Effect of Δ-9-Tetrahydrocannabinol and Cannabidiol on Nocturnal Sleep and Early-Morning Behavior in Young Adults

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Abstract: The effects of cannabis extracts on nocturnal sleep, early-morning performance, memory, and sleepiness were studied in 8 healthy volunteers (4 males, 4 females; 21 to 34 years). The study was double-blind and placebo-controlled with a 4-way crossover design. The 4 treatments were placebo, 15 mg Δ-9-tetrahydrocannabinol (THC), 5 mg THC combined with 5 mg cannabidiol (CBD), and 15 mg THC combined with 15 mg CBD. These were formulated in 50:50 ethanol to propylene glycol and administered using an oromucosal spray during a 30-minute period from 10 PM. The electroencephalogram was recorded during the sleep period (11 PM to 7 AM). Performance, sleep latency, and subjective assessments of sleepiness and mood were measured from 8:30 AM (10 hours after drug administration). There were no effects of 15 mg THC on nocturnal sleep. With the concomitant administration of the drugs (5 mg THC and 5 mg CBD to 15 mg THC and 15 mg CBD), there was a decrease in stage 3 sleep, and with the higher dose combination, wakefulness was increased. The next day, with 15 mg THC, memory was impaired, sleep latency was reduced, and the subjects reported increased sleepiness and changes in mood. With the lower dose combination, reaction time was faster on the digit recall task, and with the higher dose combination, subjects reported increased sleepiness and changes in mood. Fifteen milligrams THC would appear to be sedative, while 15 mg CBD appears to have alerting properties as it increased awake activity during sleep and counteracted the residual sedative activity of 15 mg THC.

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A potential therapeutic benefit of the use of cannabis-based extracts in the relief of pain and other chronic symptoms is an improvement in sleep quality. This may be due to hypnotic activity in addition to the therapeutic properties of cannabinoids.[1] Indeed, early studies indicated that sleep may be modulated.[2–8] However, these studies used various modes of administration, involved wide dose ranges, and were carried out in subjects of variable status with respect to their use of such drugs. Furthermore, the experimental designs were not amenable to analyses that could indicate the pharmacologic activity of individual substances. In some studies, extracts were used in which, although Δ-9-tetrahydrocannabinol (THC) could be measured, there were undetermined amounts of cannabidiol (CBD) and cannabinol. Nevertheless, the impression gained from these studies was that certain doses of THC, particularly with repeated ingestion, may reduce rapid eye movement (REM) activity and increase slow-wave sleep.

We have, therefore, investigated the effect on sleep of individual cannabinoids and cannabinoids in combination. The current studies with THC and CBD have been carried out using the doses that are currently under investigation for the relief of pain. The former cannabinoid is believed to be the principal psychoactive extract of cannabis, an effect mediated via cannabinoid $(CB)_1$ receptors. CBD may be free of such central activity but may have useful therapeutic potential arising from its reported myorelaxant and anticonvulsant properties, in addition to the attenuation of some of the effects of THC, such as euphoria and tachycardia.[9–12] The mechanism by which CBD exerts these effects is uncertain, as it cannot be completely explained in terms of CB_1 and CB_2 receptor binding. We have studied the effect of THC alone and in combination with CBD on the sleep process and on mood, performance, and sleep latencies during the morning of the day after administration.

METHODS

Protocol

The protocol was approved by the QinetiQ Ethics Committee, and the subjects were under medical supervision

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throughout the experiment. Each was provided with detailed information on the activity and potentially adverse effects of the compounds. Subjects were required to give written informed consent in the presence of the principal investigator and were informed that they could withdraw from the experiment at any time. They were warned against driving and operating machinery during the day after each experimental night.

