Pharmacology Biochemistry & Behavior, Vol 29, pp 553–557 © Pergamon Press plc, 1988 Printed in the U S A 0091-3057/88 $3 00 + 00

A Cumulative Dosing Procedure for Administering Marijuana Smoke to Humans

L. D. CHAIT,[1] R. L CORWIN AND C. E. JOHANSON

Drug Abuse Research Center, Department of Psychiatry, The Pritzker School of Medicine The University of Chicago, Chicago, IL 60637

Received 1 June 1987

CHAIT, L D , R L CORWIN AND C E JOHANSON *A cumulative dosing procedure for administering marijuana smoke to humans* PHARMACOL BIOCHEM BEHAV **29**(3) 553–557, 1988 —Subjective, behavioral and physiological effects of smoked marijuana were measured with a cumulative dosing procedure which allowed dose-related effects to be determined within a single experimental session Five male and three female occasional marijuana smokers participated Unit doses of marijuana smoke were administered in a standardized manner on four occasions during each session, each occasion spaced 20 minutes apart This procedure resulted in a cumulative dose of active (1 4%-THC) marijuana of 0, 2, 4 and 8 puffs after the four successive smoking occasions, respectively Dependent variables were measured after each smoking occasion Smoke absorption was monitored by measuring expired air carbon monoxide levels Subjects participated in three identical sessions spaced a week apart in order to assess the reliability of the procedure During a fourth session, only placebo (0 0%-THC) marijuana was administered throughout the session as a control Significant linear dose-effect functions were obtained on several measures, with good session-to-session replicability of most effects The results demonstrate the feasibility of using a cumulative dosing procedure to evaluate dose-related effects of smoked marijuana in humans The procedure would be especially useful for the assessment of shifts in dose-effect curves as a result of various experimental manipulations

Human Marijuana Cumulative dosing Carbon monoxide Subjective effects Smoking Behavioral effects

THE present study was designed to evaluate a cumulative dosing procedure for studying the effects of smoked marijuana in humans. Cumulative dosing techniques have been adopted in recent years by behavioral pharmacologists because these techniques allow the determination of a dose-effect function within a single experimental session [3, 4, 12, 21, 22] In contrast, behavioral studies using traditional single-dose testing generally require a considerable length of time to obtain dose-effect functions because of the need to space sessions several days apart to minimize "carry-over" effects The savings in time (sessions) provided by cumulative dosing methods are particularly important for human studies in which, for both practical and ethical reasons, the number of experimental sessions in which each subject can participate is limited

A recent study from this laboratory successfully employed a cumulative dosing procedure for studying the effects of ethanol on eye tracking behavior in rhesus monkeys and humans [2] The present study adapted this basic procedure for use with marijuana smoking. A standardized smoking regimen was employed to administer marijuana smoke, and changes in expired air carbon monoxide (CO) level were used to quantify smoke absorption [5,6] The effects of marijuana were evaluated on a range of dependent variables shown previously to be sensitive to acute marijuana administration [5, 6, 16, 19] Finally, in order to evaluate the reliability of the procedure, the cumulative dose-effect functions were determined on three separate occasions, spaced one week apart

METHOD

Subjects

Five male and three female adults participated They ranged in age from 18–25 years (mean=20 9) All were experienced marijuana smokers Average use of marijuana during the previous 12 months ranged from once a month to 4–6 times per week No subject had a history of substance use disorder (DSM-III criteria), except for tobacco dependence Three subjects smoked tobacco cigarettes but none smoked more than 10 cigarettes per day Subjects provided a detailed drug and medical history, and received a psychiatric and physical examination (including EKG) before beginning the study. Informed consent was obtained and subjects were paid for their participation at the end of the study

Procedure

The study consisted of four sessions, each separated by one week Sessions were held on weekday evenings from 7 00 to 10 30 p m Each subject was tested separately in a room (approximately 3.0×4 3 m) equipped with comfortable furniture, reading material and a color television or stereo

[1]Requests for reprints should be addressed to L D Chait, Department of Psychiatry, Box 411, University of Chicago, Chicago, IL 60637

equipment An attempt was made to provide a relaxed, casual environment Before the study began subjects attended a practice session to become familiar with the experimental setting and procedures and to practice the behavioral tasks

Subjects were told that the four experimental sessions would be identical procedurally, and that during the course of the study they could receive either active or placebo marijuana Subjects were instructed not to smoke marijuana or use any other drugs (except tobacco or caffeine) during the 24 hours before sessions With this exception, subjects were told not to deviate from their usual pattern of drug use outside the laboratory Tobacco smokers were asked not to smoke within 30 min of scheduled sessions and were not allowed to smoke tobacco during sessions Subjects were also not allowed to eat during sessions, but drinking water was freely available After sessions subjects were provided with transportation home

