METABOLISM, DISPOSITION AND PHARMACOKINETICS OF DELTA-9-TETRAHYDROCANNABINOL IN MALE AND FEMALE SUBJECTS*

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I. INTRODUCTION

It is well established that delta-9-tetrahydrocannabinol (THC) (I, Fig. 1) is the active psychoactive constituent found in Cannabis sativa (commonly referred to as "marijuana") (15). In recent years, a number of reports have appeared dealing with the potential therapeutic activity of THC. Its activity as an anticonvulsive agent and its potential for reducing intraocular pressure have been reviewed (4,5). Of highest interest and now well established is the antiemetic activity exhibited by THC (18,24). Knowledge of the metabolism, disposition and pharmacokinetics of any drug scheduled for therapeutic use is of great value to rational planning of dose schedules.

Although there have been a number of reports on the metabolism and disposition of THC (11,12,14,19) (cf.13,28,33 for reviews), the studies have been conducted predominantly with male volunteers. Sex differences have been observed in respect to metabolism of drugs (25) and steroids (9) by microsomal enzymes. It has been reported that microsomes from male

*Supported by NIDA grant DA-02424.

rats metabolize THC faster than those from females (2), and that a THC distillate was more potent in female rats than males in terms of behavioral response (6). Therefore, it was important to determine whether the sex differences observed with rodents would be noted in the metabolism and disposition of THC in humans.

This report presents a detailed comparison of the metabolism, disposition, and pharmacokinetics of THC in women and men.

II. MATERIALS AND METHODS

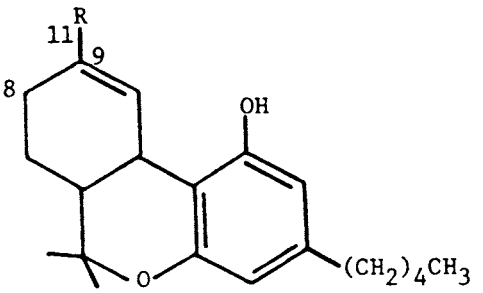
A. Subjects

Subjects who participated in the study were all healthy, female and male, paid volunteers, with normal weight in relation to their height and eating normal diets. All were familiar with the recreational use of marijuana. The female subjects had been taking oral contraceptives for at least six months prior to the study. Six male and six female volunteers were used for both the intravenous (iv) and oral (po) studies. The protocol required that different individuals be utilized in each study to minimize exposure to radiolabeled THC used in these studies.

The characteristics for the female and male subjects who volunteered for the iv studies expressed as X +/- S.D. were, respectively: age (years) 23 +/- 3 and 23+/- 2; weight, (kg) 54 +/- 7 and 72 +/- 9; height (cm), 163 +/- 7 and 175 +/- 6. Corresponding characteristics for female and male subjects in the oral group were, respectively: age 21.5 +/- 4.4 and 25.8 +/- 5.1; weight, 56.4 +/- 1.7 and 66.2 +/- 8.7; height, 165 +/- 5.5 and 175 +/- 6.9.

B. Chemicals and Materials

Tritium labeled THC-1',2'-$^{3}H_2$ or THC-4',5'-$^{3}H_2$, specific activity 150-165 mcC/mg; unlabeled THC (I); 11-hydroxy-delta-9-THC (II); and 11-nor-delta-9-THC-9-carboxylic acid (III) were obtained from the National Institute on Drug Abuse. Precoated thin-layer chromatography (TLC) plates, 20 x 20 cm, Silica Gel 60F-254 (E. Merck, Darmstadt, West Germany) were used for all chromatographic analyses. For scintillation counting, a fluor was utilized consisting of a mixture of Triton X-100/toluene/ Omnifluor (1 liter:2 liter:18 g).



I. Δ^9-Tetrahydrocannabinol R = CH_3

II. 11-Hydroxy-Δ^9-Tetrahydrocannabinol R = CH_2OH

III. 11-nor-Δ^9-Tetrahydrocannabinol-9-Carboxylic Acid R = COOH

FIGURE 1. Chemical formula for THC and its major metabolites.

C. Drug Administration

Tritium labeled THC was mixed with unlabeled drug for all dosage forms. For the iv study an ethanolic solution of THC containing approximately 150 mcC of tritium was mixed with human serum albumin (Abbott) to form a microsuspension according to the method of Perez-Reyes et al. (22). By means of an infusion pump, the preparation was administered over a 20-30 min period to six female and six male volunteers; the mean THC doses were approximately 2.2 and 4.0 mg, respectively.

In the case of the oral studies, 15 or 20 mg of THC (females and males, respectively) containing 150 mcC of radiolabeled were dissolved in 0.5 ml of sesame oil and administered in two gelatin capsules.

D. Pharmacological Measurements

To measure the magnitude of the psychological effects produced by the administration of THC, the subjects were asked to rate their degree of "high" at frequent intervals during the 90-180 min of the studies by a standard technique (20,23). Since the most consistent physiological effect of THC is cardiac acceleration, the heart rate was continuously recorded

from 10 min before drug administration and for 90-180 min thereafter.

E. Sample Collections

Blood samples were drawn at frequent intervals during the first hours of the experiments through an indwelling needle in one of the arm veins and by independent venipunctures thereafter. The blood samples were heparinized and centrifuged. The plasma obtained was immediately placed in frozen storage prior to analyses. The total urine excreted was collected at timed intervals for 72 hr, and total feces collected for the same interval of time.

F. Analytical Procedure

The basic procedure utilizes TLC to separate cannabinoid fractions, followed by scintillation counting of the radioactivity found in the separated zones.

Plasma, urine, and feces samples were analyzed for total drug, total non-conjugated and conjugated cannabinoids, THC, 11-hydroxy-delta-9-THC, and 11-nor-delta-9-THC-9-carboxylic acid by a slight modification of the procedure described by Wall et al. (31).

The major modifications were: (1) TLC developing system, for neutral cannabinoids: chloroform, ethanol, acetone, t-butanol, 92:1:3:5; for acid cannabinoids: plates pretreated in acetone, acetic acid 100:3, and dried at 110°; developing solvent was chloroform,acetone,acetic acid 60:45:0.5; and (2) extraction of urine. It had been found that preliminary chromatography on Amberlite XAD-2 resin can be omitted. The acidified urine could be extracted directly with diethyl ether.

The above procedure has been shown to give results comparable to those obtained by GC/MS procedures (30).

G. Pharmacokinetic and Statistical Analysis

The concentrations of drug in the plasma of each subject (Cp) were weighted at $1/Cp^2$, $1/Cp$, and 1 and fitted to the biexponential curve ($Cp = Ae^{-alpha \cdot t} + Be^{-beta \cdot t}$) (7), using the computer program NONLIN (17). Only data points after the peak concentration of drug in the plasma were fitted. From the three weighted analyses, the estimate of the smaller exponent which had the smallest standard deviation was used as the estimate of beta for each individual. In a few isolated cases in which the number of observed concentrations in the plasma

was seven or less or when the coefficient of variation of beta was large, the data were weighted as before and fit with a monoexponential curve ($Cp = Be^{-beta \cdot t}$). An F-test was performed in order to justify the use of the lower order model ($P > 0.1$). The estimate of the absorption rate constant for THC was found by adding an absorption term ($Ce^{-gamma \cdot t}$) to the equation which represented the concentration of THC in the plasma after its oral administration and fitting all observed data points using NONLIN (17).