The subjects were required to be between 18 and 35 years and weigh between 50 and 80 kg (female) and 60 and 90 kg (male) with a body mass index not greater than 30. Information on height and race were also recorded. Inclusion in the experiment required the absence of a significant medical history. Subjects were excluded if there was a family history of a schizophrenia-like illness, a personal history of psychiatric or emotional problems, or evidence of insomnia or daytime sleepiness. An intake of >14 U of alcohol per week for females and 21 U for males, smoking >5 cigarettes or equivalent a day, or ingesting >5 beverages containing caffeine a day were also exclusion criteria. A unit of alcohol is defined in the United Kingdom as being equivalent to 7.9 g or 10 mL of pure alcohol (ethanol).

Inclusion in the experiment required the absence of clinically significant findings in the medical examination and in the associated pathology tests. These included a 12-lead electrocardiogram and measurement of blood pressure, heart rate (both supine and erect), and oral temperature. Exclusion criteria included a resting blood pressure exceeding 140 mm Hg systolic or 90 mm Hg diastolic and a resting heart rate <40 per minute. Urine analysis with a drug screen, biochemistry, hematology, and screening for hepatitis B and C were carried out. The medical examination and the pathology tests were repeated at the end of the experiment.

All subjects agreed to use barrier methods of contraception with a spermicide for the duration of the experiment and for 3 months after the completion of the experiment. They agreed that if a hormonal method was being used, it would not be discontinued during the experiment. The initial screening of the subjects included, if appropriate, a urinary pregnancy test, and this was repeated before each treatment night and on completion of the experiment.

During the time between medical screening and the first experimental night, the subjects were instructed in the techniques that would be used to measure performance and memory. Subjects reached a plateau level of performance on all tests before the first experimental night.

Subjects

There were 4 females aged between 21 and 22 (mean 21.8) years and 4 males aged between 24 and 34 (mean 28.8) years. The females weighed between 57.7 and 68.3 (mean 61.3) kg and the males weighed between 70.6 and 78.9 (mean 74.7) kg. All subjects had experienced previously the effects of cannabis, but it was determined that this was occasional and linked to social events. Furthermore, the subjects reported that they had not used cannabis for at least 30 days before the commencement of the experiment and did not use cannabis during the experiment. This was confirmed by urinary drug screen. Subjects did not have a history of drug, alcohol, tobacco, or caffeine abuse or any history of the use of a social drug other than cannabis. This was confirmed by a urine drug screen that included that for opiates, barbiturates, benzodiazepines, cocaine, and amphetamine. The alcohol intake of the subjects did not exceed 8 U/wk in the females and 20 U/wk in the males. Two subjects were smokers—1 female (3 cigarettes per day) and 1 male (up to 4 cigarettes per day).

Experiment Design

The experiment was double-blind and placebo-controlled with a 4-way crossover design in which the acute effects of two cannabinoids (THC and a combination of THC and CBD) were observed on sleep and behavior the next day. The experiment consisted an adaptation night and 4 experimental nights. At least a week separated each experimental night. Subjects were required to retire at their normal bedtime on the nights preceding and to refrain from napping or exercise during the day before each of these nights and from exercise up to 12 hours after each night. The subjects were taken to the sleep laboratory in a chauffeur-driven car.

The adaptation night was used to familiarize the subjects with the experimental situation and to confirm that the subjects had a normal sleep pattern. As far as the adaptation night was concerned, alcohol and caffeine ingestion were prohibited for 24 hours and smoking from 5 PM before the overnight sleep.

As far as the treatment nights were concerned, alcohol was prohibited for 48 hours before and for 24 hours after drug ingestion. In addition, throughout the experiment, alcohol consumption was restricted on all other days of the week to no more than 3 U/d for males and 2 U/d for females. Caffeine was prohibited for 48 hours before and for 12 hours after, and smoking was prohibited from 5 PM before and for 12 hours after each treatment night. Subjects were also required to avoid spicy foods, Chinese food, bananas, and strong cheese during the evening before the treatment night.

