RELATION OF PLASMA DELTA-9-THC CONCENTRATIONS TO SUBJECTIVE "HIGH" IN MARIJUANA USERS: A REVIEW AND REANALYSIS[1]

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I. INTRODUCTION

Since Gaoni and Mechoulam (1) and Mechoulam and Gaoni (2, 3) first described the isolation and synthesis of delta-9-tetrahydrocannabinol or THC (which is also called delta-1-tetrahydrocannabinol, delta-1-THC) as the major active ingredient of hashish, a great deal of research has been directed toward its measurement in blood and tissues and its pharmacokinetics. Lemberger et al. (4-6) were the first to study the blood levels of ^{14}C-THC in man. Their research stimulated a great deal of research and controversy regarding possible metabolic and dispositional differences in normal volunteers compared to long-term marijuana smokers. Lemberger et al. showed that labeled THC given i.v. disappeared from the plasma of chronic marijuana smokers with a half-life of 28 hr as compared to 57 hr in nonusers. The apparent volumes of distribution did not differ between the two groups. Within 10 min after i.v. administration, these investigators found the 11-hydroxy metabolite in the blood of both groups. It was also present in the urine and feces of both groups for more than

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one week. Hence, it was readily apparent that following a single dose of THC, accumulation and persistence of active and inactive metabolites readily occurred.

Subsequently, Lemberger et al. (7) studied the temporal correlation between the psychological effects of labeled THC and blood levels after different routes of administration. They reported that the psychologic effects of oral or inhaled ^{14}C-THC were temporally correlated with plasma levels of THC and its metabolites in human volunteers who professed to be chronic marijuana users. In addition, these investigators observed that, of various routes of administration, the greatest and most prolonged radioactivity was obtained following inhalation of smoked spiked marijuana, and least after oral administration. These studies as well as those of other investigators were reviewed by Lemberger et al. (5). Lemberger (8) stressed the importance of methodology in detecting the small amounts of THC as well as active metabolites. Specificity as well as sensitivity also determine how long after dosing the cannabinoids are measured in blood and, hence, the complexity of the pharmacokinetic models proposed.

Agurell and his colleagues (11) used various methods, including radiolabeled and later gas chromatographic-mass spectrometric (GC/MS) methods, to study the metabolic fate of various tetrahydrocannabinols. Agurell et al. (12) reported on the pharmacokinetics of delta-8-tetrahydrocannabinol (delta-8-THC) in man after smoking and the relationship ofblood levels to physiological and psychological effects. They chose to study delta-8-THC because of the relative ease of synthesis of deuterated derivatives for GC-MS analysis. Their data in general are in agreement with the human data based upon radiolabeled THC. They were able to show that the increase in heart rate was well correlated with the plasma levels of delta-8-THC, whereas the alterations in mental performance were more delayed and prolonged than the peak delta-8-THC plasma level. They suggested that, from a pharmacokinetic model point of view, the receptors for altering heart rate were in a "shallow compartment," whereas those for a psychological "high" were in a "deep compartment." The possible role of active metabolites was also stressed. In any event, these investigators pointed out that if, by analogy, the effects of delta-8 and delta-9-THC are similar, plasma levels of THC were not an entirely relevant parameter for determining performance decrement.

The role of active THC metabolites further complicates the picture. Wall et al. (13) also pointed out the extensive biotransformation of various cannabinoids in animals and man. The fact that some metabolites of THC are active further suggests that no simple relationship between plasma levels and marijuana induced "high" would be expected. However, in the

case of 11-OH-delta-9-THC, one of the active metabolites of THC, its pharmacokinetics are similar to those of THC itself (14).

