Pharmacology Biochemistry & Behavior, Vol. 35, pp. 861–864. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

The Effects of Orally Administered Δ^9-Tetrahydrocannabinol in Man on Mood and Performance Measures: A Dose-Response Study

G. B. CHESHER, K. D. BIRD,* D. M. JACKSON, A. PERRIGNON AND G. A. STARMER

Department of Pharmacology, University of Sydney, N.S.W. Australia
**School of Psychology, University of New South Wales, Kinsington, N.S.W. Australia*

Received 24 July 1989

CHESHER, G. B., K. D. BIRD, D. M. JACKSON, A. PERRIGNON AND G. A. STARMER. *The effects of orally administered Δ^9-tetrahydrocannabinol in man on mood and performance measures: A dose-response study.* PHARMACOL BIOCHEM BEHAV **35**(4) 861–864, 1990.—A dose-response study of the effect of orally administered Δ^9-tetrahydrocannabinol (THC) on human mood and skills performance was conducted. Using five dose levels of THC (0, 5, 10, 15, 20 mg) with 16 volunteers per dosage group, mood and performance measures were recorded at five testing occasions, one before and four after drug administration. The slope of the linear regression of performance on the test battery was significant for up to 200 minutes after dosage. That is to say, oral THC, at the doses used, produced significant dose-dependent impairment of performance for a period in excess of three hours. A similar time course for the effect of THC on the subjective assessment of intoxication ('stone') suggested a correlation between drug-induced impairment skills and the effects on mood.

Δ^9-Tetrahydrocannabinol Oral administration Dose response Skills performance Mood states Duration of action

IN previous studies in this laboratory we have reported the effects of the orally administered cannabinoids, Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN), alone and in combination (and with ethanol) on human performance measures (1–6). These studies have indicated that both THC and ethanol produce a decrement in human performance on a battery of tests of psychomotor and cognitive function. The doses of THC used in separate experiments were adjusted to deliver approximately 143, 214 and 268 μg/kg (i.e., 10, 15 and 20 mg/70 kg body weight). The ethanol dose in all experiments was constant at 0.54 g per kg. In another experiment (3,4), all of the possible combinations between THC (214 μg/kg), CBD (286 μg/kg), CBN (286 μg/kg) and ethanol (0.54 g/kg), were administered to volunteers and their effects on performance on a battery of tests was assessed. Both THC and ethanol produced significant decrements in performance and their combined effects could be described in terms of an additive model. Both CBD and CBN were inactive in the doses used and there was no evidence that these substances modified the effects of THC or of ethanol. To our knowledge there have been no systematic studies of the dose-response effects of THC on a broad range of psychomotor and cognitive tasks as used in our laboratory. Such studies are important from a basic pharmacological viewpoint and also in a social and forensic context. The present investigation was planned as the first of a series using the same battery of tests to study the dose-response relationship of THC administered orally and by smoking, together with orally administered ethanol. In this manner it is envisaged that by using the same laboratory procedures, it may be possible to determine approximately the dose of each drug required to produce a similar degree of impairment in the human performance measures tested.

METHOD

Subjects

The subjects were healthy volunteers of both sexes drawn mainly from the population of university students. Eighty subjects were used (23 female and 57 male) with body weights of 58 kg to 84 kg (median 64.5 kg) and aged 18 years to 34 years (median 21 years). All were nonnaive as regards cannabis use, the extent of which ranged between once per week or more (64 subjects) and once per month or less (16 subjects).

All subjects were medically examined by one of us (A.P.) to ensure that no past or present illness precluded them from participation in the experiment. The purpose and design of the experiment was fully explained to the subjects and their informed consent obtained.

Drugs

Capsules containing THC dissolved in sesame oil containing

2.5, 5.0 or 10.0 mg per capsule were used. Placebo capsules contained sesame oil only. Dosage levels used were adjusted to deliver approximately 70, 140, 215 or 286 μg THC/kg (i.e., 5, 10, 15 or 20 mg per 70 kg body weight). Each subject was given three capsules.

