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Assay of Plasma Cannabidiol by Capillary Gas Chromatography/Ion Trap Mass Spectroscopy Following High-Dose Repeated Daily Oral Administration in Humans

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CONSROE, P., K. KENNEDY AND K. SCHRAM. *Assay of plasma cannabidiol by capillary gas chromatography/ion trap mass spectroscopy following high-dose repeated daily oral administration in humans.* PHARMACOL BIOCHEM BEHAV **40**(3) 517–522, 1991.—Plasma levels of cannabidiol (CBD) were ascertained weekly in 14 Huntington's disease patients undergoing a double-blind, placebo-controlled, crossover trial of oral CBD (10 mg/kg/day = about 700 mg/day) for 6 weeks. The assay procedure involved trimethylsilyl (TMS) derivatization of CBD and the internal standard delta-6-tetrahydrocannabinol (THC), capillary column gas chromatography, ion trap mass spectroscopy in positive ion chemical ionization mode using isobutane, and calculations of CBD levels based on peak ion intensity of the 387 M+H peak of delta-6-THC-TMS and the 459 M+H peak of CBD-2TMS. The sensitivity of the assay was about 500 pg/ml, and the precision was about 10–15%. Mean plasma levels of CBD ranged from 5.9–11.2 ng/ml over the 6 weeks of CBD administration. CBD levels averaged 1.5 ng/ml one week after CBD was discontinued, and were virtually undetectable thereafter. The elimination half-life of CBD was estimated to be about 2–5 days, and there were no differences between genders for half-life or CBD levels. Additionally, no plasma delta-1-THC, the major psychoactive cannabinoid of marijuana, was detected in any subject.

Cannabidiol (CBD) Oral administration Cannabinoid Cannabis Marijuana Humans
Gas chromatography/mass spectroscopy (GC/MS) Capillary column GC Ion trap MS Plasma levels of CBD
Half-life of CBD Pharmacokinetics of CBD Plasma delta-1-tetrahydrocannabinol (THC) Plasma delta-9-THC
Placebo Sesame oil vehicle Capsules of CBD and sesame oil

CANNABIDIOL (CBD) is a natural and often abundant cannabinoid of Cannabis (marijuana). While CBD is completely devoid of human psychoactive effects (22) typical of the major psychoactive cannabinoid of marijuana, delta-1-tetrahydrocannabinol (THC), it does possess pharmacological activities. CBD can inhibit (20) and induce (4) hepatic microsomal enzymes, can block seizures (7) and can reduce abnormal behaviors of other animal models of neurologic diseases (5). Further, preliminary findings in patients with epilepsy (9), dystonia (6) and Huntington's disease (HD) (25) have suggested that CBD might be of therapeutic benefit in these chronic neurologic conditions.

The metabolism and pharmacokinetics of CBD have been studied extensively in laboratory animals, and studied, to some degree, in humans [see reviews (2, 3, 13, 15)]. However, there are no published data on blood levels or related pharmacokinetic parameters of CBD following extended daily dosing of the cannabinoid. Such data would be informative, since the chronic conditions intended for CBD would require maintenance, rather than acute, doses of the cannabinoid.

Recently, we have evaluated in a controlled clinical trial the effects of 6 weeks of oral CBD administration in patients with HD. Plasma levels of CBD (and delta-1-THC) were measured by gas chromatography/mass spectroscopy (GC/MS), using published procedures modified for our use, and using an ion trap MS instrument which apparently has not been used previously for cannabinoid assays. The clinical results and a summary of the CBD blood level data of this study are presented in a companion paper (see Consroe et al., this volume). The purpose of the present paper is to detail our analytical procedures, to present additional results of the analysis, and to discuss the implications of the findings in relation to pharmacokinetic aspects of CBD and delta-1-THC.

