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Do Plasma Concentrations of Δ^9-Tetrahydrocannabinol Reflect the Degree of Intoxication?

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Abstract: Plasma concentrations of THC were measured by gas–liquid chromatography and mass spectrometry following three routes of administration and correlated with clinical effects. Plasma concentrations peaked at 3 minutes after intravenous injection and then sharply declined. The peak "high" occurred at 30 minutes while plasma concentrations were declining. This lag between plasma concentration and "high" continued during most of the span of the drug's effects. The situation was quite similar following smoking, except that peak plasma concentrations were lower. After oral administration of THC, absorption was slow, with peak concentration occurring at 1 to 2 hours. Plasma concentrations were much lower. Correlations between plasma concentrations of drug and "high" were significant but not impressive. The degree of "high" was quite variable in relation to the prevailing plasma concentration. Conjunctival injection was found so long as plasma concentration of THC could be measured. Pulse rate increases occurred at lower concentration after oral administration than after the other two routes. It is unlikely that a range of plasma concentrations can be reliably equated with impaired performance. The mode of administration will become important should THC or some homolog become a therapeutic agent.

MARIJUANA may become an accepted social drug in the United States and in other developed countries as well as in many parts of the world. Its use should be dealt with in a way similar to that of other social drugs, most notably alcohol. Because of the known impairment in driving an automobile caused by alcohol, virtually every jurisdiction has some law regarding blood concentrations of this drug associated with such impairment. Decisions about these concentrations vary with different jurisdictions. In some, any amount of detectable alcohol in blood is considered to be evidence of impairment, while in others, arbitrary levels such as 50 or 100 mg/dl have been imposed. The assumption has generally been made that blood concentrations of alcohol reflect rather closely those that prevail in the brain at any given moment. Except for instances of marked tolerance to the effects of alcohol, plasma concentrations of alcohol correlate well with intoxication or impaired performance. Now it remains to be determined whether a similar range of plasma concentrations can be defined for THC.

It is also possible that the active component of cannabis, THC, or some homolog of this compound, may find a place in therapeutics.[1] If so, the mental effects of the drug, so desired for social use, might be construed as an unwanted effect. Thus, it is pertinent to determine what plasma concentrations of the drug are associated with mental effects and what the time course of such effects is after different modes of administration.

The present study attempted to relate plasma concentrations of THC to self-

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ratings of degree of intoxication and two overt clinical signs of THC intoxication, namely, conjunctival injection and pulse rate. We wanted to see if the model provided by alcohol held for THC.

Methods

Subjects

Eleven men between the ages of 18 and 35 years were volunteer subjects. All had prior experience with marihuana, which ranged from infrequent to frequent use. All were in good physical and mental health. None was taking other psychoactive drugs. Prior to each trial, subjects were asked to abstain from cannabis for at least 72 hours and from alcohol for at least 24 hours.

Dose and Administration of THC

Three forms of THC were administered, each to each subject on successive trials. Trials were separated in time by at least one week. Assignment to treatments was randomized. Three dose forms were used:

1. Smoking. A cigarette containing about 19 mg THC was smoked in a fashion determined by the subject such as to obtain the maximum desired "high." The butt was extinguished in water and retained for analysis of residual THC.

2. Oral Administration. A chocolate cookie was prepared containing 20 mg THC added as an ethanolic solution evaporated under nitrogen. The subject ate one such cookie.

3. Intravenous. Into the injection port of a rapidly flowing intravenous infusion of normal saline, 5 mg THC in 95% ethanolic solution (2 mg/ml) was slowly injected over a period of 2 minutes. This mode of administration has been used previously by us and is effective and safe.