The test battery:

1. *Standing steadiness* (body sway: a measure of motor coordination). The apparatus consists of a platform beneath which a displacement transducer is mounted. The subject steps on to the platform and is instructed to relax and to stand as still as possible. Any body movement creates an electrical impulse which is amplified and recorded on a Grass Polygraph. The impulses are integrated to give an overall measure of body sway as frequency and amplitude which is termed epoch time and the results are expressed as this measure. For this study, body sway was measured in two conditions; eyes open and eyes closed.

2. *Pursuit rotor* (a simple tracking task to test hand-eye coordination). The subject is required to track with a photocell stylus a 15-mm square which rotates in the horizontal plane at 15 rpm in a clockwise direction. The number of times the stylus goes off the target and the total time off target are recorded. The testing time for this study was 32 sec.

3. *The Vienna Determination Apparatus* (VDA). (Apparatus of Schufried, Stuttgart, W. Germany.) This task is an experimenter paced, serial complex reaction time task involving seven colour and two auditory stimuli to which the subject must respond by pressing the appropriate button of foot pedal. In this experiment stimuli were presented at a constant rate of one stimulus per 1.22 sec for a total of 100 stimuli. Correct, incorrect and delayed responses were recorded. Actual reaction times are not recorded by this apparatus.

4. *Simple reaction time.* (Apparatus of Schufried, Stuttgart, W. Germany.) The subject sits with finger poised over a button which s/he is required to press as quickly as possible when the stimulus is presented. The stimuli used were a white light or a sound (a 1250 Hz tone). The reaction times (millisec) were recorded to both stimuli. Responses to 5 visual and 5 auditory stimuli were recorded.

5. *Complex reaction time.* The same apparatus as for the simple reaction time was used. The subject is presented with stimuli of either a red or white light or a tone. The response of a button press must be given only when the white light is presented simultaneously with the tone. Other stimuli, alone or in combination are to be ignored. The reaction time responses (millisec) to five stimuli (white light and tone) were recorded.

6. *Number test.* (Apparatus of Zack, Simbach am Inn; W. Germany.) The subject is presented with a series of single digit addition or subtraction displays and is required to key in the answers by pressing the appropriate key. Each response generates another display (i.e., the rate of stimulus presentation is subject controlled). For this study, the total number of sums attempted and the total correct responses were recorded over a two-minute period.

7. *Self-reported intoxication scales.* Subjects were asked to assess their degree of intoxication (or "stone") by means of a 0 to 10 analog scale; 0 meaning that they feel no drug effect at all, being completely "straight" and 10 as being "stoned as I have ever been." These assessments were made at each post treatment time of testing (see below).

Procedure

In order to avoid differential carry-over effects [Keppel (9)] each subject was randomly assigned to one of the five dosage groups, with 16 subjects per group. The experiment was conducted double blind such that neither the subjects nor the observers were aware of the treatment until the experiment was concluded.

The subjects arrived at the laboratory having consumed a light breakfast. The battery of tests was fully explained and each subject underwent first a practice run on all of the tests and then the first predrug, control run (T_0). The capsules of THC or placebo were then taken with water and subjects completed the test battery at 80 (T_1), 140 (T_2), 200 (T_3) and 260 min (T_4) after dosage.

Data Analysis

The experimental design is a 5×5 factorial with repeated measures on the second factor. Factors and factor levels are:

A (dose level): 0 (placebo), 5, 10, 15, 20 mg/70 kg

B (time of testing): T_0, T_1, T_2, T_3, T_4.

The analysis of the performance data was based on a linear model of the dose-response relationship. Changes over time in THC effects were examined by comparing the slope (b_0) of the regression line relating performance to dose level at time T_0 with the slopes (b_1 to b_4) of the corresponding regression lines at subsequent measurement occasions (T_1 to T_4). These slope differences (b_0–b_1, b_0–b_2, b_0–b_3, b_0–b_4) define a set of comparisons accounting for changes over time in the linear component of the dose-response relationship (A_{lin} B). Bonferroni adjusted *t*-tests [Harris (7)] were carried out on the slope differences, in order to ensure that the Type I error rate was not inflated beyond conventional levels. Because this analysis ignores any nonlinear components of the dose-response relationship, F-tests were carried out on the residual (nonlinear) components of the dose × time interaction (A_{res} B). These are tests of the fit of the linear dose-response model to the data.

