Psychopharmacology 66, 45 – 50 (1979)

Psychopharmacology

Interaction of Cannabidiol and Alcohol in Humans*

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Abstract. Six male and four female healthy volunteers were given oral placebo (glucose capsule and orange juice), cannabidiol (CBD 200 mg capsule and orange juice), alcohol (1 g/kg in orange juice and glucose capsule), and CBD (200 mg capsule) plus alcohol (1 g/kg in orange juice) in a double-blind, crossover, randomized design. Treatments were spaced one week apart. Parameters measured were a finger tap test (motor performance), cancellation and differential aptitude tests (psychomotor performance), a 1-min time production task, subjective effects (66 item adjective-pair semantic differential), and breathalyzer estimations of blood alcohol levels. Compared to placebo, alcohol and alcohol plus CBD, but not CBD alone, produced significant impairments of motor and psychomotor performances, overestimations of time production and subjective responses indicating an accurate self-perception of their intoxication and deficits. The combination of alcohol plus CBD resulted in significantly lower blood alcohol levels compared to alcohol given alone, however, there were few differences observed between the pharmacological effects of the two alcohol conditions. Thus, the inactivity of CBD, a major marijuana constituent, on motor and mental performance and effects also extends to its interaction with alcohol.

Key words: Cannabidiol – CBD – Marijuana – Alcohol – Human interaction – Psychomotor effects – Subjective effects – Blood alcohol levels – Breathalyzer

Two of the most commonly used drugs, both singly and in combination, are alcohol and marijuana (Fisher and Brickman, 1973). Several studies (Hansteen et al., 1976; Manno et al., 1971; Rafaelsen et al., 1973) have documented pharmacological interactions between alcohol and Δ^9-tetrahydrocannabinol (THC), the major psychoactive principle of marijuana. However, no human data are available concerning interactions of alcohol with cannabidiol (CBD), another major marijuana constituent (Carew, 1971). While CBD is devoid of the typical THC-produced psychoactivity and cardiotonic effects in man (Dalton et al., 1976; Hollister, 1973; Karniol et al., 1974; Perez-Reyes et al., 1973), the cannabinoid cannot be considered inactive. In rodents, CBD has been shown to produce a hypnotic effect on the sleep-wakefulness cycle (Monti, 1977), to markedly inhibit liver enzymes (Siemens et al., 1976) and to augment or block the pharmacological effects of several drugs such as barbiturates (Consroe and Wolkin, 1977; Siemens et al., 1976), various antiepileptics (Consroe and Wolkin, 1977) and THC (Dalton et al., 1976; Karniol et al., 1974). Further, CBD has potent anticonvulsant effects in various laboratory animal species (Consroe and Wolkin, 1977; Karler and Turkanis, 1976) and preliminary data suggest similar effects occur, therapeutically in epileptic patients (Cunha et al., 1979). In this latter phase 2, double-blind study, 16 patients with secondary generalized epilepsy and temporal focuses and who were refractory to several standard antiepileptic drugs, received oral 200 mg CBD (8 patients) or placebo (8 patients) daily for $4^1/_2$ months, in addition to their daily anticonvulsant medication. Based upon clinical and EEG criteria, 4 of the CBD patients remained completely free of seizures; 3 patients presented partial improvement and 1 showed no improvement. Seven placebo patients remained unchanged in their clinical condition and 1 presented clear improvement. In view of all the above considerations, the present study was designed to evaluate

* This research was supported, in part, by the University of Arizona (Sabbatical Leave), a fellowship from the Fundacão de Amparo ã Pesquisa do Estado de São Paulo (FAPESP), and the National Institute on Drug Abuse grant No. DA01448

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0033-3158/79/0066/0045/$01.20

the acute pharmacological interaction between CBD and alcohol on human motor and cognitive functions, subjective responding, and blood alcohol levels.

