Comparative Pharmacology of Δ^9-Tetrahydrocannabinol and its Metabolite, 11-OH-Δ^9-Tetrahydrocannabinol

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ABSTRACT A comparison of the psychologic and physiologic effects of intravenously administered Δ^9-tetrahydrocannabinol (Δ^9-THC) and 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC) was carried out in nine casual marihuana smokers. A marked tachycardia and psychologic "high" occurred within 3–5 min after the i.v. administration of 11-OH-Δ^9-THC (1 mg) to all subjects. In contrast, the peak psychologic "high" was delayed 10–20 min after the i.v. administration of Δ^9-THC (1 mg). There was some individual variation in response among subjects. Psychologic effects correlated well with plasma levels of unchanged [^{3}H]11-OH-Δ^9-THC. About 75% of the administered radioactive dose was excreted in urine (25%) and feces (50%) after [^{3}H]11-OH-Δ^9-THC administration. The disposition, excretion, and metabolism of [^{3}H]11-OH-Δ^9-THC appear to be similar to that previously reported after [^{14}C]Δ^9-THC administration. These findings, in conjunction with the marked psychologic high seen after 11-OH-Δ^9-THC, suggest that in man, Δ^9-THC, the active constituent in marihuana, is converted to 11-OH-Δ^9-THC, which is in part responsible for the psychologic effects.

INTRODUCTION

Marihuana and hashish are commonly used drugs which are derived from the hemp plant, *Cannabis sativa*. Gaoni and Mechoulam (1) have shown that the major pharmacologically active principle of this plant is Δ^9-tetrahydrocannabinol (Δ^9-THC).[1] Recent clinical studies (2) have suggested that the actual pharmacological agent responsible for the psychologic effects is a metabolite of Δ^9-THC, since several of the psychologic effects have been correlated to the plasma levels of metabolites of Δ^9-THC. 11-OH-Δ^9-THC, one of the metabolites of Δ^9-THC formed in vivo in man (3), has been shown to be very active when administered intravenously (4). The present study, utilizing a double-blind crossover design, compares several of the responses produced by the administration of Δ^9-THC with those produced by administration of the same dose of 11-OH-Δ^9-THC.

METHODS

Nine male volunteers, ranging in age from 22 to 24 yr, were studied in two separate experimental designs. The subjects were casual smokers of marihuana, having used this drug at least 6–12 times within the past 2 yr. Each volunteer had previously experienced a psychologic "high" while smoking marihuana. None of the subjects had a history of habitual usage of drugs or medication. The subjects were admitted to the Lilly Ward at Marion County General Hospital and were under constant medical and nursing supervision throughout each aspect of the experiment. They were given complete medical examinations and a thorough psychiatric evaluation. The procedures involved in this study and the hazards and risks associated with them were explained to the volunteers, and informed consent was obtained.

The first series of experiments employed three subjects, ranging in weight from 63 to 87 kg, who were studied on three separate occasions during a 3-mo period in a nonblinded, crossover fashion. However, the subjects were unaware of what specific effects would be anticipated from these studies and due to the nature of the study were not told what the expected response or potency of the drug to be used was. All three subjects received tritiated 11-OH-Δ^9-THC (specific activity 24.6 μCi/mg), nonradiolabeled Δ^9-THC, and absolute alcohol for parenteral administration.

The second series of experiments used six subjects, ranging in weight from 70 to 80 kg, who were studied

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[1] *Abbreviations used in this paper:* THC, tetrahydrocannabinol.

TABLE I

Comparative Pharmacology of Δ⁹-THC, 11-OH-Δ⁹-THC, and Alcohol Vehicle after their Intravenous Administration in a Nonblinded, Crossover Study

	Heart rate		Symptom sign score		Psychologic high	
	Pre	Peak	Pre	Peak	Pre	Peak
J. A. A. Vehicle	78	82	1	5	0	1
11-OH-Δ⁹-THC	80	140	2	46	0	10+
Δ⁹-THC	77	132	1	37	0	10+
J. M. A. Vehicle	85	85	7	7	0	0
11-OH-Δ⁹-THC	104	124	8	63	0	10+
Δ⁹-THC	95	116	2	20	0	1
J. C. L. Vehicle	64	65	0	1	0	0
11-OH-Δ⁹-THC	66	106	0	25	0	10+
Δ⁹-THC	65	72	0	9	0	6

during a 3-wk period using a double-blind, crossover design. The order of drug administration was randomized to eliminate any order effect. At weekly intervals each subject was administered either nonradiolabeled 11-OH-Δ⁹-THC, nonradiolabeled Δ⁹-THC, or absolute alcohol for parenteral administration. Each subject was told that he might receive any one or all of the three drugs and was told that each drug might or might not be active in the dose used.

