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Intravenous Δ9-Tetrahydrocannabinol:

Effects on Ventilatory Control and Cardiovascular Dynamics

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Δ9-Tetrahydrocannabinol (THC), the active component of marijuana, was studied to determine whether it might be useful for preanesthetic medication. Ten healthy subjects received THC intravenously in logarithmically spaced incremental doses. Four subjects received a total cumulative dose of 135 μg/kg and four others, 201 μg/kg. Two of the ten subjects discontinued the study because of anxiety reactions. Ventilatory minute volume at a controlled elevated CO_2 tension, 48 ± 2 (SD) torr, changed minimally with THC, −0.49 l/min/50 per cent increase in dose. THC shifted the ventilatory response to CO_2 2.7 torr dextrad at 20 l/min without a change in slope. Dose-related tachycardia was the most marked cardiovascular effect. Heart rates increased to more than 100/min in five of six subjects. Cardiac index increased from 4.04 ± 0.62 l/min/m² before THC to 6.92 ± 2.34 l/min/m² after 134 μg/kg. Mean arterial pressure increased slightly, and total peripheral resistance fell. The cardiovascular changes suggest beta-adrenergic stimulation. Intense mental effects and anxiety prohibited higher THC doses. (Key words: Ventilation, marijuana; Premedication, marijuana; Ataractics, marijuana.)

DELTA-9-TETRAHYDROCANNABINOL (THC) is the principal pharmacologically active component of marijuana.[1] Inhaled, swallowed or intravenously injected, THC causes sedation and euphoria without tendency toward dependence on the drug.[2–4] Previous laboratory investigations have shown minimal respiratory and circulatory effects, other than tachycardia,[5,6] although few dose-response data for man exist. We considered that THC might have useful properties for anesthetic premedication.

Occasionally patients need operations on an emergency basis soon after use of marijuana. Beaconsfield *et al.*[7] think marijuana may be dangerous for anesthetized patients, because their findings suggested a beta-adrenergic mechanism for marijuana-induced tachycardia. Pulse rates in their subjects, however, did not exceed 100 beats/min, and they did not adequately rule out vagal blockade. Other pharmacologic effects of THC suggest its use as a surgical premedicant and anesthetic adjuvant. THC relieves pain[8,9] and lowers the required dosages of inhalational and intravenous anesthetic agents in animals.[10–12] After large doses of THC, various animals manifest neurophysiologic changes resembling the classic pattern of induction and emergence from general anesthesia.[13] Short-term amnesia,[14,15] blockade of antidiuretic hormone secretion,[16] muscle relaxation[2] and bronchodilatation[17] are other THC effects potentially useful in surgical patients.

Before clinical trials of THC, more data about its cardiovascular, ventilatory, and psychologic toxicities are needed, especially dose–response data for man. Hollister and Gillespie[18] injected as much as 6 mg THC intravenously into four subjects, but did not increase this dose because of its intense mental effects (confusion, vertigo, lethargy) and the increase in heart rate. There are few scientific studies of overdoses[19] and no reliable reports of human fatalities after THC. This study of the effects of intravenous administration of THC in large doses on CO_2-mediated control of ventilation and on

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CO_2-stimulated cardiovascular dynamics in healthy volunteers should have detected serious problems if they existed. In fact, the limit to THC dose was its psychologic rather than physiologic effects.

Methods

Subjects

Ten male volunteers (ages 21 to 41 years, weights 52 to 85 kg, body surface areas 1.56 to 2.01 m^2) received THC intravenously. All subjects visited the research laboratory and learned the extent and risks of the study at least one day before giving their written consent. Subjects could stop the experiment at any time. During the experiments, an anesthesiologist representing the subject was present. The University of Pennsylvania Committee on Studies Involving Man approved our protocol.

Each subject fasted from midnight. He lay on a contour-flexed operating table with music playing in the background. Radial arterial and internal jugular venous catheters were inserted and pressures (MAP, CVP) continuously measured using Statham strain gauges zeroed at mid-thoracic level. Lead II of the electrocardiogram was continuously recorded. Subjects breathed oxygen-enriched air through a wide-bore mouthpiece from a nonrebreathing circuit.

Each subject answered a questionnaire evaluating psychologic and physiologic effects on the day of and the day after the study.