Cumulative urine data (U_C) were fitted with the equation $U_C = U_{inf.}(1-e^{-kt})$ (7). The first deviation of this equation was evaluated at four or five times for which there were corresponding plasma samples. The renal clearance (Cl_R) for each subject was estimated by taking the mean of $(dUc/dt)/Cp$ at those points.

The areas under the plasma concentration curves (AUC) were calculated from 0 to 48 hr or from 0 to 72 hr by the trapezoidal rule. The area under the curve from the last data point (48 to 72 hr) to infinity represented less than 2% of AUC in all cases and was considered to be negligible. The total clearance of drug from the plasma (Cl_T) was calculated as V_d = Dose/beta x AUC). Half-lives (t/2) were calculated from the fitted exponents ($lambda_i$ = alpha, beta, or gamma) as $t/2 = 0.693/lambda_i$.

Weighted means were used whenever the variance of an individual parameter was estimated (viz. beta and Cl_R). In these cases the formulas of Meiers were used (16).

Correlation analysis was done for the subjective "high" and heart rate data vs the concentrations of THC, total cannabinoids, 11-hydroxy-delta-9-THC, and 11-nor-delta-9-THC-9-carboxylic acid in the plasma. The subjective "high" was expressed as a percent of the maximum "high" for each subject. The heart rate was expressed as the percent increase over the basal heart rate for each subject. The coefficients of correlation (r) were determined for pooled groups of subjects using the CORR procedure in Statistical Analysis Systems (SAS). Correlation coefficients were compared using Fisher's Z-transformation of r (26).

Unless otherwise stated, statistical significance was determined at the 0.05 level.

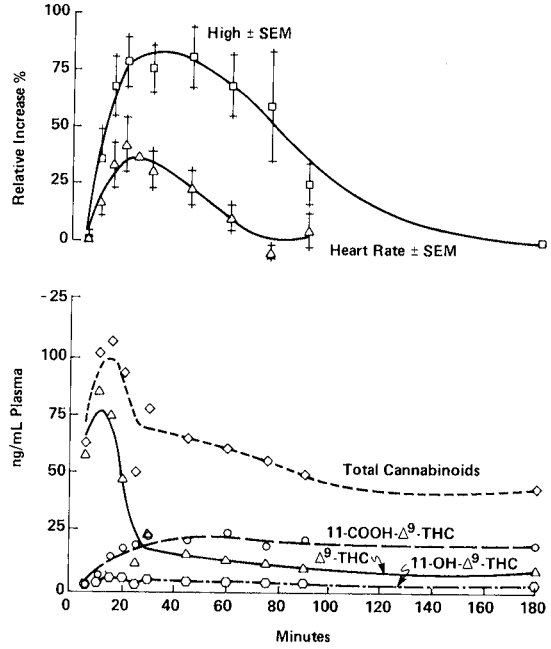
III. RESULTS

A. Correlation of Plasma Cannabinoid Levels and Pharmacodynamic Measurements

Figure 2 (a-d) compares over a 2-3 hr period the mean

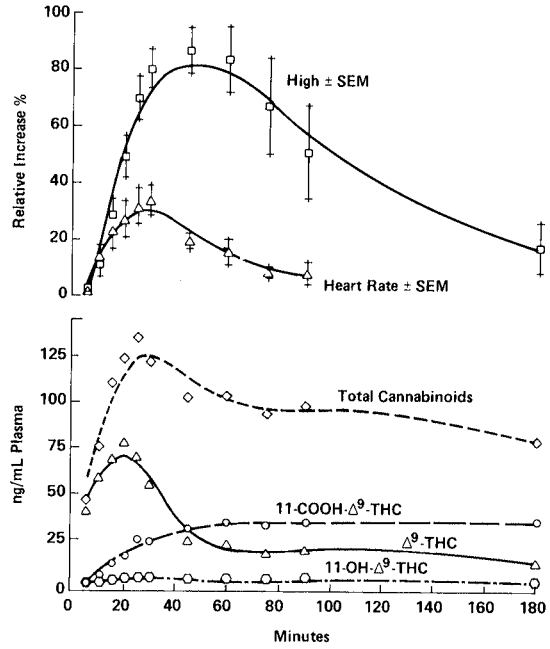
INTRAVENOUS

FEMALE



(a)

MALE



(b)

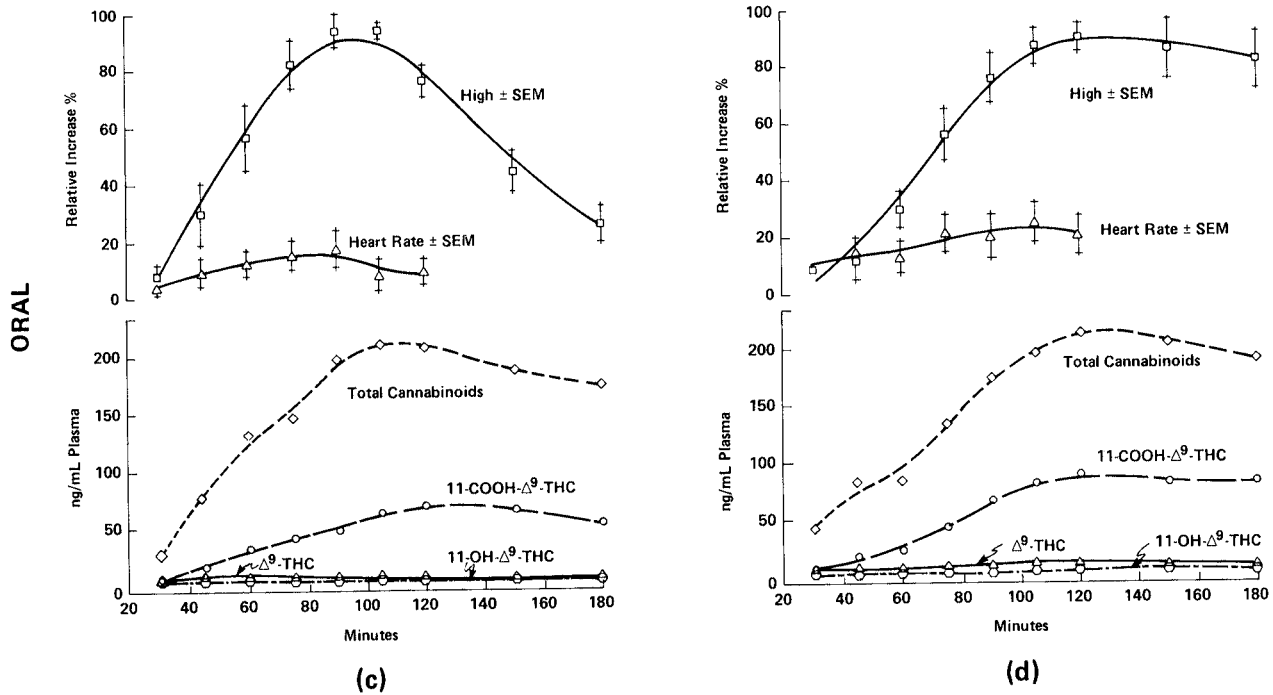


FIGURE 2. Concentration of THC and its major metabolites in plasma and their effect on subjective high and heart rate. Panels a and b represent the data from female and male subjects, resp., after intravenous administration of THC. Panels c and d represent the data from female and male subjects, resp., after oral administration of THC. Subjective high is presented as a percentage of the maximum response for each subject. Heart rates are presented as the percent increase above the heart rate prior to dosing. All curves represent the means of six subjects.

plasma concentration of THC and metabolites with the mean subjective "high" and mean heart rate of male and female subjects. Table I presents the correlation analysis of the data. In general for both sexes and both administration routes, total cannabinoid plasma levels provided better correlation with heart rate and psychological effects than corresponding THC plasma concentrations. After both iv and po administration to male subjects, correlation of THC plasma levels with heart rate was observed; $p < 0.05$. In general, no correlation of THC plasma levels with mean subjective "high" could be found.