Ampoules containing an alcoholic solution of Δ⁹-THC or 11-OH-Δ⁹-THC were prepared under aseptic conditions with a final concentration of 1 mg of drug dissolved in 1 ml of absolute alcohol. The alcoholic diluent served as the vehicle administered during the control period of these studies.

The tritiated 11-OH-Δ⁹-THC was enzymatically synthesized and labeled in the cyclohexane and benzene rings. The nonradiolabeled 11-OH-Δ⁹-THC was chemically synthesized. These materials were synthesized at the Research Triangle Institute, Research Triangle Park, N. C., and supplied by Dr. Monique Braude of the National Institutes of Mental Health, Rockville, Md. 7 mg of enzymatically synthesized, radiolabeled 11-OH-Δ⁹-THC, which initially contained 80% 11-OH-Δ⁹-THC, was purified by extraction and thin-layer chromatography. 4 mg of the pure [³H]11-OH-Δ⁹-THC was obtained. The material was shown to contain one radioactive peak on thin-layer chromatography having the same chromatographic properties as authentic 11-OH-Δ⁹-THC. The chemically prepared 11-OH-Δ⁹-THC was assayed by thin-layer and gas-liquid chromatography and shown to have a purity greater than 95%.

Δ⁹-THC and 11-OH-Δ⁹-THC were prepared for intravenous administration by dissolving 1 mg of the drug in absolute alcohol for parenteral administration. The solutions were prepared under aseptic conditions and placed in single-dose ampoules. The solutions were subjected to tests for sterility and pyrogenicity. The purity of the injected 11-OH-Δ⁹-THC and Δ⁹-THC was affirmed by thin-layer chromatography and gas-liquid chromatography coupled with mass spectrometry. All drugs were administered by injection into the antecubital vein during a 1-min interval through the tubing of a rapidly flowing intravenous infusion of 5% dextrose and water.

All subjects remained in the recumbent position for the duration of the experiments except when urine samples were to be collected. They were continuously evaluated before, during, and after the administration of drug and/or vehicle for psychologic and pharmacologic effects. Signs and symptoms were assessed and quantified at regular intervals using a modified Cornell Medical Index questionnaire. Subjects were also questioned at these time intervals about the presence or absence of a psychologic high they may have been experiencing. Subjects were instructed to rate the magnitude of their psychologic high from 0 (no effect) to 10 (maximum effect experienced in the past while they were smoking marihuana), as previously described (2). Subjects were also observed for objective signs, and a tape recording of the experimental session was evaluated at the completion of that session. They were also asked to relate their experience during the experimental session by writing a resume at the end of each session.

In addition, heart rate was determined by continuous monitoring of the standard lead II of the electrocardiogram during the first 30–45 min of the session, followed by periodic recordings for up to 8 h if deemed necessary.

After the administration of tritiated 11-OH-Δ⁹-THC, blood samples were drawn periodically into heparinized Vacutainers (Vacutainer Blood Specimen Tubes, Becton, Dickinson & Co., Rutherford, N. J.) from an indwelling catheter placed in the subject's arm opposite the site of injection, and the samples were assayed as previously described (3). Urine and feces were collected at regular intervals and analyzed for radioactivity as previously described (5).

RESULTS

Pharmacologic and psychologic effects of Δ⁹-THC and 11-OH-Δ⁹-THC. The intravenous administration of 1 ml of absolute alcohol for parenteral administration (the vehicle) produced only minimal effects on the symptom sign questionnaire and psychologic high rating in the three subjects utilized in the first experimental series. These effects were similar to those they reported during the preinjection period. Administration of the vehicle had no effect on the heart rate (Table I).

