The Effects of Delta-9-Tetrahydrocannabinol (Cannabis) on Cardiac Performance with and without Beta Blockade

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SUMMARY Systolic time intervals (STI) were measured in ten healthy male volunteers before and after intravenous (i.v.) administration of 25 μg/kg delta-9-tetrahydrocannabinol (Δ-9-THC). Mean ± SEM heart rate increased 32 ± 7 beats/min, while systolic and diastolic blood pressures were unchanged after Δ-9-THC. Total electromechanical systole lengthened 17 ± 4.2 msec, left ventricular ejection time (LVET) prolonged 24 ± 4.0 msec and pre-ejection period (PEP) shortened 17 ± 5.1 msec after Δ-9-THC. All these changes were significant (P < 0.01). In nine other subjects who underwent prior beta adrenergic blockade, similar but less marked changes were noted in heart rate, blood pressure, and STI after Δ-9-THC. The shortening of PEP after Δ-9-THC was only 9 msec (NS) in beta blocked subjects.

Thus, Δ-9-THC significantly increased heart rate, shortened PEP and prolonged LVET, without any change in afterload. Beta adrenergic blockade prevented significant shortening of PEP and blunted other responses. These findings suggest that Δ-9-THC enhanced cardiac performance. Partial inhibition of this effect was achieved with prior beta adrenergic blockade.

THE USE OF MARIJUANA is quite common among young adults in the United States. The exact prevalence varies according to geographical location, age, and education level, but a conservative estimate of prevalence of marijuana use among college age youths is approximately 25%.

Despite this widespread use of marijuana, relatively few studies of the physiological effects, especially the cardiovascular effects, of marijuana in man have been published.

The active ingredient present in marijuana is levo delta-9-tetrahydrocannabinol (Δ-9-THC),1,4 although its metabolite 11-OH-Δ-9-THC is probably the active compound in the body.4 Before the availability of pure Δ-9-THC, pharmacologic studies concerning the effects of cannabis were difficult. Now, however, pharmacologic study has been facilitated.

A detailed, systematic study of the effects of Δ-9-THC on the resting systolic time intervals in man has not been published, although shortening of the pre-ejection period (PEP) has been previously reported.4 The purpose of this study was to investigate the cardiovascular effects of intravenously administered Δ-9-THC in man, utilizing serial determinations of the left ventricular systolic time intervals and arterial pressures, and to determine whether the effects of the agent could be altered by beta adrenergic blockade.

Material and Methods

Δ-9-THC dissolved in ethanol was obtained from the National Institute of Mental Health, Center for Drug Study. It was made suitable for human intravenous use by the University of Illinois, College of Pharmacy, Manufacturing Division, by aseptic preparation and dissolving in absolute alcohol with a final concentration of 1 mg Δ-9-THC/ml. The dose administered was 25μg/kg, which for a 75–80 kg person would deliver a dose of Δ-9-THC approximately equivalent to smoking one marijuana cigarette containing 5 mg Δ-9-THC.

All subjects were normal male volunteers between the ages of 22 and 30. Prerequisites for admission to the study were a negative history of cardiovascular disease, a normal physical examination of the cardiovascular system, a normal electrocardiogram (ECG), a normal chest X-ray, a satisfactory score on the Millon Illinois self-report inventory which screens for psychotic potential, and frequency of marijuana use less than once per week. Three of the subjects had never used cannabis. All subjects gave written informed consent. The experimental protocol was approved by the Human Investigation Committee of the University of Illinois.

Protocol

The subjects were studied in the basal fasting state in the supine position. A bipolar electrocardiographic lead was obtained across the anterior thorax with the negative electrode in the second intercostal space at the right mid clavicular line and the positive electrode in the fifth intercostal space at the left anterior axillary line. A contact microphone was placed over the third intercostal space at the left sternal border and was strapped firmly to the chest. The indirect carotid pulse tracing was obtained with a pulse pick-up held manually over the right carotid artery in the neck and connected to a modified amplifier channel of the Electronics for Medicine recorder. The time constant of the pulse recording system used was 1.5 sec, which has been shown to be adequate for recordings with no significant time phase shifts and distortion.4 The electrocardiogram, phonocardiogram, and indirect carotid pulse tracings were recorded simultaneously at 100 mm/sec paper speed with 20 msec time lines on an Electronics for Medicine multichannel photographic recorder. The arterial pressure was measured with a cuff sphygmomanometer on the right arm.

A 21-gauge scalp vein needle was inserted into a vein on the dorsum of the left hand and 5% dextrose in water solution allowed to drip through plastic tubing which had an in-
jection site out of sight of the subjects; thus medication was injected without the subjects knowing the time of injection. All studies were carried out in a quiet room with subdued lighting.

