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The effects of Chronic Administration of *Trans*-Δ^9-Tetrahydrocannabinol on Behavior and the Cardiovascular System of Dogs [1]

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Abstract—The daily intravenous administration of Δ^9-tetrahydrocannabinol (Δ^9-THC) produced a marked tolerance to the behavioral effects of this compound in six mongrel dogs. Similar results were obtained with Δ^8-THC in the only dog tested. The minimal effective acute I.V. dose of Δ^9-THC to produce ataxia and other behavioral changes is 0.5 mg/kg. In one dog, the effects of 161 mg/kg Δ^9-THC given intravenously after chronic treatment were less than those observed following 0.5 mg/kg in a drug naive dog. There were no behavioral responses which would indicate a withdrawal syndrome following abrupt stopping of the medications. Tolerance to the behavioral effects of Δ^9-THC developed over a range of doses when the injections were made only once every 8 days. Behavioral tolerance could still be observed 23 days after the last injection of Δ^9-THC in a tolerant dog. Initially Δ^9-THC produced bradycardia in four of seven dogs tested but this changed to tachycardia at higher doses of Δ^9-THC on approximately day 6 or 8 of treatment. There was no significant change in blood pressure in these dogs after either acute or chronic administration.

Introduction

In 1968 it was reported (1) that tolerance develops to the effects of an alcoholic extract of *Cannabis sativa* and to the effects of Δ^9-tetrahydrocannabinol (2) in rodents. We have reported that tolerance developed to the effects of *l-trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC) on the overt behavior of dogs (3); while McMillan and his coworkers have shown that a marked tolerance develops to

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the effects of Δ^9-THC in pigeons (4). We have now expanded our studies of the production of behavioral tolerance induced by daily intravenous administrations of Δ^9-THC in dogs. The results of these experiments comprise the body of this report.

It has been reported (5, 6) that Δ^9-THC produces a dose related increase in heart rate when smoked or taken orally by man. Conversely, studies in anesthetized dogs showed that the intravenous administration of comparatively larger doses of Δ^9-THC produced a prolonged bradycardia. This bradycardia was accompanied by a pronounced hypotension which usually had a duration of up to four hours (7). These dogs were anesthetized with barbiturates and reports exist which suggest an interaction between Δ^9-THC and barbiturates (8). Therefore, we measured the effects of acute and chronic administrations of Δ^9-THC on heart rate and blood pressure in the present experiments with unanesthetized dogs.

Methods

Trans-Δ^9-Tetrahydrocannabinol (Δ^9-THC) suspended in bovine albumin was injected intravenously into mongrel dogs of either sex. The suspensions of Δ^9-THC were prepared in the following manner. A stock solution of 150 mg Δ^9-THC per cubic centimeter of absolute ethanol was prepared and refrigerated. Two cubic centimeters of this solution was placed in a 50 cc flask. The ethanol was evaporated off under a stream of nitrogen and 700 mg bovine albumin was added to the Δ^9-THC. These substances were stirred with a glass rod, about 7 cc distilled water was added and the flask was placed in a sonicator until a good suspension was achieved. Sufficient water was added to bring the volume to 10 cc. When very high doses were used the final volume was 5 cc giving a concentration of Δ^9-THC of 60 mg/cc.

Behavioral effects of Δ^9-THC were graded using a modification of the scale adopted by Walton *et al.* (9) to quantitate cannabinoidlike activity in dogs. The following scale was used in these experiments.

0 – no effect.

1 – slight depression, often characterized by a decrease in spontaneous activity or a slowing of movement, but also hyperexcitable when aroused, static ataxia or wobble as described by Walton seen only after the dog has been standing in one position for a long period of time (3-5 minutes).

2 – prance-like placement of feet, static ataxia seen between 1 and 3 minutes after standing in one position and overreacts to a swinging hand.

3 – static ataxia more pronounced and seen soon after dog stands in one position, some loss of tone in hind legs usually evident by a spreading apart of the legs or squatting; circling and increased salivation may also be seen at this stage. The tail is often tucked between the hind legs at this stage.