During each session subjects smoked marijuana on four separate occasions, spaced 20 min apart This dosing interval was chosen because most of the effects of marijuana that we intended to measure peak within 20 min of smoking Each smoking occasion (bout) consisted of four uniform puffs, spaced 60 sec apart The time it took to smoke (approximately 3 min) is included as part of the 20 min interbout interval For each puff subjects were instructed to inhale the smoke for 5 sec, hold in the smoke for 10 sec, and then exhale [5] Baseline measures (heart rate, expired air CO level, subjective effects and cognitive/psychomotor performance) were obtained during the 20 min before the first smoking bout, and during the ~17 min after each of the four smoking bouts All measures except CO level were again determined at the end of the session (about one hr after the final smoking bout) On each occasion measurements were made in the same sequence heart rate first, followed by CO, subjective effects and performance

The dosage regimen was identical for the first three sessions the first bout consisted of four puffs of placebo marijuana, the second and third bouts consisted of two puffs of placebo marijuana followed by two puffs of 1 4%-THC marijuana, and the fourth bout consisted of four puffs of 1 4%-THC marijuana Thus, after each successive smoking bout subjects received 0, 2, 4 or 8 cumulative unit doses (puffs) of active marijuana, respectively For the last session subjects received only placebo marijuana throughout all four smoking bouts This last session served as a control condition, to ensure that any dose-related changes observed in the first three sessions were not due solely to expectation effects or to other uncontrolled variables unrelated to drug administration (e g , to the passage of time) Subjects were blind to the dosing conditions

Marijuana Cigarettes

Standard, pre-rolled marijuana cigarettes weighing approximately 800–900 mg were supplied by the National Institute on Drug Abuse (NIDA) The cigarettes contained either 0 0 or 1 4% delta-9-THC (assayed by NIDA) Cigarettes were stored in airtight containers in a cold room, and were humidified for 48 hr at room temperature before use, according to instructions provided by NIDA Cigarettes were cut in half before smoking and were smoked through hollow plastic cigarette holders Cigarettes were lit mechanically by the experimenter Subjects took two puffs from each half-length cigarette Further details on cigarette preparation appear elsewhere [5]

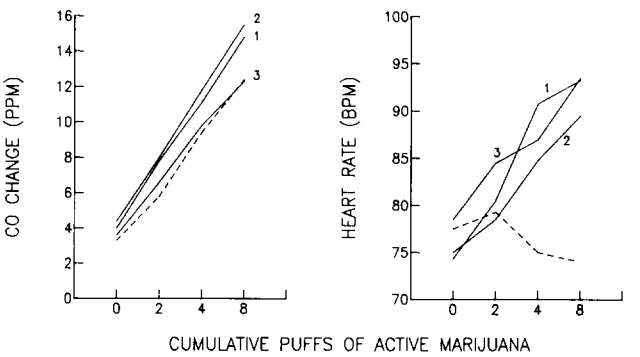

FIG 1 Group (N=8) dose-effect functions for expired air carbon monoxide level (expressed as change from pre-smoking baseline) and heart rate The numbers 1, 2 and 3 indicate the first, second and third session The dashed lines show the results obtained during the fourth session, when only placebo marijuana was administered

Dependent Variables

Sitting radial heart rate was measured digitally End alveolar expired air was collected according to the procedure described in [7] Samples were read immediately with a portable CO meter (MiniCO Model 1000, Catalyst Research Corp , Baltimore) Readings are presented as ppm and were corrected for ambient level

Subjective effects were measured with two brief questionnaires One consisted of 20 true-false items from the Addiction Research Center Inventory (ARCI) There were 8 "dummy" items and 12 items shown previously to be sensitive to the effects of smoked marijuana (M scale, [6]) The other questionnaire was a series of six 100-mm visual analog scales (VAS), labelled "stimulated," "high," "anxious," "sedated," "down" and "hungry" [6]

Performance effects of marijuana were measured with a computerized version of the digit span test (forward only) and a visual divided attention task Subjects performed the digit span twice on each occasion, and the better of the two scores (number of successive digits correctly recalled) was recorded The divided attention task lasted for 5 min and required subjects to respond as quickly as possible to a target stimulus (the digit zero) in a continuous string of random digits while at the same time counting the number of occurrences of a second target stimulus (the digit five followed immediately by a digit larger than five) Detailed descriptions of these two tasks can be found in McLeod *et al* [17]