METHOD

Subjects and Experimental Design

Fifteen Huntington's disease patients completed the 15-week clinical trial, although 1 patient refused venipuncture/collection

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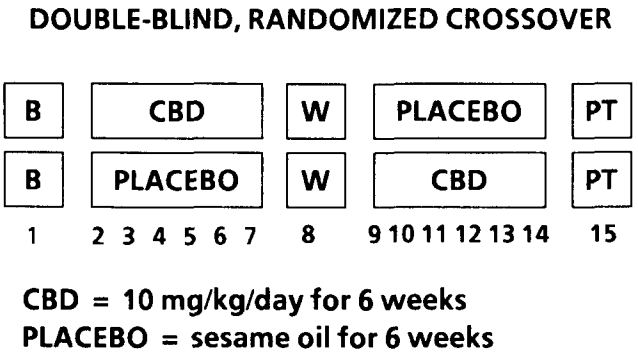

FIG. 1. Study design of the cannabidiol (CBD) trial in Huntington's disease. Patients, randomly assigned to one of the two treatment orders above, were evaluated weekly for 15 weeks during baseline (B), CBD or placebo administration (weeks 2–7 and 9–14), washout (W) and post-treatment (PT) conditions.

of blood for the CBD assay. Thus data for the assay were derived from 14 subjects, 8 men and 6 women, aged 17–66 (median of 52.5 years) and weighing between 47.6–101 kg (median and mean of 71.4 and 68.9 kg, respectively). A schematic of the (double-blind, randomized crossover study) design is presented in Fig. 1. CBD and placebo (PBO) were given for 6 weeks each wherein 6 patients were evaluated in the baseline (B)-CBD-washout (W)-PBO-posttrial (PT) order, and 8 patients were evaluated in the B-PBO-W-CBD-PT order. CBD powder (>99% pure and with no other cannabinoids detected) was obtained from the U.S. National Institute on Drug Abuse (Rockville, MD) and was kept frozen (−20°C) and in the dark until used. CBD was dissolved in sesame oil, N.F. (Ruger Chemical Co., Hillside, NJ), and the drug solution was incorporated into soft gelatin, amber-colored capsules (R. P. Scherer Corp., Troy, MI). Capsules (in a light-resistant glass vial) were dispensed on a weekly basis. The total daily dose of CBD (10 mg/kg) or PBO (sesame oil, N.F.) was divided into 4 capsules, and patients were instructed to take 2 capsules twice a day (8:00 a.m. and 2:00 p.m.) on an empty stomach, with an 8-ounce glass of water (and to store the medication in a cool place). Blood samples were taken at weekly intervals (i.e., at baseline and every 7 days for a total of 15 weeks) and at the same time of day for a given patient (between 11:00 a.m. and 2:00 p.m.). The blood was drawn into heparinized Vacutainer glass tubes (Becton Dickinson Co., Lincoln Park, NJ). The plasma was immediately separated by centrifugation and stored in silanized glass tubes at −20°C until time of analysis. All analyses of patients' samples were carried out blindly.

Analytical Procedures

Materials. CBD is described above. Delta-6-THC (also known as delta-8-THC) was used as the internal standard. Delta-6-THC and delta-1-THC (also known as delta-9-THC) were purchased from Sigma Chemical Co. (St. Louis, MO) and were greater than 99% pure. The cannabinoids were stored in the dark at −20°C. Dimethyldichlorosilane was purchased from Supelco, Inc. (Bellefonte, PA), and acetonitrile, N,O-bis (trimethylsilyl) trifluoroacetamide (BSTFA) and Reactivials were purchased from Pierce Chemical Co. (Rockford, IL). All solvents used were H.P.L.C. grade.

