THE PHARMACOKINETICS OF DELTA-9-TETRAHYDROCANNABINOL IN MAN AFTER SIMULTANEOUS INTRAVENOUS AND ORAL ADMINISTRATION*

Brian M. Sadler
Monroe E. Wall

Research Triangle Institute
Research Triangle Park, North Carolina

Mario Perez-Reyes

University of North Carolina
Chapel Hill, North Carolina

I. INTRODUCTION

Cannabinoid research recently has been branched into a number of clinically important areas. Mechoulam cited several potential clinical applications for delta-9-tetrahydrocannabinol (THC) and related cannabinoids, including the treatment of glaucoma, nausea, ulcers, and hypertension (1). As a result the metabolism and disposition of THC have been studied to a great degree (2,3).

One piece of important information which has been lacking has been an accurate measure of the bioavailability of orally administered THC. Ohlsson et al. reported bioavailability of THC at 0.06, but their study terminated in six hours and used a chocolate cookie as a vehicle (4). Wall et al. reported values of 0.11 and 0.19 for female and male subjects, respectively, using sesame oil capsules, but their protocol prohibited the simultaneous administration of oral and intravenous doses of the same subjects.

*Supported by NIDA grant DA-02424.

This study is an effort to assess the bioavailability of THC in male subjects after simultaneous administration of a tracer intravenous (i.v.) dose and a 20 mg oral dose.

II. MATERIALS AND METHODS

A. Subjects

Six, healthy, male paid volunteers of average height and weight and eating normal diets were used in this study. All had used marijuana in a recreational manner.

B. Chemicals and Materials

[^{3}H]-delta-9-THC, THC, and various standard cannabinoids were obtained from the National Institute on Drug Abuse (NIDA). Precoated thin layer chromatography (TLC) plates, 20 x 20 cm, silica gel 60F-245 (E. Merck, Dramstadt, West Germany) were used for all TLC. Scintillation counting was performed using Triton X-100:toluene:Omniflor (1 l.:2 l.:18 g). Radioimmunoassay (RIA) kits for THC and 9-COOH-11-nor-delta-9-THC were obtained through NIDA from Dr. C. E. Cook (Research Triangle Institute, Research Triangle Park, NC).

C. Drug Administration

Each subject was given a single-bolus intravenous injection of [^{3}H]-delta-9-THC (0.141 mg/123 mcCi) dispersed in human serum albumin (5) and a simultaneous oral dose of 19.98 mg THC dissolved in sesame oil (0.5 ml) and administered in a gelatin capsule.

D. Sample Collection

Blood samples were drawn by means of an indwelling venous catheter for the first 4 hours and by independent venipuncture for all other periods. Samples were taken from all subjects for 24 hours. Samples from three subjects were collected for 96 hours. Samples from three subjects were collected for 96 hours. Urine samples were obtained for all subjects for 24 hrs while feces was collected only for the three subjects studied for 96 hours.

E. Analytical Procedure

The procedure described by Wall et al. (3), as modified in Wall et al. (6), was used for quantitation of tritiated cannabinoids. Briefly, the system involves solvent extraction followed by TLC and scintillation spectrophotometry. Non-radiolabeled THC and 9-COOH-11-nor-delta-9-THC were assayed by RIA according to published procedures (7,8). Gas chromatography/mass spectrometry (GC/MS) was used to quantitate the 11-OH-metabolite of THC in plasma (9).

F. Pharmacokinetics

All nonlinear curve fitting was done using NONLIN (10). Plasma concentrations of [^{3}H]-delta-9-THC were weighted as $1/C^2$ and fitted with a biexponential function. The cumulative urinary excretion curves (A_e vs. time) for total [^{3}H]-cannabinoids and [^{3}H]-9-COOH-11-nor-delta-9-THC were fitted with a monoexponential accumulation function. The first derivative of the fitted curve was evaluated at at least six time points for which there were corresponding plasma values (C_i) for the species, respectively, and the renal clearances calculated as the mean of $(dA_e/dt)_i/C_i$. AUC (0-t) for [^{3}H]-delta-9-THC and THC were calculated by use of the log-trapezoidal rule. AUC (t-infinity) was calculated by use of the weighted mean estimate of lambda$_z$ (or beta) and the last observed plasma concentration. AUC (0-infinity) was adjusted to account for the area contributed by any THC present at t = 0. Standard formula were used for all pharmacokinetic calculations (11).