B. Metabolism and Excretion

The plasma concentrations of THC and major metabolites at various time periods are presented in Tables II (iv administration) and III (po administration). A similar pattern was observed for both sexes. THC plasma levels decreased rapidly after iv infusion of drug was terminated (usually 15-25 min). After 1-1.5 hr, a much slower decrease in plasma THC levels was noted (cf. Fig. 3,4).

The active metabolite, 11-hydroxy-delta-9-THC (II), was present in the plasma in low concentrations, varying from 5-10% of THC levels at most time periods. The inactive metabolite 11-nor-delta-9-THC-9-carboxylic acid (III) was the major metabolic product found in plasma. Conjugated cannabinoids (defined as the radiolabeled plasma fraction insoluble in diethyl ether) were absent.

After oral administration, the composition of plasma cannabinoids was again similar for both sexes, exhibiting, however, characteristic differences from the data obtained after iv dosing. The major differences noted were (1) that after po administration, THC plasma levels increased to rather constant concentrations up to 4-6 hr after dosing, and (2) that the ratio of the plasma levels of active metabolite II relative to those of parent drug I showed a considerable increase (cf., Tables II and III). After oral administration, the concentrations of acid metabolites also increased considerably over the levels noted after iv dosing, and small quantities of conjugated cannabinoids were noted.

C. Urinary Excretion.

THC was excreted in urine as non-conjugated or conjugated acid metabolites (Tables IV, V). The mean cumulative cannabinoid excretion found in 72 hr after iv administration was 16.7 +/- 2.6% and 15.2 +/- 4.2% of the total dose for females and

TABLE I. Correlation of "High" and Heart Rate with Plasma Levels of THC and Metabolites

Correlation Coefficient (r)[a] for 6 Subjects

	Male (iv)		Female (iv)		Male (po)		Female (po)	
Cannabinoid	High	Heart	High	Heart	High	Heart	High	Heart
Δ^9-THC	-0.0998	0.5460*	0.0879 (0.0399)	-0.0187 (0.0785)	0.0729	0.4840*	0.3862*	0.2348
Total Drug	0.4674*+	0.7393*	0.1072 (0.2873)	0.1433 (0.4752)*+	0.5438*+	0.6093*	0.6409*+	0.1352

[a]R values receiving an asterisk showed significance at $P < 0.05$. R values in parentheses under the heading "Female (iv)" were obtained by dropping the data of one subject.

+Total drug significantly better correlated with parameter than Δ^9-THC ($P < 0.05$).

TABLE II. THC and Metabolites Found in Human Plasma after Intravenous Administration

ng/ml (Mean ± SD)

Time (hr)	Total Cannabinoids	Nonconjugated Cannabinoids	Polar Acids	11-nor-Δ^9-THC-9-COOH	11-OH Δ^9-THC	Δ^9-THC
			Six Female Subjects - Average Dose 2.2 mg			
* 0.08	62 ± 18	62 ± 18	Trace	0.6 ± 0.3	0.7 ± 0.4	58 ± 17
0.17	102 ± 31	102 ± 31	4.1 ± 1.5	4.8 ± 1.0	2.3 ± 1.5	85 ± 26
0.25	107 ± 40	106 ± 40	11 ± 2.2	13 ± 4.2	3.6 ± 2.4	75 ± 40
0.33	93 ± 39	92 ± 39	16 ± 3.1	16 ± 6.5	3.8 ± 2.8	47 ± 30
0.5	77 ± 22	76 ± 21	15 ± 6.4	22 ± 7.4	3.2 ± 2.3	23 ± 12
* 1.0	60 ± 13	60 ± 14	15 ± 8.6	24 ± 10	2.5 ± 1.14	12 ± 6.1
* 1.5	49 ± 6.3	48 ± 6.2	11 ± 4.6	21 ± 7.3	1.6 ± 0.7	8.7 ± 2.7
* 3.0	43 ± 3.8	48 ± 4.9	11 ± 4.7	18 ± 6.4	1.1 ± 0.6	7.9 ± 3.0
6.0	30 ± 3.4	30 ± 3.0	5.3 ± 1.9	14 ± 4.2	0.5 ± 0.3	5.6 ± 2.4
* 12.0	24 ± 7.5	23 ± 7.9	3.2 ± 1.0	12 ± 7.8	Trace	4.4 ± 3.7
* 24.0	16 ± 2.3	16 ± 2.1	2.4 ± 1.2	8.0 ± 3.1	Trace	2.7 ± 1.3
48.0	11 ± 3.2	11 ± 3.3	1.8 ± 1.4	4.8 ± 1.5	Trace	2.3 ± 1.1
			Six Male Subjects - Average Dose 4.0 mg			
0.08	46 ± 20	46 ± 20	1.1 ± 1.0	1.3 ± 0.8	0.5 ± 0.4	41 ± 20
* 0.17	75 ± 19	75 ± 22	5.0 ± 3.4	5.5 ± 2.6	1.4 ± 0.8	59 ± 21
0.25	110 ± 34	109 ± 35	8.8 ± 5.9	11 ± 7.5	2.7 ± 1.6	70 ± 30
0.33	123 ± 33	122 ± 33	17 ± 6.7	15 ± 3.2	3.0 ± 1.4	63 ± 34
0.42	135 ± 46	133 ± 46	20 ± 7.8	21 ± 15	3.6 ± 1.2	71 ± 34
0.5	122 ± 41	120 ± 40	25 ± 7.4	24 ± 9.0	3.7 ± 2.3	55 ± 31
* 0.75	102 ± 28	100 ± 28	29 ± 10	31 ± 11	3.1 ± 1.8	25 ± 5.2
1.0	103 ± 35	100 ± 34	29 ± 12	34 ± 13	2.8 ± 1.2	23 ± 8.3
* 1.25	93 ± 28	91 ± 29	24 ± 9.7	33 ± 18	2.7 ± 0.6	18 ± 2.9
1.5	97 ± 33	94 ± 31	25 ± 8.9	34 ± 15	3.0 ± 0.7	20 ± 6.2
* 2.0	93 ± 31	91 ± 30	27 ± 9.8	38 ± 16	2.2 ± 0.6	19 ± 6.2
2.5	90 ± 31	87 ± 30	23 ± 11	35 ± 15	2.1 ± 1.0	16 ± 6.3
3.0	78 ± 29	76 ± 29	18 ± 7.8	34 ± 14	1.4 ± 0.6	13 ± 5.9
6.0	57 ± 19	55 ± 20	12 ± 3.6	28 ± 12	0.7 ± 0.3	6.8 ± 2.8
* 8.0	52 ± 26	50 ± 26	10 ± 3.5	27 ± 15	0.6 ± 0.3	6.2 ± 3.5
12.0	34 ± 12	33 ± 13	6.5 ± 3.0	15 ± 6.5	Trace	5.0 ± 1.0
24.0	31 ± 14	29 ± 13	5.5 ± 2.6	15 ± 7.6	Trace	3.7 ± 1.2
* 30.0	32 ± 12	29 ± 13	6.7 ± 2.3	16 ± 7.0	Trace	3.8 ± 1.8
48.0	24 ± 11	21 ± 10	4.4 ± 2.0	11 ± 5.2	Trace	3.2 ± 1.8