Materials and Methods

Subjects were ten healthy post graduate student volunteers: six males and four females, with an age range of 21–33 years and a weight range of 52–85 kg. Medical histories indicated that 5 subjects had smoked marijuana infrequently (maximum of once per week) but only several years ago. Alcohol consumption (generally 1–4 glasses of beer or wine) included once per day (1 subject), 1–4 times per week (7 subjects), and 3 times per month (2 subjects). Except for cigarettes (7 subjects) and coffee or tea (9 subjects), no other drug consumption was reported. Each volunteer was told in detail the purpose and design of the experiment, and informed consent was obtained. Subjects were instructed to refrain from drinking alcohol on the day before and on the day of their experiment, to refrain from drinking coffee and tea and smoking cigarettes at least 1.5 h before their test, and to teat one sandwich with fruit juice 1.5 h before their experiment. Experiments were conducted between 11.00 a.m. and 4.00 p.m. Crystalline cannbidiol, about 99% pure (supplied by R. Mechoulam, Israel), was stored in a glass vial at −20°C and protected from light. Thin layer chromatographic analyses (using cyclohexane on dimethylformamide-impregnated plates) in our laboratory indicated relative purity of the CBD. The batch source and dose of CBD were the same for the present study and the previous investigation in epileptic patients cited above. Cannabidiol or glucose in single doses of 200 mg, were incorporated into opaque gelatin capsules whereas alcohol (99% ethanol, Merck Co.) was dissolved in orange juice in a total volume of 300 ml. Each subject was given 4 treatments as follows: (1) placebo (orange juice with 4 ml ethanol floating on top plus 1 glucose capsule); (2) CBD (1 CBD capsule plus orange juice as above); (3) alcohol (1 g/kg ethanol in orange juice plus 1 glucose capsule); (4) CBD + alcohol (1 CBD capsule plus 1 g/kg ethanol in orange juice). In each case the capsule and drink were ingested simultaneously and drinking time was completed within about 5 min. Treatments were given to each subject in a random order. One week between treatments was standard throughout, and a double-blind procedure was employed. For each treatment, objective and subjective tests, described below, were administered to each subject immediately before and at 30, 60, 120 and 240 min following drug or placebo ingestion. The complete test battery took about 25 min per session.

The cancellation test used was a modification of a visual-motor test developed by Sack and Rice (1974) and was intended to measure various psychomotor processes of attention and concentration. It consisted of a closely spaced block of 400 numbers on a piece of paper with each number (0–9) occurring equally and randomly spaced throughout the matrix. Subjects were instructed to draw a line through a particular digit (e.g., every number 4) as rapidly as possible. Speed and accuracy were measured by ascertaining the total time to take the test and the number of correct and incorrect responses.

The differential aptitude test (Form A, the Psychological Corporation, N.Y.) was a visual-motor test measuring attention and concentration (Anastasi, 1969). It consisted of a series of 2-digit trigams on a question sheet (e.g., A 7, 7 A, B 7, 7 B, AB) with one of them underscored for recognition. Subjects were instructed to underline the correct response (e.g., 7 B, B 7, 7 A A 7) on an answer sheet for each item as rapidly as possible. Clerical speed and accuracy were determined by measuring the total time/50 item trial and the number of correct and incorrect responses.

The time production task (Karniol et al., 1974), a measure of internal perceptual function, was performed by asking subjects to estimate when he/she thought a 60-s interval had passed, on each of 5 successive trials. Time estimations were recorded and averaged for each subject.

The finger tap test (Halstead, 1947) measured undirected motor speed of upper extremities and consisted of a round (2.5 cm) telegraph key attached to a mechanical digital counter that was shielded from subject view by an enclosed box. Subjects were instructed to tap, with the index finger of their dominant hand, as rapidly as possible during a timed 1-min interval. Total number of taps/trial were recorded.