Lindgren et al. (15) determined the plasma concentrations of THC given by smoking and i.v. administration to groups of light and heavy users of marijuana. The marijuana cigarettes contained about 19 mg of THC. A dose of 5.0 mg of THC was given i.v. The investigators used a mass fragmentographic assay for THC as described by Ohlsson et al. (16-18). After i.v. injection of THC, the area under the curve for 0 to 240 min for the plasma levels of THC tended to be lower in the heavy users compared to the light users, but this was not statistically significant ($p = 0.08$). Inasmuch as a marijuana "high" is almost gone by 4 hr after either i.v. administration or via inhalation (18), these investigators only determined THC plasma levels up to 4 hr and were not able to confirm or deny the finding of Lemberger et al. (4-6) that the "apparent" terminal or beta-phase half-life of THC was shorter in chronic marijuana users. Likewise, in the smoking experiments, Lindgren et al. (15) were unable to determine any significant difference in plasma levels of THC between light and heavy users. They did note a tendency ($p = 0.06$) that heavy users showed higher THC levels, probably due to more efficient smoking than light users. The area under the curve for 0 to 240 min of the THC plasma levels was also greater in the heavy users ($p < 0.05$), again suggesting more efficient smoking by heavy users. The psychological effects on both groups from i.v. administration and inhalation were comparable. Their findings were similar to those of Perez-Reyes et al. (19) who found no differences in total plasma radioactivity or the amount of ^{14}C-THC needed i.v. to produce a maximal "high" in infrequent and frequent marijuana users. Hence, the findings of Lindgren et al. (15) and Perez-Reyes et al. (19) are in agreement with each other, but do not confirm or deny the findings of Lemberger and associates regarding a very marked reduction in the late half-life of THC in heavy marijuana users. Furthermore, insofar as maximal high is concerned, both studies find no difference in light vs. heavy users. Neither sensitivity nor tolerance to THC was observed.

Ohlsson et al. (20) studied the single dose kinetics of deuterium labeled THC in light and heavy cannabis users by both i.v. administration and smoking. Plasma levels of $^{2}H_{3}$-delta-9-THC were measured for 48 to 72 hr. After 5.0 mg i.v. or 8.6 to 9.9 mg by smoking, there was little difference between both groups with regard to the amounts smoked or plasma levels and areas under the curve. Heavy cannabis users tended to have statistically significantly higher THC levels by preference. A plasma clearance of 760 to 1190 ml/min and an elimination half-life of THC of more than 20 hr were calcu-

lated. This study, like their previous one, showed no evidence for either sensitivity or tolerance to THC in heavy users.

Hollister et al. (21) addressed the question of whether THC levels reflected the state of cannabis intoxication in 11 volunteers. They gave about 19 mg of THC in a marijuana cigarette for smoking, 20 mg of THC orally in a chocolate cookie, and 5 mg i.v. These investigators then measured THC in the plasma up to 4 hr after administration by the GC/MS method of Ohlsson et al. (16). In addition, both heart rate and subjective "high" were measured. The increases in pulse rate often returned to baseline or below even while the patient felt "high" and still had plasma concentrations of THC above 5 ng/ml. They concluded that the relationship between pulse rate and plasma concentrations of THC was similar to that previously observed by Agurell et al. (12) for delta-8-THC. Hollister et al. also pointed out that they saw no clear cut relationship between plasma concentrations of THC and the degree of intoxication in contrast to the case for ethyl alcohol.

Hunt and Jones (22) administered 30 mg of THC orally every 4 hr for 10 to 12 days to six subjects in an attempt to induce tolerance. They tested the hypothesis that development of tolerance may be due to alterations in THC biotransformation and disposition. Labeled ^{14}C-THC was given i.v. before and after the chronic oral doses of THC. The plasma and urine levels of labeled THC and metabolites were measured by HPLC separation and scintillation counting. Development of tolerance was accompanied by a statistically significant increase in the apparent volume of distribution from 2.6 to 6.4 liter/70 kg man and the plasma clearance increase from 605 to 977 ml/min. The steady state volume of distribution was not altered. The half-life for THC was unchanged (19.6 vs 18.7 hr) while the terminal half-life for the metabolites increased from 48.7 to 52.9 hr. The steady state volume of distribution was not changed (626 vs 742 liter/70 kg). Hunt and Jones (22) proposed a four compartment mammalary model with elimination from the central compartment to explain their data. The mean terminal half-lives of THC of 18.7 to 19.6 hr were shorter than those reported by Lemberger et al. (6) of 28 hr for chronic users. Since the Hunt and Jones subjects were experienced marijuana users, they could not provide data on the observation of Lemberger et al. of a 57 hr terminal half-life of THC in non-users.