Extraction and derivatization procedures. Prior to use, all glassware was silanized by treatment with dimethyldichlorosilane and then rinsed with appropriate solvents (23). The extraction procedure used for the isolation of cannabinoids from plasma was modified slightly from a procedure reported earlier (10). One ml of plasma was transferred to a 16 × 100 mm glass culture tube with a teflon-lined screw cap. The internal standard (delta-6-THC in ethanol, 10 ng/ml, 10 μl) was added, the tube quickly capped, vortexed for 10 seconds and allowed to equilibrate overnight at 4°C. Two ml of acetonitrile were then added, the sample vortexed for 30 seconds and then centrifuged at 2,000 rpm for 10 minutes. The supernatant was carefully decanted into a clean 16 × 100-mm glass culture tube and the volume reduced to less than 1 ml by evaporation at 40°C under a dry nitrogen stream. One ml of 0.2 N NaOH and 2 ml of a hexane-ethylacetate mixture (9:1, v/v) were added. The tube was shaken for 30 minutes on a reciprocating shaker at 60 cycles/minute followed by centrifugation at 2,000 rpm for 5 minutes. The organic phase was transferred to a clean 16 × 100-mm glass culture tube and 2 ml of 0.1 N HCl added. The tube was again agitated (15 minutes) and centrifuged (10 minutes) as previously described. The organic layer was transferred to a Reactivial, evaporated to dryness, and the trimethylsilyl (TMS) derivative prepared by addition of 20 μl acetonitrile and 40 μl of BSTFA with heating at 60°C for 12 minutes. After cooling to room temperature, the derivatization reagents were evaporated to dryness under a stream of nitrogen and the residue reconstituted in 10 μl of acetonitrile. Blank plasma samples spiked with known quantities of (single and combined) CBD, delta-6-THC and delta-1-THC were extracted and derivatized as above. All samples were analyzed immediately after extraction and derivatization. Tests of efficiency of the reaction were carried out by derivatizing 1 μgm of the cannabinoids and then examining their profiles using a GC/MS program which could resolve both the derivatized and underivatized cannabinoids. No underivatized or partially derivatized material was detected for CBD or the THCs. Tests of efficiency of the extraction procedure indicated that it recovered approximately 60% of known quantities of CBD or the THCs added to blank plasma.

Gas chromatography conditions. The GC used in this study was a Varian 3400 fitted with a 30-m DB-5 WCOT capillary column (J and W Scientific, Folsom, CA) with helium as the carrier gas at 20 psi head pressure. One μl of the sample solution was injected onto the column in the splitless mode using the following temperature program: initial temperature, 230°C with a 2-minute hold time followed by programming at 1.5°C/minute to 250°C, then an increase to 280°C at 15°C/minute with a final hold time of 5 minutes. Using this program, the retention times for CBD-2TMS, delta-6-THC-TMS and delta-1-THC-TMS were approximately 8, 9.5 and 9 minutes, respectively.

Mass spectrometry and quantitation. A Finnigan-MAT ITDS 800 was operated in the positive chemical ionization mode under the following conditions: reagent gas, isobutane at a pressure such that the ratio of m/z 57 to 41 was 30/1; temperatures of the interface, transfer line, exit nozzle and main manifold were all 300°C. Best sensitivity was achieved by performing a narrow scan over the mass range m/z 370 to 470 giving a scan time of 1 second with a reaction time of 200 milliseconds and ionization time of 450 microseconds. Quantitation was achieved by monitoring MH+ ions of delta-6-THC-TMS (m/z 387) and CBD-2TMS (m/z 459) and comparing peak areas with relation to the calibration curve. A separate calibration curve was created for each group of extractions. The curve was generated using plasma blanks to which was added 10 ng of the internal standard (delta-6-THC) and 1, 2, 5, 10 and 20 ng of CBD and comparing peak areas of the respective MH+ ions from 2 determinations, proceeding first with the most concentrated sample. Each of the patient samples was analyzed in duplicate. The minimum detectable quantity of CBD was 500 pg/ml extracted

TABLE 1

PLASMA LEVELS OF CANNABIDIOL (CBD) IN PATIENTS WITH HUNTINGTON'S DISEASE

Sample Collections*	N†	Mean(±SD) Level§	Range¶	95% CL‡
1 week before CBD	14	ND		
1 week on CBD	14	6.7 (5.2)	ND#–20	3.7–9.7
2 weeks on CBD	14	8.1 (6.5)	ND#–20	4.4–11.9
3 weeks on CBD	14	8.1 (6.2)	ND#–20	4.5–11.7
4 weeks on CBD	14	5.9 (4.2)	1.5–15	3.5–8.3
5 weeks on CBD	13‡	9.5 (4.4)	4.0–17.5	6.8–12.1
6 weeks on CBD	14	11.2 (7.5)	2.5–25	6.7–15.7
1 week off CBD	13‡	1.5 (0.8)	ND**–2.5	1.1–1.9
2 weeks off CBD	6	<1 (N=3) ND (N=3)		
3–8 weeks off CBD	6	ND		

*Timing of blood sample collections during the crossover trial which included a baseline (B) period, 6 weeks oral administrations of CBD (10 mg/kg/day) and placebo (PBO), a washout (W) week between the treatments and a posttrial (PT) period (see Fig. 1).