III. RESULTS

The concentrations of [^{3}H]-delta-9-THC and its major metabolites in plasma are present in Table I. The concentration of [^{3}H]-delta-9-THC in plasma is plotted in Figure 1 along with the fitted biexponental curve. A mean elimination phase half-life of 50 hours was observed. The mean terminal phase volume of distribution (V_z) was 578 +/- 76 (mean +/- S.E.M.) liters. The total body clearance of [^{3}H]-delta-9-THC from plasma (CL) was 135 +/- 13 ml/min.

The concentrations of THC, 9-COOH-11-nor-delta-9-THC, and 11-OH-delta-9-THC in plasma as determined by RIA and GC/MS are presented in Table II. The observed and fitted concentration of THC in plasma is plotted in Figure 2. The systemic bioavailability (f) of orally administered THC was 0.13 +/- 0.02.

TABLE I. [^{3}H]-Delta-9-THC and Metabolites Found in Human Plasma after Intravenous Administration of 0.141 mg [^{3}H]-delta-9-THC and Oral Administration of 19.98 mg THC

	ng/ml								
				Acids			Neutrals		
Time	Total Cannabinoids	Total Free	Total Conjunction	Total Acid	Polar	11-COOH	Total Neutrals	11-OH	Δ^9-THC
5 min	6.4 ± 2.1	6.1 ± 2.0	0.24 ± 0.1	0.84 ± 0.3	0.35 ± 0.2	0.39 ± 0.2	5.3 ± 2.1	0.36 ± 0.2	4.6 ± 1.9
10	5.1 ± 1.4	4.8 ± 1.3	0.35 ± 0.2	2.3 ± 0.5	1.0 ± 0.5	0.96 ± 0.6	2.5 ± 1.1	0.41 ± 0.3	1.8 ± 0.8
20	4.6 ± 1.0	4.2 ± 1.0	0.36 ± 0.1	2.6 ± 0.5	1.4 ± 0.5	0.83 ± 0.4	1.6 ± 0.5	0.21 ± 0.1	1.3 ± 0.5
30	4.3 ± 0.8	4.0 ± 0.9	0.30 ± 0.2	2.8 ± 0.5	1.0 ± 0.5	1.31 ± 0.7	1.3 ± 0.5	0.17 ± 0.05	0.97 ± 0.4
60	3.8 ± 0.5	3.3 ± 0.5	0.36 ± 0.2	2.4 ± 0.2	0.83 ± 0.4	1.26 ± 0.7	0.96 ± 0.4	0.11 ± 0.05	0.76 ± 0.3
90	3.5 ± 0.5	3.1 ± 0.6	0.37 ± 0.3	2.4 ± 0.4	1.1 ± 0.2	0.91 ± 0.5	0.75 ± 0.4	0.10 ± 0.06	0.58 ± 0.3
120	3.3 ± 0.5	2.9 ± 0.5	0.41 ± 0.2	2.2 ± 0.3	1.2 ± 0.1	0.61 ± 0.2	0.67 ± 0.4	0.07 ± 0.02	0.52 ± 0.3
150 [a]	3.0 ± 0.3	2.7 ± 0.2	0.35 ± 0.1	2.2 ± 0.3	1.0 ± 0.08	0.72 ± 0.2	0.45 ± 0.09	0.06 ± 0.02	0.34 ± 0.1
180	3.1 ± 0.5	2.8 ± 0.6	0.27 ± 0.1	2.3 ± 0.4	0.97 ± 0.3	0.87 ± 0.3	0.52 ± 0.3	0.06 ± 0.02	0.40 ± 0.3
4 hr	2.7 ± 0.5	2.5 ± 0.5	0.18 ± 0.1	2.1 ± 0.4	0.62 ± 0.5	1.1 ± 0.6	0.41 ± 0.2	0.05 ± 0.02	0.31 ± 0.1
6	2.3 ± 0.4	2.1 ± 0.3	0.23 ± 0.2	1.7 ± 0.3	0.55 ± 0.3	0.91 ± 0.5	0.36 ± 0.1	0.04 ± 0.01	0.28 ± 0.1
8	2.0 ± 0.4	1.8 ± 0.3	0.23 ± 0.2	1.5 ± 0.3	0.58 ± 0.3	0.57 ± 0.4	0.30 ± 0.09	0.03 ± 0.01	0.24 ± 0.1
11	1.7 ± 0.2	1.5 ± 0.2	0.16 ± 0.1	1.2 ± 0.2	0.48 ± 0.3	0.55 ± 0.3	0.33 ± 0.2	0.03 ± 0.01	0.27 ± 0.2
24	1.1 ± 0.2	1.0 ± 0.2	0.12 ± 0.05	0.84 ± 0.1	0.34 ± 0.2	0.30 ± 0.1	0.19 ± 0.07	0.02 ± 0.01	0.14 ± 0.1
30 [b]	0.81 ± 0.04	0.67 ± 0.04	0.14 ± 0.03	0.49 ± 0.03	[c]0.21 ± 0.1	[c]0.17 ± 0.1	0.18 ± 0.06	0.02 ± 0.01	0.15 ± 0.04
48 [b]	0.61 ± 0.05	0.49 ± 0.06	0.12 ± 0.06	0.38 ± 0.06	0.11 ± 0.04	0.20 ± 0.1	0.11 ± 0.00	0.01 ± 0.01	0.10 ± 0.00
72 [b]	0.41 ± 0.06	0.30 ± 0.05	0.11 ± 0.02	0.18 ± 0.05	0.06 ± 0.01	0.070 ± 0.01	0.12 ± 0.02	0.01 ± 0.01	0.11 ± 0.01
96 [b]	0.31 ± 0.06	0.22 ± 0.08	0.08 ± 0.03	0.15 ± 0.08	0.04 ± 0.01	0.073 ± 0.07	0.07 ± 0.00	trace	0.062 ± 0.00