*Five subjects

TABLE III. THC and Metabolites Found in Human Plasma after Oral Administration

ng/ml (Mean ± SD)

Time (hr)	Total Cannabinoids	Nonconjugated Cannabinoids	Polar Acids	11-nor-Δ^9-THC-9-COOH	11-OH Δ^9-THC	Δ^9-THC
			Six Female Subjects - Average Dose 15 mg			
0.50	28 ± 26	26 ± 26	11 ± 14	4.1 ± 3.9	1.4 ± 1.3	4.8 ± 4.6
0.75	76 ± 58	69 ± 53	27 ± 23	15 ± 10	3.8 ± 4.2	9.0 ± 8.4
1.0	112 ± 67	104 ± 63	49 ± 27	27 ± 18	3.7 ± 2.8	7.7 ± 5.9
1.25	146 ± 61	135 ± 56	56 ± 23	41 ± 21	4.2 ± 2.6	8.4 ± 5.3
1.5	196 ± 66	184 ± 65	91 ± 31	48 ± 28	5.5 ± 2.6	9.1 ± 4.7
1.75	210 ± 53	194 ± 54	79 ± 28	62 ± 28	5.9 ± 2.8	9.4 ± 4.5
2.0	207 ± 40	192 ± 40	80 ± 21	68 ± 20	5.3 ± 1.6	7.4 ± 2.2
2.5	185 ± 32	173 ± 33	70 ± 26	64 ± 10	4.5 ± 2.5	7.2 ± 3.8
3.0	172 ± 34	160 ± 39	70 ± 26	51 ± 14	4.4 ± 2.9	6.8 ± 3.1
4.0	140 ± 30	130 ± 31	50 ± 22	48 ± 8.0	2.5 ± 1.7	6.2 ± 3.2
6.0	119 ± 30	109 ± 30	45 ± 17	38 ± 8.6	1.6 ± 0.9	5.4 ± 4.2
8.0	96 ± 39	95 ± 37	29 ± 19	39 ± 13	1.2 ± 0.5	3.8 ± 2.3
12.0	76 ± 23	68 ± 24	25 ± 15	28 ± 6.4	0.9 ± 0.5	3.2 ± 1.9
24.0	56 ± 11	48 ± 11	16 ± 3.7	21 ± 6.4	0.7 ± 0.5	1.9 ± 0.6
30.0	46 ± 12	39 ± 10	19 ± 8.2	15 ± 2.6	Trace	1.5 ± 1.0
48.0	35 ± 11	27 ± 10	8.4 ± 3.0	12 ± 7.4	Trace	0.9 ± 0.5
72.0	28 ± 10	23 ± 11	7.7 ± 3.9	8.4 ± 5.3	Trace	0.8 ± 0.9
			Six Male Subjects - Average Dose 20 mg			
0.75	84 ± 14	62 ± 18	39 ± 8	18 ± 6	2.7 ± 0.8	9.1 ± 4.0
1.0	85 ± 42	81 ± 40	29 ± 19	23 ± 12	3.4 ± 3.1	8.0 ± 7.3
1.25	134 ± 41	127 ± 39	52 ± 26	47 ± 22	3.8 ± 1.9	11 ± 9.3
1.5	173 ± 41	164 ± 42	60 ± 27	66 ± 32	5.2 ± 1.7	11 ± 6.6
1.75	194 ± 51	185 ± 51	58 ± 20	82 ± 39	5.1 ± 2.1	13 ± 7.5
2.0	213 ± 68	201 ± 69	66 ± 17	89 ± 40	6.6 ± 3.4	13 ± 9.1
2.5	204 ± 61	191 ± 62	56 ± 26	80 ± 39	5.9 ± 3.0	14 ± 9.7
3.0	190 ± 67	180 ± 68	57 ± 13	82 ± 37	5.6 ± 3.2	11 ± 8.2
4.0	176 ± 68	167 ± 67	45 ± 19	82 ± 36	5.6 ± 3.6	11 ± 6.6
6.0	142 ± 47	134 ± 46	42 ± 11	62 ± 31	4.0 ± 1.8	10 ± 6.0
8.0	122 ± 37	115 ± 37	36 ± 10	51 ± 21	3.4 ± 2.3	8.4 ± 4.8
11.0 - 12.0	94 ± 31	87 ± 31	25 ± 9	37 ± 18	1.9 ± 1.3	6.4 ± 3.9
24.0	63 ± 22	56 ± 23	15 ± 4	29 ± 14	1.3 ± 1.2	3.3 ± 2.4
30.0	51 ± 15	44 ± 13	14 ± 4	23 ± 8	0.8 ± 0.6	3.2 ± 2.1
48.0	38 ± 12	30 ± 11	10 ± 3	14 ± 6	0.6 ± 0.5	2.2 ± 1.7
72.0	25 ± 7	17 ± 7	6 ± 3	8 ± 5	Trace	1.0 ± 0.6

TABLE IV. THC and Metabolites Found in Human Urine after Intravenous Administration Cumulative % Dose* (Mean ± SD)

Time (hr)	Total Cannab.	Nonconjugated Cannabinoid			Conjugated Cannabinoids		
		Total	Polar Acids	11-nor-Δ^9-THC-9-COOH	Total	Polar Acids	11-nor-Δ^9-THC 9-COOH
			Six Female Subjects - Average Dose 2.2 mg				
1-1.5	1.8 ± 1.3	1.2 ± 0.9	0.8 ± 0.5	0.08 ± 0.04	0.6 ± 0.5	0.1 ± 0.1	0.05 ± 0.02
3	4.1 ± 0.2	2.6 ± 0.3	1.8 ± 0.5	0.4 ± 0.1	1.4 ± 0.4	0.3 ± 0.1	0.1 ± 0.06
6	5.4 ± 1.9	3.6 ± 1.1	1.9 ± 0.8	0.6 ± 0.3	1.8 ± 0.9	0.4 ± 0.2	0.2 ± 0.08
11-12	7.5 ± 1.2	4.9 ± 0.6	2.6 ± 0.9	0.9 ± 0.4	2.4 ± 0.9	0.5 ± 0.2	0.2 ± 0.03
24	11 ± 2	7.1 ± 1.6	3.3 ± 1.1	1.8 ± 1.0	3.7 ± 0.9	0.8 ± 0.3	0.4 ± 0.07
48	14 ± 2	14 ± 2	4.1 ± 1.3	2.6 ± 1.3	5.1 ± 1.4	1.0 ± 0.3	0.5 ± 0.05
72	16 ± 3	10 ± 3	4.4 ± 1.6	3.2 ± 1.7	5.5 ± 1.5	1.2 ± 0.3	0.6 ± 0.08
			Six Male Subjects Average Dose 4.0 mg				
1.5-2	3.2 ± 1.1	2.1 ± 0.6	1.6 ± 0.7	0.3 ± 0.3	1.2 ± 0.6	0.3 ± 0.2	0.1 ± 0.1
2.5-3	4.9 ± 4.1	3.9 ± 3.2	1.5 ± 1.2	0.8 ± 0.8	1.9 ± 1.7	0.4 ± 0.4	0.3 ± 0.2
6	4.4 ± 0.1	2.8 ± 0.1	1.4 ± 0.1	0.6 ± 0.3	1.6 ± 0.3	0.3 ± 0.1	0.2 ± 0.2
11-12	5.9 ± 2.4	3.8 ± 1.5	1.5 ± 0.7	1.0 ± 0.7	2.1 ± 0.9	0.4 ± 0.1	0.3 ± 0.2
24	10 ± 5	6.4 ± 2.3	2.5 ± 0.9	2.0 ± 1.4	3.9 ± 1.5	0.7 ± 0.3	0.6 ± 0.5
48	14 ± 4	8.4 ± 2.3	5.8 ± 3.2	2.8 ± 1.6	5.2 ± 1.3	1.0 ± 0.3	0.8 ± 0.5
72	15 ± 4	9.5 ± 2.8	3.4 ± 1.1	3.2 ± 1.7	6.0 ± 1.7	1.1 ± 0.3	0.9 ± 0.5

*Data may not be consecutive due to missing values.