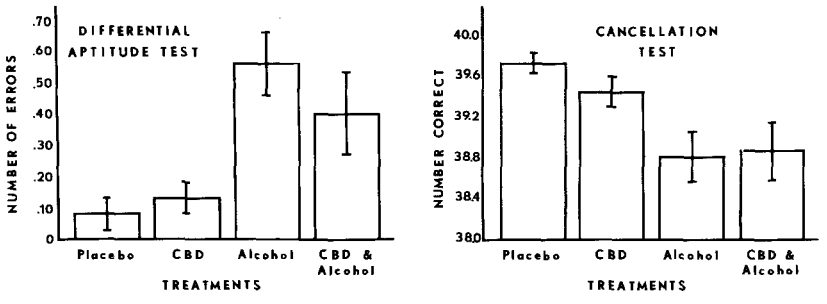
The subjective drug reaction scale (DRS), modelled after the semantic differential of Osgood et al. (1957), consisted of 66 subjective word pairs and associated degrees of intensity, e.g., cold 1, 2, 3, 4, indifferent, hot 1, 2, 3, 4. Subjects were asked to circle the choice which represented their feelings with the higher numbers indicating the strongest intensity and the indifferent response indicating either an intermediate state or one that does not apply at the moment. The DRS was broken down into 7 factors as follows (Karniol et al., 1975): a) perception of state: drugged-undrugged, sober-drunk (2 pairs); b) alertness and attention: e.g., alert-drowsy, etc. (5 pairs); c) physical feelings: e.g., cold-hot, etc. (17 pairs); d) perception: e.g., seeing details-seeing the whole, etc. (6 pairs); e) emotion: e.g., euphoric-depressed, etc. (13 pairs); f) cognitive: e.g., coherent-incoherent, etc. (18 pairs); g) sociability: e.g., friendly-unfriendly, etc. (5 pairs). Responses were tabulated and total time to take the DRS was ascertained.

The blood alcohol concentration (g/l) was estimated using the routine technique of measuring the level of breath alcohol using a standard breathalyzer apparatus (Bafômetro; Icatel Inc. e Comm., Ribeirão Preto, S. P., Brasil).

Data for each variable were analyzed by a repeated measures analysis of variance (ANOVA) FORTRAN IV program (Weldon and Humphrey, 1972) incorporated within the University of Arizona Data Corporation (Cyber 175) Computer. Subsequent differences between means for significant ANOVA factors and levels were determined by the Duncan's New Multiple Range (DNMR) test (Winer, 1971).

Results

Although the ANOVA revealed no significant ($P > 0.1$) main subject or period effects, or interactive period × treatment effects on any motor or cognitive measure, reliable main effects due to treatments were found for several dependent variables. The finger tap test yielded a significant treatment effect ($F = 3.34$; df 3, 27; $P < 0.05$) as did the number correct ($F = 3.4$; df 3, 27; $P < 0.05$) and number incorrect ($F = 3.01$; df 3, 27; $P < 0.05$) responses on the cancellation test, and the number of errors on the differential aptitude test ($F = 6.39$; df 3, 27; $P < 0.01$). There was also a nonsignificant trend for a main treatment effect on the time production task ($F = 2.84$; df 3, 27; $0.1 > P > 0.05$). As illustrated in Fig. 1, each of the drug treatments produced mean decrements of responses compared to placebo, although in general significant differences (as evaluated by DNMR tests) occurred between means of placebo and/or CBD treatments and those of alcohol and/or alcohol and CBD. In the differential aptitude test, subjects under alcohol and alcohol and CBD conditions committed significantly



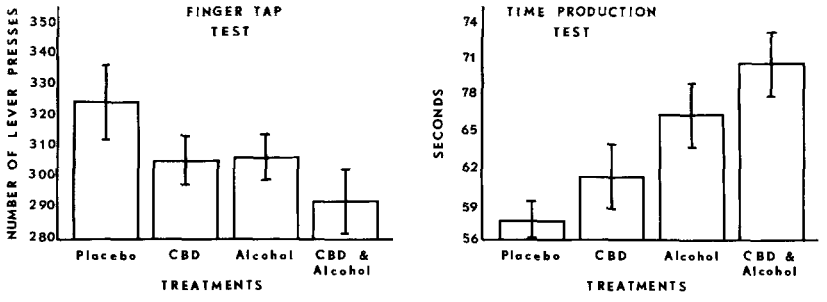


Fig. 1
Main placebo and drug (cannabidiol = CBD; alcohol; and CBD + alcohol) treatment effects on objective responding. Each bar represents the mean response (± standard error) recorded from 10 subjects on each test