[a] Mean of 5 subjects

[b] Mean of 3 subjects

[c] Mean of 2 subjects

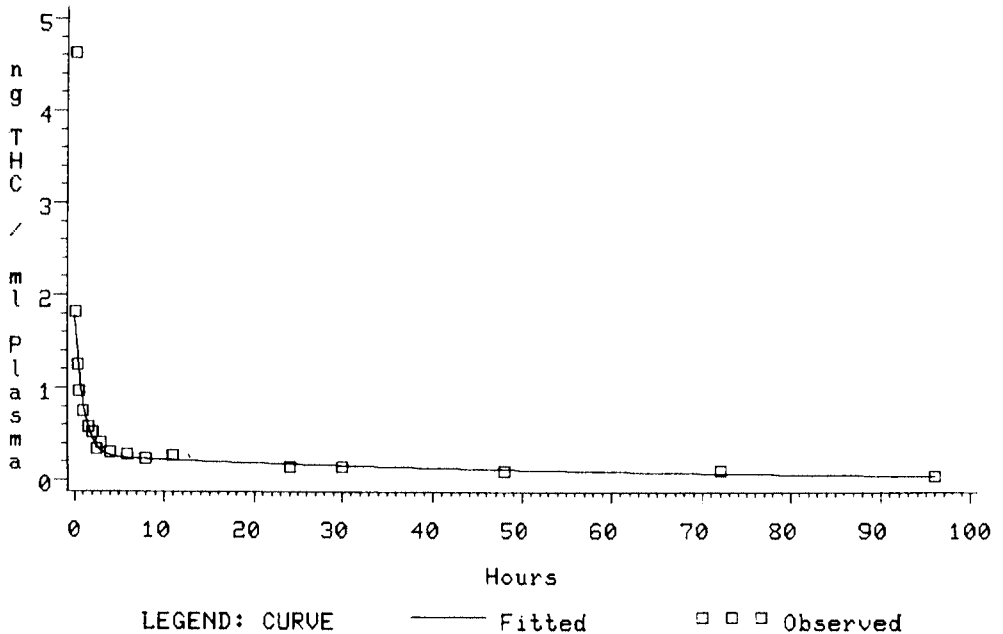

FIGURE 1. [^{3}H]-delta-9-THC (0.141 mg) was administered i.v. simultaneously with an oral dose of non-radiolabeled THC (19.98 mg) to six male subjects. The observed concentrations of tritiated THC in the plasma were weighed as $1/C^2$ and fitted with a biexponential function using NONLIN. The fitted (solid line) and observed (open squares) curves are presented above.