Valentine (23) studied the plasma levels of THC in four male volunteers following smoking marijuana cigarettes with three different doses of THC. Plasma samples were analyzed for THC using a HPLC-MS assay for up to 12 hr post-smoking. The mean data for each dose could be fitted to a two compart-

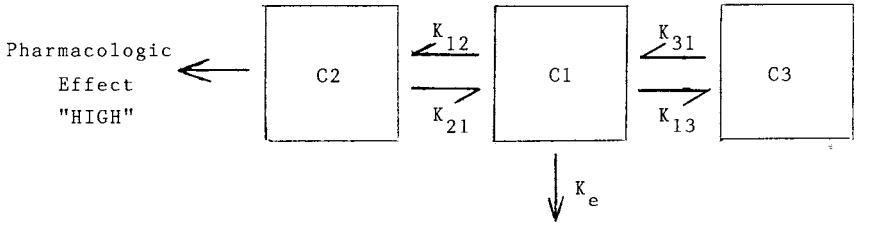
ment model with no absorption phase. No dose dependent pharmacokinetics were noted. A compartmental model was described that was consistent with the earlier reports of Lemberger et al. (5, 6).

Although the use of compartmental models in pharmacokinetics is currently a hotly debated issue, we have used a compartmental model approach in which subjective "high" was fit to a compartment (presumably brain) other than the plasma compartment. The results obtained indicate that, after about 1 hr, plasma levels of THC predict subjective "high" when these two compartments are in equilibrium. The results of this reanalysis are presented herein to act as a stimulus for further research on the relationship of plasma THC levels to degree of mental impairment.

II. METHODS

We have assumed that the effects of THC are related to its concentration at active sites and is dose related. Although no specific THC receptors have been found to date, it is reasonable to assume that there is a specific site of action for THC in the brain, with a dose response curve which may be modeled by the Hill equation (24).

We reanalyzed the reported data of Ohlsson et al. (20) and Lindgren et al. (15) according to a three compartment model with amounts in the second compartment related to the pharmacologic action, i.e., subjective "high." Ohlsson et al. administered five mg i.v. of deuterium-labeled THC ($^2H_3$-THC) to four light and five heavy marijuana users who ranged in age from 18-35 yr. Plasma levels of $^2H_3$-THC in plasma was extracted and purified by liquid chromatography, silylated and assayed via mass fragmentography. The assay is reported to be sensitive to approximately 0.1 ng/ml THC. Mean subjective "high" for light and heavy users were obtained from Lindgren et al. (15) under similar conditions. Subjects in this group consisted of 16 men and 2 women between the ages of 19 and 35, with 8 men and one women in each group. The three compartment model which we used in a reanalysis of this data may be illustrated as follows:



Standard abbreviations are used for the first order rate parameters, and are similar to those proposed by Hull (25). C1, C2, and C3 are "compartments", of which amounts in C2 were related to the time course of subjective "high" by means of the Hill equation (24):

$$E = E_{max} A^S / (1/Q + A^S)$$

E = pharmacologic effect, which in this case is subjective "high". E_{max} is the maximal effect, which is assumed to be 10. "A" is the amount of drug at an active site, which is related to concentration by the relationship: concentration = amount/volume of distribution. The Hill equation has been shown to be valid in classical pharmacological receptor assays (26,27). It predicts zero and maximal response, is sigmoidal in shape, and is continuous over the entire dose range. The use of a three compartment model was justified when F-test (28) was used on the NONLIN plasma curve fit to individual subjects.

NONLIN (29) was used with weights of reciprocal concentration to fit a three exponential equation to mean plasma concentrations in light and heavy users. First order rate parameters were calculated according to the method of Wagner (30). Amounts in the second compartment were calculated utilizing standard techniques (31). Mean subjective "high" in light and heavy users were fit according to the Hill equation by means of NONLIN regression with weights of reciprocal "high".