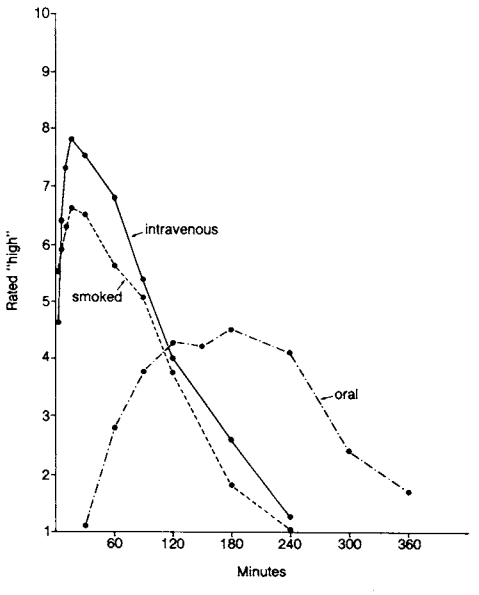

Fig. 1. Time course of "high" ratings following three modes of administration of THC.

During the intravenous and smoking sessions, 10-ml blood specimens were drawn before administration of the drug and after termination of smoking or of the intravenous injection at periods of 3, 6, 10, 15, 30, 60, 90, 120, 180, and 240 minutes. Each blood sample was obtained from a heparin lock. Heparinized plasma was separated immediately and frozen in silanized glass tubes for the chemical determinations.

During the oral administration session, blood specimens were obtained before giving the drug and at 30, 60, 90, 120, 150, 180, 240, 300, and 360 minutes thereafter. Specimens were handled as noted above.

Analysis of THC in Plasma

The procedures for analysis of THC by gas-liquid chromatography and mass spectrometry using a deuterated THC internal standard have been described in detail elsewhere.[2]

Clinical Evaluations of Drug Effects

The following clinical evaluations were made:

1. Pulse rate was read constantly through an ear lobe monitor. Several baseline records were made as well as records at

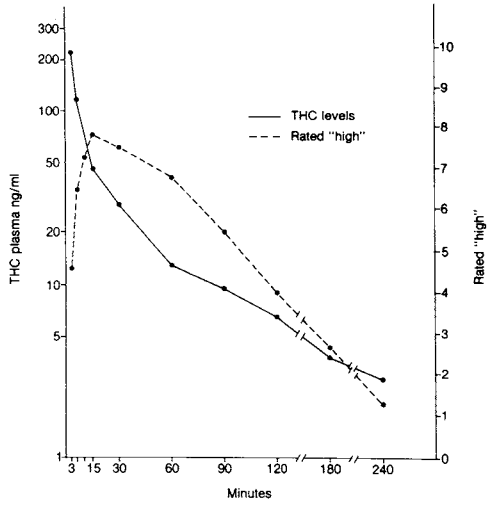

Fig. 2. Time course of "high" and relation to plasma concentration of THC following intravenous administration of THC.

every point in time when plasma samples were taken.

2. Conjunctival injection was rated on a 0 to 4 scale at the same time periods.

3. A rating of the degree of "high" on a 0 to 10 scale was made by subjects before treatment and at 3, 6, 10, 15, 30, 60, 120, and 240 minutes after smoking or intravenous administration. With oral administration, ratings were made before treatment and at 30, 60, 90, 120, 180, 300, and 360 minutes after administration. "High" was defined as the total level of drug intoxication experienced, with a score of 10 representing the maximum effect the subject could imagine. Such estimates have been highly reliable in past studies.

Results

Time Course of "High"

The time course of the degree of "high" following the three modes of administration of THC is shown in Fig. 1. Patterns were rather similar after both intravenous injection as well as smoking. Peak "high" was reached at 30 minutes, with a rather rapid decline toward baseline by the end of 4 hours. After oral administration, the degree of "high" was not nearly so great, and it was delayed in onset and prolonged in duration. The peak occurred between 2 to 4 hours after ingestion, with a decline to low levels at 6 hours.

Plasma Concentrations and "High" After Intravenous THC

In Fig. 2, both plasma concentrations of THC and the degree of "high" are plotted over time. Due to the route of administration, peak plasma concentrations were reached within 3 minutes following termination of injection, but the peak "high" was delayed to 30 minutes. This early trend for plasma concentrations of THC to decline more rapidly than the degree of "high" continued throughout the next 2 hours. Figure 3 plots the degree of "high" against the log concentrations of THC in plasma after intravenous injection. Although the correlation was significant, it was relatively low ($r = 0.35$).