Data Analysis

Each dependent variable was analyzed by two-way univariate analysis of variance for repeated measures (BMDP2V) The two factors were Dose (0, 2, 4, 8 puffs) and Session (1st, 2nd, 3rd) Because the primary purpose of the study was to evaluate the reliability (replicability) of the dose-effect functions, data from the fourth (placebo) session were not included in the analyses, but are shown in the figures for comparison With this method of analysis, a significant main effect of Dose would indicate that the variable was sensitive to the cumulative dosing manipulation (assuming that the change could not reasonably be attributed simply to the passage of time) A significant main effect of Session would indicate change in the variable between sessions, which could be due to an unstable baseline or practice ef-

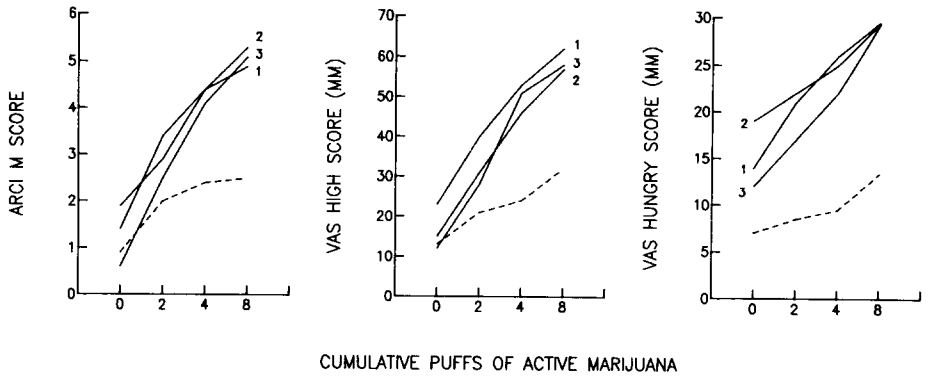

FIG 2 Group (N=8) dose-effect functions for subjective effects

fects. Finally, a significant Dose × Session interaction would indicate differences between sessions in sensitivity of the variable to the dosing regimen, possibly the result of tolerance or sensitization Significant Session effects or Dose × Session interactions would raise serious questions about the reliability and usefulness of the cumulative dosing procedure.

When significant ($p \leq 0$ 05) F values were obtained from the analyses of variance, orthogonal polynomial trend analysis was used to characterize trends across dose Huynh-Feldt adjustments of within-factors degrees of freedom were used to protect against violations of sphericity assumptions [9].

RESULTS

Significant Dose effects were obtained for eight dependent variables. No significant effect of Session or Dose × Session interaction was obtained for any of the dependent variables, indicating that the dose-effect functions did not differ across the three replications.

Carbon Monoxide

Expired air CO level increased as a linear function of dose (Fig. 1), $F(3,21)=16$ 7, $p<0.005$ CO levels increased to a similar degree after placebo smoking during the fourth session. This result demonstrates the efficacy and reliability of the standardized smoking regimen. However, there was much variability between subjects in the mean increase in CO that occurred after each smoking bout, from about 1 ppm to 7 ppm

Heart rate

Heart rate also increased as a linear function of dose (Fig 1), $F(3,21)=26.4$, $p<0.0001$. When placebo only was administered during the final session, heart rate decreased slightly, demonstrating that the increased heart rate observed during the first three sessions was a pharmacological response to THC

Subjective Effects

Linear increases as a function of dose were obtained for three of the subjective effects scales (Fig. 2). ARCI M, $F(3,21)=14.4$, $p<0$ 0005, VAS "high," $F(3,21)=61$ 8, $p<0.0001$, and VAS "hungry," $F(3,21)=21.1$, $p<0.0005$ For the M scale and rating of "high" the dose-related increases were clearly greater during the first three sessions than during the final placebo session, evidence that these subjective changes can be attributed to the pharmacological effects of THC The situation was not as clear for ratings of "hungry," however, due to baseline (0 puffs) differences between the placebo session and the other three sessions. However, the mean increase in ratings of "hungry" from 0 to 8 puffs was significantly greater than zero in each of the first three sessions (Student t-tests, p's<0.025) but not in the placebo session ($p=0$ 13) This suggests that at least part of the increase in ratings of "hungry" was dependent upon the presence of THC.