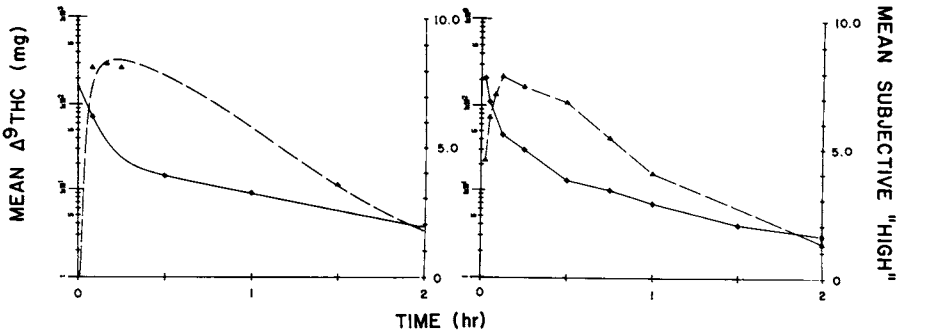


FIGURE 1. Comparison of plasma THC levels and subjective "high" after 5 mg i.v. THC. The solid line in the left graph is the triexponential fit of mean plasma THC levels from Ohlsson et al. (20), and the dashed line is the predicted time course of subjective "high" in light marijuana users based on "second" compartment amounts. The right graph shows actual mean data without curve fitting of THC plasma concentrations and subjective "high" from Hollister et al. (21) in a mixed group of light and heavy marijuana users. THC concentrations on the y-axis range from 1 to 1000 ng//ml.

CSTRIP (32) was used for initial estimates for the NONLIN fit of the plasma curve. The initial estimates for the Hill equation were obtained by linear regression of Log [Amount of THC in compartment 2] vs. Log ["high" / Max "high" - "high")]. A pharmacokinetic model for light and heavy users was also determined for smoke administration on the same subjects for mean plasma concentrations by nonlinear regression utilizing NONLIN. Calculation of first order rate parameters was performed utilizing the same method.

III. RESULTS

The time course of subjective "high" after an i.v. dose of THC appeared to show a course with initial elevation, peak effect at 15 min, followed by a decline. The calculated results for light marijuana users are shown in the left panel of Fig. 1, while the second panel shows the reported mean data of Hollister et al. (21) for a group of mixed light and heavy users. Note the general similarity, as subjective "high" rises while plasma levels of THC fall at early time points.

Mean plasma levels of THC are shown in Fig. 2 for light and heavy marijuana users following i.v. administration of 5 mg THC. A model for each group of the distribution of THC into the compartment which contains the presumed active site is shown in Fig. 3. Compartment 2 was assumed to contain the active site. It can be seen that the model predicts an equilibration and subsequent parallel decline of THC in plasma at approximately 40-60 min.

Table I shows the parameters of the pharmacodynamic model. These results are preliminary and are meant only for generation of further testable hypotheses.

IV. DISCUSSION

The use of models in scientific endeavors provides methods of obtaining new hypotheses and must be judged according to parsimony and predictive value. Clearly, distribution into brain cannot be studied directly in humans, and even imaging methods such as PET (Position Emission Tomography) require use of compartmental models for analysis (33). Despite such analysis, total brain levels may not correlate with a pharmacologic effect, as specific as well as nonspecific binding is measured. For example, no significant decreases in total brain concentrations of THC were found in groups of tolerant and nontolerant dogs and pigeons (34,35). When synaptic vesi-

cles were isolated from brain, Martin et al. (34,35) reported a significant decrease in THC concentrations in this fraction of the brains of tolerant dogs.

There is a complex relationship between the ingestion of marijuana and the time course of its subjective effects. The peak subjective "high" occurs about 15-30 min following smoking of marijuana, and about 15 min following i.v. injection of THC. Plasma levels of THC are elevated initially, and appear to be falling as subjective high increases. Although it was suggested that regional distribution at the site of action in the brain might account for the dissociation between plasma levels and subjective high (4), the discovery of active metab-