Δ9-Tetrahydrocannabinol Dosage

The National Institutes of Mental Health supplied us with THC dissolved in ethanol at a nominal concentration of 1 mg/ml. We prepared the THC for intravenous infusion by diluting it tenfold in 5 per cent human serum albumin.[4] Dr. Calton Turner[¶] quantitatively assayed our THC by gas chromatography.[20]

We administered the THC in increments to give the following logarithmically scaled cumulative doses: 27, 40, 60, 90, 134, and 201 μg/kg. Maximum dosage was first established in two of us (TCS, LAM). Four of the remaining eight subjects received 201 μg/kg and two received 134 μg/kg. Two subjects quit before receiving all the planned doses: one after the first dose and one during the fifth dose. Each drug dose was infused over one minute. Doses were given 10–12 minutes apart. The first subject received THC by peripheral intravenous infusion; all others received THC through a central venous catheter to eliminate infusion pain associated with the peripheral route.

Ventilatory Measurements

The apparatus, as previously described, included a nonrebreathing ventilatory circuit (of wide-bore tubing, Sadd valves, mixing chamber, wedge spirometer and recycler), infrared CO_2 analyzer, paramagnetic O_2 analyzer and potentiometric recorder for ventilatory minute volume ($\dot{V}_E$), frequency, and $P_{ET_{CO_2}}$.[21] First we determined the ventilatory responses to 0, 3, 5 and 7 per cent CO_2. Added oxygen kept the inspired concentration between 30 and 50 per cent. Inspired CO_2 was returned to 5 per cent, and this steady-state end-tidal CO_2 tension ($P_{ET_{CO_2}}$) recorded. We held this $P_{ET_{CO_2}}$ constant, by varying the amount of inspired CO_2, while administering incremental doses of THC. This adaptation of Lambertsen's alveolar P_{CO_2} control concept[22] allowed rapid determination of ventilatory drive after each THC dose and magnified any depression. Twelve minutes after the last dose of THC, we repeated the steady-state CO_2–ventilatory response curve to interpret accurately isohypercapnic ventilatory changes. Respiratory minute ventilation ($\dot{V}_E$) and $P_{ET_{CO_2}}$ were continuously recorded during the experiment. Data from the last 5 minutes of each measurement period were analyzed. All ventilatory data were corrected to BTPS.

Cardiovascular Measurements

We measured cardiac output with indocyanine green by duplicate dilution curves at 0 and 5 per cent inspired CO_2 before administering THC, and 8–10 minutes after

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THC injection during isohypercapnia. Cardiac index (CI), stroke index, total peripheral resistance and left ventricular minute work index were calculated in standard fashion. Complete cardiovascular data were collected for three subjects through 201 μg/kg and for three subjects through 134 μg/kg.

Analysis

The dose–response relationships were analyzed by fitting loglinear least-squares regression equations to each subject's data. To determine whether there were significant differences in responses from subject to subject, the James[23]–Welch[24] technique of weighing slopes by their individual variances was used to derive a G statistic. This statistic has a chi-square distribution under the null hypothesis that all slopes are equal. Student's t test for matched pairs also determined statistical significance between pre- and post-THC data.

Results

Respiratory

Each subject had a normal pre-drug ventilatory response to CO_2. THC usually caused small dose-related decreases in $\dot{V}_E$ and tidal volume. Average ventilatory frequency remained constant at 21 breaths/min. Ventilation had always stabilized by 7 minutes after drug injection. Figure 1 shows the individual effects of each THC dose on $\dot{V}_E$ for nine subjects. Individual dose–response curves had slopes that ranged from −5.09 to 2.74 l/min/50 per cent increase in THC dose (average −0.49). These regression slopes varied significantly among subjects ($P < 0.05$). Average ventilatory response to CO_2 after THC was significantly displaced (2.7 torr to the right at 20 l/min, $P < 0.05$) despite several subjects whose ventilation increased with THC. The responses were not significantly changed in slope (fig. 2). Inspection of the individual data suggests mild dose-related respiratory depression with irregularly occurring episodes of increased breathing, probably secondary to psychologic effects.

Cardiovascular

Tachycardia was the most marked cardiovascular effect. Figure 3 shows the individual effects of THC on heart rate. Average heart rate (HR) increased from 58 ± 11 (SD) to 65 ± 14 beats/min as CO_2 inhalation in-

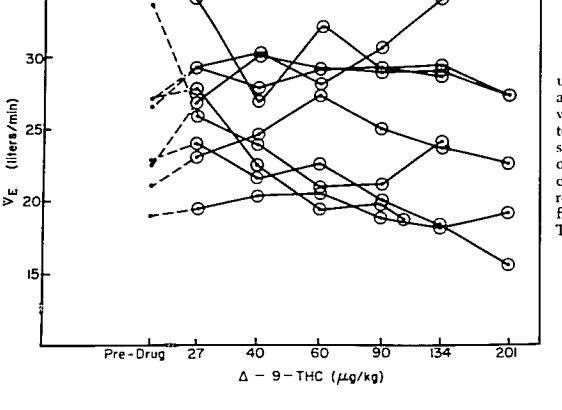

FIG. 1. Ventilatory minute volume was measured as each subject's PET_{CO_2} was held constant (48 ± 2 torr). Dashed lines represent responses to first dose of THC. One subject received 106 μg/kg, three received 134 μg/kg, and five received 201 μg/kg THC.