On each treatment night, it was ascertained whether any of the subjects had experienced adverse effects or illnesses since the previous visit. Breath alcohol levels were measured and urine samples collected for drug screening and, if appropriate, for pregnancy testing. Negative results for the alcohol, drug, and pregnancy tests were required for the subjects to continue with the experiment. Treatments were administered during a 30-minute period from 10 PM. The subjects retired to bed at approximately 11 PM (30 minutes

after completion of treatment administration) and remained in bed until approximately 7 AM the next day (8 hours after retiring). Breakfast was provided between 7:15 and 8:15 AM. At approximately 8:30 AM (10 hours after completion of treatment administration), the subjects completed subjective assessments of sleepiness and commenced a battery of performance tasks. They left the laboratory at approximately 10:30 AM in a chauffeur-driven car after a medical practitioner had discharged them.

Treatments

There were 4 treatments: THC (15 mg) and 2 combinations of THC and CBD (5 mg THC with 5 mg CBD; 15 mg THC with 15 mg CBD), together with placebo. The drugs and placebo were prepared for the experiment by GW Pharmaceuticals plc. THC and the THC/CBD combinations were formulated in 50:50 ethanol to propylene glycol and administered by means of a pump action oromucosal spray. Each actuation was 100 μL. The 15-mg dose of THC, the 2 combinations of THC and CBD, and the placebo were each delivered by 6 actuations during a 30-minute period given at 6-minute intervals from approximately 10 PM. Subjects were trained before the study not to swallow the liquid to maximize drug absorption through the buccal mucosa. This technique of administration has been validated.[13]

Polysomnography

The subjects slept in single, light-proofed, sound-attenuated, and temperature-controlled (18°C ± 2°C) rooms. Silver–silver chloride electrodes were used to record electroencephalograph activity from the O_1-A_2 and C_4-A_1 positions, together with bilateral electrooculograms and the submental electromyogram, on to EMBLA 16-channel recorders (Flaga, Iceland). The electrocardiogram and myographic activity from the anterior tibialis muscles were also recorded throughout the night. A simulated paper speed of 10 mm/s was used and the sampling rates for the various measures were as follows: electroencephalograph, 100 Hz; electrooculograms, 100 Hz; electromyogram, 200 Hz, respectively. The records were scored manually from the screen into 30-s epochs upon completion of the experiment by one analyst according to the criteria of Rechtschaffen and Kales.[14] Various measures were derived from the data for subsequent statistical analysis.

Cannabinoid Plasma Levels

A blood sample was obtained at approximately 9 PM as a control for the estimation of cannabinoid plasma levels the next morning. At approximately 8:15 AM (9.75 hours after the last actuation), a blood sample was taken for the measurement of plasma levels of the cannabinoids. Samples were collected in tubes containing lithium heparin and placed immediately into ice and water to chill before being centrifuged at 1000 × *g* for 10 minutes at 0°C to 4°C and stored at −20°C within 30 minutes of the sampling time. The serum levels of THC, 11-hydroxy THC (a major active metabolite of THC), and CBD were determined by a high-performance liquid chromatography method. The limit of quantification of the assay was 0.1 ng/mL.

Cardiovascular Measurements

Blood pressure and heart rate were recorded using an Accutorr Plus automatic blood pressure monitor (Datascope, Paramus, NJ) before, during, and after the 30-minute period of drug administration when the subjects were seated. The next morning on waking the subjects (at approximately 7 AM), blood pressure was measured both supine and erect.

Subjective Assessments

Before the administration of the treatments, the subjects rated their level of sleepiness using the 7-point Stanford Sleepiness Scale.[15] Approximately 30 minutes after awakening, the subjects assessed the quality of their sleep and their level of alertness. The extremes of the 100-mm scales were as follows: I slept *very poorly* (0) to *very well* (100); Now I feel *very sleepy* (0) to *wide awake* (100); I fell asleep *never* (0) to *immediately* (100); after I fell asleep, I slept *very badly* (0) to *very well* (100); I wanted to sleep *much more* (0) to *much less* (100). Subjects also estimated the time to sleep onset and the sleep duration. They also rated their level of sleepiness using the Stanford Sleepiness Scale.