†N = number of patients for each respective blood sample collections; the 14 (and 13) patients are from the conditions of the 2 orders combined, and the 6 patients are from conditions of the B-CBD-W-PBO-PT order (see Fig. 1).

‡One blood sample tube was cracked and thus could not be analyzed.

§Mean ± standard deviation (SD) level of CBD in ng/ml; ND = CBD not detected down to 500 pg/ml; <1 = less than 1 ng/ml but more than 500 pg/ml.

¶Numbers are ranges of CBD levels in ng/ml.

#ND in 1 patient (S.O.).

**ND in 2 patients (F.D. and N.B.).

††Numbers are 95% confidence limits (CL) of the mean levels in ng/ml.

from plasma. Accuracy was ±10% when levels were 1 ng/ml or greater, and ±15% for levels below 1 ng/ml of plasma. Additionally, all plasma samples were monitored for the MH+ ion of delta-1-THC (m/z 387) at the GC retention time for this cannabinoid.

Statistics

Friedman's (two-way analysis of variance by ranks) test (26) followed by Nemenyi's (post hoc pairwise comparison) test (19) were used to assess within-subjects differences of CBD levels among/between weeks. Other statistical tests used (19,26) were the Mann-Whitney test (to assess between-subjects differences), Spearman rank-order correlation test (to evaluate the strength of association between variables), and standard descriptive statistical tests. A two-tailed probability level of 0.05 was used for the inferential tests of significance. Additionally, an apparent terminal elimination rate constant (Ke) and half-life ($t_{½}$) of CBD were calculated for each patient using standard formulas (12). The Ke was calculated from the linear regression of the Ln (natural log) plasma concentration versus time for the last two (for 10 patients), or last three (for 2 patients) data points, and the $t_{½}$ was computed as Ln 2/Ke.

RESULTS

Table 1 shows the plasma levels of CBD before, during and after CBD administration. During the 6 weeks of CBD administration, CBD levels were present in low ng concentrations and within a relatively narrow range. Mean levels (of 14 patients) ranged from a low of 5.9 ng/ml to a high of 11.2 ng/ml, and the 95% confidence limits (CL) of each mean level were relatively tight. One week after CBD was discontinued, CBD levels were still present but at a much reduced concentration. The mean level (of 13 patients; 1 patient sample lost) was 1.5 ng/ml (with 95% CL of 1.1–1.9 ng/ml). The weekly median levels were 5.5, 6, 6.25, 4.5, 8, 9.5 and 2 ng/ml, respectively, and statistical analyses of these data indicated a significant effect over time (Friedman test, $p=0.0001$). Subsequent analyses between weeks (by the Nemenyi's test) revealed that the washout week was significantly different from each week of CBD administration ($p<0.05$, each comparison). However, there were no significant differences between any weeks during the CBD administration ($p>0.05$, each comparison).

Six (of the 14) patients could be followed for longer periods after their CBD was discontinued (Table 1), because they were evaluated in the B-CBD-W-PBO-PT order (Fig. 1). Two weeks after CBD was discontinued, CBD was detected in only 3 of these 6 patients (who were now taking placebo). The levels detected were very low, i.e., about 750 pg/ml. On each of the subsequent 6 weeks of analyses, no CBD was detected (down to 500 pg/ml, our lowest limit of detection) in any of these 6 patients. Similarly, no CBD was detected in the other 8 patients under their PBO, or washout from PBO, conditions (not shown in Table 1).

Further, plasma samples of all 14 patients were analyzed also for the presence or absence of delta-1-THC, the major psychoactive ingredient of marijuana. No delta-1-THC was detected in any patient at any time during the trial.