4 – marked static ataxia, sways forward and backward as well as from side to side and at times is unable to catch himself. Can stand for greater than 1 minute without support.

5 – plunges about, the dog cannot stand alone without support for more than 1-minute.

6 – the dog cannot plunge about but lies prostrate on the floor.

Often, three observers independently rated the behavior of each dog two hours after the injection and any two of them never differed by more than 1 rank for the same observation time throughout the study. Often the three scores were identical.

The syndrome described in this scale represents the behavioral effects of Δ^9-THC over a range of doses on acute injection. Five individual experiments were conducted during a six month period. In the first experiment behavioral observations and heart rate were measured prior to and 2 hours after each injection. Two dogs were given Δ^9-THC and one dog was given Δ^8-THC. In the second experiment blood pressure, heart rate and the behavioral score was determined prior to and two hours after the daily injections of Δ^9-THC to two dogs. The third experiment differed from the second in that a different dosage schedule was used and the measurements were determined 30 minutes after as well as prior to and 2 hours after each injection of Δ^9-THC. In the fourth experiment doses of 0.5, 5, 8, 16, and 32 mg/kg Δ^9-THC were tested in drug free dogs to serve as a control for the experiment described above. Eight days later each dog received a second injection of his initial dose of Δ^9-THC. This was repeated the third and fourth time at eight day intervals. One additional dog was given 5 mg/kg Δ^9-THC daily for seven of eight days and then not injected for 23 days at which time a dose of 8 mg/kg Δ^9-THC was injected intravenously. These animals were observed 2 hours after each injection and their behavior rated according to the scale as described above.

Blood pressure was measured indirectly with the use of a pediatric cuff and stethescope on the femoral artery. Heart rate measurements were made by placing the stethescope on the chest of the animal and counting the beats over a 15 second period. The magnitude of the range in values that were obtained during training were larger than those obtained during the experiment. In experiment 3 these measures were also taken prior to and 30 minutes and 2 hours after each daily injection of control vehicle.

Results

The results of the first experiment are presented in Table I. Tolerance to the behavioral effects of Δ^8- and Δ^9-THC occurred in each dog in this experiment. Often a one hundred percent increase in dose did not significantly increase the value on the behavioral rating scale. There did not appear to be a

TABLE I

Day	Dose	Behavior			Heart Rate					
					Dog 1		Dog 2		Dog 3	
		Dog 1	Dog 2	Dog 3±	Before	After	Before	After	Before	After
1	0.5	3	3	3	86	85	80	90	84	80
2	1	2	2+	2	92	94	92	96	98	96
3	1	2	2	2	82	92	114	120	98	92
4	1	1	1	0	84	88	108	100	102	108
5	1	1	0	0	92	94	132	108	92	94
6	2	2	2	1	102	104	110	112	104	100
7	2	1	1	1	110	112	106	100	114	110
8	2	2	2	2	100	102	112	108	120	116
9	4	2	2	2	92	112	104	116	112	120
10	8	3+	3+	2	108	116	120	112	100	88
11	8*	3+	N.T.	2	120	112	112	—	112	116
12	0	1−	0	1	132	—	100	—	120	—
13	0	0	0	0	—	—	—	—	—	—
14	0	0	0	0	—	—	—	—	—	—
15	8*+	N.T.	0	4	120	—	108	—	114	114
16	16*	3	0	3	100	100	—	—	120	116
17	0	0	0	1	120	—	116	—	96	—
18	0	0	0	1	104	—	—	—	120	—
19	0	0	0	0	120	—	—	—	128	—

* Dog 2 not injected on these days
\+ Dog 1 not injected on this day
± Dog 3 was given Δ^8-THC suspended in albumin.