Total electromechanical systole or QS2 interval was measured from the onset of the Q wave of the electrocardiogram to the first high frequency component of the second heart sound. Left ventricular ejection time (LVET) was measured from the onset of the rapid rise of the carotid pulse tracing to the trough of its incisura. The pre-ejection period (PEP) was obtained by subtracting the LVET from the QS2 interval. All intervals were determined as the average of measurements of ten consecutive beats, each read to the nearest 5 msec. Heart rate was derived by dividing the average R-R interval into 60. The LVET and QS2 intervals were corrected for the effects of heart rate by using the regression equations developed by Weissler and will be referred to as LVETc and QS2c. The pre-ejection period was not corrected for heart rate because of previous studies with right atrial pacing and atropine showing that changes in heart rate by themselves do not alter the pre-ejection period.10, 11

After a 15-minute rest period, three sets of recordings and measurements of systolic time intervals and arterial blood pressure were obtained at five-minute intervals. The average of these is reported as control measurements. In ten subjects (group A), Δ-9-THC was then administered at a rate of 1 mg/min through the tubing of the i.v. infusion set. Systolic time intervals and arterial blood pressure were recorded at 5, 10, 15, 30, 60, 90, and 120 minutes after drug administration. If a striking change in heart rate was noted on the heart rate meter at times other than the standard recording intervals, additional measurements were made. This occurred only twice.

In nine other age-matched subjects (group B), 0.1 mg/kg propranolol was injected intravenously after resting control measurements which were repeated 5, 6, and 7 minutes after completion of the propranolol injection. Δ-9-THC was then administered and post Δ-9-THC measurements of systolic time intervals and blood pressure obtained similar to group A.

In eight subjects receiving propranolol, adequacy of beta adrenergic blockade was demonstrated at the termination of the study by infusion of isoproterenol at a rate of 2.5 μg/min for five minutes, without demonstrable effect on heart rate.

Control values for systolic time intervals and blood pressure (group A) and post-propranolol values (group B) were compared to peak responses after Δ-9-THC, using standard statistical methods.

Results

The time course of action of Δ-9-THC in subject 8 (table 1) is shown in figure 1. Peak changes in systolic time intervals coincided with peak changes in heart rate. In all cases, peak effects of Δ-9-THC occurred between 5 and 25

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Abbreviations: CON = control; THC = post Δ-9-THC; HR = heart rate; DBP = diastolic blood pressure; SBP = systolic blood pressure.
minutes. The total duration of action, as determined by heart rate, was variable. Return to control heart rates occurred from 30 to 120 minutes (mean 90 min) after Δ-9-THC administration.

Table 2 lists heart rate, blood pressure, and STI of the ten subjects before and after Δ-9-THC administration. Control values reflect the mean of three sets of determinations. Mean ± SEM changes in heart rate and blood pressure in the non-beta adrenergic blocked subjects receiving Δ-9-THC are illustrated in figure 2. Mean heart rate increased 32 ± 7 beats/min (BPM) (P < 0.001), while systolic and diastolic pressures did not change significantly after drug administration. Mean STI before and after Δ-9-THC are illustrated in figure 3. Mean Q2c lengthened 17 ± 2 msc. Mean LVETc lengthened 24 ± 4 msc and PEP shortened 19 ± 5 msc. All these changes were significant at the 1% level or less.

Table 2 lists heart rate, blood pressure, and STI in the nine subjects with beta adrenergic blockade before Δ-9-THC administration. Determinations represent the mean of three sets of resting values obtained five, six and seven minutes after propranolol administration. The post-Δ-9-THC values are again peak responses. The effects of propranolol on mean heart rate, blood pressure and selected STI are illustrated in figure 4. As expected, propranolol caused slight but significant decreases in heart rate and systolic blood pressure, and increases in QS2 and PEP. The change in LVETc after propranolol was not significant.

The effects of Δ-9-THC on mean heart rate and blood pressure in the beta adrenergic blocked subjects are illustrated in figure 5. The heart rate increase after Δ-9-THC was 19 ± 1.8 BPM, (P < 0.001), while the effects on blood pressures were insignificant. The effects of Δ-9-THC on mean STI in the beta adrenergic blocked subjects are illustrated in figure 6. Q2c and LVETc prolonged an average of 15 ± 3.8 msc and 14 ± 3.4 msc, respectively (P < 0.001 and < 0.01). PEP shortened only 7 msc (NS).

Figure 7 compares the changes in heart rates and STI after Δ-9-THC in subjects with and without prior beta adrenergic blockade. The directional changes in heart rate, Q2c, PEP, and LVETc after Δ-9-THC were not altered by beta adrenergic blockade although the magnitude of the changes was less in the group with prior beta adrenergic blockade. Except for the difference in PEP, these changes were not statistically different.

**Discussion**

At rest, the systolic time interval measurements in both groups of subjects were well within the normal range.12, 13 After beta adrenergic blockade in group B subjects, heart rate and systolic arterial blood pressure decreased slightly but significantly, while PEP and Q2c lengthened. These effects were quite consistent with the known pharmacologic actions of beta adrenergic blockade on the cardiovascular system.14 The failure of LVETc to change significantly after propranolol was not altogether surprising. By decreasing cardiac inotropy and velocity of contraction during ejection, beta adrenergic blockade would tend to cause prolongation of LVETc. On the other hand, a simultaneous reduction in cardiac output and stroke volume would tend to shorten the ejection time. These two opposing effects may offset each other, leaving an essentially unchanged LVETc.