Plasma Concentrations and "High" After Smoked THC

The pattern of plasma concentrations of THC after smoking marihuana was similar to that after intravenous injection of THC, although peak concentrations were lower

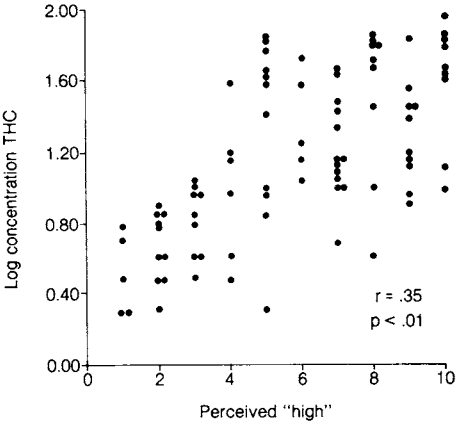

Fig. 3. Correlations between log concentration of plasma THC and "high" following intravenous injection of THC.

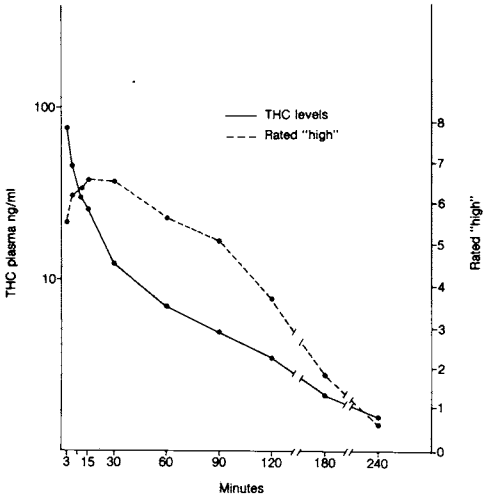

Fig. 4. Time course of "high" and relation to plasma concentration of THC following smoking of cannabis.

(Fig. 4). The pattern of "high" was also similar to that after intravenous injection, with a slower rise and slower decline of the "high" than that of the plasma concentrations. Only when both reached low levels did they parallel each other. Figure 5 shows the plot of log concentration of THC in plasma after smoking against "high." The correlation was significant and somewhat higher ($r = 0.53$) than for the intravenous mode of administration.

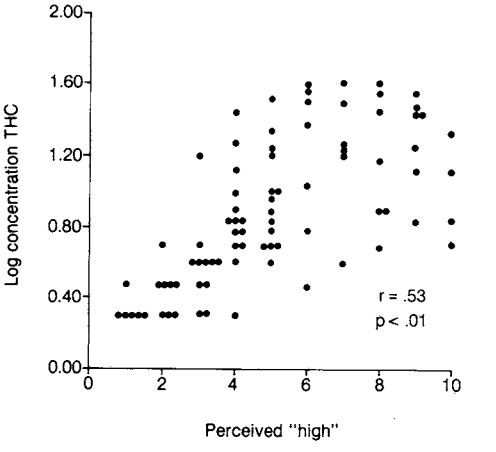

Fig. 5. Correlations between log concentration of plasma THC and "high" following smoking of cannabis.

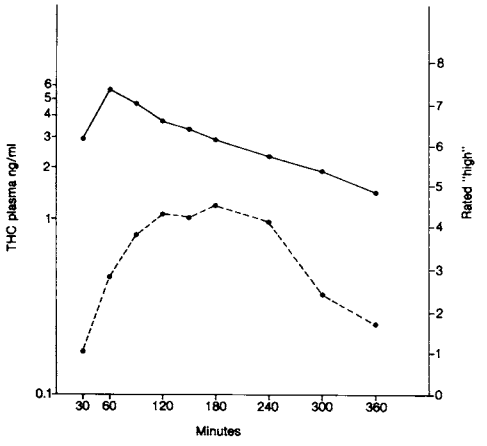

Fig. 6. Time course of "high" (lower curve) and relation to plasma concentration of THC (upper curve) following oral administration of THC.

