SINGLE DOSE KINETICS OF CANNABIDIOL IN MAN[1]

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I. INTRODUCTION

Cannabidiol (CBD) is one of the main constituents in most Cannabis preparations. CBD possesses no psychotomimetic activity in humans in contrast to the highly active delta-1-tetrahydrocannabinol (THC) the major compound in the plant (1-3). However, CBD has anticonvulsant properties in animals and possibly also in man (4,5), and, consequently, the potential of CBD as an antiepileptic drug is under investigation. Despite CBD being a main constituent of Cannabis preparations and an interest in the medical use of CBD, very few reports have been published concerning the kinetics of this cannabinoid (3,8). This report presents data on the single dose kinetics of CBD after smoking and intravenous administration.

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II. METHODS

A. Subjects

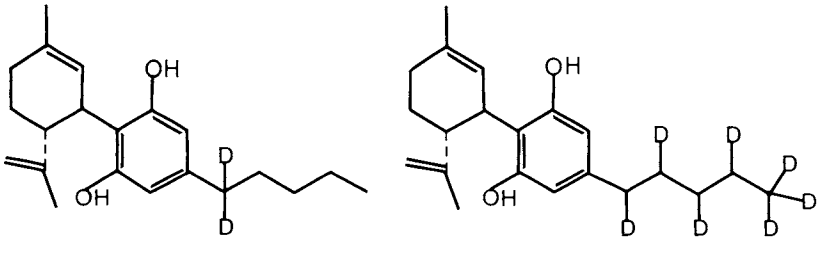
Five healthy young men volunteered to participate in this study. All had previous experience with marijuana ranging from infrequent to frequent use. All were in good physical and mental health and none were taking other psychoactive drugs. Prior to the trial, subjects were asked to abstain from cannabis for at least 72 hours and from alcohol for at least 24 hours.

B. Compounds

Deuterium-labeled CBD (CBD-d_2; Fig. 1) was administered to follow the plasma levels without disturbances from non-allowed smoking of cannabis during the experiment. The synthesis of CBD-d_2 as well as CBD-d_7 (see Fig. 1 for labeling), the latter was used as internal standard, have been described earlier (9). The unlabeled CBD in CBD-d_2 was 1.4% and in CBD-d_7 0.3%. The d_2-content in the internal standard was 0.4%. The chemical purity checked by gas chromatography was over 92%.

C. Doses and Routes of Administration

Deuterated CBD, viz CBD-d_2, was administered by an intravenous injection during 2 minutes of 20 mg.--a technique used



CBD-d_2 CBD-d_7

FIGURE 1. Structural formulas of deuterium labeled CBD, CBD-d_2, and CBD-d_7, the internal standard.

earlier for THC (10)--and by smoking marijuana placebo cigarettes (furnished by NIDA, Rockville, MD) spiked with 20 mg of the compound. The smoked dose was estimated by subtracting the remaining amount of CBD in the butt from the original amount in the cigarette (11). No exchange of deuterium atoms was observed after the smoking process. The two trials were performed in a randomized order with at least one week between the treatments.

D. Blood Sampling

Blood samples were drawn prior to the sessions and at 3, 6, 10, 15, 30, 60, 90, 120, 180 and 240 minutes after termination of smoking or intravenous injection. The samples were collected in heparinized glass tubes and immediately centrifuged. The plasma, usually 3 ml, was transferred to silanized glass vials and stored at $-20^{o}C$ until analysis.

E. Analytical Procedure

After addition of internal standard, the plasma samples were extracted with organic solvents and purified by liquid chromatography according to a method described earlier (8,9). The trimethylsilylated CBD extracts were submitted to the mass spectrometric quantification. The gas chromatographic-mass spectrometric procedure, using a LKB 2091-051 instrument, has been described previously (8). The base peaks $[M-68]^{+\cdot}$ in the mass spectra of the disilylated CBD analogues were selected for monitoring: m/z 392 for CBD-d_2 and 397 for CBD-d_7. The standard curves with a range of 0.04-10 ng/ml and 10-2000 ng/ml (Fig. 2) were prepared by mixing different dilutions from stock solutions.