TABLE V. THC and Metabolites Found in Human Urine after Oral Administration
Cumulative % Dose* (Mean ± SD)

Time (hr)	Total Cannab.	Nonconjugated Cannabinoid			Conjugated Cannabinoids		
		Total	Polar Acids	11-nor-Δ^9-THC-9-COOH	Total	Polar Acids	11-nor-Δ^9-THC-9-COOH
Six Female Subjects - Average Dose 15 mg							
1.25-1.5	0.9 ± 0.8	0.6 ± 0.5	0.4 ± 0.3	0.1 ± 0.1	0.4 ± 0.3	0.1 ± 0.1	0.1 ± 0.1
4	6.2 ± 2.0	3.6 ± 0.7	1.9 ± 0.3	0.8 ± 0.1	2.6 ± 1.3	1.0 ± 0.6	0.6 ± 0.6
5-6	5.5 ± 0.6	2.6 ± 0.6	1.7 ± 0.1	0.5 ± 0.4	2.9 ± 1.3	0.9 ± 0.5	0.8 ± 0.5
8	8.8 ± 1.9	4.7 ± 0.7	2.5 ± 0.4	1.0 ± 0.2	4.1 ± 1.3	1.8 ± 0.7	0.9 ± 0.6
11	9.4 ± 2.4	4.6 ± 1.2	2.7 ± 0.5	1.0 ± 0.5	4.8 ± 1.9	2.0 ± 0.8	1.1 ± 0.7
24	12.5 ± 3.0	6.3 ± 0.7	3.4 ± 0.7	1.4 ± 0.4	6.2 ± 2.6	2.4 ± 1.2	1.4 ± 0.8
30	14.1 ± 3.5	6.8 ± 0.7	3.9 ± 0.9	1.5 ± 0.5	7.3 ± 3.4	2.9 ± 1.5	1.6 ± 1.1
48	15.4 ± 3.0	7.7 ± 0.8	4.0 ± 0.7	1.9 ± 0.5	7.7 ± 2.9	2.9 ± 1.4	1.8 ± 1.0
72	15.9 ± 3.6	8.1 ± 1.0	4.3 ± 1.0	1.9 ± 0.5	7.8 ± 3.4	2.9 ± 1.5	1.8 ± 1.1
Six Male Subjects - Average Dose 20 mg							
1.5-2	1.3 ± 0.3	0.7 ± 0.1	0.47 ± 0.01	0.118 ± 0.004	0.5 ± 0.2	0.3 ± 0.1	0.12 ± 0.01
2.5-3	2.4 ± 0.3	1.4 ± 0.1	0.8 ± 0.1	0.3 ± 0.2	1.0 ± 0.2	0.5 ± 0.1	0.2 ± 0.1
4	3.7 ± 0.2	1.9 ± 0.3	1.1 ± 0.2	0.5 ± 0.2	1.8 ± 0.5	0.6 ± 0.2	0.5 ± 0.1
6	5.7 ± 1.0	3.1 ± 0.6	1.6 ± 0.1	0.8 ± 0.3	2.6 ± 0.3	1.1 ± 0.2	0.7 ± 0.1
8	5.9 ± 0.6	3.3 ± 0.6	1.8 ± 0.1	0.9 ± 0.4	2.6 ± 0.2	1.0 ± 0.2	0.7 ± 0.3
11	8.1 ± 0.8	4.4 ± 0.8	2.2 ± 0.1	1.2 ± 0.5	3.7 ± 0.5	1.5 ± 0.1	0.9 ± 0.4
24	10.3 ± 2.1	5.5 ± 1.4	2.7 ± 0.4	1.7 ± 0.8	4.8 ± 1.0	1.9 ± 0.5	1.2 ± 0.3
30	11.2 ± 2.0	5.9 ± 1.4	2.8 ± 0.4	1.8 ± 0.9	5.3 ± 1.0	2.1 ± 0.5	1.3 ± 0.3
48	12.7 ± 1.8	6.5 ± 1.5	3.0 ± 0.4	2.0 ± 0.9	6.1 ± 1.0	2.4 ± 0.5	1.5 ± 0.4
72	13.4 ± 2.0	6.9 ± 1.6	3.2 ± 0.4	2.2 ± 1.0	6.5 ± 1.1	2.5 ± 0.5	1.6 ± 0.4

*Data may not be consecutive due to missing values.

males, respectively; after po administration corresponding values were 15.9 +/- 3.6% and 13.4 +/- 2.0%. Analyses were conducted for neutral non-conjugated and conjugated cannabinoids but only traces were found. The composition of the cannabinoid urinary metabolites was similar for both sexes. After iv administration the ratio of non-conjugated to conjugated fraction increased, the non-conjugated-conjugated ratio approximating 1:1 at many time periods. The 11-nor-acid metabolite (III) and the less well defined "polar acid" fraction were the major constituents in urine. Other acid metabolites intermediate in polarity were present but were not quantitated.

D. Fecal Excretion

After iv administration, mean cumulative cannabinoid excretion in feces after 72 hr was 25 +/- 19% and 20 +/- 16% for female and male, respectively; after po administration corresponding values were 48 +/- 6% and 53 +/- 19%. The composition of cannabinoids found in the feces was similar for both sexes but was affected by the route of administration (cf. Tables VI and VII). In general, the cannabinoids in feces were non-conjugated -- the conjugate fraction amounting to only 5-10% of the total. After iv administration, both the 11-hydroxy and 11-nor-acid metabolites comprised the major components of the cannabinoid fractions which were analyzed; whereas after po administration, the 11-nor-acid was the major metabolite.

E. Pharmacokinetic Parameters

Figures 3 and 4 present graphical plots of the observed and calculated THC plasma concentrations vs time. The observed and calculated data were in agreement and consistent with a two compartment model with a biexponential decline in plasma levels as a function of time. The mean values of certain pharmacokinetic parameters are shown in Table VIII. After iv administration, the t/2 values for the rapid disposition alpha-phase calculated for THC were 0.4 and 0.6 hr, female, and male, respectively. Corresponding terminal phase (beta) half-lives were 29 and 36 hr, respectively. After oral administration, the t/2 values fo the absorption phase (gamma-phase) were 0.7 and 0.9 hr, female and male, respectively; t/2 of alpha-phase 3.8 and 3.9 hr; and t/2 beta-phase 25 hr for both sexes. Biological half-lives were also calculated from the beta-exponentials of metabolites (Table VIII). The terminal phase half-lives of the total drug and 11-nor-acid approx-

TABLE VI. THC and Metabolites Found in Human Feces after Intravenous Administration
Cumulative % Dose* (Mean ± SD)