Intravenously administered Δ-9-THC in a dose approximating that delivered by smoking one marijuana cigarette significantly increased heart rate, shortened PEP and lengthened LVETc, without any change in arterial pressure or afterload. These effects became maximally evident 5-25 minutes after drug administration, suggesting, in accordance with previous studies, that the phar-
The major determinants of the systolic phases of the left ventricle have been well studied. Shortening of the pre-ejection period may be due to an accelerated rate of rise of the left ventricular pressure and cardiac performance, small alterations in LVEDP do not appreciably change the pre-ejection period or the true isovolumic contraction time. Marked increases in LVEDP, when they occur, tend to reflect a deterioration in left ventricular performance; under these circumstances the PEP lengthens, due to the predominant effect of a reduced rate of force development by the left ventricle. Finally, preliminary hemodynamic observations in our laboratory have shown a decrease or no change in LVEDP after Δ-9-THC (unpublished observations). It seems reasonable, therefore, to conclude that shortening of the pre-ejection period after Δ-9-THC reflected an enhancement of cardiac performance, manifested by an increase in the rate of rise of isovolumic pressure.

When corrected for the effects of heart rate, the duration of left ventricular ejection varies directly with afterload, with venous return, stroke volume or cardiac output, and inversely with myocardial inotropy. Thus, in any given case, the duration of left ventricular ejection is determined by the interplay of these factors.

As previously stated, our subjects showed no significant change in systolic or diastolic arterial blood pressure after Δ-9-THC, and were all healthy young volunteers with normal heart size. There was, therefore, no increase in afterload. With afterload remaining constant, and a directional change in PEP consistent with an increased rate of isovolumic pressure rise, the most reasonable explanation for prolongation of LVET, in our subjects is that it must be caused by an increased venous return with a concomitant increase in cardiac output and stroke volume. This increase in preload, operating through the Starling mechanism, could perhaps explain the enhanced cardiac performance manifested by shortening of the pre-ejection period, without having to postulate a direct inotropic effect of Δ-9-THC, for which there is no current evidence.

Previous studies of the cardiovascular effects of Δ-9-THC have given somewhat conflicting results and are difficult to interpret. This is probably due in part to differences in experimental design, species, and dose and route of Δ-9-THC administration. Several previous human studies are relevant to the present investigation. Beaconsfield et al., investigating the effects of cannabis on human volunteers without prior marijuana experience, demonstrated marked sinus tachycardia and a pronounced increase in peripheral blood flow without change in arterial pressure. Weiss et al., studying the effects of oral Δ-9-THC on young healthy male volunteers, also showed marked shortening of the pre-ejection period, slight increase in mean blood pressure, increased heart rate and increased forearm blood flow, as well as forearm vascular conductance. In a letter to the editor, Goodeday and Perloff found in a chronic marijuana user greater heart rate and cardiac output and a greater drop in peripheral resistance during exercise after smoking two marijuana cigarettes. These and other studies suggest decreased vascular resistance and/or increased peripheral blood flow in man after exposure to cannabis.

It has been suggested that these effects are probably mediated by increased sympathetic activity induced by Δ-9-THC. Thus, Bright et al. and Beaconsfield et al. reported abolition of marijuana-induced tachycardia in man after beta adrenergic blockade. Beaconsfield gave his subjects 160 mg oral propranolol per day for 48 hours prior to marijuana smoking. Weiss et al. also showed in their study increased urinary excretion of epinephrine after Δ-9-THC.

It is therefore likely that increased sympathetic activity secondary to Δ-9-THC accounts for all or part of our results. This increase could reflect either reflex mechanisms secondary to decrease in peripheral resistance and/or direct central nervous system stimulation. With either of these latter mechanisms, it is possible that vagal withdrawal may
also being occurring, resulting in atropine like effects. It should be pointed out that isolated nonmyelinated rabbit vagus nerve fibers show a decrease in size of compound action potential with exposure to Δ-9-THC.  

Since changes in heart rate and systolic time intervals occur simultaneously, it is likely that these are caused by similar mechanisms. The possibility that these changes reflect different mechanisms cannot be excluded. In order to further examine these possibilities, nine subjects (group B) were studied after beta adrenergic blockade. As shown in table 2 and figure 7, significant increases in heart rate, LVETc and Q2c still occurred after Δ-9-THC in these subjects. Shortening of the PEP, however, was no longer significant. These results suggest that while Δ-9-THC induced beta adrenergic stimulation is undoubtedly present to some degree (abolation of PEP shortening and attenuation of other STI responses after propranolol), it does not account for all of the changes observed in this study. It is possible that the dosage of propranolol received by our subjects was insufficient to suppress intense beta adrenergic stimulation resulting from Δ-9-THC administration.

We conclude that intravenous Δ-9-THC in a dose approximating that delivered by one marijuana cigarette significantly increases heart rate, LVETc, Q2c, and shortens PEP without any change in systolic or diastolic arterial pressure. The exact pharmacological mechanism or mechanisms responsible for these changes need further definition utilizing other noninvasive techniques such as echocardiography, as well as possibly direct hemodynamic investigation.

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