After the intravenous administration of [³H]11-OH-Δ⁹-THC (1 mg) to these same subjects, there were marked pharmacologic and psychologic effects (Fig. 1, Table I). All subjects responded to the effect of this drug within 2–3 min. There was an increase in heart rate ranging from 20 to 60 beats/min. In all subjects the symptoms were most intense within 15 min and reached their maximal effect during this period. The return of the symptom sign score to predrug levels varied with each of the subjects and appeared to be correlated with the subject's body weight.

All subjects reported a maximum psychologic high within 2–3 min after the intravenous administration of 11-OH-Δ⁹-THC that was more intense than that previously experienced after smoking marihuana. In subjects J. A. A. and J. M. A. this high was initially so intense that they felt it to be unpleasant. They later perceived it as being more pleasant and similar to previous highs they had experienced with marihuana. Again, the dura-

tion of these effects appeared to be correlated to body weight.

After a 1–2 mo hiatus, each subject was given an intravenous injection of 1 mg of Δ⁹-THC in a manner identical to the previous administrations. The results are shown in Fig. 2 and Table I. Subject J. A. A. experienced a psychologic high that he rated as being greater than any previous high after smoking marihuana; however, it was not as intense as after 11-OH-Δ⁹-THC administration. This subject reported the effects as being entirely pleasant. The effect did not reach its maximum until 15 min after administration and was of long duration. The symptom sign score was increased above the predrug score and peaked at 30–45 min after the injection. The tachycardia produced by Δ⁹-THC in subject J. A. A. appeared to be similar to that produced by 11-OH-Δ⁹-THC administration in this subject. After the intravenous administration of Δ⁹-THC (1 mg), subject J. C. L. had a psychologic high that was pleasant; however, at its peak he rated it at a value of 6. This

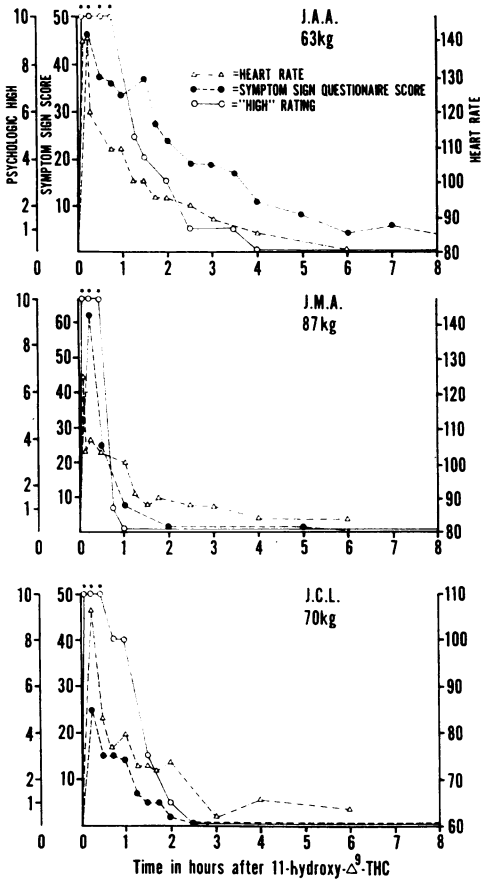

FIGURE 1 The effect of 11-OH-Δ⁹-THC (1 mg) on heart rate, psychologic high, and symptom sign score after its intravenous administration to three human volunteers.
* Indicates value greater than 10.