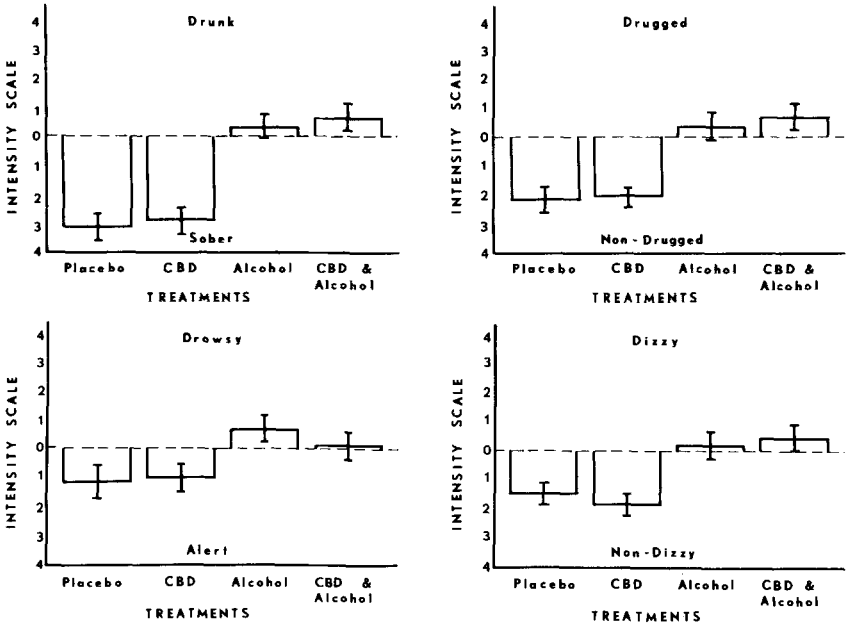


Fig. 2
Main placebo and drug (cannabidiol = CBD; alcohol; and CBD + alcohol) treatment effects on 4 items of the drug reaction scale. Each bar represents the mean subjective response (± standard error) of 10 subjects on each item

more errors ($P < 0.05$) than when under CBD and placebo conditions. On the cancellation test, the mean numbers of correct responses were significantly ($P < 0.05$) greater with placebo and CBD groups than with alcohol and alcohol and CBD treatments. In the finger tap test, mean responding differed significantly ($P < 0.05$) between placebo and alcohol and CBD treatments. Additionally, each drug treatment produced overestimates of time production compared to placebo, although only the difference between alcohol and CBD and placebo treatment means was statistically significant ($P < 0.05$).

With respect to subjective responding, ANOVA results of the 66 items scores on the DRS showed a large number (58 items) of significant ($P < 0.05$) main subject effects, although generally there were no clear correlational trends between individual subject responding and subject characteristics (e.g., gender, body weight, drug history factors) or experimental conditions (e.g., treatment orders). Significant ($P < 0.05$) main treatment effects (14 items) were interspersed among various DRS factors in the following manner. On perception of state (Fig. 2, top left and right), both alcohol and alcohol + CBD produced feelings of being

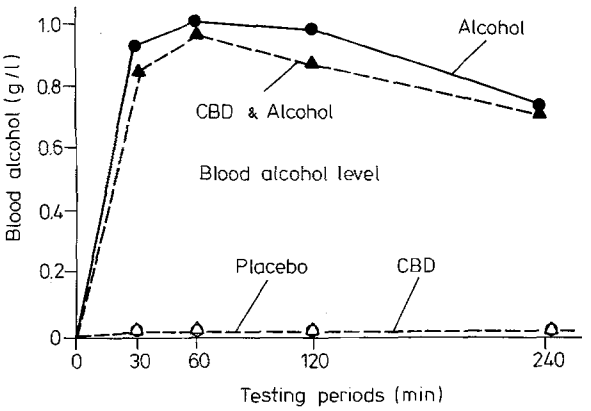


Fig. 3. Interactive period × treatment effects of breathalyzer-estimated blood alcohol levels. Each point represents the mean value (± standard error) obtained from 10 subjects following placebo and drug (cannabidiol = CBD; alcohol; and CBD + alcohol) treatments