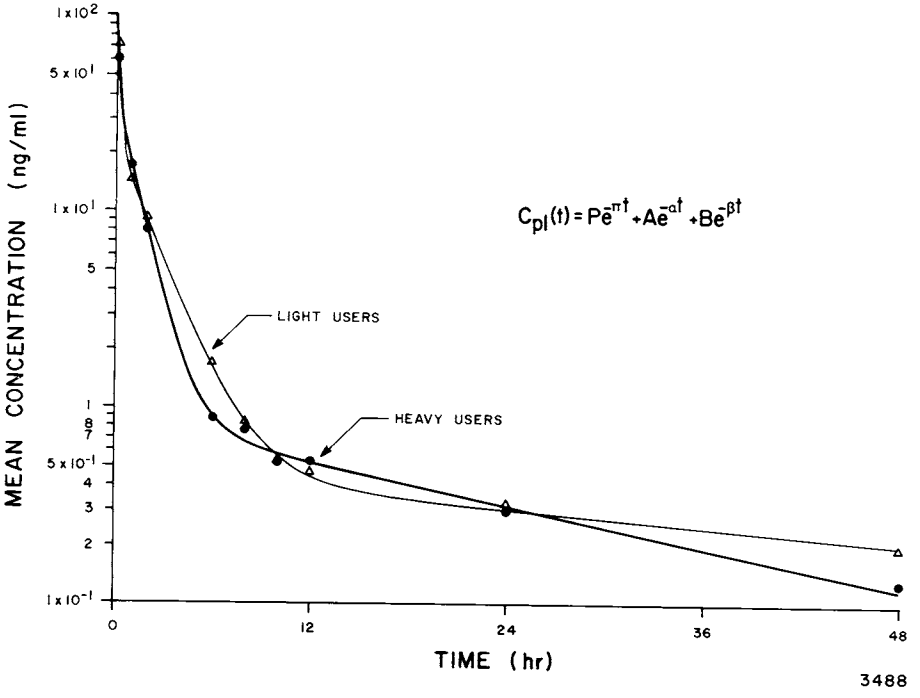


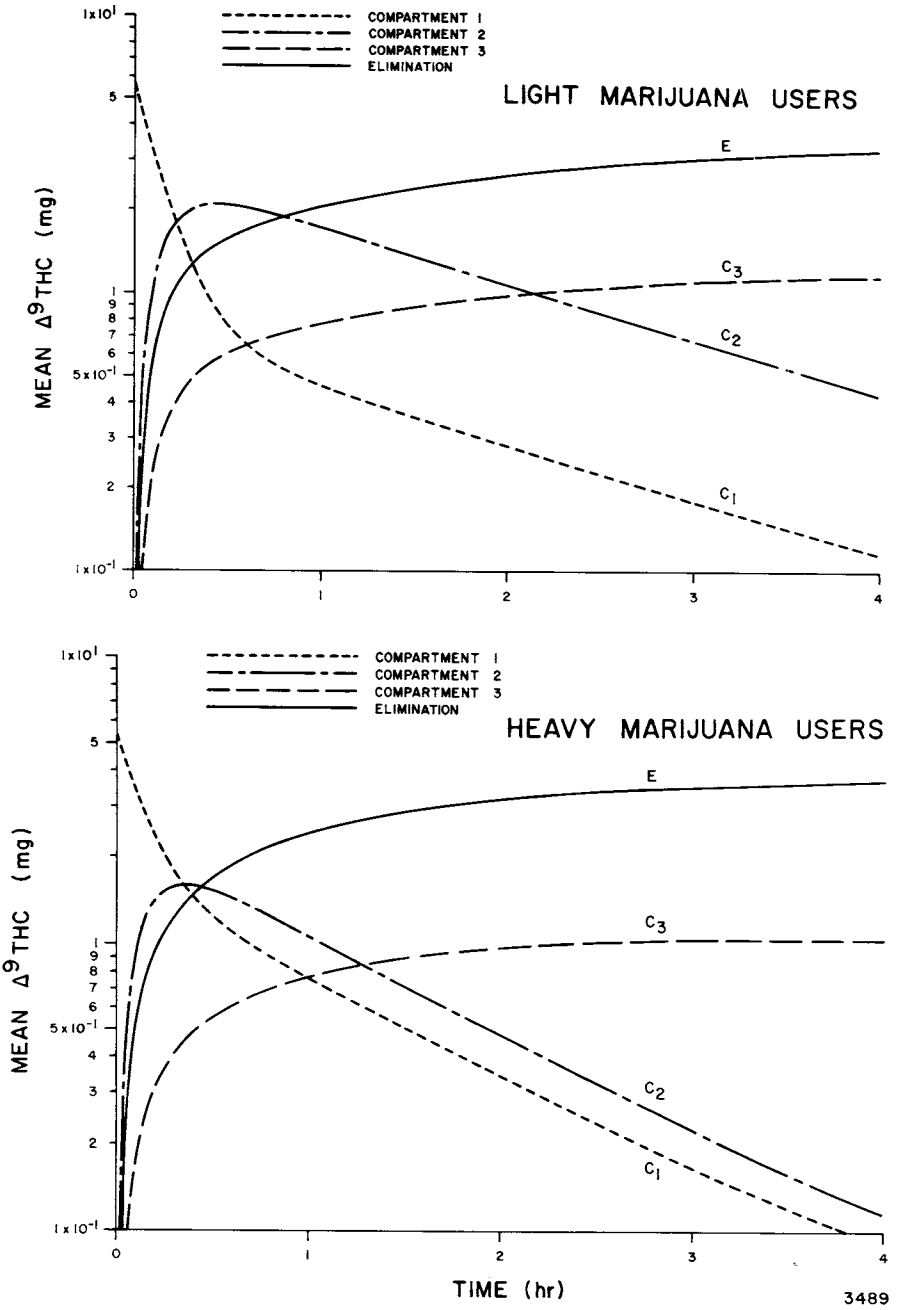
FIGURE 2. Mean plasma concentrations of deuterated THC in light and heavy marijuana users after a 5 mg i.v. dose. Mean plasma concentrations of $^{2}H_{3}$-THC in four light (open triangles) and five heavy (solid circles) marijuana users were determined by Ohlsson et al. (20). The solid lines are the fit according to the model described in the text. Parameters for light users are: P = 151 ng/ml, pi = 6.53 h^{-1}, A = 22.4 ng/ml, alpha = 0.483 h^{-1}, B = 0.460 ng/ml, beta = 0.0168. For heavy users: P = 85.9 ng/ml, pi = 7.13 h^{-1}, A = 38.4 ng/ml, alpha = 0.839 h^{-1}, B = 0.844 ng/ml, beta = 0.0405.