TABLE II

Effect of Chronic Injections of Δ^9-THC on the Behavior, Heart Rate, and Blood Pressure in Dogs

		Behavior		Heart Rate				Blood Pressure			
				Dog 1		Dog 2		Dog 1		Dog 2	
Day	mg/kg Dose	Dog 1	Dog 2	Before	After	Before	After	Before	After	Before	After
1	1	1	1	88	—	96	—	90	—	90	—
2	2	2	2	92	96	88	68	108	104	105	110
3	3	3	3	96	76	84	76	102	113	120	107
4	6	4	4	94	72	76	64	143	113	113	127
5	6	4	4	76	76	84	76	140	133	126	122
6	6	4−	4	88	88	84	60	126	116	97	127
7	6	3	3	80	76	84	78	116	110	112	123
8	6	3	2 +	84	84	88	84	90	105	123	137
9	6	3	4	92	84	84	84	116	104	123	133
10	6	2	3−	84	88	90	92	90	88	122	123
11	12	died	2 +	92	died	108	92	121	died	117	127

significant change in heart rate from any of these injections. However, the heart rate did increase over the duration of the experiment in all three dogs. The results of the second experiment are presented in Table II. Again, some tolerance to the behavioral effects of Δ^9-THC was observed in both dogs. This may be most evident on day 10 when the ratings after 6 mg/kg Δ^9-THC were less than those observed after 3 mg/kg Δ^9-THC on day 3. Some bradycardia appeared in each of these dogs during the early days of this experiment but this was not seen after day 7. Also, the increase in heart rate seen during the first experiment was not seen in experiment 2. There were no consistent changes in blood pressure throughout this study. The dog that died during this study was very apprehensive and had to be forcibly restrained for the injections during the later part of the study.

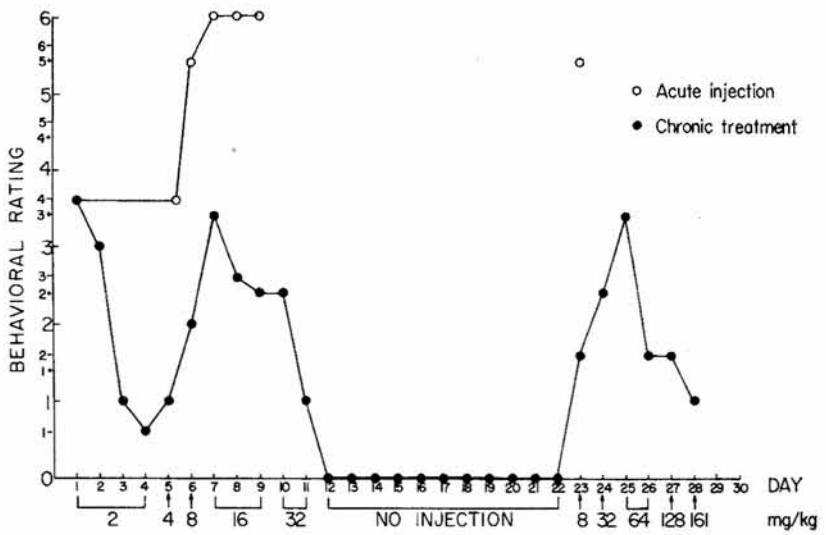

FIG. 1

The effect of chronic intravenous administration of *l-trans*-Δ^9-THC on the overt behavior of dog #1. The numbers on the ordinate represent the behavioral rating as described in the methods. Plus and minus signs are used to indicate that either a slightly greater or less effect was observed than described. The days of the experiment and the dose of Δ^9-THC given on each day are presented on the abscissa. The open circles represent the readings obtained when previously drug free dogs were given the dose of Δ^9-THC indicated on the abscissa. The closed circles indicate the behavioral rating for the dog which received the chronic injections of Δ^9-THC indicated on the abscissa. (*Ann. N. Y. Acad. Sci.* **191**, 83, 1971).

The effects of Δ^9-THC on the overt behavior of the two dogs used in the third experiment are presented in Figures 1 and 2. Effects similar to these were observed in the two prior studies. That is, tolerance has been observed to the behavioral effects of Δ^9-THC in each of six dogs tested in our laboratories.

Four daily intravenous injections of 2 mg/kg Δ^9-THC produced a marked tolerance in both dogs in this experiment. Similar results were seen in the first experiment when 1 mg/kg was given daily, but when 6 mg/kg was repeated for 7 days in experiment 2 the tolerance, although clearly evident, was not as pronounced. In the experiments summarized in figures 1 and 2, doses of Δ^9-THC gradually increased to 32 mg/kg did not produce a disruption of behavior to the extent observed with the initial dose of 2 mg/kg. The behavioral rating for each dose used in a drug free dog are presented on the top of the figures.