drunk and being drugged, whereas placebo and CBD were without effect (i.e., feelings of sobriety and not drugged). On the alertness and attention factor, subjects reported they felt drowsy under the influence of alcohol and alcohol + CBD but felt alert under the influence of placebo and CBD (Fig. 2, bottom left). Similarly, on another item, alcohol and alcohol and CBD treatments caused feelings of inactivity, whereas placebo and CBD conditions provoked responses of feeling active. On the third factor, physical feelings, both alcohol and alcohol and CBD caused subjects to feel dizzy, and placebo and CBD were without effects (Fig. 2, bottom right). On an additional item (tense relaxed), subjects felt relaxed under alcohol and alcohol + CBD treatments but indifferent under placebo and CBD conditions. On perceptual factors, alcohol and alcohol + CBD treatments elicited feelings of dreaming and abnormal hearing, whereas CBD and placebo were without effects. On item (good-bad) of the emotional factor elicited alcohol and alcohol + CBD treatment responses of feeling bad as opposed to feeling good or indifferent with the other 2 conditions. On the cognitive factor, alcohol and alcohol + CBD, but not placebo and CBD treatments, caused subjects to feel irrational, confused, careless and incapable. Further, no significant changes were found on any items of the sociability factor. On all of the above reliable factor items, the responses elicited under alcohol did not differ statistically from those under alcohol + CBD. Additionally, significant ANOVA period × treatment interactive effects of items suggested a trend of responses, due to the two alcohol conditions, to occur about equally at all testing periods (30, 60, 120 and 240 min) following drug ingestion.

The ANOVA for blood alcohol levels yielded significant period ($F = 8.28$; $df\,3, 27$; $P < 0.01$), treatment ($F = 237.41$; $df\,3, 27$; $P < 0.01$) and period × treatment ($F = 2.89$; $df\,12, 108$; $P < 0.01$) effects, the latter is illustrated in Fig. 3. As shown, the alcohol treatment produced a slightly greater elevation of blood alcohol than did the alcohol + CBD condition and the differences were statistically significant ($P < 0.05$) at the 30, 60 and 120 min testing periods following drug ingestion.

Discussion

The salient findings of the present study indicate that alcohol and alcohol + CBD, but not CBD given singly, produce decrements of motor and cognitive responses and subjective alterations, and that with concurrent ingestion, CBD decreases blood alcohol levels. However, the interactive pharmacological effects between CBD and alcohol, where present, are not antagonistic but are either negligible or at best only minimally enhancing to the predominant effects of alcohol in the combination.

That alcohol, at the blood levels observed (ranging from about 0.75 g/l or 0.07% to 1 g/l or 0.1%), produced evidence of psychomotor deficits as measured by our cancellation and differential aptitude tests is not unexpected. The dose of alcohol administered (1 g/kg) was chosen to yield these relatively high blood alcohol levels that have previously been associated with reliable pharmacological effects in similar experimental tests. For example, alcohol resulting in blood levels of 0.05–0.09% increased errors and decreased accuracy in similar types of cancellation tests (Nash, 1962; Rafaelsen et al., 1973) and in other pencil-and-paper tests (Nash, 1962) involving clerical speed and accuracy. Moreover, it appears that alcohol depresses one or more of the mental processes (e.g., degree of selectivity, resistance to distraction, shifting of attention), since these factors are considered to underlie performance on the above types of tests (Sack and Rice, 1974). Additionally, as judged by subjective responding, subjects under the influence of alcohol appeared to express an accurate self-perception of their intoxication and deficits. In these regards, subjects perceived their intoxicated state on several DRS factors, i.e., perception of state (drugged; drunk), physical feelings (dizzy; relaxed), perception (dreaming; abnormal hearing) and emotions (bad); specific deficits were also realized on alertness/attentional (drowsy; inactivity) and cognitive (irrational; confused; careless; incapable) factors. These responses appear to reflect a generalized depressant effect of alcohol and are within the norm of subjective responses elicited by the drug at comparable blood levels in other studies of self perceived mood (see review by Wallgren and Barry, 1970).