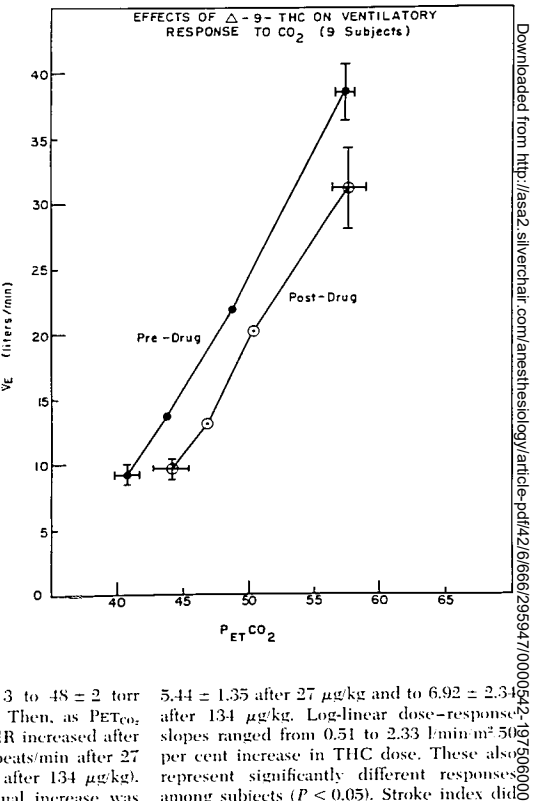

FIG. 2. Post-drug curve after 106 to 201 μg/kg THC. Standard-error bars are shown.

creased $P_{ET}CO_2$ from 41 ± 3 to 48 ± 2 torr during the control period. Then, as $P_{ET}CO_2$ was held constant, mean HR increased after each THC dose (89 ± 17 beats/min after 27 μg/kg, 101 ± 15 beats/min after 134 μg/kg). The most extreme individual increase was from 50 to 120 beats/min following 27 μg/kg THC. Heart rate changes ranged from −12 to 25 beats/min/50 per cent increase in dose. The fastest HR was 133. Again, significantly different responses existed among subjects ($P < 0.05$). The individual data suggest a direct, dose-related tachycardia with non-dose-related episodes of further tachycardia secondary to psychologic effects.

Cardiac index also increased in dose-dependent fashion (fig. 4) Cardiac index increased from 3.35 ± 0.48 to 4.04 ± 0.62 l/min/m², as $P_{ET}CO_2$ increased from 41 ± 3 to 48 ± 2 torr during the control period. Then, with $P_{ET}CO_2$ held constant, CI increased to 5.44 ± 1.35 after 27 μg/kg and to 6.92 ± 2.34 after 134 μg/kg. Log-linear dose-response slopes ranged from 0.51 to 2.33 l/min·m² 50 per cent increase in THC dose. These also represent significantly different responses among subjects ($P < 0.05$). Stroke index did not change significantly: 63 ± 8 ml/m² before THC, 61 ± 9 after 27 μg/kg, and 68 ± 20 after 134 μg/kg.

Mean arterial pressure increased only slightly with THC dosage, from 95 ± 12 torr before THC to 96 ± 5 torr after 27 μg/kg and 103 ± 9 torr after 134 μg/kg. Central venous pressure did not change significantly, being 9 ± 4 torr before THC and 7 ± 4 torr after 134 μg/kg. Left ventricular minute work index increased from 5,140 ± 380 g/m·min before THC to 7,050 ± 1,640 g/m·min after 27 μg/kg and 9,630 ± 3,290 g/m·min after 134 μg/kg (significantly different than control, $P < 0.05$). Total peripheral resistance de-