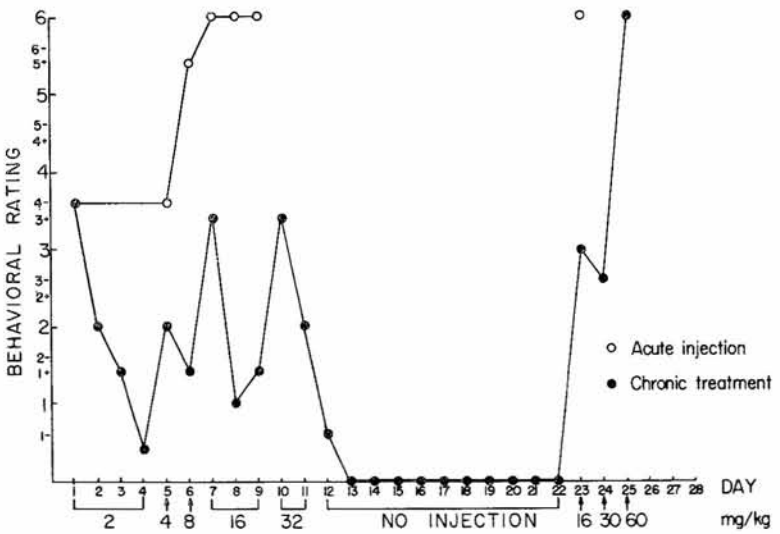

FIG. 2

The effect of chronic intravenous administration of *1-trans*-Δ^9-THC on the overt behavior of dog #2. The numbers on the ordinate represent the behavioral rating as described in the methods. Plus and minus signs are used to indicate that either a slightly greater or less effect was observed than described. The days of the experiment and the dose of Δ^9-THC given on each day are presented on the abscissa. The open circles represent the readings obtained when previously drug free dogs were given the dose of Δ^9-THC indicated on the abscissa. The closed circles indicate the behavioral rating for the dog which received the chronic injections of Δ^9-THC indicated on the abscissa. This dog died following the injection of 60 mg/kg Δ^9-THC on day 25 of the experiment.

There were some striking differences in the onset of tolerance to a number of the effects of Δ^9-THC in dogs. One of the most obvious effects of Δ^9-THC in dogs is that the animals overract (duck and retreat) to a swinging hand soon after their exposure to the drug. This effect has been observed in almost every dog tested in our laboratory. However, the dogs become tolerant to this effect very quickly and often it is not observed following the second injection. A second effect of Δ^9-THC in dogs is the static ataxia which is observed. The animals become tolerant to this effect considerably more slowly than they do to

their hyperreaction to a swinging hand. Dogs do not appear to become tolerant to certain effects of Δ^9-THC. Most noticeably of these were sedation and loss of appetite which were more pronounced as the dose of Δ^9-THC was increased during these studies. In this regard Δ^9-THC appears to be similar to the opiates and other drugs in that tolerance develops to certain of its effects but not to others. The behavioral patterns returned to normal almost immediately after cessation of daily drug treatment. Rales which appeared on the eleventh day of the experiment subsided soon after medication stopped. There were no behavioral signs that might suggest withdrawal in either dog. It is obvious from figures 1 and 2 that when the injections were resumed some 11 days later