The cumulative excretion of radiolabeled cannabinoids in urine and feces is presented in Tables III and IV, respectively. After 72 hours 21 +/- 1% and 40 +/- 2% of the administered radiolabel was accounted for in urine and feces, respectively. Cumulative urinary excretion of total tritiated cannabinoids and tritiated 9-COOH-11-nor-delta-9-THC were fitted with an exponential accumulation function using NONLIN.

TABLE II. THC, 11-Nor-9-carboxy- and 11-Hydroxy-delta-9-THC in Human Plasma (see text for doses)

IV Dose 0.141 mg [^{3}H]-Δ^9-THC
Oral Dose 19.98 mg Δ^9-THC

ng/ml

	Δ^9-THC		11-Nor-9-COOH-Δ^9-THC		11-OH-Δ^9-THC	
Time	(n)		(n)		(n)	
0'	(6)	2.8 ± 1.5	(6)	13.7 ± 12.3		
5'	(6)	7.3 ± 2.3	(6)	17.4 ± 12.4		
10'	(6)	4.0 ± 1.5	(6)	17.6 ± 13.7		
20'	(6)	3.4 ± 1.8	(6)	17.3 ± 13.5		
30'	(6)	5.1 ± 3.1	(6)	20.9 ± 18.4	(5)	1.5 ± 1.1
60'	(6)	19.4 ± 13.2	(6)	101.8 ± 74.5	(5)	7.8 ± 1.3
90'	(6)	20.7 ± 4.3	(6)	206.9 ± 79.1	(6)	9.5 ± 2.1
120'	(6)	21.2 _ 5.3	(6)	223.8 ± 23.6	(5)	8.4 ± 2.1
150'	(5)	17.6 ± 6.1	(5)	231.0 ± 58.1	(5)	6.9 ± 2.4
180'	(6)	14.4 ± 2.9	(6)	214.7 ± 71.4	(6)	5.2 ± 1.5
4h	(6)	9.7 ± 1.5	(6)	136.1 ± 30.8	(5)	3.2 ± 0.9
6h	(6)	8.5 ± 3.6	(6)	103.9 ± 27.3	(6)	2.3 ± 0.8
8h	(6)	10.0 ± 6.7	(6)	97.6 ± 32.8	(5)	2.0 ± 1.1
11h	(6)	6.0 ± 1.2	(6)	82.0 ± 23.8	(5)	1.4 ± 0.5
24h	(6)	4.4 ± 1.5	(6)	50.6 ± 25.8		
30h	(3)	3.6 ± 0.4	(3)	25.1 ± 9.7		
48h	(3)	2.6 + 0.4	(3)	17.6 ± 4.2		
72h	(3)	2.3 ± 0.5	(3)	9.2 ± 3.4		
96h	(3)	2.3 ± 0.7	(3)	7.1 ± 4.0		

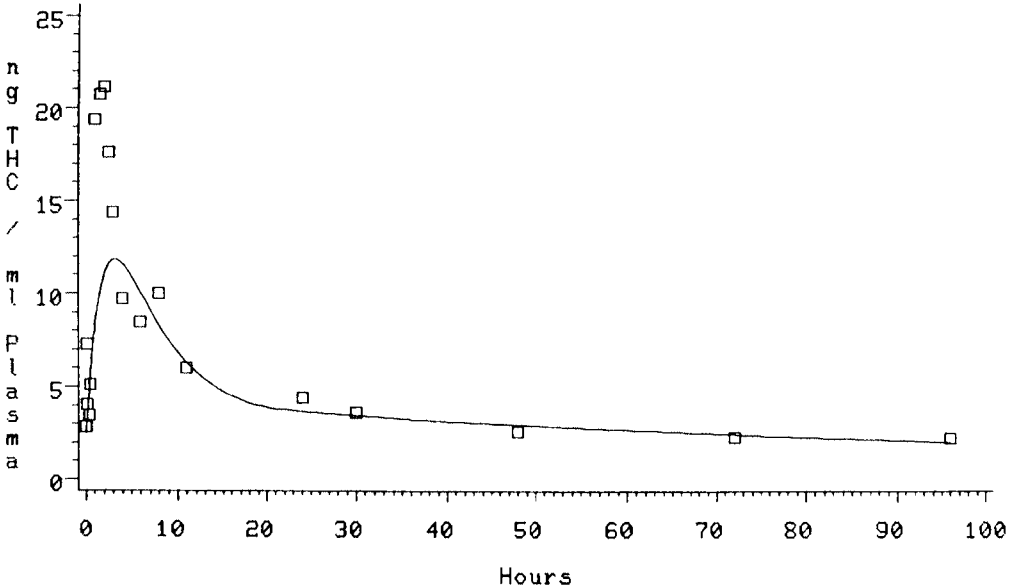

FIGURE 2. THC (19.98 mg) was administered orally with a simultaneous dose of tritiated THC (0.141 mg, i.v.) to six male subjects. RIA was used to determine the plasma concentrations of THC, which were weighted as $1/C^2$ and fitted with a triexponential function using NONLIN. The fitted (solid line) and observed (open squares) curves are presented above.