Plasma Concentrations of THC After Oral Administration

Plasma concentrations of THC after oral administration were considerably lower than those after either smoking or intravenous administration (Fig. 6). Peak concentrations were not reached until 60 minutes (usually subjects showed a double

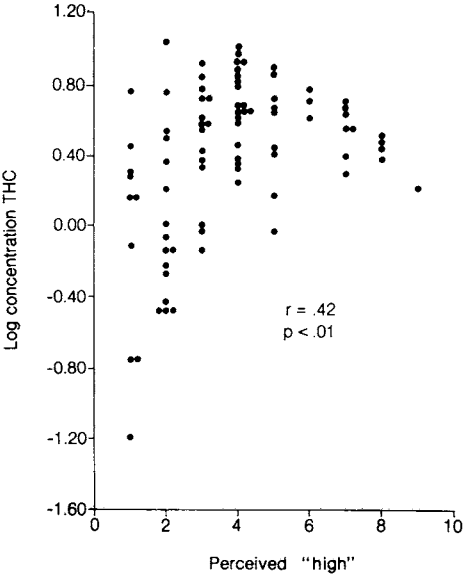

Fig. 7. Correlations between log concentrations of plasma THC and "high" following oral administration of cannabis.

TABLE I

Correlation Between Plasma Concentrations of THC and Degree of "High": Three Routes of Administration

Time (min)	Intravenous	Smoked	Oral
3	−.27	.52	
6	.35	.69	
10	.44	.59	
15	.44	.40	
30	.30	.51	.70
60	.23	.23	.55
90	.28	.45	.66
120	.42	.45	.48
180	−.11	.21	−.05
240	−.32	—	.10

peak), after which the decline was gradual over the next few hours. Peak "high" lagged behind the plasma concentrations by 1 to 3 hours. The correlation between plasma concentrations and degree of "high" shown in Fig. 7 was significant, although not strong ($r = 0.42$).

Plasma Concentrations of THC and Degree of "High" at Various Time Periods

Table I shows these correlations for each of the three routes of administration. Correlations were best after the initial very rapid distribution phase of THC was completed after intravenous or smoking routes of administration. They were slightly better overall from smoking, but in general were most reliable for both routes from 10 to 120 minutes after administration. Correlations were also highest for oral administration during the period when absorption was nearly complete or complete. With any route of administration, correlations became relatively poor after 2 hours.

Relationship Between Prevailing Plasma Concentrations of THC and "High"

Table II shows these relationships for different time periods. Those for intravenous and smoking routes of administration were combined, as their kinetics were so similar. During the distribution phase after the intravenous or smoking routes, the subjects were often not aware of being intoxicated despite the presence of relatively high plasma concentrations. After that phase, the relationship between plasma concentration and degree of "high" became somewhat linear for all routes of administration. Nonetheless, individual variability was considerable.

TABLE II

Relationship Between Prevailing Plasma THC Concentrations (ng/ml) and Reported "High": Three Routes of Administration

	Intravenous and smoked			Oral		
Degree of "high"	Range	Median	Mean	Range	Median	Mean
0	2-190	4	61	tr-6	1	—
1	2-6	3	3	tr-6	1	—
2	2-317	4	29	tr-6	1	—
3	3-240	4	31	tr-8	4	—
4	2-251	8	27	2-10	5	5
5	2-250	19	43	1-8	5	5
6	3-210	27	44	4-6	5	5
7	4-112	17	31	2-4	3	3
8	4-215	47	59	2-3	3	3
9	7-196	25	46	2	2	2
10	5-160	44	46	—	—	—

Clincal Signs in Relation to Plasma Concentrations

Conjunctival Injection. Reddened conjunctivae are one of the most reliable clinical signs produced by THC. With intravenous administration of THC, it was often maximal 3 minutes after termination of the injection. It was always maximal by 10 minutes after completion of the injection. Reddening tended to subside in some patients 180 minutes after injection. A similar situation prevailed following smoking, although one subject returned to normal by 180 minutes. With oral administration of THC, reddening of the conjunctivae occurred within 30 to 60 minutes, was maximal from 60 to 180 minutes, and then gradually lessened. One subject, whose pattern of plasma concentrations suggested delayed absorption of the drug, showed virtually no reddening of the conjunctivae. In general, this effect of THC was present so long as plasma concentrations of drug were above 5 ng/ml, even though subjects may no longer perceive themselves as "high."