Measurement of Next-Day Performance, Memory, and Sleepiness

After each overnight experiment, performance was measured from approximately 8:30 AM the next morning using psychomotor and cognitive tasks, together with assessments of mood, sleepiness, and fatigue, and the electroencephalographic determination of sleep latency. The tasks were presented in the following order (with elapsed time in brackets): mood assessment (0 to 1 minute), Samn-Perelli fatigue rating (1 to 2 minutes), immediate memory word recall (2 to 4 minutes), digit symbol substitution (4 to 8 minutes), 6-letter memory recall (8 to 13 minutes), multiattribute task (MAT) battery and subjective workload ratings (13 to 63 minutes), digit memory recall (63 to 66 minutes), choice reaction time (66 to 68 minutes), sustained attention (68 to 78 minutes), delayed memory word recall (78 to 79 minutes), mood assessment (79 to 80 minutes), Samn-Perelli fatigue rating (80 to 81 minutes), Stanford Sleepiness Scale (81 to 82 minutes), and sleep latency test (82 to 107 minutes).

Digit Symbol Substitution

The subjects were presented with one of a series of 30 different sheets with 200 randomized digits (0 to 9) arranged

in 10 rows on both sides of the sheet.[16] In the space below each digit, they were required to insert the appropriate symbol indicated by a code at the top of the page. They were given 2 minutes for each of the 2 sides of the sheet to complete as many substitutions as possible, and the total for each session was recorded.

Multiattribute Task Battery

The MAT battery has been developed to provide a standardized test for use in laboratory studies of performance and workload.[17] The battery incorporates 4 simulation tasks that aircrew would expect to perform. The MAT battery was displayed on a screen divided into 6 windows, of which 4 were tasks: system monitoring (''dials'' and ''lights''), tracking, communications, and resource (fuel) management, and 2 provided information about the communications and resource management tasks. Subject responses were made using keys on a standard computer keyboard, and the battery lasted 50 minutes. Response data and reaction times were recorded for all tasks except tracking, for which the root mean error score was recorded.

Choice Reaction Time

An asterisk was displayed in 1 of 4 corners of a monitor screen, and subjects were required to respond by pressing 1 of 4 buttons in the same spatial arrangement as the asterisks on the screen.[18] The task was self-paced with a total of 160 asterisks presented. Response data and reaction times were recorded.

Sustained Attention

A random sequence of letters was presented one at a time on a monitor screen at a rate of 1 each second.[19] Two letters (the critical stimulus) were displayed continuously at the top left-hand corner of the screen. Subjects were required to press a button whenever the letters of the critical stimulus were presented consecutively during the random sequence. Response times and the nature of the responses (correct, missed, and wrong) were recorded.

Immediate and Delayed Word Memory Recall

The immediate word memory recall task presented a list of 16 unrelated words (2-syllable nouns with a frequency of >12 per million in general usage) on a monitor screen at a rate of 1 every 3 seconds. Immediately after the presentations, subjects were given 45 seconds to recall as many of the words as possible. Delayed memory recall was tested 76 minutes later when they were again asked to recall the words within 45 seconds. The number of words recalled and the number of words correctly recalled were recorded.

Six-Letter Memory Recall

Subjects were given 15 s to memorize a set of 6 letters. Then, a series of randomly generated letters was displayed individually on a monitor, and they were required to indicate whether the letter was contained in the memory set by pressing the appropriate button.[20] This procedure was repeated a further 9 times, so that a total of ten 6-letter memory sets were presented during this test. Response times and the nature of the responses (correct, missed, and wrong) were recorded during this 5-minute task.

Digit Memory Recall

Series of single-digit numbers (1 to 9) were presented simultaneously above and below a horizontal line on a monitor.[20] Subjects were required to memorize the digit below the line, compare it with the digit above the line in the subsequent presentation, and respond by pressing the appropriate button for ''same'' or ''different'' number. The 3-minute task was self-paced with a maximum reaction time of 2 seconds per response. Response times and the nature of the responses (correct, missed, and wrong) were recorded.