Time (hr)	Total Feces**	MeOH Soluble**		MeOH Insoluble**	Nonconjugated			
		Non-conjugated	Conjugated		Polar Acids	11-nor-Δ^9-THC 9-COOH	11-OH Δ^9-THC	Δ^9-THC
				Four Female Subjects - Average Dose 2.2 mg				
21-24	9 ± 11	7 ± 9	0.4 ± 0.4	1.4 ± 2.0	1.2 ± 1.3	2.3 ± 2.8	4.4 ± 6.5	0.4 ± 0.5
44.5-48	19 ± 17	15 ± 13	1.0 ± 0.4	0.9 ± 0.5	2.2 ± 1.7	4.4 ± 4.5	2.3 ± 1.4	0.9 ± 0.8
72	26 ± 19	19 ± 14	1.2 ± 0.4	5.0 ± 4.7	2.9 ± 1.9	5.9 ± 5.5	3.1 ± 1.6	1.3 ± 0.8
				Five Male Subjects - Average Dose 4.0 mg				
24	14 ± 11	11 ± 9	0.6 ± 0.5	1.9 ± 1.8	1.0 ± 1.0	2.2 ± 1.8	4.1 ± 4.5	0.8 ± 1.2
48	40 ± 6	32 ± 6	2.2 ± 0.1	5.7 ± 0.6	3.3 ± 2.7	5.9 ± 4.7	10 ± 3	2.0 ± 0.6
72	35 ± 11	27 ± 10	1.9 ± 0.7	5.9 ± 2.2	2.9 ± 1.7	6.3 ± 2.6	9.9 ± 5.7	2.7 ± 1.4

*Data may not be consecutive due to missing values.

**Total feces, MeOH soluble, and MeOH insoluble were measured independently.

TABLE VII. THC and Metabolites Found in Human Feces after Oral Administration
Cumulative % Dose* (Mean ± SD)

Time (hr)	Total Feces**	MeOH Soluble**		MeOH Insoluble**	Nonconjugated			
		Non-conjugated	Conjugated		Polar Acids	11-nor-Δ^9-THC-9-COOH	11-OH Δ^9-THC	Δ^9-THC
			Five Female Subjects - Average Dose 15 mg					
22-24	9 ± 11	7 ± 8	2.1 ± 2.4	2 ± 2	1.1 ± 1.8	1.4 ± 1.8	0.8 ± 1.0	1.3 ± 1.3
48	37 ± 6	24 ± 2	4.2 ± 1.4	8 ± 1	4.4 ± 1.8	6.1 ± 0.5	3.0 ± 0.6	2.8 ± 0.6
72	48 ± 6	33 ± 3	4.4 ± 2.0	11 ± 2	6.0 ± 2.2	8.1 ± 1.7	4.0 ± 0.3	4.1 ± 1.9
			Six Male Subjects - Average Dose 20 mg					
24	24 ± 24	18 ± 19	1.8 ± 1.9	4 ± 5	2.3 ± 2.3	4.3 ± 4.5	1.9 ± 2.1	2.8 ± 2.9
40-48	55 ± 13	39 ± 11	5.1 ± 0.8	12 ± 4	5.8 ± 0.9	11 ± 2	4.0 ± 1.1	5.6 ± 3.5
72	53 ± 18	39 ± 12	4.0 ± 2.3	11 ± 6	6.1 ± 2.2	11 ± 5	3.7 ± 1.2	5.7 ± 1.7

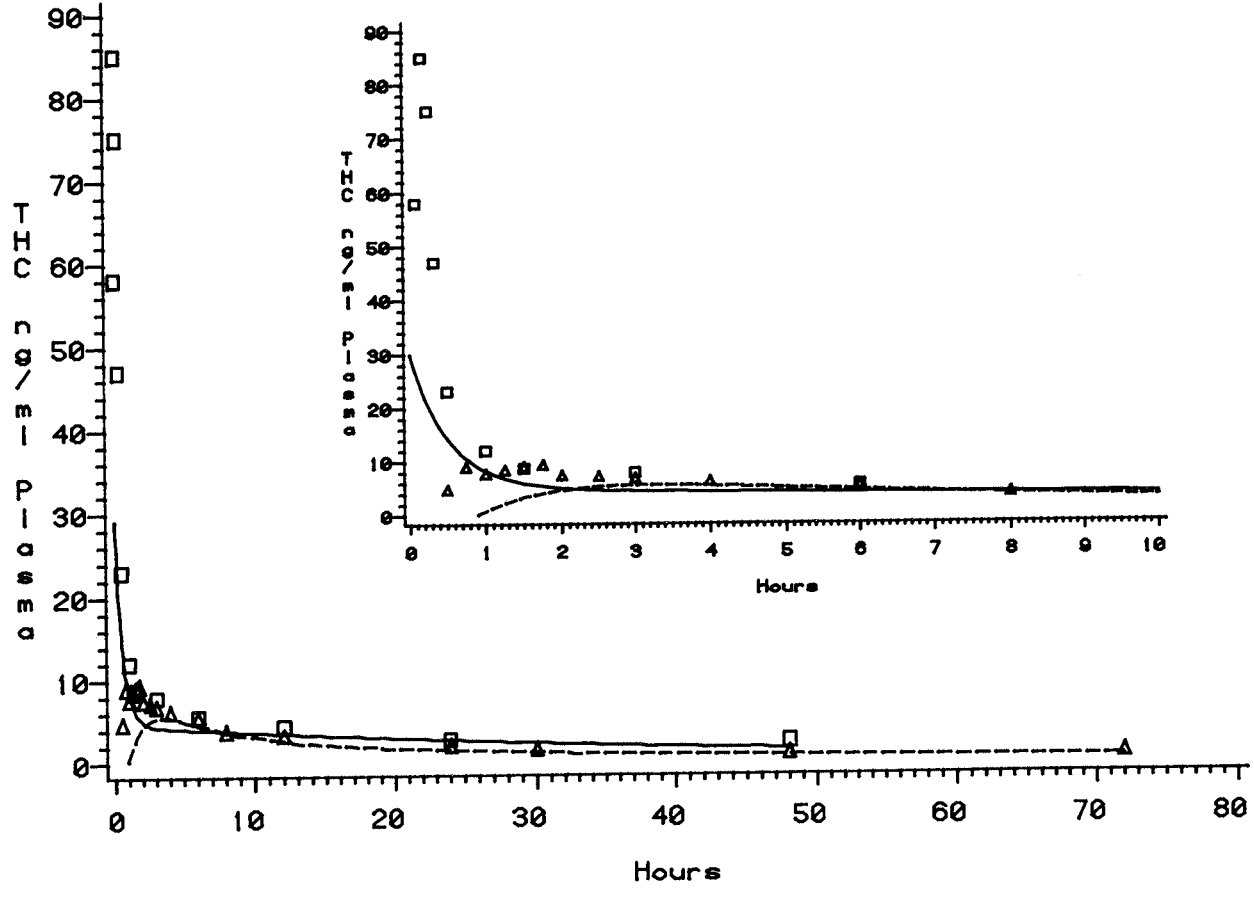
*Data may not be consecutive due to missing values.