In contrast to the effects of alcohol given alone, the administration of CBD, alone, did not result in any reliable alterations in either objective performances or subjective responding. Although there were trends of a decreased motor performance on the finger tap test, decreased accuracy on the cancellation and differential aptitude test, and an increase of time estimation on the time production task with CBD, none of these effects reached statistical significance. Additionally, subjective responses under the influence of CBD were essentially identical to those elicited by the placebo. Our results and conclusion that CBD has negligible effects on mentation and performance are congruent with those of many previously published reports. That is, CBD in acute oral doses of up to 100 mg per subject (Hollister, 1973; Karniol et al., 1974), inhalational doses of 0.15 mg/kg (Dalton et al., 1976) and intravenous doses of up to 30 mg per subject (Hollister, 1973; Perez-Reyes et al., 1973) does not affect subjective measurements, pulse rate, and various psychomotor tasks (e.g., pursuit meter; wobble board; delayed auditory feedback), the latter of generally greater complexity than those used in the present study. While we cannot predict the effects of higher acute doses of CBD on these or other paradigms, the range of CBD doses above are certainly large in comparison to equivalent doses of THC that have very significant effects on human mentation and performance (Dalton et al., 1976; Hollister, 1974; Karniol et al., 1974, 1975; Manno et al., 1971; Perez-Reyes et al., 1973; Rafaelsen et al., 1973).

Compared to placebo, the combination of alcohol and CBD resulted in a consistent decrease in accuracy on both cancellation and differential aptitude test. In these respects the decrements produced were not statistically different from those produced by alcohol given alone. Alcohol + CBD also produced a significant reduction in finger tapping responses and a consistent overestimation of the 1-min period on the time production task, compared to placebo. On these latter two measures, similar nonsignificant trends were observed with alcohol given alone compared to placebo but there were no significant differences between the two alcohol conditions. While CBD could have slightly augmented the effects of alcohol on the latter two tasks, the relatively high subject variability observed on these measures probably accounts for the statistical discrepancies found. Thus we suggest that the alterations observed on these latter measures are largely the result of alcohol. In this respect, even though CBD consistently reduced blood alcohol levels, these values (ranging from about 0.072 – 0.098 %) are within the range that have been associated with previously reported effects of alcohol. In studies of finger tapping speed (Enzer et al., 1974; Idestrom and Cadenius, 1968) alcohol at blood levels of about 0.08 % decreased performance on this test. Additionally, several experiments on perceived time duration (see review by Wallgren and Barry, 1970) have shown that alcohol given in comparable doses caused time to be perceived as passing more quickly, so that, as in the present study, a 60 s time interval is judged to be longer than it is, i.e., 66 s for alcohol and 70 s for alcohol + CBD. This suggests a central depressant effect of alcohol, i.e., slowing the subjective processes in relation to the fixed rate at which time passes. Moreover, the effects of alcohol + CBD on subjective responding of the DRS were identical to the effects of alcohol given alone. This provides further evidence that the generalized depressant effects of alcohol predominated in the CBD + alcohol condition and that the subjects expressed a rather accurate self-perception of their demonstrated psychomotor deficits.

Concerning the statistically significant reductions in blood alcohol levels in the alcohol + CBD treatment compared to alcohol given alone, it is improbable that these differences were due to sampling errors. The calculated accuracy of our breathalyzer apparatus, using standard alcohol test solutions, was never less than 99.98 % and, further, any potential errors in breath sampling within our experimental design would be expected to be distributed equally among all treatment conditions. Alcohol blood levels predominantly reflect processes of gastrointestinal absorption, metabolism and distribution, but it is unlikely that CBD could have altered the latter two factors. In rodents, CBD is a potent inhibitor (and not a stimulator) of certain drug metabolizing enzymes (Siemens et al., 1976) and further, in rats, the cannabinoid neither alters the liver metabolism nor the rate of disappearance of ethanol from blood (Siemens and Khanna, 1977). Considering that in the present study both drugs were given concurrently, an inhibitory effect of CBD on some processes related to alcohol gastrointestinal absorption might account for the reduced blood alcohol levels observed. Nevertheless, the effect of CBD on blood alcohol levels was of little pharmacological consequence with regard to objective and subjective responding. Clearly there was no evidence that CBD antagonized any pharmacological effects of alcohol and, in general, there were few measurable differences between the two alcohol conditions. Thus, under the present experimental conditions it is concluded that CBD in a relatively high oral dose has little pharmacological effect by itself or when combined with alcohol.

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Received April 9, 1979