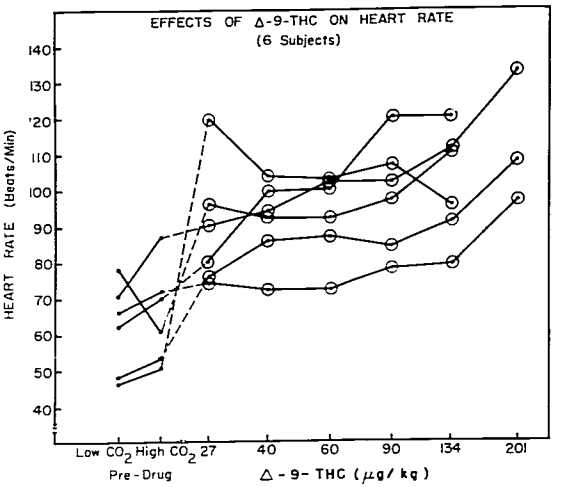

FIG. 3. Solid lines with small circles on the left show heart-rate responses to an increase in CO_2 from 41 ± 3 to 48 ± 2 torr before THC administration. Dashed lines represent responses to first THC dose while PET_{CO_2} was held constant at 48 torr. Solid lines with open circles show further dose–response information while PET_{CO_2} continued to be held constant.

clined slightly, from 967 ± 344 dyne·sec/cm^5 before THC to 755 ± 241 dyne·sec/cm^5 after the first dose and 676 ± 304 dyne·sec/cm^5 after the last dose (significantly different from control, $P < 0.05$). No arrhythmias were noted.

SYMPTOMS

All subjects except one reported prior experience with marijuana. All felt drowsy after receiving THC. When asked to rate the maximum drug effect (0, no effect; 10, as "high as you can get"), answers ranged from 5 to 10 (average 8). Four subjects reported odd dreams. Four felt excited or alert immediately after drug injection. Five reported interference with concentration and four with logical thinking. Six subjects felt dizzy, and seven complained of nausea or vomited after the study. All complained of a very dry mouth, and two thought this interfered with breathing. One thought he had uvular swelling (not confirmed by uvular photographs), and two worried about airway obstruction. Six noticed blurred vision and two complained of burning eyes.

One volunteer quit after the first dose of THC (27 μg/kg) because of anxiety. This subject, an anesthesia research fellow, described his experience as follows: "First there was a 'rush' with muscle discomfort, then in a minute, tinnitus and hyperacusis. I developed a feeling of detachment. This feeling seemed like it might go on forever and I wouldn't be able to control my mind." Intravenous injection of diazepam relieved his anxiety, and in a few minutes he fell asleep. Another subject became anxious during the fifth injection (total dose 106 μg/kg) and asked not to receive any more.

Discussion

The THC dosages used in this study (to as much as 201 μg/kg) were deliberately large. Since THC has been proposed as an anesthetic adjuvant, we searched for doses causing hypnosis. Very large THC doses are needed to lower minimal anesthetic concentrations in animals. THC, 500 μg/kg administered intravenously in dogs and 1,000 μg/kg given intraperitoneally in rats significantly lowered anesthetic requirements, but 100 and 5000

μg/kg, respectively, do not.[10-11] Even larger doses may produce general anesthesia.[13] Our subjects would not tolerate such doses.

Mental and motor impairment occurs after 6 μg/kg THC inhaled by smoking.[25] Subjects of Perez-Reyes *et al.* perceived a drug "high" after 10 μg/kg THC intravenously.[4] Hollister and Gillespie infused as much as 6 mg intravenously and did not increase this dose because of its intense effects on mental state and heart rate.[18] Fifteen subjects of Johnson and Domino smoked marijuana cigarettes containing 30 mg THC; 14 reported they were "as high as or higher than ever before."[26] Smokers retain no more than 50 per cent of the THC content of a marijuana cigarette, even if they hold each breath 30 seconds or more.[27] Thus, our total intravenous THC dose of approximately 14 mg was as large as or larger than other reported doses.

THC is insoluble in water and is supplied by the NIMH in absolute ethanol. Total ethanol dose for our subjects was 158 mg/kg. Johnstone and Reier showed that ethanol (350 mg/kg intravenously) has no effect on heart rate, blood pressure, or ventilatory response to CO_2.[28] Although our administered ethanol dose was small, ethanol modification of THC effects is possible. Manno *et al.* found additive effects of THC (2.5 and 5 mg inhaled) and ethanol (521 mg/kg orally) on subjective sensations and pulse rate.[29] In rats, THC increases ethanol sleeping time and immobility in dose-related fashion.[30]

THC, 134 and 201 μg/kg, usually sedated our subjects without causing unconsciousness. They appeared partly dissociated from surrounding activity. They seemed calm and occasionally talked inappropriately. Their feelings, reported later, indicated considerable anxiety. Two of ten subjects dropped out before receiving all planned drug doses due to panic reactions during infusion, and each of these subjects worried about losing control over his mind. Subjects of Isbell *et al.* reported marked distortion of auditory and visual perceptions, derealization and hallucinations after large oral doses of THC.[31] Talbot and Teague observed 12 soldiers in Vietnam with acute toxic psychosis associated with environmental stress and cannabis derivatives.[32] Stress associated with our laboratory setting and invasive techniques may have caused or exaggerated anxiety. Several recent studies suggest that the psychologic effects of THC depend on the

