Interactions in man of delta-9-tetrahydrocannabinol

II. Cannabinol and cannabidiol

Oral doses of delta-9-tetrahydrocannabinol (THC) 20 mg, combined with placebo or with 40 mg doses of cannabinol (CBN) and cannabidiol (CBD), were given to volunteers. The combination of THC with CBN produced no detectable changes in the quality, intensity, or duration of the effects of THC alone. The THC-CBD combination tended to delay onset and prolong effects of THC, while making them somewhat more intense. Even this interactive effect was slight, providing no reason to abandon the current practice of basing doses of marihuana for clinical studies solely on THC content.

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Besides delta-9-tetrahydrocannabinol (THC), the other two major cannabinoids of marihuana are cannabinol (CBN) and cannabidiol (CBD). Previous studies by us have indicated that the last two are essentially inactive in man.[7] It is still possible that they might affect activity of THC, either by altering its metabolism or by competing for its receptors.

Studies of interaction between major cannabinoids have suggested a potentiating effect of CBD and a blocking action of CBN. CBN was reported to antagonize the prolongation of hexobarbital sleeping time in mice.[15] Pentobarbital anesthesia in mice, which is prolonged by THC alone, was further enhanced by adding CBD, while CBN reduced the effect, the latter result being consistent with the previous study.[3] Hexobarbital sleeping time in rats was prolonged both by THC and CBD, showing an additive effect; CBN blocked the effect of THC. This result also is consistent with the previous study. The enhancement by CBD was thought possibly to be due to inhibition of THC metabolism.[4] This explanation was supported by a study showing that CBD was the most potent cannabinoid for inhibiting hepatic drug-metabolizing enzymes.[5] Intestinal motility in mice from a combination of both THC and CBD was more depressed than by a comparable single dose of THC alone; 10 mg/100 gm of THC combined with 40 mg/100 gm of CBD induced depression equivalent to that of 40 mg/100 gm dose of THC alone.[1] CBD given prior to THC reduced the magnitude and duration of hypothermic effects of THC in rats, as well as its depressant effects on heart rate, respiration, and rectal temperature in rabbits. The action was thought due to competitive

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Table I. *Comparison of quantitative measures of THC interactions with CBN and CBD (mean scores, 15 subjects)*

	THC-Pl	*THC-CBN*	*THC-CBD*
Pulse rate	+13	+15	+13
Global ratings	6.7	6.7	7.0
ARCI scores			
Hallucinogen 2 hr	6.0	6.3	6.6
Hallucinogen 4 hr	4.5	4.0	6.0
Marihuana 2 hr	7.3	7.2	7.3
Marihuana 4 hr	7.0	5.9	8.0

antagonism.[2] A more complex interaction between THC and CBD was described in rabbits, mice, and rats. CBD was thought to antagonize the excitatory effects of THC while potentiating the depressant effects.[13]

The situation in regard to these interactions in man is somewhat less clear. Oral doses of 30 mg of THC produced strong psychological responses in man, while doses of 15 to 60 mg of CBD alone produced nothing. When the former dose of THC was combined with 15, 30, or 60 mg doses of CBD, most of the effects of THC were blocked.[14] A comparison between smoked THC and marihuana indicated that the subjective, cognitive, and physiologic changes tended to be greater for marihuana.[6] Rather than a blocking effect of other constituents in marihuana, the latter study suggested enhanced effects, even though the amount of other cannabinoids present in the marihuana was miniscule.

As most experimental studies of marihuana base doses on THC content, ignoring the presence of the other two major constituents, it seemed desirable to determine whether interactions were of such magnitude that other cannabinoids must also be taken into account. The present study tested these interactions in man, using oral doses of the pure materials.

Methods

Fifteen volunteers who had previous exposure to marihuana in limited amounts were recruited. They were all men over the age of 18, in good physical and mental health. Each subject was exposed to three trials with THC, either alone or combined with the other cannabinoid.

Three treatments were given; the drugs were administered orally in the form of chocolate cookies to which the materials had been added: (1) THC 20 mg with extracted marihuana placebo; (2) THC 20 mg with 40 mg of CBN; (3) THC 20 mg with 40 mg of CBD.

Each trial was run one week apart and the treatments were administered in a Latin-square order. The basis for selecting the 2:1 ratio between CBN and CBD and THC was that marihuana may occasionally contain this ratio of these constituents (seldom is it higher) and that when one of the other cannabinoids is that high in proportion to THC, the other is practically nonexistent. Thus, these ratios represent extreme cases.

The comparative effects of each treatment were evaluated with the following clinical criteria: (1) a narrative summary of effects with time cues included so as to delineate the course of drug effect; (2) measurements of pulse rate and reddening of the eyes prior to treatment and hourly thereafter for 5 hr; (3) subjects completed the card-sort version of the Addiction Research Center Inventory (ARCI) at 2 and 4 hr following doses of drug; (4) upon completion of each trial, subjects made a rating of total intensity based on a 0 to 10 scale; a retrospective comparative rating on the same scale was obtained at the end of the third trial.

Urine was collected prior to treatment and at timed intervals following each treatment for determination of urinary metabolites by thin-layer chromatography (TLC) using techniques described previously.[10–12] Changes in the metabolism of THC induced by the presence of the other cannabinoid might be detected.

Results

Clinical appraisal of the subjects, as well as review of the narrative summaries, gave a distinct impression that the onset of effects from the THC-CBD combination was slightly slower, but that the intensity of the reaction was increased and duration was somewhat prolonged. No quantitative or temporal difference was observed between THC-placebo and THC-CBN in terms of clinical effects. Qualitively each treatment produced identical effects.

The remainder of quantifiable clinical data are shown in Table I. Pulse rate changes were about the same among the three treatments. So were global ratings of peak intensity of the experience, although slightly higher for the THC-CBD combination. This latter trend was somewhat more striking in regard to mean ARCI scores for hallucinogen and marihuana factors. Both scores were higher 4 hr following the THC-CBD combination.

Both CBD and CBN could be detected unchanged in thin-layer chromatograms, but their presence, as well as that of other metabolites, obscured detection of unchanged THC, which we have previously been able to demonstrate.[9] Metabolites were more numerous following both combinations than after THC alone, the increase representing additional metabolites of the other cannabinoids. Formation of possible dihydroalcohol and other polar metabolites of THC may have been enhanced by the presence of CBD.

Discussion

At the very most, the presence of comparatively large amounts of CBD in combination with THC may have increased slightly its clinical effects. CBD has been reported to be a potent inhibitor of hydroxylating enzymes.[16] Such an action could delay formation of the 11-hydroxymetabolite, one which is known to be somewhat more potent than the parent substance.[8] This action might also delay formation of dihydroxymetabolites, which are generally assumed to be inactive. Thus, the clinically observed slower onset and longer duration of the THC-CBD combination might possibly be explained by this mechanism. In any case, the difference is relatively slight. Thus, the present practice of ignoring the amounts of other cannabinoids in marihuana and basing doses solely on THC content is justified.

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