**Total feces, MeOH soluble, and MeOH insoluble were measured independently.

TABLE VIII. Mean Values of Pharmacokinetic Parameters[a]

DRUG FORM	AUC/DOSE i.v. (min/ml) x 10^3	AUC/DOSE p.o. (min/ml) x 10^3	β[c] i.v. (hr^{-1}) x 10^2	β[c] p.o. (hr^{-1}) x 10^2	$t_{\frac{1}{2}\beta}$[b] i.v. (hr)	$t_{\frac{1}{2}\beta}$[b] p.o. (hr)	V_d[d] i.v. (liters)	Cl_T i.v. (ml/min)	Cl_R[c] i.v. (ml/min)	Cl_R[c] p.o. (ml/min)
				MALES						
Total Drug	28 (10)	13 (4)	1.6 (1.0)	1.8 (0.6)	43	39	226 (129)	40 (16)	4.5 (0.7)	14.3 (1.1)
Δ^9-THC	4.2 (1.0)	0.8 (0.5)	2.0 (1.7)	2.7 (0.7)	36	25	734 (444)	248 (62)	-	-
11-OH-Δ^9-THC	-	-	4.6 (1.8)	3.8 (2.3)	15	18	-	-	-	-
11-nor-Δ^9-THC-9-COOH	-	-	1.3 (1.2)	2.8 (0.8)	55	25	-	-	1.6 (0.1)	4.4 (0.6)
				FEMALES						
Total Drug	26 (8)	16 (2)	2.3 (1.4)	1.4 (0.7)	31	48	130 (87)	44 (24)	8.0 (0.9)	14.2 (2.5)
Δ^9-THC	5.5 (2.1)	0.6 (0.3)	2.4 (2.8)	2.8 (1.4)	29	25	523 (217)	197 (50)	-	-
11-OH-Δ^9-THC	-	-	2.1 (3.0)	5.8 (2.2)	33	12	-	-	-	-
11-nor-Δ^9-THC-9-COOH	-	-	2.8 (1.1)	1.9 (1.3)	25	37	-	-	1.8 (0.4)	4.2 (0.7)

(a)Figures in parentheses are standard deviations.
(b)Calculated from mean β.
(c)Weighted mean and standard deviation.
(d)Apparent volume of distribution corrected for β.

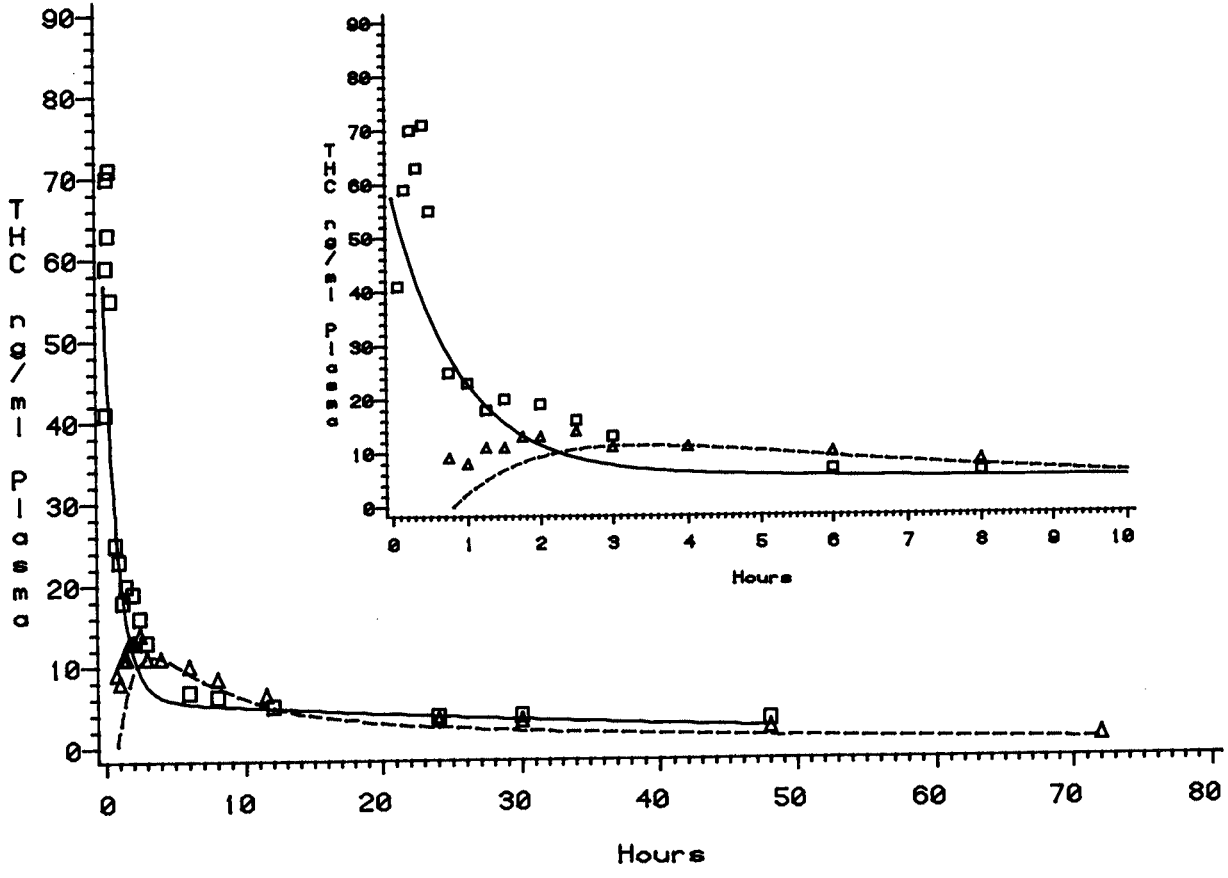

THC ng/ml Plasma
Hours
0
10
20
30
40
50
60
70
80
90
THC ng/ml Plasma
Hours
0
1
2
3
4
5
6
7
8
9
10

imated those noted for THC. AUC/Dose calculated for total drug and THC were similar for both sexes. The magnitude of the area uder the curve corrected for dose, calculated for total cannabinoids and THC, was unaffected by the sex of the subjects, but was markedly influenced by the route of administration, cf., Table VIII. The values obtained after po dosing were much lower than the corresponding values noted after iv administration. The volume of distribution corrected for beta was of the same order for both sexes, approximately 10 L./kg. Total clearance values were also of the same order for both sexes, 197 and 248 mL/min for females and males, respectively. Renal clearance values for 11-nor-delta-9-THC-9-carboxylic acid were of the same order for both sexes (1.5-2.0 mL/min). There seemed to be some increase in these values after oral administration, although the difference may not be significant.

IV. DISCUSSION

Although the metabolism of THC in man has received extensive study (cf.10,28,32,33 for reviews), previous studies have been conducted largely with male volunteers (31). Moreover, in most of the earlier studies, analyses of plasma for THC or metabolites were not conducted for sufficiently long periods to obtain reasonable estimates for beta-parameters and corresponding half-lives. The studies reported in this paper present a comprehensive study of the metabolism, excretion and pharmacokinetics of THC administered to female and male volunteers by iv and oral dosing. In agreement with other workers (3,8), we could not demonstrate a consistent relationship between plasma THC concentrations and subjective "high" or heart rate. With male volunteers correlation was observed (iv and po, Table I) between THC levels and heart rate. However, better correlation was observed for both sexes between the total cannabinoid plasma concentrations found after iv or po administration and both heart rate and psychological "high". This relationship is probably coincidental. However, we have noted that the shape of the plots for total cannabinoids, "high", and heart rate shown in Figs. 2a-d, which depict these

FIGURE 3. Observed and calculated concentrations of THC in plasma of female subjects. The observed data represent the means of six subjects for oral (triangles) and intravenous (squares) administration of THC. The corresponding calculated curves (oral ---; intravenous ——) were constructed from the weighed parameter means from individual fitted plasma data.