Subjective Measurements

Mood and well-being were assessed using a series of twelve 100-mm visual analogue scales.[21] The subjects assessed their level of sleepiness using the Stanford Sleepiness Scale and rated their fatigue level against 10 separate criteria, from which a score in the range 0 (*extremely fatigued*) to 20 (*extremely alert*) was calculated.[21] Subjects also assessed their level of workload during the MAT battery when the scale was presented on the screen at 10-minute intervals by giving a rating between 1 (*workload insignificant*) and 10 (*task abandoned—unable to apply sufficient effort*).[23]

Sleep Latency Test

Subjects were instructed to lie in bed and to try to fall asleep. The electroencephalograph, electrooculograms, and electromyogram were recorded as described previously. The test was ended 20 minutes after ''lights out.'' Subsequently, one analyst determined the latency to stage 1 (drowsy) sleep for all recordings.

Adverse Events

Adverse events whether considered to be related to the use of the drug were recorded with details of their onset and cessation, severity, and relation to treatment.

Statistical Analysis

The statistical power for the experiment was calculated using the method of Owen.[24] Estimates of variance from previous studies[25,26] were used to calculate the minimum

detectable difference between the 2 drugs for a sample of sleep and psychometric tests and for 1 subjective measurement for 8 subjects with 80% power at the 5% level of significance. The order of drug ingestion was based on a Latin-square design, balanced for carryover effects.

The data were analyzed by analysis of variance as a general test at the 5% significance level. A 1-factor model (treatment) with subjects as a random factor was used for all variables except MAT battery tracking, workload ratings, mood assessment, and the Samn-Perelli fatigue rating. For these variables, a 2-factor model (treatment and ''run'') was used as these variables were presented at the beginning and the end of the morning test session. Significant effects in the analysis of variance of the factors were examined using Newman-Keuls.[27] Planned comparisons were made between the cannabinoids and placebo using Dunnett procedure, which adjusts for multiple comparisons with a control, so that the overall error rate remains at 5%.[28] The assumptions of analysis of variance (homogeneity of variance, normality, and additivity) were studied by considering transformations of the raw measures using the maximum likelihood method.[29] Each measure was examined for a possible order effect and, if significant, was included as a linear covariate in the analyses of these measures.

A principal component analysis was carried out on the subjective assessments of mood, and 2 major varimax-rotated components were identified for analysis. The first component included measures related to lethargy, inefficiency, an inability to concentrate, dullness, sleepiness, and withdrawal. The second component included measures related to anxiety, agitation, tension, irritability, and aggression.

For the sleep latency data, on those occasions when stage 1 sleep did not occur within the 20 minutes allowed (6 of the 32 sleep latency tests), an iterative extension to a standard analysis of variance procedure was used. This method follows a standard expectation/maximization algorithm for handling data censored beyond 20-minute duration, and it overcomes a downward bias, which would otherwise be created if the value was removed altogether or if it was treated as 20 minutes.[30]

RESULTS

Sleep, Subjective Measures, Next-Day Performance, Memory, and Sleepiness

The effects of the cannabinoids on nocturnal sleep and early-morning performance, memory, and sleepiness are given in Tables 1–3. Back-transformed means corrected for bias are shown, where appropriate, together with the transformation required.

There was no difference in the subjects' ratings of sleepiness before the administration of the 4 treatments, nor were there any differences in the subjects' assessments of sleep onset, duration, or quality following the administration of the cannabinoids.

There were no effects of 15 mg THC on sleep. In the case of the latency to rapid eye movement sleep, although the mean data with 15 mg THC appear to be increased, the statistical analysis failed to demonstrate a significant change for the group as a whole due to the variability of the data. The next day, the subjects reported increased sleepiness 30 minutes after rising, and there were decreased latencies to early-morning sleep. The subjects also reported changes in mood. Several aspects of memory were impaired. There was a reduction in the number of words remembered correctly in the immediate and delayed recall tests.