TABLE III. [^{3}H]-Delta-9-THC and Metabolites Found in Human Urine after Intravenous Administration of 0.141 mg [^{3}H]-delta-9-THC and Oral Administration of 19.98 mg THC Expressed in Cummulative % Dose

Sample (n)	Total Cannabinoids	Total Free	Free Acids			Free Neutrals		
			Total Acids	Polar Acids	11-COOH-Δ^9-THC	Total Neutrals	11-OH-Δ^9-THC	Δ^9-THC
0-4h (5)	4.5 ± 2.2	3.3 ± 1.9	3.3 ± 1.8	1.8 ± 0.8	0.9 ± 0.8	0.05 ± .03	0.02 ± .01	.006 ± .001
6-11h (3)	5.7 ± 0.8	3.9 ± 0.4	3.8 ± 0.3	1.8 ± 0.4	1.2 ± 0.4	0.07 ± .02	0.02 ± .01	.005 ± .003
24h (4)	12.4 ± 2.6	8.7 ± 1.6	8.6 ± 1.6	3.4 ± 0.8	3.4 ± 0.8	0.12 ± .02	0.05 ± .02	.01 ± .008
30h (2)	16.6 ± 0.8	11.4 ± 0.3	11.2 ± 0.2	4.3 ± 0.2	5.1 ± 0.6	0.14 ± .01	0.06 ± .01	.02 ± .008
48h (2)	19.2 ± 1.0	13.0 ± 0.5	12.9 ± 0.5	4.8 ± 0.4	5.6 ± 0.6	0.16 ± .02	0.07 ± .01	.02 ± .009
72h (2)	21.3 ± 1.6	14.5 ± 1.0	14.4 ± 1.0	5.2 ± 0.6	6.4 ± 0.4	0.17 ± .03	0.07 ± .02	.03 ± .01
96h (2)	22.3 ± 2.2	15.2 ± 1.4	15.1 ± 1.3	5.4 ± 0.7	6.7 ± 0.3	0.18 ± .04	0.08 ± .02	.03 ± .01

Sample (n)	Total Conjugated	Total Cleaved	Cleaved Acids			Cleaved Neutrals		
			Total Acids	Polar Acids	11-COOH-Δ^9-THC	Total Neutrals	11-OH-Δ^9-THC	Δ^9-THC
0-4h (5)	1.2 ± 0.7	0.7 ± 0.4	0.7 ± 0.4	0.3 ± 0.2	0.11 ± .06	0.05 ± .03	.01 ± .01	.007 ± .000
6-11h (3)	1.8 ± 0.5	1.1 ± 0.4	1.0 ± 0.4	0.4 ± 0.2	0.24 ± .08	0.07 ± .03	.02 ± .01	.01 ± .008
24h (4)	3.7 ± 1.0	2.2 ± 0.7	2.1 ± 0.7	0.8 ± 0.3	0.41 ± .04	0.12 ± .03	.04 ± .01	.03 ± .004
30h (2)	5.2 ± 0.5	3.0 ± 0.7	3.0 ± 0.5	1.1 ± 0.5	0.46 ± .03	0.17 ± .01	.05 ± .01	.02 ± .007
48h (2)	6.2 ± 0.4	3.5 ± 0.7	3.4 ± 0.4	1.3 ± 0.5	0.54 ± .08	0.19 ± .01	.06 ± .01	.02 ± .01
72h (2)	6.8 ± 0.6	3.9 ± 0.8	3.8 ± 0.5	1.4 ± 0.5	0.62 ± .09	0.21 ± .02	.06 ± .01	.03 ± .01
96h (2)	7.1 ± 0.7	4.0 ± 0.9	4.0 ± 0.5	1.4 ± 0.6	0.64 ± .08	0.22 ± .02	.07 ± .01	.03 ± .01