The novel design of our trial gave us the opportunity to estimate the apparent terminal $t_{½}$ of CBD following a probable steady-state condition of the drug. Complete data (i.e., nonzero and nonmissing plasma level data from the last day of CBD administration and 1 week following its discontinuation) were available from 10 of our patients, and their $t_{½}$s are illustrated in Fig. 2. The distribution of $t_{½}$s was curvilinear, and it approximated a normal distribution (calculated skewness and kurtosis values were 0.95 and −0.11, respectively). The mean (±standard deviation) was 68.2 (24.6) hours, the range was 41.4–113.0

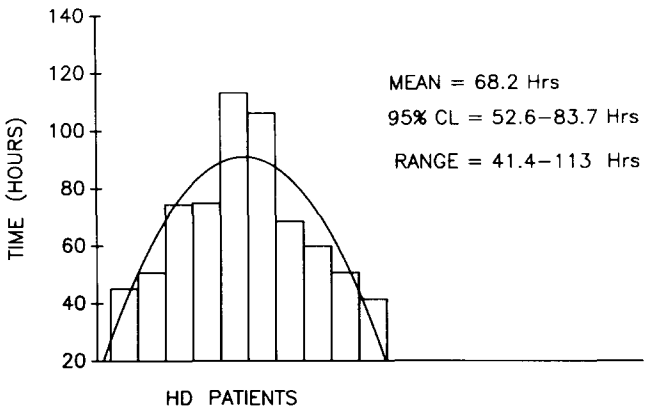

FIG. 2. The bars represent the estimated half-lives ($t_{1/2}$s) in hours (Hrs) of cannabidiol (CBD) in the 10 Huntington's disease (HD) patients who had measurable levels of CBD the last day of CBD administration and 1 week following CBD discontinuation. 95% CL = 95% confidence limits of the mean $t_{1/2}$. The curved line is the calculated curvilinear regression of the 10 $t_{1/2}$s.

hours, and the 95% CL of the mean was 52.6–83.7 hours. Additionally, complete plasma level data were available for 2 of the patients who were off CBD treatment for 2 weeks. Their calculated $t_{1/2}$s (and 95% CL) were 104 (66–244) and 112 (79–192) hours (data not shown in Fig. 2).

Lastly, the plasma level and kinetic data were subjected to some inferential and correlational testing. The plasma levels of CBD were averaged over the 6 weeks of CBD administration, and the medians (and means $\pm$ standard errors) were 9.8 (8.9 ± 0.9) ng/ml for the 8 men and 6.7 (7.1 ± 1.3) ng/ml for the 6 women. Analysis of these data indicated no significant difference between the genders (Mann-Whitney test, $p = 0.19$). Similarly, there was no significant difference between the men and women for the CBD plasma levels at the 1-week washout period (Mann-Whitney test, $p = 0.16$). Additionally, analyses of association between variables were made from the data of the genders combined. Comparisons of averaged CBD levels versus body weight, averaged CBD levels versus age, washout CBD levels versus body weight and washout CBD levels versus age yielded correlation coefficients (Spearman rho's) of .31, .47, $-.03$ and .04, respectively. Also, comparisons of $t_{1/2}$s versus body weight and $t_{1/2}$s versus age yielded rho's of $-.17$ and $-.19$, respectively. Each of the above correlations was not significant ($p > 0.05$).

DISCUSSION

The present data were obtained from a double-blind, placebo-controlled, randomized crossover trial of oral CBD administration (10 mg/kg/day) for 6 weeks in patients with HD (see Consroe et al., this volume). Although the trial was not designed as a pharmacokinetic or metabolic assay study, there are a number of salient findings of the present study that are novel and germane to the assay and pharmacokinetics of CBD and of delta-1-THC as well.

One conspicuous finding was that the CBD plasma levels were low (average of about 8 ng/ml) following a high oral dose of CBD (about 700 mg/day/patient on the average). This suggests a low bioavailability, perhaps due to deficient absorption, degradation by stomach acidity and/or a first pass (gastrointestinal and/or liver metabolic) effect.

There are no published data concerning the quantitative amount of CBD in blood and feces following oral administration, so it is impossible to assess whether or not gastrointestinal absorption of CBD is deficient. Concerning the possible degradation of CBD, it is well known that CBD in vitro isomerizes readily in the presence of acidic reagents to form various products, including notably delta-1-THC (11). Further, a recent study (14) has reported on the identification of delta-1-THC (and delta-6-THC), but not THC metabolites, in the urine of a patient given a large dose (600 mg daily) of CBD. The latter authors hypothesized that the cyclization of CBD to THC may have occurred in the urine itself, although a blood sample from this patient was not available to verify this supposition. While it is theoretically possible that a similar conversion could take place in the highly acidic stomach, the lack of findings of plasma delta-1-THC in the present study suggests that such a conversion does not take place under normal physiological conditions.