The statistical tests outlined above were carried out on each measure and also on the centroid (the unweighted mean) of the standard scores on the set of measures. Previous research using the same battery (1,2) has shown that a single measure of the general level of performance on the test battery as a whole is likely to be particularly sensitive to the effects of ethanol or cannabis. Since intoxication ratings were not obtained before the drug was administered (T_0), they cannot be subjected to the analysis outlined above.

RESULTS

(a) *Performance measures:* The outcomes of the statistical tests on the performance measures are shown in Table 1, and the dose-response relationship at each time of testing on the centroid of the measures is depicted in Fig. 1. The points plotted in Fig. 1 are adjusted means, corrected for (1) differences between groups at T_0, and (2) differences across measurement occasions in the placebo group (practice effects).

As can be seen from the nonsignificant F ratios in the final column of Table 1 there is no suggestion of departures from linearity in the dose-response relationship observed on any of the performance measures. The analysis of scores on the centroid, the measure of general level of performance, showed a significant dose-response relationship at all times of testing up to 200 min after drug ingestion (T_3). It can be seen from Fig. 1 and Table 1 that the slopes of the best fitting straight lines on the centroid are very similar at times T_1, T_2, and T_3 (as the *t* ratios of 6.66, 6.04 and 5.07 suggest). By T_4 however, the slope is not significantly different from zero ($t = 2.25$).

The influence of THC on individual performance measures can

TABLE 1

ANALYSIS OF THE DOSE × TIME INTERACTION OF PERFORMANCE DATA

Variable	T_0-T_1	T_0-T_2	T_0-T_3	T_0-T_4	A_{res} B F ratios (12,300 *df*)
	A_{lin} B *t* ratios (300 *df*)				
Centroid	6.66†	6.04†	5.07†	2.25	0.48
Standing Steadiness (eyes open)	5.56†	5.51†	4.24†	2.60*	1.30
Standing Steadiness (eyes closed)	6.02†	5.87†	2.89*	1.48	0.75
Pursuit Rotor (No. of errors) (−)	3.36†	2.71*	2.84*	1.23	0.58
Pursuit Rotor (time on target)	3.14*	2.08	1.32	0.51	0.50
VDA (number correct)	4.41†	3.31†	1.25	0.48	0.87
Reaction Time (visual) (−)	1.04	0.95	3.44†	1.08	0.72
Reaction Time (auditory) (−)	0.93	2.55*	1.92	−0.04	0.55
Complex Reaction Time (−)	0.58	−0.05	0.52	−0.02	0.55
Number Test (number correct)	5.74†	5.39†	3.90†	3.45†	1.63

*$p<0.05$/k, †$p<0.05$/kp, where k = No. of planned contrasts (4) and p = number of variates (10).

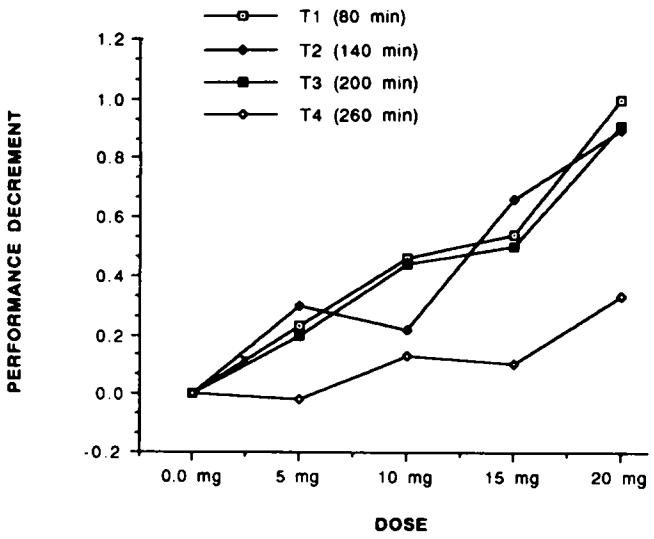

FIG. 1. The dose-response relationship of the scores on the performance measure across all testing times.