TABLE IV. [^{3}H]-Delta-9-THC and Metabolites Found in Human Feces after Intravenous Administration of 0.141 mg [^{3}H]-delta-9-THC and Oral Administration of 19.98 mg THC Expressed as Cummulative % Dose

(n)		Total Cannabinoids	Fecal Residue	Methanol Extract: Total Methanol Extract Cannab.	Methanol Extract: Total Free	Methanol Extract: Total Conjugates
(1)	8h	0.06	0.006	0.05	0.05	0.004
(1)	24h	11.6	1.2	10.4	10.0	0.4 ± 0.3
(2)	48h	21.3 ± 15.4	2.8 ± 1.6	18.5 ± 13.9	17.7 ± 13.2	0.9 ± 0.7
(2)	72h	39.6 ± 2.7	6.5 ± 1.4	33.1 ± 4.1	31.0 ± 4.5	2.1
(1)	96h	45.8	6.3	39.5	37.6	2.0

(n)		Methanol Extract: Acids: Total Acids	Acids: Polar Acids	Acids: 11-COOH-Δ^9-THC	Neutrals: Total Neutrals	Neutrals: 11-OH-Δ^9-THC	Neutrals: Δ^9-THC
(1)	8h	0.03	0.004	0.02	0.01	0.006	0.005
(1)	24h	5.5	1.5	2.5	4.5	3.1	0.9
(2)	48h	10.3 ± 7.8	2.9 ± 2.1	5.0 ± 3.5	7.3 ± 5.4	4.9 ± 3.9	1.8 ± 0.8
(2)	72h	19.5 ± 2.2	5.2 ± 1.0	10.1 ± 0.6	11.5 ± 2.3	7.3 ± 2.3	3.1 ± 0.3
(1)	96h	23.7	6.5	12.2	13.9	9.4	3.0

The observed and fitted curves are presented in Figure 3. The renal clearances of total tritiated cannabinoid and [^{3}H]-9-COOH-11-nor-delta-9-THC were calculated by dividing the first derivative of the fitted accumulation curves by corresponding concentrations in the plasma. The renal clearances were 7.9 +/- 0.3 ml/min and 11.1 +/- 0.8 ml/min for total cannabinoids and 9-COOH-11-nor-delta-9-THC, respectively.

IV. DISCUSSION

The observed concentrations of cannabinoids in various biological samples in this experiment are in general consistent with the previous work of Wall et al (6). The elimination half-life reported here (50 hours) is longer than that reported by Wall et al (6). This may be accounted for by the fact that THC with a higher specific activity was used in the present study and more accurate estimates of the concentrations of THC at 72 and 96 hours were obtained.

Plasma samples taken before dosing revealed the presence of small amounts of THC in the plasma. Subjects were asked to refrain from the recreational use of marijuana for at least two days prior to the start of the experiment. The AUC (0-infinity) was corrected for the levels of THC at zero time by subtracting C_0/beta from the AUC for each subject.

The contribution of the present work is that for the first time the systemic bioavailability of orally administered THC was assessed after simultaneous oral and IV administration of the drug. Simultaneous use of two routes of administration appeared to have no significant effect on the pharmacokinetic parameters of either when used alone. The relatively low bioavailability (f = 0.13) is likely due to a significant first pass effect in the liver since previously reported values for oral absorption of THC are over 90% (6,12). This value for the bioavailability of THC is higher than that reported by Ohlsson et al. (4) and is probably due to the difference in the choice of oral vehicles. Sesame oil appears to be the more effective vehicle.

ACKNOWLEDGMENTS

The authors express their thanks to Carolyn Foust and Elizabeth Strawn for their technical assistance.