Only a few human studies have assayed CBD in plasma, and each has involved administration of low acute doses of the cannabinoid. The one study employing oral administration, i.e., 40 mg of (deuterium-labelled) CBD in a chocolate cookie (1), obtained peak CBD plasma levels of only 5–8 ng/ml, and an estimated systemic availability of only about 6% (21). The other human studies, employing CBD by smoking (21) or intravenous (IV) administration (21, 28, 29), also report low ng/ml concentrations of CBD after a short period of time. The metabolism of CBD in humans (14, 28, 29) and animals (13,15) is rapid and diverse, yielding nearly 100 or so metabolites. The major metabolic path in man is hydroxylation to 7-OH-CBD and then oxidation to CBD-7-oic acid (15). The metabolites of CBD are excreted in feces and urine, although, surprisingly, a major excretory product in humans is unchanged CBD (14,28). In a recent pharmacokinetic study in the dog (24), the bioavailability of oral CBD was low (13–19%), and this was due to a high extraction ratio (74%) in the liver leading to a first-pass effect. Taken together, the available evidence suggests that the bioavailability of oral CBD is low across species, and this may be due primarily (but not necessarily exclusively) to first-pass metabolism in the liver. Although no attempt was made to measure CBD metabolites in the present study, the huge differential between the dose administered and plasma levels obtained suggests that the magnitude of this metabolic effect would be substantial. This could result in large quantities of 7-OH-CBD and other oxidative metabolites which, if active, could contribute substantially to the activity of CBD. CBD metabolites have not been evaluated directly for any pharmacological activity. However, the time courses in mice of anticonvulsant activity and brain levels of CBD and CBD metabolites suggest that CBD itself is responsible for its anticonvulsant effect in this species (17). Further, CBD clearly was not effective in relieving symptoms of HD in the present clinical trial, and thus CBD metabolites, even if present in high levels, apparently were not active in this situation either.

Depending on the actual cause of this low bioavailability of CBD, several strategies might be employed in future studies to increase its systemic availability following oral administration. Some examples are the administration of CBD after food has been ingested, and the use of other vehicles and other dosage forms of CBD. Further, chemical modification of the CBD molecule which results in the formation of a "prodrug" of CBD also might enhance the oral bioavailability of this cannabinoid. Obviously, experimental data are required to verify or refute these speculations. In the interim, the current evidence indicates that oral CBD, in an encapsulated sesame oil vehicle and given in repeated high doses without prior food, or in a chocolate cookie and given in a low acute dose, has a very low systemic availability in humans.

Another notable finding of the present study was the plasma

concentration-time course curve and its decay. The plasma levels of CBD were relatively constant (about 6–11 ng/ml), and not reliably different, over the 6 weeks of administration of the drug. However, plasma levels of CBD were significantly lower (about 1.5 ng/ml) after 1 week discontinuation of CBD. Subsequently, CBD plasma levels were barely detectable (about 750 pg/ml) in 3 of 6 subjects at 2 weeks post CBD. CBD was not detectable (down to 500 pg/ml) in all 6 subjects 3–8 weeks after CBD was discontinued. Calculations of these data yielded an estimated terminal t½ of CBD ranging from about 2 to 5 days. The latter must be considered only approximate since our calculations involved only 2 or 3 data points in the relevant portion of the plasma level curves. Nevertheless, the plasma level data suggest that CBD was at steady-state during CBD administration, and that CBD was slowly eliminated, i.e., from tissue stores to plasma, after termination of the CBD. Further, this elimination occurred up to a maximum of 3 weeks and, within the practical limit of our assay sensitivity, the calculated apparent t½ of several days is compatible with this relatively slow elimination of CBD. In the previous human study (21) which measured CBD plasma levels over 72 hours following IV and smoking administration of 20 mg (deuterium-labelled) CBD, an estimated t½ of about 24–31 hours was found. These authors also stated that the terminal elimination phase was not reached at 72 hours. Thus their terminal elimination t½ for CBD was probably underestimated because of too short sampling time—in turn, dependent upon limited assay sensitivity (2). Additionally, the terminal elimination t½s of CBD have been reported to be 9 hours in the dog (24) and 11 hours in the rat (27), and these values appear to be underestimated for the same reasons as mentioned above.