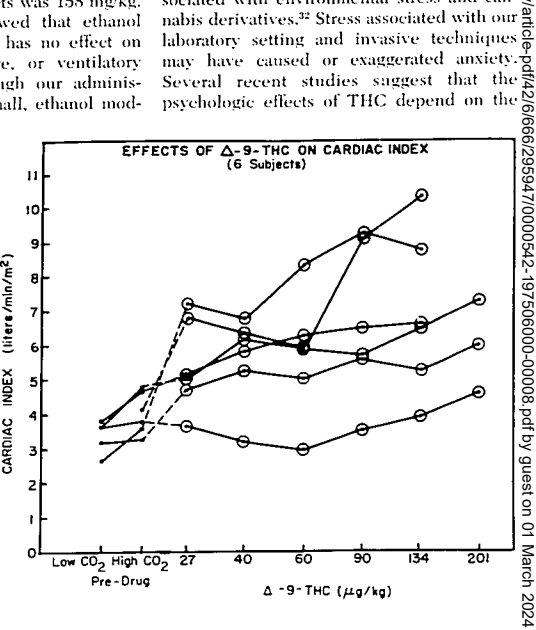

FIG. 4. Solid lines with small circles on the left show cardiac index responses to an increase in CO_2 from 41 ± 3 to 48 ± 2 torr before THC administration. Dashed lines represent responses to first THC dose while $P_{ET}CO_2$ was held constant at 48 torr. Solid lines with open circles show further dose–response information while $P_{ET}CO_2$ continued to be held constant.

expectations held by a subject and the setting in which the drug is taken.[33,34] In the research laboratory, subjects sometimes cannot differentiate social doses of THC from placebo.

THC causes respiratory depression and death in rats and mice after 27 to 49 mg/kg, intravenously.[35] Little depression occurred in our subjects at doses of as much as 200 μg/kg. THC displaced the CO_2 response curve about as much as morphine, 5 mg, intramuscularly.

Tachycardia was the most prominent physiologic effect. Heart rate exceeded 100 beats/min in five of six subjects and increased 50 beats/min above control values in two subjects. Wide intersubject variability was present, and the tachycardia was not regularly dose-related. Human studies have consistently shown increases in heart rate with THC, usually in a dose-dependent fashion.[36] Perez-Reyes measured a 25 per cent acceleration in HR after 22 μg/kg THC, intravenously.[4] Beaconsfield *et al.*[7] and Martz *et al.*[37] blocked the tachycardia induced by marijuana with propranolol, and Beaconsfield postulated beta-adrenergic stimulation as the mechanism. Johnson and Domino detected premature ventricular contractions in two of 15 subjects who had smoked 30 mg of marijuana.[26] Tachyarrhythmias may be the limiting toxicity of THC in human subjects who tolerate the psychologic effects.

Cardiac index and left ventricular minute work index increased as a result of the tachycardia. Mean arterial pressure increased slightly and total peripheral resistance decreased slightly. Weiss *et al.* measured increases in forearm blood flow and urinary excretion of epinephrine and a shortening of ventricular pre-ejection period after THC.[38] These cardiovascular effects are consistent with beta-adrenergic stimulation. However, the variability of individual responses is considerable, suggesting a direct dose-related sympathetic stimulation and an indirect, episodic activation secondary to psychologic arousal. Both share a final adrenergic pathway.

THC, 1 mg, intravenously, caused immediate unpleasant feelings before producing a pleasant high in two subjects of Lemberger *et al.*,[39] as well as in one of our subjects who received 27 μg/kg. Thus, although THC has little significant respiratory or cardiovascular toxicity at doses of as much as 201 μg/kg, it offers little promise as an ataractic drug, even in reduced dose. THC is also unsuitable as a general anesthetic because its duration of action is prolonged, a rapid reversal technique does not presently exist, and unpleasant psychologic effects occur before sleep. On the other hand, in doses likely to be inhaled by marijuana smokers, no serious derangement of cardiovascular or respiratory function occurred. The "direct effects" of THC on respiration and circulation, *i.e.*, those with clear dose–response relations, were small in magnitude compared with the "indirect effect," presumably due to panic reactions. It is possible that these effects could be moderated with other drugs.

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