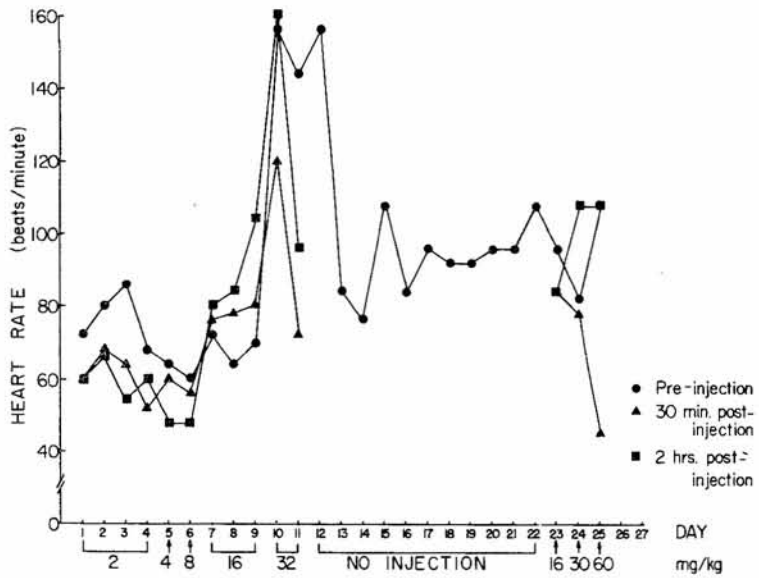

FIG. 3

The effect of chronic intravenous administration of *1-trans*-Δ^9-THC on the heart rate of dog #1. The heart rates were determined by placing a stethescope on the chest of the dog and counting the beats during 15 seconds. The circles represent the heart rate determined prior to the injection of Δ^9-THC. The triangles represent the value determined 30 minutes after the injection and the squares the value obtained 2 hours after the injection. The days of the experiment and the dose of Δ^9-THC given on each day are given on the abscissa.

considerable tolerance was still present. One dog in this study died after receiving 60 mg/kg Δ^9-THC. Upon necropsy a blood colored exudate was found in the bronchial tubes but there was no evidence that the dog had aspirated vomitus. The lungs were very red and full of blood. Similar observations were made upon necropsy of dogs who died from acute injections of 24, 32, or 42 mg/kg Δ^9-THC. The stomach and the rest of the G.I. tract of the chronic

dog were empty indicating that the dog had not eaten for some time. The dog lost 14 % of her weight during the experiment, appeared emaciated and was not seen eating on days when large doses of Δ^9-THC were given.

The second dog survived increasing doses of Δ^9-THC up to and including 161 mg/kg. The behavioral effects observed after this dose were less than those usually observed after an I.V. injection of 0.5 mg/kg Δ^9-THC in a naive dog

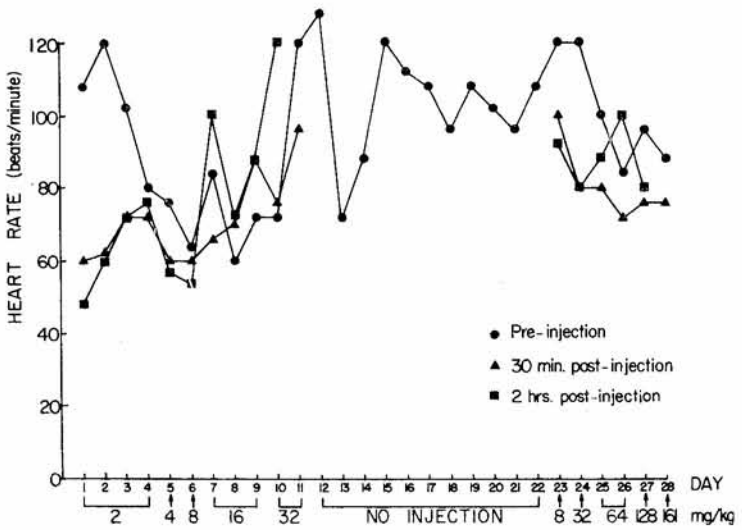

FIG. 4

The effect of chronic intravenous administration of *l-trans*-Δ^9-THC on the heart rate of dog #2. The heart rates were determined by placing a stethescope on the chest of the dog and counting the beats during 15 seconds. The circles represent the heart rate determined prior to the injection of Δ^9-THC. The triangles represent the value determined 30 minutes after the injection and the squares the value obtained 2 hours after the injection. The days of the experiment and the dose of Δ^9-THC given on each day are given on the abscissa.