Lastly, the present findings indicated there were no significant differences between the two genders with regard to plasma levels or t½s of CBD. Further, neither the body weight nor age of the subjects was correlated to any significant degree with plasma levels or t½s of CBD.

The assay, metabolism and pharmacokinetics of delta-1-THC have been studied extensively in man following its administration by IV, smoking and oral routes [see reviews (2, 3, 8, 15) and citations therein]. Virtually all of these studies have used acute administration, i.e., one or only a few repeated doses (about 20–30 mg/subject) of delta-1-THC, although 1 study (and presumably the only one) has utilized a more extended dosing schedule, i.e., 12 days of oral (about 180 mg/day) delta-1-THC (16). Several aspects and findings of these studies pertain to the present and previous data of CBD.

Assay of delta-1-THC and its metabolites in plasma most often has made use of GC/MS techniques with practical detection limits of low ng/ml, and in some cases down to low pg/ml (2,8). The latter sensitivities are lower than those achieved in the present study, and the differences may reflect many aspects of the respective assays including the use of sophisticated ion detection equipment (2,8). In the present study, an ion trap MS was used (18) and, to our knowledge, this is novel for a cannabinoid assay. The major practical advantage of this relatively new instrument over the other types of the more sophisticated MS instruments is that it is much lower in cost (perhaps tenfold). Considering that a good sensitivity (down to 500 pg/ml) is obtained with the ion trap detector for CBD, similar detection limits might be obtainable for other cannabinoids as well. The cost advantage of this instrument could make quantitative assay of cannabinoids a routine and more widely used procedure.

A consistent finding following oral administration of delta-1-THC is that peak plasma levels are in the low ng/ml range (2). The oral bioavailability of delta-1-THC ranges from 4–20 %, with the higher systemic availability resulting from the use of sesame oil as a vehicle (3,30). A consensus view is that a first-pass effect of liver metabolism is responsible for the relatively low bioavailability of the cannabinoid (2,30). While 100 or more metabolites are formed (15), delta-1-THC is metabolized preferentially to 7-OH-delta-1-THC (a major active metabolite) and, in turn, to delta-1-THC-7-oic acid (a major inactive metabolite). While it is believed that delta-1-THC itself is mainly responsible for the pharmacological effects of delta-1-THC after smoking and IV injection, 7-OH-delta-1-THC may contribute equally to the pharmacological effects of delta-1-THC after oral administration of the latter cannabinoid (2). Most recent evidence (2) indicates that the average terminal t½ of delta-1-THC is about 4 or 5 days. Also, new evidence (2) indicates that the redistribution from fat tissue to blood is the major factor that governs the terminal elimination t½ of delta-1-THC. Because of the latter, there could be a difference in t½ between lean and obese individuals (16), and between men and women (who generally have a higher percentage of body fat than men). The latter comparison has been evaluated (30), and the results indicate there are no major differences between the genders concerning metabolism, excretion and pharmacokinetic parameters of delta-1-THC.

In summary, the present data show that the plasma levels of CBD are within a low, narrow range (6–11 ng/ml) over 6 weeks of daily, oral, high-dose (about 700 mg) CBD administration. Following CBD discontinuation, plasma levels of CBD appeared to decline over about 2–3 weeks, with an approximate t½ of about 2–5 days. There were no differences in levels or t½ of CBD between the male and female subjects, and no plasma delta-1-THC was detected in any subject during the trial. From these findings and others, it appears that there are many similarities between CBD and delta-1-THC with respect to their pharmacokinetics in humans. Aside from a difference in the quantity of free versus metabolite disposition, the major difference between the 2 cannabinoids remains to be pharmacodynamic, in that delta-1-THC is psychoactive and CBD is not. Because of these factors and findings which suggest a rather substantial safety of this cannabinoid, CBD might serve as a useful cannabinoid to model delta-1-THC in long-term, high-dose pharmacokinetic studies in humans.

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