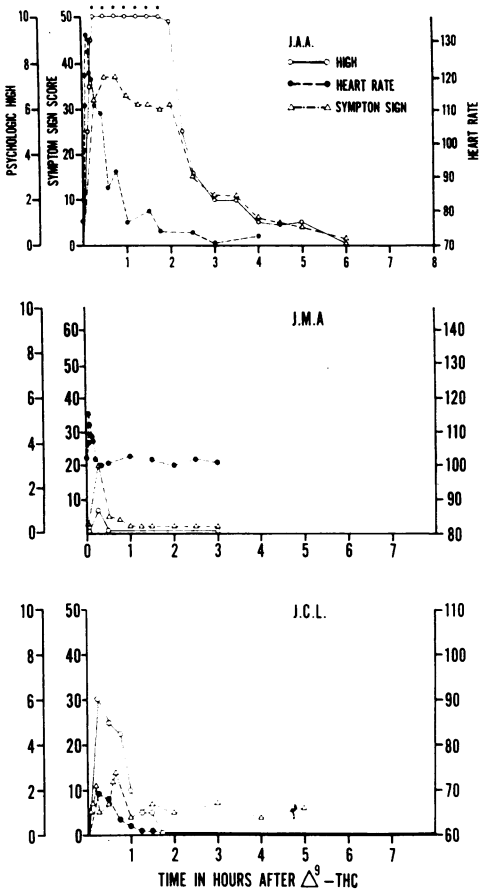

FIGURE 2 The effect of Δ⁹-THC (1 mg) on heart rate, psychologic high, and symptom sign score after its intravenous administration to three human subjects.
* Indicates value greater than 10.

would be approximately one-half of the rating given for 11-OH-Δ⁹-THC by the same subject. The maximum effect occurred 15 min after Δ⁹-THC administration. Subject J. M. A. reported only minimal effects on the psychologic "high" rating (a rating of 1 at 15 min), and similarly, the symptom sign score was minimal. Both subjects J. M. A. and J. C. L. had small increases in heart rate. The effects of Δ⁹-THC seen in these three subjects also appeared to be related to body weight, the lightest subject having the greatest intensity and duration of effects, whereas the heaviest showed minimal effects of short duration.

As a result of the variability and response among subjects, the second series of experiments was conducted utilizing a double-blind, crossover design with a randomized order of drug administration. At the conclusion of the experiment, the data was statistically analyzed, and the code was broken. The results are shown in Table II and Fig. 3. As in the previous study, there were essentially no effects produced after the intravenous adminis-

tration of the vehicle. After the intravenous administration of 11-OH-Δ^9 THC, all subjects responded with an increase in symptom sign score as determined by a modified Cornell Medical Index. Five of the six subjects reported a markedly greater psychologic high after the 11-OH-Δ^9-THC administration than after Δ^9-THC. In all these subjects the difference was clearly discernible. In the sixth subject the effects of 11-OH-Δ^9-THC were quantitatively equal to or slightly greater than the effects experienced after Δ^9-THC, although the time of onset was much shorter after 11-OH-Δ^9-THC. All subjects in this study found the effects to be entirely pleasant. As in the previous series of experiments, all subjects experienced and responded to the effects of 11-OH-Δ^9-THC within 2–3 min, whereas the onset of effects was delayed for a considerably longer time after Δ^9-THC administration (Fig. 3). In all subjects there was an increase in heart rate ranging from 20 to 70 beats/min after 11-OH-Δ^9-THC administration, and from about 20 to 55 beats/min after Δ^9-THC administration. The mean effects of the alcoholic vehicle, 11-OH-Δ^9-THC, and Δ^9-THC on the psychologic high, symptom sign score, and heart rate are illustrated in Fig. 3.

Plasma levels of Δ^9-THC and 11-OH-Δ^9-THC. Previous studies (2) have demonstrated a correlation between the plasma levels of metabolites of Δ^9-THC and the

TABLE II

Comparative Pharmacology of Δ^9-THC, 11-OH-Δ^9-THC, and Alcohol Vehicle after their Intravenous Administration in a Double-Blind, Crossover Experiment with Randomization of Order of Drug Administration

	Heart rate		Symptom sign score		Psychologic high	
Subject	Pre	Peak	Pre	Peak	Pre	Peak
B. B. Vehicle	76	77	1	2	0	0
11-OH-Δ^9-THC	84	101	0	52	0	9
Δ^9-THC	78	97	5	21	0	4
M. D. Vehicle	66	66	1	1	0	0
11-OH-Δ^9-THC	60	99	0	28	0	8
Δ^9-THC	60	78	1	11	0	2
J. H. Vehicle	67	59	4	1	0	0
11-OH-Δ^9-THC	86	110	5	44	0	9
Δ^9-THC	64	75	1	39	0	9
A. H. Vehicle	73	76	0	0	0	0
11-OH-Δ^9-THC	77	100	3	13	0	3
Δ^9-THC	68	88	0	2	0	0
B. D. Vehicle	63	66	0	1	0	0
11-OH-Δ^9-THC	64	92	0	28	0	9
Δ^9-THC	70	99	2	34	0	2
J. P. Vehicle	70	66	0	3	0	0
11-OH-Δ^9-THC	56	132	2	81	0	10
Δ^9-THC	66	119	3	54	0	7