With the concomitant administration of THC and CBD, there was evidence of decreased stage 3 sleep, and at the higher dose combination (15 mg THC with 15 mg CBD), awake time was increased. At the lower dose combination (5 mg THC and 5 mg CBD), there were no changes in mood, sleepiness, fatigue, or performance the next morning. With the higher dose combination (15 mg THC and 15 mg CBD), subjects reported increased sleepiness with fatigue and changes in mood. For both combination doses, there were no changes in performance on the memory tests, except for a reduced reaction time with the lower doses in digit recall.

Blood Pressure

Inspection of the blood pressure and pulse rate recordings did not indicate changes in blood pressure or pulse rate related to the 30-minute period of drug administration. Recordings of these measures in the morning on awakening revealed postural systolic hypotension with 15 mg THC when given alone or in combination with 15 mg CBD. There were compensatory increases in pulse rate, both supine and erect.

Cannabinoid Plasma Levels

The pharmacokinetic data showed that during the evening before drug administration, the mean serum concentrations of THC, 11-hydroxy THC, and CBD were less than the limit of quantification of the assay. The serum levels of the cannabinoids the next morning were related to the dose that had been administered the previous evening. The mean serum concentrations of THC 9.75 hours after the ingestion of 5 and 15 mg THC in combination with CBD and of 15 mg THC when ingested alone were 0.405, 1.348, and 1.170 (with standard deviations of 0.359, 0.739, and 0.700) ng/mL, respectively. Similarly, the concentrations of 11-hydroxy THC 9.75 hours after the ingestion of the 2 dose combinations of THC with CBD and of 15 mg THC alone were 0.714, 2.178, and 1.663 (with standard deviations of 0.762, 1.325, and 1.293) ng/mL, respectively. The serum

TABLE 1. Effect of the Cannabinoids (Δ-9-THC and CBD) on the Electroencephalographic Measures of Nocturnal Sleep (Means for 8 Subjects)

Measure	Transform	SE*	Placebo	15 mg THC	5 mg THC and 5 mg CBD	15 mg THC and 15 mg CBD
Total sleep time, min	log	0.3879	429.13	429.25	443.83	404.56
Sleep efficiency index†	log	0.2190	0.89	0.89	0.92	0.84
Sleep onset latency, min		3.9145	24.63	25.94	22.56	23.50
Latency to slow-wave sleep, min		1.5351	10.13	12.13	11.44	10.81
Latency to REM sleep, min	log	0.1487	106.56	140.13	107.44	107.44
REM to non-REM ratio	log	0.1980	0.24	0.21	0.27	0.18
Number of REM periods		0.3934	4.50	3.88	4.25	3.91
Number of awakenings		2.1375	13.63	14.13	12.50	14.25
Number of stage shifts		7.4232	106.50	103.88	100.13	100.00
Duration of wakefulness, min	log	0.3194	17.06	17.19	11.25	41.06‡
Duration of stage 1 sleep, min		6.4665	45.88	43.19	44.75	42.56
Duration of stage 2 sleep, min		11.4059	234.19	233.81	235.50	233.19
Duration of stage 3 sleep, min		3.2203	32.88	28.06	24.19§	23.75§
Duration of stage 4 sleep, min		6.9455	40.06	53.38	48.31	49.81
Duration of stages 3 and 4, min		6.3538	72.94	81.44	72.50	73.56
Duration of REM sleep, min		11.5244	84.75	74.31	93.13	61.88

*Standard error for comparison. Where data were transformed, the SE is given on a transformed scale.
†Sleep efficiency index (total sleep time divided by time in bed).
‡$P < 0.05$ compared with 5 mg THC and 5 mg CBD.
§$P < 0.05$ compared with placebo.

concentrations of CBD following the ingestion of 5 and 15 mg CBD in combination with THC were 0.309 and 0.863 (with standard deviations of 0.187 and 0.425) ng/mL. There was no CBD detectable following the administration of THC alone.