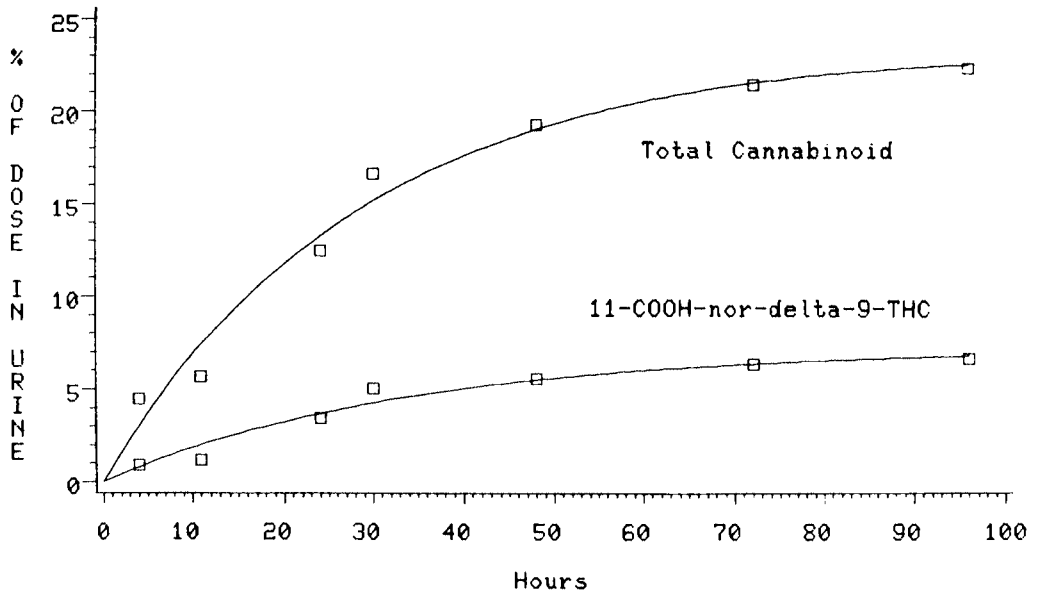

FIGURE 3. Drug was administered as in Fig. 2. The cummulative excretion of radiolabel and of [^{3}H]-11-COOH-delta-9-THC was fitted with a monoexponentail accumulation function using NONLIN. The fitted (solid line) and observed (open squares) curves are presented above.

REFERENCES

1. Mechoulam, R., J. Clin. Pharmacol. 21:23 (1981).
2. Lemberger, L., and Rubin, A., Life Sci. 17:1637 (1975).
3. Wall, M. E., Brine, D. R., and Perez-Reyes, M., The metabolism of cannabinoids in man, in "Pharmacology of Marihuana" (M. C. Braude and S. Szara, eds.), p. 93. Raven Press, New York, 1976.
4. Ohlsson, A., Lindgren, J. E., Wahlen, A., Agurell, S., Hollister, L. E., and Gillespie, B. A., Clin. Pharmacol. Ther. 28:409 (1980).
5. Perez-Reyes, M., Timmons, M. C., Lipton, M. A., Davis, K. H., and Wall, M. E., Science 177:633 (1972).
6. Wall, M. E., Sadler, B. M., Brine, D. R., Taylor, H., and Perez-Reyes, M., Metabolism, disposition and pharmacokinetics of delta-9-tetrahydrocannabinol in male and female subjects, submitted to Clin. Pharmacol. Therap. 1982.
7. Cook, C. E., Schindler, V. H., Tallent, C. R., Chin, K. M., and Pitt, C. G., Radioimmunoassay for cannabinoids, in "Cannabinoid Assays in Biological Fluids" (R. L. Hawks, ed.), NIDA Research Monograph No. 42, U.S. Government Printing Office, Washington, D. C., 1982.
8. Cook, C. E., Schindler, V. H., Tallent, C. R., Seltzman, H. H., and Pitt, C. G., Fed. Proc. 40:278, Abstr. 245 (1981).
9. Wall, M. E., Brine, D. R.,Bursey, J. T., and Rosenthal, D., Detection and quantitation of tetrahydrocannabinol and its metabolites, in "Cannabinoid Assays in Humans" (R. E. Willette, ed.), p. 197. NIDA Research Monograph No. 7, U.S. Government Printing Office, Washington, D. C., 1976.
10. Metzler, C. M., Elfring, G. L., and McEwen, A. J., "A Users Manual for NONLIN and Associated Programs". The Upjohn Company, Kalamazoo, MI, revised edition, 1976.
11. Allen, L., Kimura, K., MacKichan, J., and Ritschel, W. A., (eds.), "Manual of Symbols, Equations & Definitions in Pharmacokinetics". Committee for Pharmacokinetic Nomenclature of the American College of Clinical Pharmacology, Philadelphia, PA 1982.
12. Lemberger, L., Axelrod, J., Kopin, J. J., Ann. N. Y. Acad. Sci. 191:142 (1971).