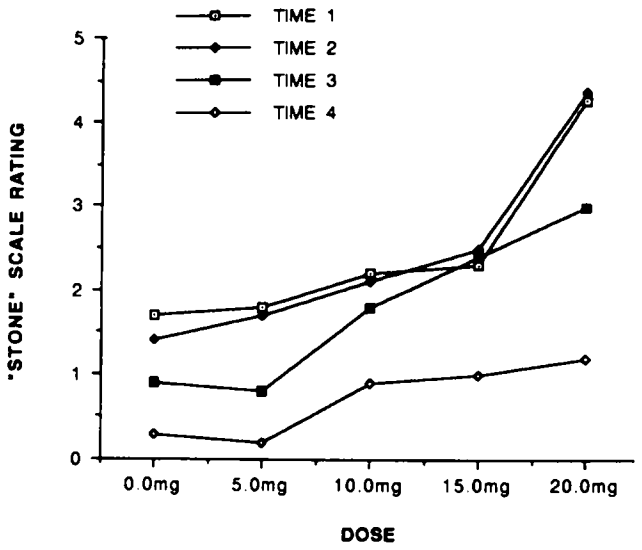

FIG. 2. The dose-response relationship across all testing occasions of the subjective assessment of intoxication ("Stone scale"). Time 1, 2, 3, 4 = 60, 140, 200, 260 minutes (respectively) after dosing.

be seen in Table 1. The most striking effects were those on the arithmetic test and the standing steadiness (eyes open condition). In these tests the t ratios for the A_{lin} B interaction (indicating a significant dose-response relationship) were significant at each time point. Similarly, significant ratios were recorded up to T_3 for pursuit rotor (errors) and standing steadiness (eyes closed). The drug effect on the VDA was significant up to 140 min after dosage (T_2).

(b) *Intoxication ratings:* The dose-response relationship between THC and the mood effects determined by the 'stone' rating scale is depicted in Fig. 2. The lowest (5 mg) dose was clearly not distinguishable from placebo, though the remaining doses exhibited a dose-dependent effect. When examined across time the peak of the subjective stone rating occurred at or about T_1 or T_2 (80 and 140 min after dosing respectively) and was little changed across this time period for all doses. The duration of subjective intoxication appeared to be dependent upon dose because, as can be seen in Fig. 2, a trend for a dose-response difference still existed at T_4 (260 min after the drug had been taken).

DISCUSSION

The centroid of the set of measures is a sensitive index of the performance on the battery as a whole and is, therefore, a powerful indicator of the degree of impairment produced by the drug. The scores on the centroid indicate that the slope of the linear regression of performance on dose levels was significantly different from that at T_0 (predrug) for up to 200 min after dosage. That is to say, the drug produced significant impairment of performance skills for a period in excess of 3 hours. The F ratios for the residual interaction variation (A_{res} B, Table 1) indicated that there were no significant departures from linearity in these dose-response relationships. These data, therefore, suggest that the dose-response relationship for orally administered THC, administered at four dose levels, on the performance of human volunteers on the test battery is essentially linear.

It is interesting to compare with the above performance measures, the dose-response relationship of THC on the self-assessment of intoxication. Apart from the 5 mg dose which was not distinguishable from placebo, the doses of THC were clearly and constantly delineated across time. Although subjects were

used once only, the ability of the simple analogue scale to detect the dose-response relationship was clearly demonstrated in this study. The time course of the effects of the drug on the performance measures and on the subjective assessment of intoxication at the various dose levels were quite similar, suggesting a correlation between the drug induced impairment of skills performance and the effects on mood.