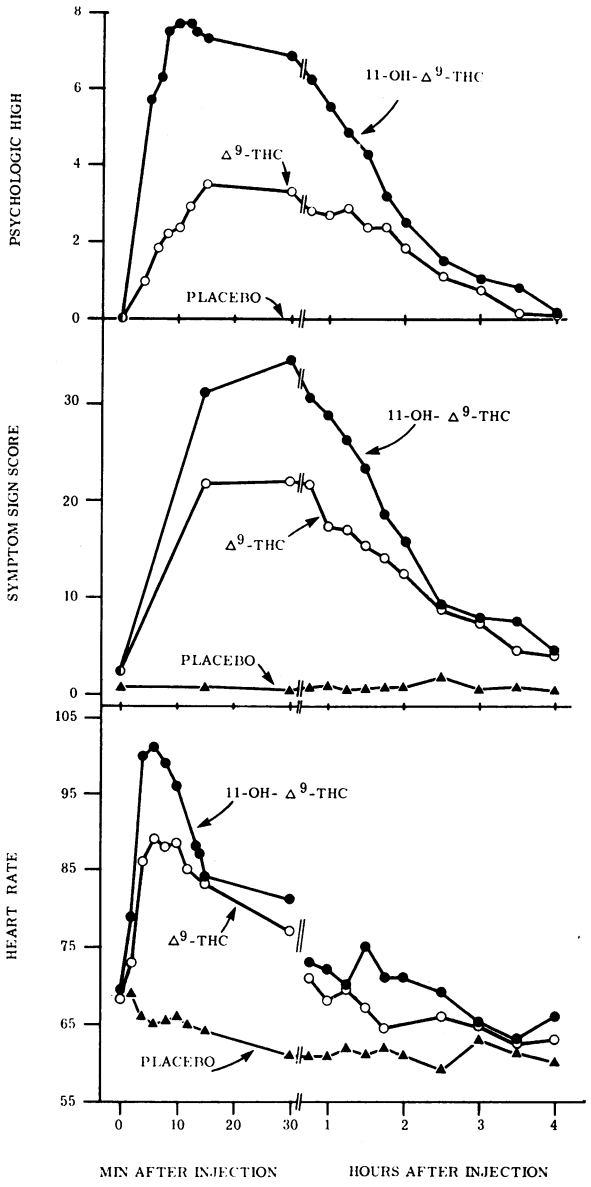

FIGURE 3 Comparison of the effects of the intravenous administration of alcoholic vehicle, Δ^9-THC, and 11-OH-Δ^9-THC on psychologic high, symptom sign score, and heart rate. Each point represents the mean value obtained from six subjects to whom the drugs were administered in a double-blind, crossover fashion.

psychologic effects they produced after oral administration or inhalation. After the intravenous administration of [^{3}H]11-OH-Δ^9-THC, the plasma levels of unchanged [^{3}H]11-OH-Δ^9-THC and total radioactivity declined in a biphasic fashion (Fig. 4). The levels of unchanged [^{3}H]11-OH-Δ^9-THC were highest at the onset and the peak of the pharmacologic effect. In contrast, the levels of radioactive metabolites of [^{3}H]11-OH-Δ^9-

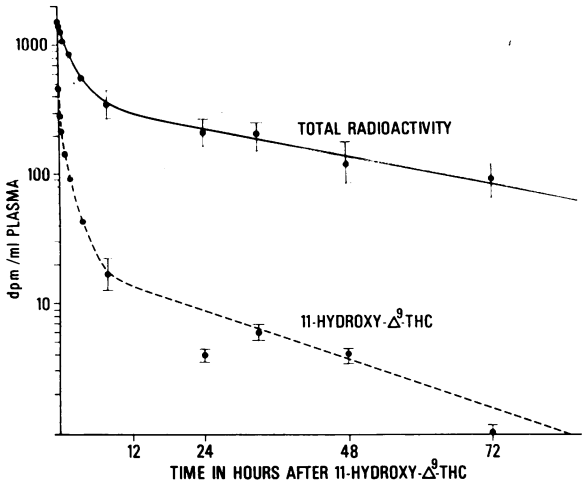

FIGURE 4 Plasma levels of 11-OH-Δ^9-THC and total radioactivity after the intravenous administration of [^{3}H]11-OH-Δ^9-THC to three human volunteers. Values represent the mean ±SEM.