(Fig. 7 and ref. 7); therefore, we have observed more than a 300-fold increase to the behavioral effects and approximately a 4-fold increase in the lethal dose of Δ^9-THC. All dogs given an initial dose of 24 mg/kg Δ^9-THC intravenously died soon after the medication. The quantity of drug needed, its lack of solubility and the apparent poor health of the animal caused us to conclude the experiment at this point. The dog was emaciated, hadn't eaten for a number of days and was given dextrose orally on the day following the last injection. There were no indications of withdrawal observed. This dog fully recovered and appeared in good health about 2 weeks after the experiment. There were no behavioral changes nor rales in the dog given repeated injections of albumin. He maintained good health and appetite throughout the experiment.

The initial injections of Δ^9-THC in experiment 3 produced bradycardia in

both dogs at both 30 and 120 minutes after the injections (Figs. 3 and 4). The bradycardia decreased during the first week of the experiment. The heart rate prior to the injection was considerably less on day 4, 5, and 6 than on the first three days.

We expect that this is due to a prolonged effect of the drug rather than an indication of tolerance to the bradycardia. However, when the dose was increased to 16 mg/kg (day 7 or 8) a tachycardia was observed in each dog. The heart rate was high in both dogs on day 12, 24 hours after the second injection of 32 mg/kg. An injection was not given on day 12 and the heart rates fell dramatically. Bradycardia was observed in each dog when the injections were started again on day 32. There was no change in the blood pressure of any of the three dogs used in this experiment (Figs. 5 and 6).

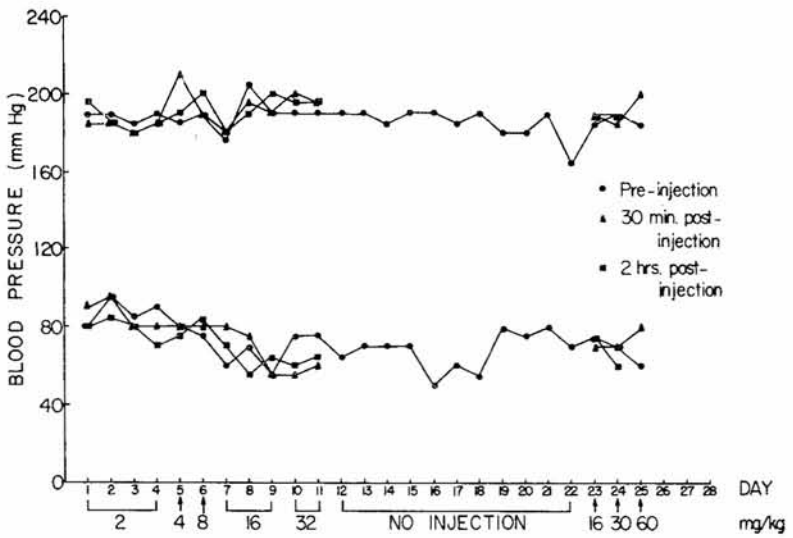

FIG. 5

The effect of chronic intravenous administration of *l-trans*-Δ^9-THC on the blood pressure of dog #1. The blood pressure was determined by applying a pediatric cuff around one hind leg and listening for blood flow with the aid of a stethescope. Readings were taken prior to (●———●), 30 min after (▲———▲) and 2 hours after (■———■) each injection of Δ^9-THC indicated on the abscissa. The days of the experiments and the dose of Δ^9-THC given on each day of the experiment are presented on the abscissa.

The nature of the experiment required large quantities of the suspensions to be given each day. On two occasions (in different dogs) a swelling appeared on one of the limbs. The animal favored this leg, did not walk on it and would snap at the experimenter if he touched it. One of the investigators accidently grasped the damaged limb while taking the animal's blood pressure after an injection of Δ^9-THC. The animal did not respond in the expected manner and

walked normally putting weight on that leg. The next day he favored the leg prior to the injection of Δ^9-THC but not during the post injection observation period. Similar effects were observed in the other dog. Although not quantitated these observations suggest the need for experiments to investigate the possible analgesic effects of Δ^9-THC in dogs.