Adverse Events

There were no serious adverse events and no adverse events that led to withdrawal of a subject. All 8 subjects reported at least one adverse event. Inspection of reported adverse events showed that the high dose combination of THC and CBD was likely to be associated with symptoms related to the nervous system.

DISCUSSION

It would appear that the cannabinoids, THC and CBD, when given in the doses and in the combinations used in the present study, are unlikely to have adverse clinical effects on sleep. THC would appear to be a sedative compound, whereas CBD would appear to have some alerting properties. The distinct activity of these compounds suggests that they could be complementary in clinical practice. The alerting activity of CBD may be particularly useful in the concomitant administration of THC and CBD when the therapeutic activity of both compounds is sought.

The present analysis did not provide evidence that 15 mg THC altered the sleep process, although inspection of

TABLE 2. Effect of the Cannabinoids [Δ-9-THC and CBD] on Subjective Assessments of Sleep and Sleepiness 30 Minutes After Rising, 9 Hours After Administration (Means for 8 Subjects)

Measure	SE*	Placebo	15 mg THC	5 mg THC and 5 mg CBD	15 mg THC and 15 mg CBD
Stanford Sleepiness Scale (from 1.0 = *wide awake* to 7.0 = *extremely sleepy*)	0.4157	2.38	3.75†	2.88	3.71†
Visual Analogue Scale (from 100 = *wide awake* to 0 = *very sleepy*)	9.7679	70.75	43.75†	56.75	35.13‡

*Standard error for comparison. Where data were transformed, the SE is given on a transformed scale.
†$P < 0.05$ compared with placebo.
‡$P < 0.01$ compared with placebo.

TABLE 3. Effect of the Cannabinoids [Δ-9-THC and CBD] on Performance, Memory, Mood, Subjective Sleepiness, and Sleep Latency the Next Morning 10 Hours After Administration (Means for 8 Subjects)

Measure	Transform	SE*	Placebo	15 mg THC	5 mg THC and 5 mg CBD	15 mg THC and 15 mg CBD
Digit symbol substitution						
Number of substitutions		4.5883	158.75	152.00	162.00	153.63
Choice reaction time						
Reaction time, s	Reciprocal	0.0284	0.42	0.42	0.41	0.42
Wrong, %	Square root	0.3130	2.27	3.59	3.91	3.05
Sustained attention						
Reaction time, s		0.0198	0.42	0.42	0.40	0.40
Errors (wrong and missed), %	Square root	0.5525	7.21	7.39	6.64	11.70
Immediate word recall						
No. words correctly recalled		0.8522	11.25	9.00†	10.50	9.25
Delayed word recall						
No. words correctly recalled		0.9316	8.13	5.06†‡	8.25	6.46
Six-letter memory recall						
Reaction time, s	Log	0.0373	0.93	0.96	0.88	0.96
Wrong, %	Log	0.1917	12.50	12.67	13.50	13.50
Digit memory recall						
Reaction time, s		0.0231	0.81	0.78	0.74†	0.79
Errors (wrong and missed), %		0.0139	6.43	6.60	6.41	4.57
Mood (mean)						
First component§		0.1590	0.1821	−0.1586†‡	0.2467	−0.2702†‡
Second component§		0.2935	−0.6173	0.2670†	−0.0662	0.4165†
Fatigue rating (mean)						
From 20 (*extremely alert*) to 0 (*extremely fatigued*)		1.1742	11.13	8.50	9.94	7.19†
Stanford sleepiness scale						
Before sleep latency test (from 1.0 = *wide awake* to 7.0 = *extremely sleepy*)		0.4613	3.25	4.13	3.88	4.50†
Sleep latency						
To stage 1 sleep, min		1.3989	10.15	5.85†	7.97	9.31