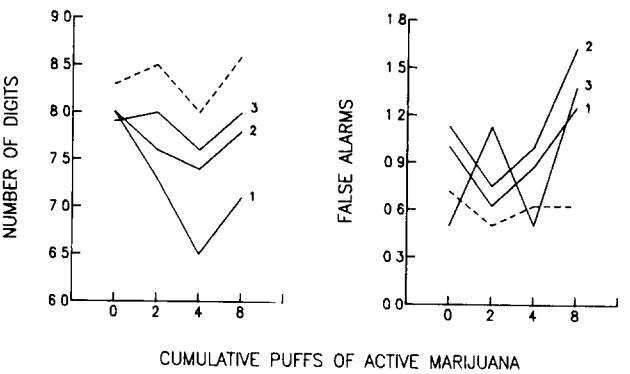

FIG 3 Group (N=8) dose-effect functions for the number of digits correctly recalled on the digit span task, and the number of false alarms made during the divided attention task

Performance Measures

Both behavioral tasks showed dose-related effects (Fig. 3) The number of digits correctly recalled in the digit span task decreased as a function of dose of active marijuana, $F(3,21)=4$ 9, $p<0$ 01, both linear and quadratic trends were significant, and, unexpectedly, peak effects were consistently observed after 4 puffs. There was no evidence of a performance decrement during the placebo session There was a tendency for the decrement in digit span performance to diminish across the first three sessions, suggesting tolerance development; however, this effect did not approach statistical significance (Dose × Session interaction, $F(6,42)=0$ 8, $p>0$ 5)

In the divided attention task, there were no effects of marijuana dose on the number of misses of the zero stimulus or on mean reaction time to the zero stimulus False alarm rate (the number of zero-appropriate responses to the five target) increased as a function of dose of active marijuana, $F(3,21)=3\ 9$, $p<0\ 05$, but was unchanged during the placebo session (Fig 3) The increased false alarm rate was not apparent until after 8 puffs of active marijuana

There was also a significant effect of dose on accuracy in estimating the number of occurrences of the five target stimulus in the divided attention task, $F(3,21)=5\ 3$, $p<0\ 01$ However, this effect was slight, showed a complex relation to dose and was not outside the range obtained during the placebo session, making interpretation difficult

DISCUSSION

This study demonstrates that a cumulative dosing procedure can be successfully employed in evaluating the effects of marijuana smoking in humans Linear dose-related changes were obtained on most of the dependent variables that were selected for study These effects were replicable when the dose-effect functions were twice redetermined at weekly intervals The fact that these effects were absent or considerably attenuated during the final (placebo only) session is evidence that these effects were primarily the result of THC absorption It was notable that placebo effects were observed for the three subjective effects scales (Fig 2), but not for the physiological measure of heart rate (Fig 1) Subjective responses to placebo marijuana are not uncommon [5,15], and the design of the present study should have been particularly conducive to showing conditioned placebo effects, since the placebo session was scheduled after three seemingly identical sessions at which active marijuana was administered [20]

Most of the dose-related effects of smoked marijuana obtained here with a cumulative dosing procedure have been observed in other studies using single-dose administration of marijuana or THC expired air CO level, heart rate, subjective "high" [5, 6, 13], digit span [19], and visual divided attention [16] The apparent marijuana-induced increase in self-reported "hungry" ratings was an interesting finding in view of anecdotal and experimental reports of increased appetite and food intake in humans after marijuana smoking or oral THC [1, 10, 11, 14]

It remains to be determined whether single-dose administration of marijuana smoke would yield dose-effect functions equivalent to those obtained with the cumulative dosing technique Several studies have directly compared the behavioral effects of drugs with cumulative vs single dosing techniques [3, 18, 21, 22] In all cases, qualitatively similar effects were obtained with the two dosing procedures, and in most cases the effects were quantitatively similar as well Whether a cumulative dosing procedure will produce the same dose-effect function as a single dosing procedure depends upon a number of factors, including the particular drug under study and the particular response being measured For example, for a drug with a rapid onset and a long duration of action, the effect of a cumulative dose should approximate the effect of the corresponding non-cumulative (single) dose [4]

A previous study from this laboratory [5] is relevant to this issue That study examined the effects of four puffs of 1 4%-THC marijuana administered as a single dose to six subjects similar to those studied in the present report The smoking procedure was identical to that employed here The single-dose administration resulted in a mean "high" rating (20 min after smoking) of 43, and a mean heart rate increase (5 min after smoking) of 28 bpm In the present study, this same dose of marijuana administered cumulatively resulted in a mean (across the three determinations) "high" rating of 50, and a mean heart rate increase of 14 bpm Thus, "high" ratings were similar with the two procedures, but heart rate change was less with the cumulative dosing procedure This may reflect acute tolerance development to the cardiovascular effects of marijuana, an effect reported elsewhere [6,8] This difference also points out the fact that the comparability of dose-effect functions obtained from single vs cumulative dosing depends upon the response being studied