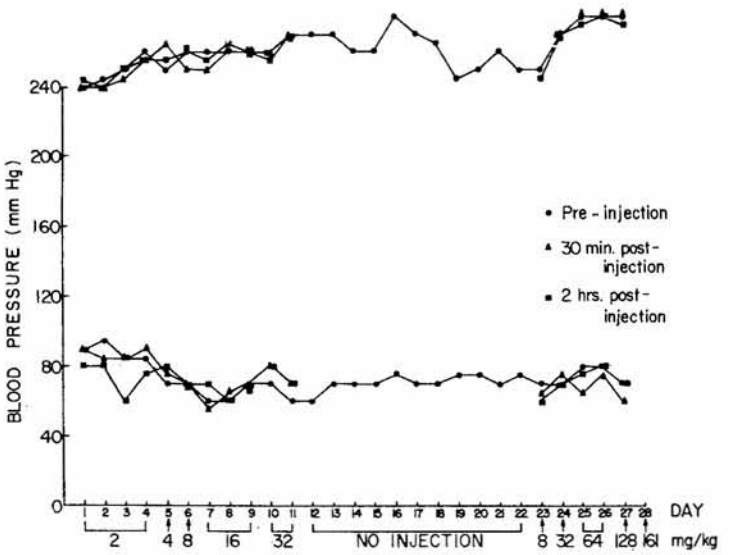

FIG. 6

The effect of chronic intravenous administration of *l-trans*-Δ^9-THC on the blood pressure of dog #2. The blood pressure was determined by applying a pediatric cuff around one hind leg and listening for blood flow with the aid of a stethescope. Readings were taken prior to (●———●), 30 min after (▲———▲) and 2 hours after (■———■) each injection of Δ^9-THC indicated on the abscissa. The days of the experiments and the dose of Δ^9-THC given on each day of the experiment are presented on the abscissa.

The results of the fourth and fifth experiments are presented in Figure 7. They indicate that a pronounced tolerance to Δ^9-THC develops when the drug is administered as infrequently as once every 8 days. The tolerance on this dose schedule was observed over a wide range of doses 0.5–8 mg/kg and appeared more quickly with lower than with the higher doses. Dog #1169 died following the third injection of 16 mg/kg Δ^9-THC. Dog #4020 salivated profusely prior to and immediately after each injection of Δ^9-THC. There was no tolerance observed to this effect. Dog #1120 also salivated following the injections during the final portions of this experiment. Dog #4066 was given an intravenous injection of 5 mg/kg Δ^9-THC on 7 of 8 days and not medicated again for 23 days. On the 23rd day 8 mg/kg Δ^9-THC was given and pronounced tolerance still was observed (Fig. 7).

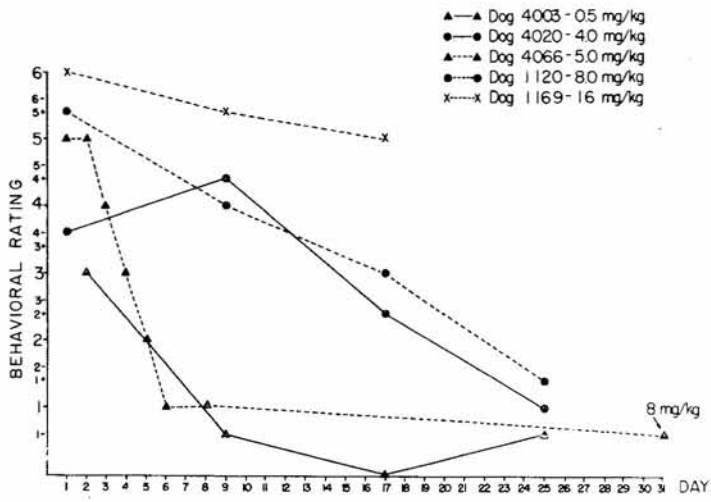

FIG. 7

The production of tolerance to the behavioral effects of *l-trans*-Δ^9-THC given only once every eight days to dogs. The numbers on the ordinate represent the readings on the behavioral rating scale described in methods. Plus and minus signs are used to indicate the behavioral effect observed was somewhat more or less than described. Injections of Δ^9-THC were given only on those days where the character is presented. The animals were drug free on the other days and had food and water presented *ad libitum*. (*Ann. N. Y. Acad. Sci.* **191**, 83, 1971).

