Stone, 1983; Nicholson *et al.*, 1982).

Change in dynamic visual acuity and visuo-motor coordination suggest that altered neuromuscular mechanisms are likely to be the common denominator (Borland & Nicholson, 1984). Indeed, morphine-like compounds modulate saccadic and smooth pursuit eye movements (Griffiths *et al.*, 1984; Rothenberg *et al.*, 1980a,b), and such effects would displace the target image from the fovea with loss of visual acuity. It is, however, unlikely that the sensory components of saccadic eye movements would be modified by codeine, as decreased accuracy and increased reaction time of saccades in the absence of any change in the peak velocity or duration of saccades, has only been observed with the more potent morphine-like drugs such as methadone (Rothenberg *et al.*, 1980a; Griffiths *et al.*, 1984). Further, altered performance is unlikely to be related to change in pupil size. A minimal miosis with codeine (Jasinski *et al.*, 1971; Liljequist, 1981) would only tend to reduce peripheral aberration, and this would be of no consequence as, in the present study, the task was well illuminated and targets were highly contrasted with the background.

Drowsiness and sedation are often reported after codeine (Kantor *et al.*, 1966, 1981), but there was no evidence from the present studies that arousal, at least as measured by critical flicker fusion, was altered. Drowsiness was reported by three subjects with the highest dose of codeine, but careful examination of individual data failed to link this feeling with impairment of performance. On the other hand nausea appeared to be related to impairment of performance. Three subjects complained of nausea after ingestion of 90 mg codeine, and they had the greatest deterioration of visuo-motor coordination, though there was no obvious relationship with dynamic visual acuity. With visuo-motor coordination the subject's head was free to move, and nausea is known to be more likely with opioid analgesics in ambulatory than in supine individuals (Jaffe & Martin, 1985).

The present study raises the issue of the mechanism and the site of action of codeine. Eye movement control (Keller, 1974), nausea (Jaffe & Martin, 1985) and sedation (Martin & Sloan, 1977) all involve brain stem mechanisms. Indeed, altered oculomotor function could be the basis of impaired visuo-motor coordination and dynamic visual acuity, though codeine may also have activity at higher levels. As most of the effects of codeine such as analgesia, sedation, respiratory depression and hypothermia involve μ-receptors (Hayes & Tyers, 1983; Pickworth & Sharpe, 1979) it is reasonable to suggest that impaired performance may also involve these receptors. However, different subsets of receptors may be concerned with analgesia on the one hand and with sedation and respiratory depression on the other (Goodman & Pasternak, 1984), and the possibility arises that impaired performance may involve different receptors than those involved with sedation.

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