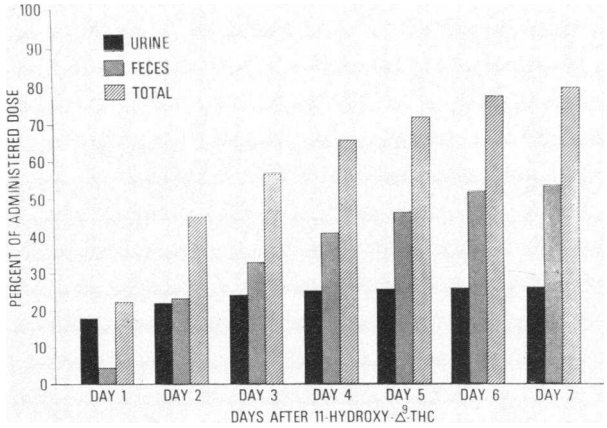

FIGURE 5 Excretion of radioactive metabolites of 11-OH-Δ^9-THC after the intravenous administration of [^{3}H]11-OH-Δ^9-THC to three human subjects. Values represent the mean of the three subjects.

THC were present in lower concentrations at these times.

Excretion and metabolism. After the intravenous administration of [^{3}H]11-OH-Δ^9-THC, radioactively labeled compounds were excreted in the urine and feces (Fig. 5). About 16% of the administered dose of tritiated 11-OH-Δ^9-THC was excreted in the urine during the first day: of this, 5% was excreted during the first 2 h and 12% during the first 12 h. After 1 wk, 22% (range 19–26%) of the administered radioactive dose was excreted in the urine. During this period 50% of the administered dose of tritium was excreted in the feces.

The major urinary metabolite(s) of 11-OH-Δ^9-THC were polar acidic compounds and had extraction and chromatographic properties similar to the acidic urinary metabolites reported after [^{14}C]Δ^9-THC administration in man (5). In addition to these acidic compounds, about 5% of the urinary radioactivity was present in the form of unchanged 11-OH-Δ^9-THC. Two radioactive metabolites identified in feces after 11-OH-Δ^9-THC administration were shown by chromatography to be unchanged 11-OH-Δ^9-THC and 8,11-dihydroxy-Δ^9-THC. The metabolic fate of 11-OH-Δ^9-THC (Table III) in man appears to be similar to that reported previously for Δ^9-THC (3, 5–7).

DISCUSSION

Δ^9-THC is the major psychoactive constituent of marihuana (8). Administration of this compound to man produces effects similar to those seen after the use of cannabis preparations (9–11). Investigations in animals (12) and man (3) have shown that Δ^9-THC is converted to 11-OH-Δ^9-THC in vivo. In several ani-

TABLE III

The Excretion and Metabolism of Δ^9-THC and 11-OH-Δ^9-THC in man

	After Δ-9-THC*	After 11-OH-Δ-9-THC
Percent dose recovered in urine	22–31%	20–25%
Percent dose recovered in feces	41–45%	50%
Total percent dose recovered	67–71%	70–75%
11-OH-THC in urine	5%	5%
Acid metabolite(s) in urine	20%	19%
11-OH-THC excreted in feces	20%	20%
8, 11 di-OH-THC excreted in feces	18%	18%
Material unaccounted for in feces (possibly conjugates of 11-OH-THC)	7%	10%

* Based upon earlier studies (5).

mal species this compound was shown to be pharmacologically active (13–17). Previous studies in man (2) have suggested that metabolites of Δ^9-THC were actually responsible for the psychologic effects of Δ^9-THC and cannabis. Recent preliminary reports (4, 18) have shown direct evidence that 11-OH-Δ^9-THC is a potent pharmacologic substance in man.