F. Pharmacokinetic Analysis

The area under the plasma concentration versus time curve (AUC), for the time 0-240 minutes, were estimated using the trapezoidal rule. The systemic availability of CBD-d_2 after smoking was calculated by comparisons of the AUC with that obtained after intravenous injection.

III. RESULTS AND DISCUSSION

The single dose kinetics of deuterium labeled cannabidiol

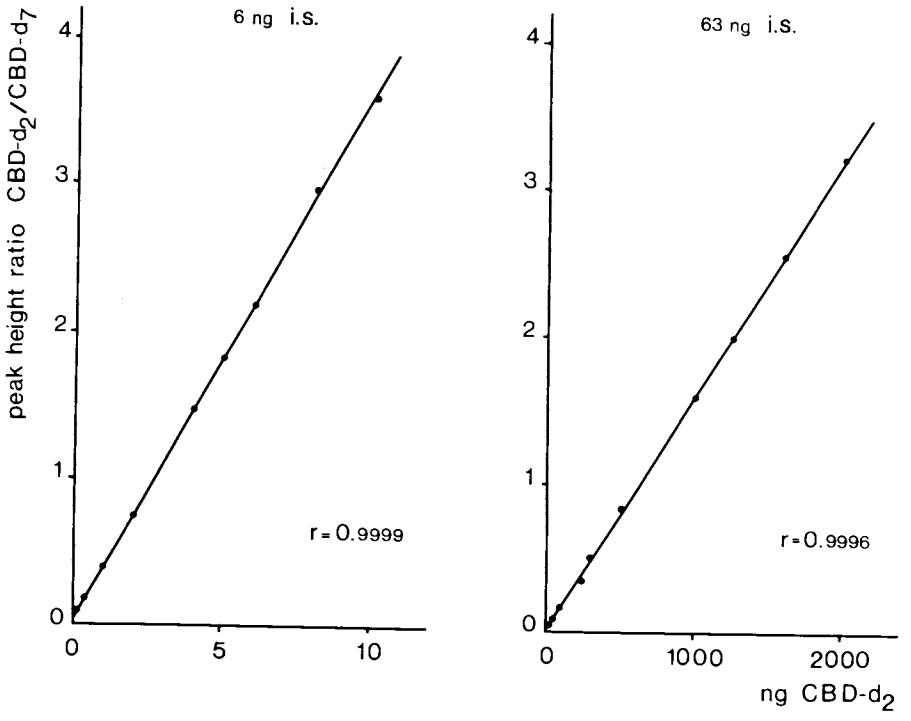


FIGURE 2. Standard curves for CBD-d_2, 0-10 ng/ml and 10-2000 ng/ml.

(CBD-d_2, Fig. 1) has been studied in man after intravenous injection of 20 mg and by smoking a placebo marijuana cigarette spiked with 20 mg CBD-d_2. The average dose smoked was estimated to 19.2 +/- 0.3 mg by subtracting the compound remaining in the butt from the original amount in the cigarette. The plasma levels were followed for four hours and the mean plasma levels for the five subjects are shown in Fig. 3. After both routes of administration a marked fall in the plasma levels occurred during the first fifteen minutes whereafter the levels declined smoothly. At three minutes the plasma levels were 684 +/- 240 (mean +/- S.D.) (range356-972) ng/ml at fifteen minutes and had declined to 10.3 +/- 4.5 (range 3.4-15.5) ng/ml at four hours. These values, except for the earliest time points, are in good agreement with those determined in an earlier report (3), where plasma levels of 20 mg tritium labeled CBD was followed in man after intravenous infusion. Since a more rapid infusion time was used in the present study, higher initial plasma levels were obtained.