Although cannabis is most commonly smoked it is, nevertheless, eaten in various forms by many users of the drug. There have been very few studies of the effect of cannabis on human performance in which the drug has been given by mouth, and of these even fewer have attempted to determine a dose-response relationship for these effects. Kielholz and colleagues (10), using three doses of THC (in olive oil) all of which were greater than those used in the present study, did not demonstrate a dose-response relationship for the drug on the measures used. Rafaelsen *et al.* (11), on the other hand, administered cannabis resin in baked cakes to provide doses within the range of those employed in the present study, did provide data that suggested a dose-response effect though they did not present a formal regression analysis. The present study has demonstrated that a dose-response relationship exists for the effects of orally administered THC for both performance skills and for the subjective assessment of intoxication. Furthermore, the study indicates that the potency of orally administered THC is greater than that previously estimated (8). In an evaluation of the literature, this author considered that a dose of THC of approximately 30 mg by mouth was needed to produce easily measurable physiological and subjective effects.

REFERENCES

1. Belgrave, B. E.; Bird, K. D.; Chesher, G. B.; Jackson, D. M.; Lubbe, K. E.; Starmer, G. A.; Teo, R. K. C. The effect of (−)trans delta-9-tetrahydrocannabinol, alone and in combination with ethanol, on human performance. Psychopharmacology (Berlin) 62:53–60; 1979.
2. Belgrave, B. E.; Bird, K. D.; Chesher, G. B.; Jackson, D. M.; Lubbe, K. E.; Starmer, G. A.; Teo, R. K. C. The effect of cannabidiol, alone and in combination with ethanol on human performance. Psychopharmacology (Berlin) 64:243–246; 1979.
3. Bird, K. D.; Boleyn, T.; Chesher, G. B.; Jackson, D. M.; Starmer, G. A.; Teo, R. K. C. Interactions among the cannabinoids (THC, CBD and CBN) alone and when combined with ethanol: effects on human performance. In: Goldberg, L., ed. Alcohol, drugs and traffic safety. vol. 3. Stockholm: Almqvist Wiksell; 1981:1111–1125.
4. Bird, K. D.; Boleyn, T.; Chesher, G. B.; Jackson, D. M.; Starmer, G. A.; Teo, R. K. C. Intercannabinoid and cannabinoid-ethanol interactions and their effects on human performance. Psychopharmacology (Berlin) 71:181–188; 1980.
5. Chesher, G. B.; Franks, H. M.; Hensley, V. R.; Hensley, W. J.; Jackson, D. M.; Starmer, G. A.; Teo, R. K. C. The interaction of ethanol and delta-9-tetrahydrocannabinol in man. Effects on perceptual, cognitive and motor functions. Med. J. Aust. 2:159–163; 1976.
6. Chesher, G. B.; Franks, H. M.; Jackson, D. M.; Starmer, G. A.; Teo, R. K. C. Ethanol and delta-9-tetrahydrocannabinol interactive effects on human perceptual, cognitive and motor functions II. Med. J. Aust. 1:478–481; 1977.
7. Harris, R. J. A primer of multivariate statistics. 2nd ed. Orlando, FL: Academic Press; 1985.
8. Jones, R. T. Human effects: An overview. In: Petersen, R., ed. Marijuana research findings: 1980. N. I. D. A. Research Monograph Series No. 31. Washington, DC: U.S. Government Printing Office; 1980.
9. Keppel, G. Design and analysis: A researcher's handbook. Englewood Cliffs, NJ: Prentice-Hall; 1982.
10. Kielholz, P.; Hobi, V.; Ladewig, D.; Miest, R.; Richter, R. An experimental investigation about the effect of cannabis on car driving behaviour. Pharmacopsychiatry 6:91–103; 1973.
11. Rafaelsen, O. J.; Bech, P.; Christiansen, J.; Nyroe, J.; Rafaelsen, L. Cannabis and alcohol: effects on simulated car driving. Science 179:920–923; 1973.