*Standard error for comparison. Where data were transformed, the SE is given on a transformed scale.
†$P < 0.05$ compared with placebo.
‡$P < 0.05$ compared with 5 mg THC and 5 mg CBD.
§The first component of mood included measures related to anxiety, agitation, tension, irritability, and aggression. Negative values indicate greater levels of these variables. The second component of mood included measures related to lethargy, inefficiency, an inability to concentrate, dullness, sleepiness, and withdrawal. Positive values indicate greater levels of these variables.

the data could suggest that in some individuals, the duration of slow-wave sleep may have been increased. However, there was evidence, the next morning, of increased sleepiness and changes in mood and of reduced latencies to early-morning sleep. Increased sleepiness and changes in mood the next day, but not the decreased latencies to early-morning sleep, were also seen when 15 mg THC was given with 15 mg CBD.

Modulation of slow-wave sleep was observed when 5 or 15 mg CBD was ingested with the same doses of THC, as there was a decrease in stage 3 sleep. It would appear possible that CBD may increase slow-wave activity usually associated with stage 4, as there were no changes in the duration of stage 2 itself or in the combined duration of stage 2 and slow-wave sleep. This could be due to the activity of CBD alone or to its activity in combination with THC. It is also of interest that an increase in awake activity occurred with the ingestion of 15 mg CBD and 15 mg THC, but not with 5 mg CBD and 5 mg THC (or with 15 mg THC alone). This would suggest that CBD may have an alerting effect that is dependent on dose. The analysis did not provide any evidence that CBD reduced total sleep time for the group as a whole, but again, inspection of the data

could suggest that in some individuals, it was curtailed, together with rapid eye movement sleep.

In the present study, assessment of performance detected residual activity of the cannabinoids somewhat more than 10 hours after ingestion. At this time, impaired performance was limited to the effect of 15 mg THC on memory, and this observation is in broad accord with the published literature (reviewed by Ashton[31]) and with the studies of Curran et al.[32] In the latter study, episodic memory and verbal learning were impaired only with 15 mg THC and not with 7.5 mg THC. These effects were contained within the 8-hour period after ingestion and were not present 24 hours after ingestion.

Although impaired memory was observed the next day when 15 mg THC was given alone overnight, there were no effects on memory when 15 mg THC was ingested with 15 mg CBD. This could be due to an alerting effect of CBD. Indeed, such an effect would be consistent with increased wakefulness during the night, absence of an effect on early-morning sleep latencies when the higher dose combination was ingested, and reduced reaction time in digit recall with the low dose combination. However, although the activity of 15 mg CBD may have counteracted the effects of 15 mg THC on memory, the subjective impression of sleepiness persisted, as did changes in mood. The possibility that CBD may counteract, at least partially, the activity of THC has been raised in connection with the psychologic effects of THC.[12]

Overall, these observations would suggest that the effects of overnight administration of THC and CBD on the sleep process and early-morning behavior are dependent on dose. This would accord with both the pharmacokinetic data and the recordings of blood pressure and pulse rate. The mean serum concentrations of these cannabinoids and of 11-hydroxy THC (a major active metabolite of THC) are clearly related to the administered dose. Persistent activity of the high dose cannabinoids when given alone or in combination was also evident from postural systolic hypotension with compensatory increases in pulse rate, both supine and erect, observed the next morning.

Clearly, the present studies on cannabis-related compounds have shown that overnight administration leads to dose-related serum concentrations and dose-related effects on the sleep process and early-morning activity. The studies have identified the discrete activities of THC and CBD related to their sedative and alerting properties and have explored the potential of sleep studies to establish dose combinations that are likely to provide the optimum balance of their activity.

It is suggested that combinations of THC and CBD are unlikely to prejudice any improvement in sleep brought about by the effects of these drugs in alleviating pain and other chronic symptoms. However, although 15 mg THC is free of adverse effects of clinical significance on the sleep process, its activity is associated with residual effects. In this context, the coadministration of THC and CBD has advantages beyond the therapeutic benefits that both drugs may bring individually. An equal dose of CBD appears to counteract the residual effects of THC on daytime sleep latencies and memory, although the subjects may still report sleepiness.

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