THC ng/ml Plasma
Hours
0
10
20
30
40
50
60
70
80
90
THC ng/ml Plasma
Hours
0
1
2
3
4
5
6
7
8
9
10

correlations, and the plots of THC concentration in mouse brain vs time after iv administration, are similar (21,29). In the mouse model it has been shown (21,29) that after iv administration of cannbinoids, brain concentrations of parent drug reach a maximum within 0.5 min after administration, and a steady state is maintained for at least 30 min before brain levels decrease; whereas, mouse plasma cannabinoid levels decreased rapidly. If similar effects occur in man, this would account for psychological effects persisting for long time periods after plasma cannabinoid levels have decreased.

It is now well established from in vitro and in vivo animal studies and in vivo in man that THC is extensively metabolized by liver enzymes (27,28). In man allylic hydroxylation at the C-8 or C-11 positions by microsomal enzymes convert the parent drug to metabolites hydroxylated at C-8 (8-alpha or 8-beta), C-11, or both positions. Hydroxylation in the side chain frequently occurs in animals but many not be an important process in man. The primary alcohol at C-11 is metabolized to the corresponding 11-nor-acid or more polar acids by liver alcohol-dehydrogenase enzymes.

Our studies indicate that after administration of THC, no significant differences in metabolic pattern or excretion were observed between women and men. As noted in our earlier studies (31), certain major differences can be noted due to the route of administration. Of particular interest are the differences noted in the ratio of plasma THC (I) concentration to that of its 11-hydroxy metabolite (II). After iv administration, the ratio of II:I varies from 1:10-20; whereas after oral administration, the ratio increases to 1:2. The increase in the plasma levels of II after oral administration has been noted in our earlier studies (28,31). We attribute this to first-pass effects which both increase the concentration of II and decrease that of I. The increased proportion of the active 11-hydroxy metabolite may account for the fact that the subjective "high" noted with subjects receiving oral THC dosing is of the same order as noted with subjects receiving iv dosing, even though in the latter case THC plasma concentrations are initially much higher. Previous studies with mice have shown that THC metabolites with one additional hydroxyl moiety (8-beta, 11, or 3') penetrate the blood-brain barrier more rapidly and achieve much higher concentrations in

FIGURE 4. Observed and calculated concentrations of THC in plasma of male subjects. The observed data represent the means of six subjects for oral (triangles) and intravenous (squares) administration of THC. The corresponding calculated curves (oral ---; intravenous ——) were constructed from the weighed parameter means from individually fitted plasma data.

the brain than parent drug (21,29).

The cannabinoid acids, which include the 11-nor acid (III), as well as other less defined and more polar compounds, constitute the end products of cannabinoid metabolism. These acids comprised the major metabolite fraction found in plasma, urine and feces. No differences were found in the metabolism of these compounds that could be attributed to differences in sex. However, the route of administration did play a role, particularly in the degree of conjugation. We define urinary cannabinoid conjugates as the radiolabeled fraction that cannot be extracted from urine with diethyl ether. After oral administration, concentration of the conjugated fraction in urine was larger than the comparable fraction found after iv dosing. Similarly, in the feces, after iv administration, little conjugation was noted, whereas the concentration of total conjugates increased after oral administration. Little is known about the composition of the cannabinod conjugate fraction except that some of it can be hydrolyzed by glucuronidase. This represents at times only a small fraction of the total conjugates. The nature of the remaining forms of conjugation is still largely unknown.

Acidic cannabinoids comprise almost the entire cannabinoid fraction found in the urine. Neutral cannabinoids, both free and conjugated, are found only in trace quantity. Urinary excretion is the minor route of elimination of cannabinoids. Approximately 13-16% of the total dose is found in urine after 72 hr with both administration routes and for both sexes.

As noted previously (31), biliary excretion via the feces is the major route of cannabinoid excretion. Approximately 30% of the total dose was recovered in feces after iv administration, and about 50% after oral administration. The composition of the cannabinoids found in the feces is noteably different from the pattern of urinary metabolites. Fecal cannabinoids were found only in the non-conjugated form. In addition to acid metabolites, neutral cannabinoids, particularly 11-hydroxy-delta-9-THC, were important constituents. Whether the cannabinoids are excreted partially or totally as conjugates in bile and then enzymatically cleaved by endogenous intestinal enzymes or enzymes from microbial flora is uncertain. In the rat, an animal in which THC is also excreted in metabolized form primarily in feces (1), biliary cannulation studies of animals dosed with THC demonstrated that 60% of the metabolites were eliminated as water-soluble conjugates (34).

Pharmacokinetic parameters were similar for both sexes but differed in some cases due to the administration route. After termination of iv infusion of THC, the plasma decay curves for THC, when plotted as concentration vs time, yielded a biexponential curve which could be fitted by a digital computer

program to provide a non-linear regression analysis of the curve (17), from which could be calculated the constants of the equation: $C = Ae^{-alpha.t} + Be^{-beta.t}$. The actual and calculated plots of THC concentrations vs time (Figs. 3,4) are in reasonable agreement. The half-lives calculated for THC from the terminal phase constant beta were in excellent agreement for both sexes and both routes of administration, the range being 25-36 hr (Table VIII). Similar values were noted for total drug and the 11-nor-acid metabolite. Our results were in excellent agreement with an earlier study by Lemberger et al. (14), which covered approximately the same time period (72 hr) as our study. These workers report terminal phase half-lives of 28 hr for subjects who were experienced marijuana users. They noted similar half-lives for total radioactivity (total drug) and "ether extractable" radioactivity (which may have included the 11-nor-acid metabolite).

Similar apparent volumes of distribution were found for THC after iv administration of the drug to female and male volunteers. The high values observed, 523 and 734 liters (9.9 and 10.2 l./kg), are in accord with the results reported by Lemberger et al. (14) and can be ascribed to sequestration of the lipid soluble drug in fatty tissues.

After oral administration of THC, the values for AUC/dose were of the same order for both sexes but were markedly lower than corresponding values noted after iv dosing. The bioavailability of THC ranged from 10.9% (female) to 19.0% (male). Ohlsson et al. (19) report a systemic availability of 6% for THC utilizing a protocol with a shorter time period and a different vehicle for the drug.

From Table VII, it can be noted that the maximal quantity of THC found in feces ranges from 3-6% of the total dose, some of which may be due to biliary excretion. It follows therefore that absorption of THC through the gastrointestinal wall was high. Consequently, the low bioavailability of THC observed in our studies after oral administration must be due to extensive biotransformation of the drug by liver enzymes as a result of the "first pass" effect.

Renal clearance values Cl_R were determined for non-conjugated 11-nor-delta-9-THC-9-carboxylic acid, which is the major acidic metabolite found in urine. It should be noted that a number of other acids are present, some of which are probably included in what we term the polar acid fraction. In accord with the previously discussed pharmacokinetic data, no differences in Cl_R values were found due to the sex of the subjects. The data does indicate increased renal clearance after oral administration. The reason for this is not clear-cut. Possibly there may be greater saturation of the binding protein in plasma by the higher levels of the 11-nor-acid metabolite formed after oral administration. The renal clearance values

were not corrected for plasma binding as this constant has never been determined for the 11-nor-acid. In all likelihood, it would be of the order of at least 80-90% based on other cannabinoids binding values. Even correcting for an assumed 90% plasma binding of the 11-nor-acid (III), it is evident that the clearance ratio would be much lower than unity compared to inulin. This suggests that the metabolite may be subject to reabsorption (7).

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