After smoking, a plasma curve with a very similar slope as the curve after intravenous administration was achieved. However, the plasma levels after smoking were lower 114 +/- 62

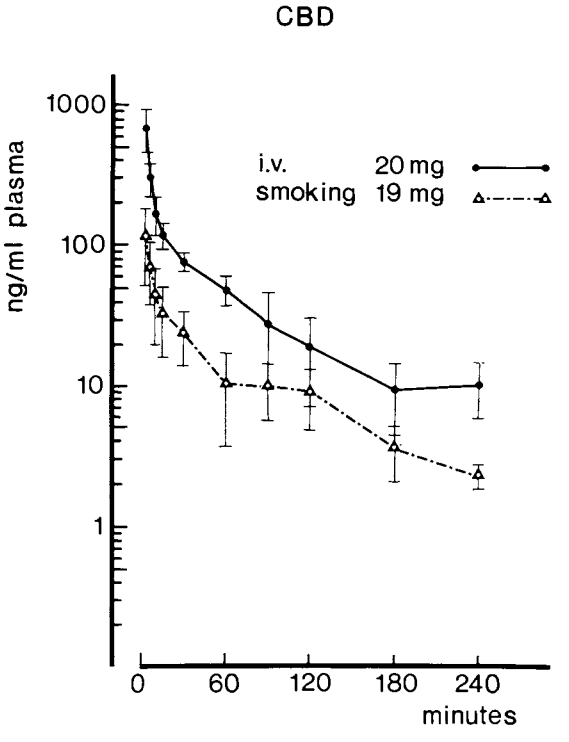


FIGURE 3. Mean plasma curves (mean +/- SD) of CBD-d_2 after intravenous administration and smoking in five healthy users.

(range 42-191) at three minutes, 33 +/- 17 (range 12-51) at fifteen minutes and 2.3 +/- 0.05 (range 1.9-2.8) ng/ml at four hours.

Both after smoking and infusion the shape of the mean plasma curves of CBD-d_2 very much resemble those obtained after THC administration in a previous study with a similar experimental design (10). However, doses given were lower for THC and therefore the actual plasma levels were lower.

The interindividual variations in plasma levels were relatively small, both after smoking and infusion. A greater difference in the individual plasma levels after smoking could perhaps have been expected since the subjects smoked in their usual fashion. Rather small interindividual differences after smoking THC have also been noted (10).

The AUC and estimated availability in the five subjects are listed in Table I. The subjects smoked very similar amounts, range 18.8-19.4 mg of CBD-d_2, a dose that was very close to the injected dose of 20 mg. The estimated systemic availability was 31 +/- 13 (range 10-42) % of CBD-d_2 after

TABLE I. Kinetic Parameters of CBD-d_2 Disposition in Man after Intravenous Administration (20 mg) and Smoking

Subject	Intravenous AUC[a]	Smoking: Estimated Amount Smoked (mg)	Smoking: AUC[a]	Smoking: Estimated Systemic Availability (%)
PF	9.13	19.4	3.69	42
BM	10.54	19.3	3.17	31
IP	14.78	19.3	1.45	10
RP	11.44	18.8	3.14	29
IW	12.93	19.0	4.99	41
Mean[b]	11.76 (2.18)	19.2 (0.3)	3.29 (1.27)	31 (13)

[a] $\text{AUC} = \frac{\text{AUC}_{1-240}}{(\text{ng/ml}) \times \text{min}} \times 10^{-3}$

[b] Mean (+/- S.D.).

smoking. The main loss of CBD is probably due to pyrolysis and disappearance of CBD through the side-stream smoke during the smoking process.

The estimated systemic availability after smoking an average of 13.0 mg THC was 18 +/- 6 (range 7-25) % in a group of subjects with a comparable use of cannabis as the presently investigated group. If that possible difference in availability of the cannabinoids is due to differences in the transfer of the cannabinoids during the smoking process, or due to metabolic or kinetic factors is not yet known.

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