Pulse Rate. A second highly reliable sign of cannabis effect is an increase in pulse rate. After intravenous THC, the maximum increase in pulse rate varied from +25 to +100 beats per minute, with a median increase of +40 beats per minute at a median THC level of 100 ng/ml. After smoking of THC, the increase in pulse rate varied from 0 to +80 beats per minute, with a median of +34 beats per minute at a median THC level of 45 ng/ml. Following oral ingestion of THC, the pulse rate increase varied from +4 to +68 beats per minute, with a median increase of +26 beats per minute at a median THC level of 4.5 ng/ml. The pulse rate often returned to baseline or below, even while the patient felt "high" and had plasma concentrations of THC above 5 ng/ml. A similar relationship between pulse rate and plasma concentrations of the Δ^8-THC isomer has also been found.[3]

Discussion

A clear-cut relationship between plasma concentrations of THC and degree of intoxication, as has been shown for alcohol, could not be demonstrated. The kinetics of THC following smoking was almost the same as following intravenous injection, with rapid attainment of peak plasma concentrations. This peak was followed by a distribution phase in which THC rapidly left the blood. Owing to its high lipid solubility, it entered relatively rapidly into the brain and other lipid depots of the body. Thus, following these two routes of administration, the degree of intoxication actually increased as plasma concentrations decreased. Such a lag between plasma concentrations and degree of intoxication continued throughout most of the time span of the major effects of the drug. Studies in mice have shown that while plasma levels are falling initially, brain concentrations are rising or are constant.[4]

The situation following oral administration was considerably different. Here, the degree of intoxication paralleled the peak concentrations in plasma over time following completion of absorption. What was most interesting was that the degree of intoxication following oral dosage was attained with much lower concentrations of plasma THC than following the other two routes of administration. Quite possibly, oral administration permits a greater amount of THC to enter the liver and to be metabolized to its more potent active metabolite, 11-hydroxy-Δ^9-tetrahydrocannabinol.[5] Indeed, preliminary data indicate that after oral administration of THC, plasma levels of the 11-hydroxylated metabolite are more than twice that of THC itself. The plasma peak of 11-hydroxy-THC is, however, not particularly delayed compared to the THC peak.[6]

Thus, it seems evident that one will not be able to make the neat correlations between plasma concentrations of THC and intoxication that have been made in the case of alcohol. The degree of intoxication at any

given moment may vary considerably with plasma concentrations in the same individual and even over a greater degree with different individuals. One will not be able to determine reliably some relatively narrow range of plasma concentration that will coincide linearly with intoxication.

So far as therapeutic applications of THC are concerned, the route of administration will become very important. Both the intravenous route and smoking of the drug tend to produce too severe a degree of intoxication and too short a span of action for any sustained use. Oral administration is somewhat more suitable, although absorption is erratic, in the sense that effects are sustained longer and are not as severe. This route would be most applicable if one could predict in advance the span of time during which the effects were desired and if the desired effect could be obtained with relatively low concentrations of the drug.

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Discussion of the Paper

Dr. Wall: Why do you use chocolate cookies as the route of administration in preference to the sesame oil capsules that NIDA makes available? Do you have comparative absorption data?

Dr. Hollister: The cookie is used to simulate "real world" ingestion of THC. Cookies do have a fairly high fat content which would facilitate absorption.

Dr. Nahas: The gastric acid of the stomach will inactivate up to 50% of THC, if it remains there for about an hour. If THC is given by mouth for therapeutic purposes, it would be preferable that it should by-pass the stomach and go directly into the intestine, with a gastric-coated vehicle, instead of using a chocolate cookie, or even the presently available gelatin capsules which dissolve in the stomach.

Dr. Hollister: We calculated the bioavailability by the cookie route to be about 6% which is close to the 3:1 ratio that Isbell estimated earlier for smoking *vs.* oral administration.