Discussion

The results presented in this paper clearly indicate that pronounced tolerance develops to the behavioral effects of Δ^9-THC in dogs. The magnitude of the tolerance is at least 300 fold, which suggest that it is in the range of opiate tolerance and exceeds barbiturate tolerance (10). Although a phenomenon of increased sensitivity has been reported for the chronic effects of marihuana in man (11), these results confirm our previous findings (3) of tolerance in dogs and support the observations of others that tolerance is observed from cannabinoids when administered chronically to laboratory animals (12, 13). One must consider a number of differences between the experiments in man and those in laboratory animals. One of considerable importance is the difference in dose. The doses used in these and other laboratory experiments are considerably higher than those used in the human studies. Secondly, one must consider the route of administration. The drug was administered by inhalation in the human studies when reverse tolerance was described and was given intravenously in our experiments. In the human experiments smoke was the vehicle whereas in these experiments Δ^9-THC was given bound to bovine serum albumin. The most important consideration may be that we cannot

study many of the subjective effects such as the "high" produced in man in lower species. We do not have tests which quantitate these types of drug effects. Further experimentation is necessary to establish the significance of these differences in experimental design on what appears to be contrasting results in man and laboratory animals although one report has suggested that tolerance was observed to marihuana in experienced human subjects (14).

When the administrations of Δ^9-THC were discontinued there were no behavioral changes in the dogs which could be interpreted as a portion of a withdrawal syndrome. Thus, Δ^9-THC differs from morphine and other drugs which produce such a high level of tolerance.

As mentioned above, the animals were somewhat sedated and often emaciated following large doses of Δ^9-THC. The dogs appeared to recover gradually from both of these effects when the drug was discontinued.

A number of dogs that have died following injections of Δ^9-THC have been autopsied. In each dog the lungs were red and were distended, and when cut exuded copious quantities of blood. Dogs that have been on chronic medication appeared emaciated and when autopsied the gastrointestinal tract was often empty which indicated that the dog had not eaten for a prolonged period of time. There were no other gross or microscopic pathological abnormalities in the vital organs that were examined.

The observation that tolerance develops to the behavioral effects of Δ^9-THC when it is given as infrequently as every eight days and still can be observed twenty-three days after a previous injection might be due to the slow excretion of the drug. It has been shown by Black *et al.* (12) that tolerance develops to the effects of Δ^9-THC when administered once a week to pigeons. Agurell *et al.* (15) and Ho *et al.* (16) have reported that a small portion of a tritium label is recovered in urine or feces one week following the injection of tritiated Δ^9-THC to rabbits or rats respectively. This slow excretion indicates a long biological half life which allows the cells to be exposed to Δ^9-THC or an active metabolite for a long period of time. This may be relevant in the lack of withdrawal signs when the drug was stopped. Conversely, this slow excretion has been suggested (17) as a possible explanation for the increased sensitivity observed in man.

Dogs anesthetized with barbiturates show a prolonged and dose related bradycardia and hypotension after an intravenous injection of 0.3 mg/kg or higher doses of Δ^9-THC (18). We did not observe hypotension in the unanesthetized dogs following the acute or chronic injection of Δ^9-THC in this study. Further experimentation is needed to determine if the hypotension observed in the anesthetized dog is due to an interaction between Δ^9-THC and the barbiturate. Kubena and Barry (8) have reported synergistic effects of barbiturates and Δ^9-THC in rodents.

Bradycardia was observed initially in two of our chronic experiments in unanesthetized dogs. In the third experiment, the degree of the bradycardia decreased about the fourth or fifth day and when higher doses of Δ^9-THC

(16 mg/kg) were given tachycardia was observed in both dogs. It appears that the magnitude of the bradycardia decreased prior to the reversal of the effect. A few days later when the dose was increased to 32 mg/kg Δ^9-THC the heart rate was very high 2 hours after the injection and was still elevated the next day during the control period. A dose related increase in pulse rate is observed in man following much lower doses of Δ^9-THC.

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