Cumulative dosing techniques are most useful for determining the variety of effects from a range of drug dosages, where the precise quantitative details of dosage are not important [4] The type of procedure described here would be particularly useful for studying relative shifts in the dose-effect functions of smoked marijuana in response to experimental manipulations, for example, in drug interaction studies (to demonstrate antagonism or potentiation of marijuana effects) or in studies examining the effects of chronic drug administration on sensitivity to marijuana (cross-tolerance or sensitization)

ACKNOWLEDGEMENTS

This research was supported by grant DA-03517 from the National Institute on Drug Abuse The authors wish to thank Drs S McCracken and K G Chua for subject screening

REFERENCES

1 Abel, E L Effects of marihuana on the solution of anagrams, memory and appetite *Nature* **231:** 260–261, 1971
2 Ando, K , C E Johanson and C R Schuster The effects of ethanol on eye tracking in rhesus monkeys and humans *Pharmacol Biochem Behav* **26:** 103–109, 1987
3 Bertalmio, A J , S Herling, R Y Hampton, G Winger and J H Woods A procedure for rapid evaluation of the discriminative stimulus effects of drugs *J Pharmacol Methods* **7:** 289–299, 1982
4 Boren, J J The study of drugs with operant techniques In *Operant Behavior Areas of Research and Application*, edited by W K Honig New York Appleton-Century-Crofts, 1966, pp 531–564
5 Chait, L D , S M Evans, K A Grant, J B Kamien, C E Johanson and C R Schuster Discriminative stimulus and subjective effects of smoked marijuana in humans *Psychopharmacology (Berlin)*, in press, 1988
6 Chait, L D , M W Fischman and C R Schuster "Hangover effects the morning after marijuana smoking *Drug Alcohol Depend* **15:** 229–238, 1985
7 Chait, L D and R R Griffiths Smoking behavior and tobacco smoke intake Response of smokers to shortened cigarettes *Clin Pharmacol Ther* **32:** 90–97, 1982
8 Cocchetto, D M , S M Owens, M Perez-Reyes, S DiGuiseppi and L L Miller Relationship between plasma delta-9-tetrahydrocannabinol concentration and pharmacologic effects in man *Psychopharmacology (Berlin)* **75:** 158–164, 1981
9 Dixon, W J *BMDP Statistical Software* Berkeley University of California Press, 1983
10 Foltin, R W , J V Brady and M W Fischman Behavioral analysis of marijuana effects on food intake in humans *Pharmacol Biochem Behav* **25:** 577–582, 1986

11 Greenberg, I , J Kuehnle, J H Mendelson and J G Bernstein Effects of marihuana use on body weight and caloric intake in humans *Psychopharmacology (Berlin)* **49:** 79–84, 1976
12 Hanson, H M , J J Witoslawski, E H Campbell and A G Itkin Estimation of relative antiavoidance activity of depressant drugs in squirrel monkeys *Arch Int Pharmacodyn* **161:** 7–16, 1966
13 Herning, R I , W D Hooker and R T Jones Tetrahydrocannabinol content and differences in marijuana smoking behavior *Psychopharmacology (Berlin)* **90:** 160–162, 1986
14 Hollister, L E Hunger and appetite after single doses of marihuana, alcohol, and dextroamphetamine *Clin Pharmacol Ther* **12:** 44–49, 1971
15 Jones, R T Marihuana-induced "high" Influence of expectation, setting and previous drug experience *Pharmacol Rev* **23:** 359–369, 1971
16 MacAvoy, M G and D F Marks Divided attention performance of cannabis users and non-users following cannabis and alcohol *Psychopharmacologia* **44:** 147–152, 1975
17 McLeod, D R , R Hoehn-Saric, A S Labib and D J Greenblatt Six weeks of diazepam treatment in normal women Effects on psychomotor performance and psychophysiology *J Clin Psychopharmacol,* in press, 1988
18 McMillan, D E , D A Cole-Fullenwider, W C Hardwick and G R Wenger Phencyclidine discrimination in the pigeon using color tracking under second-order schedules *J Exp Anal Behav* **37:** 143–147, 1982
19 Melges, F T , J R Tinklenberg, L E Hollister and H K Gillespie Marihuana and temporal disintegration *Science* **168:** 1118–1120, 1970
20 Stewart, J , H de Wit and R Eikelboom Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants *Psychol Rev* **91:** 251–268, 1984
21 Thompson, D M , J M Moerschbaecher and P J Winsauer Drug effects on repeated acquisition Comparison of cumulative and non-cumulative dosing *J Exp Anal Behav* **39:** 175–184, 1983
22 Wenger, G R Cumulative dose-response curves in behavioral pharmacology *Pharmacol Biochem Behav* **13:** 647–651, 1980