olites of THC focused efforts upon the possible correlation between the appearance of these substances in plasma and the time course of subjective "high". Thus subjective "high" was seen to parallel the plasma time course of 11-OH-delta-9-THC (14), and polar metabolites of THC (13). Temporal correlation alone of subjective high and plasma levels of possible active metabolites is not sufficient to determine the relative importance of distribution vs. metabolism in the onset of subjective "high;" metabolites must also distribute into brain. We describe a model which assumes only distribution and a dose-

TABLE I. Pharmacodynamic Model of Deuterated THC in Light and Heavy Marijuana Users*

First Order Rate Parameters		Use Level			
		Light i.v. (N = 4)	Heavy i.v. (N = 5)	Light Smoking (N = 4)	Heavy Smoking (N = 5)
K_{12}	h^{-1}	3.34	3.00	4.13	3.27
K_{21}	h^{-1}	1.35	2.95	1.65	1.91
K_{13}	h^{-1}	0.643	0.499	0.776	0.598
K_{31}	h^{-1}	0.0234	0.0548	0.0302	0.0523
K_e	h^{-1}	1.68	1.50	1.40	1.93
V_d (central)	l	31.7	43.6		
Hill Parameters					
S		2.03	1.28		
Q		1.17	0.95		

*This table lists the parameters calculated from mean plasma data reported by Ohlsson et al. (20) and Lindgren et al. (15) according to the model outlined in the text. The kinetic parameters for smoking were fit to mean plasma THC only. Standard abbreviations are used for the parameters and are similar to those proposed by Hull (25).