In the present investigation we compared the effects produced by the administration of Δ^9-THC and 11-OH-Δ^9-THC. Particular concern was placed on the onset and duration of the effects. Each subject served as his own control, and these studies were conducted in a double-blind, crossover fashion with the order of drug administration being randomized. Both drugs were given in the same 1-mg dose by the intravenous route in order to circumvent any differences in absorption, and essentially, each subject was bioassaying the two drugs. This design was chosen because individual variations in the psychologic effects of psychotropic drugs are well known.

The drugs were given in the same dose and were not of equimolar concentrations; however, since the differences in their molecular weights are negligible (less than 5%), this should have no significant bearing on the experiment. All subjects utilized during the initial study responded qualitatively to each of these drugs; however, there was some degree of intersubject variation in the quantitative effect as well as the duration of effect. The most probable explanation for this is that, although each received the same total dose, the dose per kilogram of body weight varied from 16 μg/kg for subject J. A. A. to 11.5 μg/kg for subject J. M. A. Subject J. C. L. was intermediate in weight and received a dose of 14 μg/kg of each drug. In addition, subject J. A. A. was ectomorphic, whereas subject J. M. A. had an endomorphic build, and perhaps the shorter duration of effects in this subject was related to a redistribution of drug into adipose tissue. Subjects for the second study (double-blind, crossover design) were selected who were closer in weight (70–80 kg). Again, in this study there was individual variation in the response to Δ^9-THC and 11-OH-Δ^9-THC. However, in all subjects the 11-OH metabolite was reported to produce a greater psychologic high.

After the intravenous administration of 11-OH-Δ^9-THC, there were pronounced psychologic and pharmacologic effects seen within 2–3 min. A marked tachycardia, an intense psychologic high, and considerable symptoms were produced. After the intravenous administration of Δ^9-THC, eight of nine subjects had effects that were qualitatively similar, subject A. H. being the exception. However, in the case of the psychologic high and symptom sign score, these effects did not reach their maximal effect until 15–30 min after the intravenous infusion. This suggests that after the administration of Δ^9-THC (or marihuana or hashish), this compound is converted by biotransformation to 11-OH-Δ^9-THC, which is in part responsible for the psychologic effects of Δ^9-THC. This is consistent with earlier studies that suggested that metabolites of Δ^9-THC are responsible for its psychologic effects (2) in man. It has been shown that after the administration of [^{14}C]-Δ^9-THC, 11-OH-Δ^9-THC and other radioactive metabolites are present in plasma and their concentration exceeds that of Δ^9-THC at 15 min (the time of the maximal psychologic effects of Δ^9-THC after inhalation).

Further evidence to support the hypothesis that Δ^9-THC is producing its psychologic effects via an active metabolite (11-OH-Δ^9-THC) comes from the excretion and metabolic studies. After tritiated 11-OH-Δ^9-THC administration, the metabolic fate of this compound is both qualitatively and quantitatively similar to that previously reported for Δ^9-THC, suggesting that Δ^9-THC and 11-OH-Δ^9-THC have a common metabolic pathway.

Recent studies by Perez-Reyes, Timmons, and Lipton (18) have reported that Δ^9-THC and 11-OH-Δ^9-THC are equally potent in producing typical marihuana-like psychologic effects. Unfortunately, their experimental design could not be expected to give any differential effects. These investigators infused the drugs intravenously at a very slow rate (1 mg every 5 min; doses that are about three times that used in the present experiment) into different individuals until they each achieved their desired level of high. Perhaps the differences between the present study and theirs are related to the method of administration. With the slow infusion of Δ^9-THC, it may be rapidly converted to the 11-OH-Δ^9-THC, thereby causing the effects to be similar. An alternative explanation is that during the slow infusion of the 11-OH-Δ^9-THC, it is more easily metabolized to inactive compounds, thus giving it the appearance of being less active than is actually the case.

In general the results of this present investigation indicate than in man 11-OH-Δ^9-THC, at the dose used, is more potent than Δ^9-THC and further suggest that the psychologic effects of Δ^9-THC are dependent upon its conversion to an active metabolite.

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