COMPARTMENT 1
COMPARTMENT 2
COMPARTMENT 3
ELIMINATION
LIGHT MARIJUANA USERS
MEAN Δ9THC (mg)
1x10¹
5
1
9
8
7
6
5x10⁻¹
4
3
2
1x10⁻¹
E
C3
C2
C1
0
1
2
3
4
COMPARTMENT 1
COMPARTMENT 2
COMPARTMENT 3
ELIMINATION
HEAVY MARIJUANA USERS
MEAN Δ9THC (mg)
TIME (hr)
3489

relationship ofTHC to subjective "high". Following these assumptions, a time course of subjective "high" is predicted to occur which is similar to that observed.

The model suggests several hypotheses, two of which follow. Hypothesis 1: The time course of marijuana subjective "high" is determined by the delivery of THC and its active metabolites to brain. Prediction: Following pseudoequilibrium between blood and active sites in brain, plasma levels of THC and its active metabolites will correlate with subjective "high."

The model predicts a parallel decline between the active site and blood approximately 40 min following an i.v. dose in heavy users, and 60 min in light users of marijuana. A plasma concentration-response curve may, therefore, be predicted to apply at any time following the attainment of this equilibration. We have converted amounts in the "second" compartment to equivalent plasma concentrations after pseudoequilibrium, and present the resultant relationship between plasma levels and mean subjective "high" in Fig 4. There appears to be a relative right shift predicted in the concentration response curve for heavy users, suggesting tolerance. The estimates at plasma concentrations greater than 20 ng/ml are extrapolations, and hence, are not predicted to be as reliable as estimates at lower plasma concentrations.

The predictions of Fig 4 are testable under further empirical conditions. Preliminary evidence may support such a concept, as can be seen when completely separate data from Perez-Reyes et al. (36) is plotted. Three men and three women who smoked from 4 to 12 marijuana cigarettes a month were administered three different potencies of marijuana: 1.32%, 1.97% and 2.54% THC. The subjective "high" was determined. Contrary to the authors' opinion of a lack of correlation, after sixty min following smoking, mean plasma concentrations of THC significantly correlated with mean subjective "high". Addition of the 45 min points lowered the correlation. These data are shown in Fig. 5. Half maximal effect was seen at 15 ng/ml, which is between the bounds predicted from the model shown in Fig. 4. This group of marijuana users would, in fact, corre-

FIGURE 3. Amounts of deuterated THC in each compartment of a three compartment open model in light and heavy marijuana users. The "second" compartment, which is presumed to contain the site of action of THC, shows a peak at about 15-20 min with a parallel decline with plasma starting 60 min following an i.v. dose of 5 mg of THC in light users, and 40 min in heavy users. Compartmental amounts were based on the model described in the text.

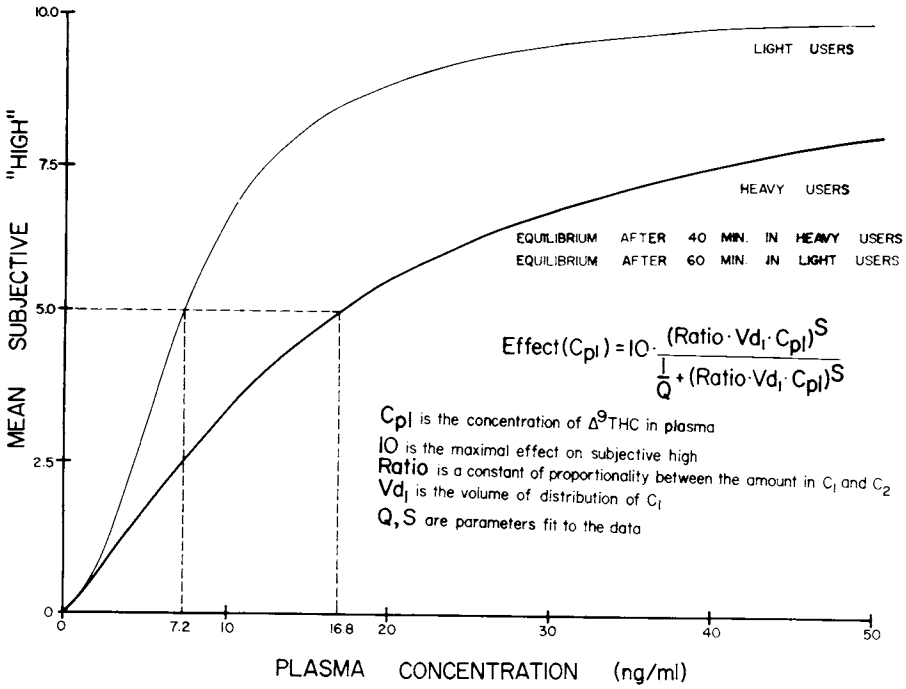


FIGURE 4. Relation of plasma THC concentration vs. subjective "high" estimates in light and heavy marijuana users at pseudoequilibrium. Following equilibration of THC between blood and active sites in brain, plasma concentrations of THC are predicted to show a dose-response relationship with subjective "high." The presence of large amounts of active metabolites would invalidate this specific relationship, and correlation would be better predicted to arise from concentrations of THC and active metabolites.

spond to slightly less frequent smokers than the heavy smokers of Ohlsson et al. (20).

Hypothesis 2: The elimination of THC from the body is determined by slow (net) release of THC from tissues (perhaps fat). Prediction: Calculations of half-life in man from blood data measured with current analytic techniques may underestimate terminal half-life when compared to that determined from fat (or other tissue).

Wagner (24,30) has discussed artifacts in calculated terminal half-lives when plasma levels fall to limits of detectability before all tissues equilibrate with blood. Thereis, in addition, much evidence which supports the possibility of a prolonged half-life of THC. Kreuz and Axelrod (37) have noted a terminal half-life of 5 days of THC in the rat when calcu-

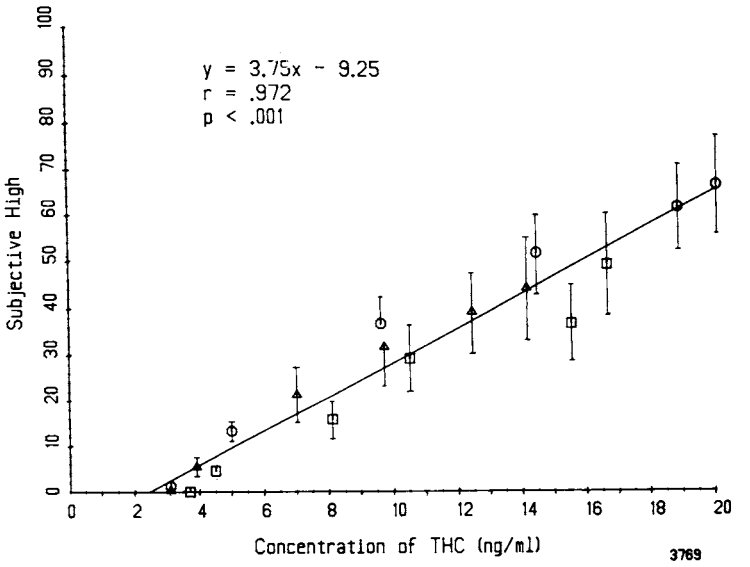


FIGURE 5. Correlation of plasma THC concentration and subjective "high" after pseudoequilibrium. The data of Perez-Reyes et al. (36) are shown for time points 60 min following smoking of 1.32% (triangles), 1.97% (squares), and 2.54% (circles) THC cigarettes. Error bars correspond to +/- S.E.M.

lated from fat and Garrett and Hunt (38) predicted a terminal half-life of 8 days in the dog.

The prediction of this model is consistent with findings of Hunt and Jones (22) that enhanced metabolism of THC will have a minimal effect on its terminal phase half-life. Our model suggests that the rate of metabolism (and excretion) is at least 50-100 times faster than release from tissue stores.

The prediction of a prolonged half-life of THC is of potential importance in the clinical treatment of patients with substance abuse, and is consistent with clinical reports of a relatively prolonged detoxification phase associated with treatment of marijuana dependence (39,40). Simultaneous measurement of plasma and some representative measurements of THC fat concentrations may provide clarification of this point.

The above two hypotheses are readily testable with additional research and will allow one to further understand the complex pharmacology of THC. Furthermore, additional new data will help validate or reject the present compartmental model

which predicts that plasma THC levels correlate with subjective "high".

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