Bronchial Effects of Aerosolized \( \Delta 9 \)-Tetrahydrocannabinol in Healthy and Asthmatic Subjects

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SUMMARY

Effects on airway dynamics, heart rate, and the central nervous system of various doses of \( \Delta 9 \)-tetrahydrocannabinol administered in a random, double blind fashion using a Freon\(^\circledR\)-propelled, metered-dose nebulizer were evaluated in 11 healthy men and 5 asthmatic subjects. Effects of aerosolized \( \Delta 9 \)-tetrahydrocannabinol were compared with aerosolized placebo and isoproterenol and with 20 mg of oral and smoked \( \Delta 9 \)-tetrahydrocannabinol. In the normal subjects, after 5 to 20 mg of aerosolized \( \Delta 9 \)-tetrahydrocannabinol, specific airway conductance increased immediately, reached a maximum (33 to 41 per cent increase) after 1 to 2 hours, and remained significantly greater than placebo values for 2 to 3 hours. The bronchodilator effect of aerosolized \( \Delta 9 \)-tetrahydrocannabinol was less than that of isoproterenol after 5 min, but significantly greater than that of isoproterenol after 1 to 3 hours. The magnitude of bronchodilatation after all doses of aerosolized \( \Delta 9 \)-tetrahydrocannabinol was comparable, but 5 mg of \( \Delta 9 \)-tetrahydrocannabinol caused a significantly smaller increase in heart rate and level of intoxication than the 20-mg dose. Smoked \( \Delta 9 \)-tetrahydrocannabinol produced greater cardiac and intoxicating effects than either aerosolized or oral \( \Delta 9 \)-tetrahydrocannabinol. Side effects of aerosolized \( \Delta 9 \)-tetrahydrocannabinol included slight cough and/or chest discomfort in 3 of the 11 normal subjects. Aerosolized \( \Delta 9 \)-tetrahydrocannabinol caused significant bronchodilatation in 3 of 5 asthmatic subjects, but caused moderate to severe bronchoconstriction associated with cough and chest discomfort in the other 2. These findings indicate that aerosolized \( \Delta 9 \)-tetrahydrocannabinol, although capable of causing significant bronchodilatation with minimal systemic side effects, has a local irritating effect on the airways, which may make it unsuitable for therapeutic use.

Introduction

Previous studies have demonstrated that the smoking of marijuana or the ingestion of its principle psychoactive ingredient, \( \Delta 9 \)-tetrahydrocannabinol (\( \Delta 9 \)-THC), causes acute bronchodilatation both in healthy young men (1, 2) and in patients with either chronic, stable bronchial asthma (3) or experimentally induced bronchospasm (4). The mechanism of \( \Delta 9 \)-THC-induced bronchodilatation has been shown not to be due to a sympathomimetic or atropine-like effect (5). This suggests that cannabinoid compounds may have therapeutic utility, because they appear to relax bronchial smooth muscle

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by a mechanism different from that of currently available bronchodilator agents. Smoking would not appear to be a satisfactory route of administration of Δ9-THC for possible therapeutic purposes, however, in view of the potential of smoked marijuana for depressing alveolar macrophage bactericidal activity (6) and for causing bronchial irritation and impaired airway dynamics in heavy users (7, 8). Oral Δ9-THC, although capable of causing significant, prolonged bronchodilatation in man (2, 3), is also not suitable for therapeutic use, because of unwanted psychotropic and cardiovascular effects. The possibility was considered that inhalation of pure Δ9-THC as an aerosol might have potentially useful therapeutic advantages over smoked marijuana by causing less irritation of the airways than the smoked plant material. In addition, it was believed that aerosolized Δ9-THC might have advantages over both smoked marijuana and oral Δ9-THC, by producing more bronchodilatation by topical action while minimizing systemic physiologic effects. In the present study, the cardiopulmonary effects, intoxicating influence, and side effects of various doses of aerosolized Δ9-THC were evaluated both in healthy men and in asthmatic subjects. In addition, the effects of aerosolized Δ9-THC were compared with those of a comparable quantity of smoked or ingested Δ9-THC.

Materials and Methods

Healthy subjects. Eleven young, male, experienced marijuana smokers 22 to 33 years of age and without evidence of significant medical, pulmonary, or psychiatric disease were studied on 7 separate days with at least 48 hours intervening between each study day. On the first study day, a medical, psychiatric, and drug-use history, a detailed questionnaire concerning respiratory symptoms, a physical examination, a 12-lead electrocardiogram, and a battery of pulmonary function tests were administered. The latter included spirometry, with calculation of forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1), and forced expiratory flow during the middle half of the FVC (FEF25-75%); single-breath diffusing capacity for CO (DLco) (9); and whole-body plethysmographic measurements of airway resistance (Raw), thoracic gas volume (Vtg), and specific airway conductance (SGaw), calculated as the ratio of the reciprocal of Raw to the simultaneously measured Vtg (10-12). Spirometric and plethysmographic measurements were repeated at serial intervals after inhalation of a standard therapeutic dose (1.25 mg) of isoproterenol for comparison with results of subsequent administration of Δ9-THC by aerosol, smoking, and ingestion.

During the remaining 6 study days, subjects inhaled 0, 5, 10, or 20 mg of synthetic Δ9-THC as an aerosol; smoked a cigarette containing 900 mg of marijuana assayed at 2.2 per cent Δ9-THC, or ingested 20 mg of synthetic Δ9-THC dissolved in sesame oil within a gelatin capsule. The order in which the various test preparations were administered was randomized in a crossover fashion, and administration of the various doses of aerosolized Δ9-THC was double blind. The aerosol device consisted of a 15-ml capacity cannister fitted with a 0.067-ml metered-dose valve (Emson Research, Inc., Bridgeport, Conn.) and containing various quantities of Δ9-THC dissolved in 6 ml of ethyl alcohol (U.S.P.), 3 ml of alcohol (U.S.P.), 0.068 g of sorbitan trioleate (detacifer), 5 g of difluorodichloromethane (propellant 12), and 2.5 g of tetrafluoro dichloroethane (propellant 114) (13). Four aerosol preparations were used: one did not contain Δ9-THC (placebo), and the other 3 delivered 0.5, 1, and 2 mg of Δ9-THC per actuation, respectively. On the days when subjects were scheduled to receive aerosol preparations, they exhaled to near residual volume, wrapped their lips around the mouth-piece of the nebulizer, inspired deeply while activating the nebulizer, and held their breath for several seconds. This procedure was repeated 10 times at 30-sec intervals, so that subjects inhaled a total dose of 0, 5, 10, or 20 mg of Δ9-THC, depending on which aerosol preparation was used.

On each test day, subjects were studied beginning at approximately 9 A.M., after an overnight fast and after having refrained from use of cannabis or other drugs for more than 12 hours. Measurements consisted of systolic and diastolic blood pressure, heart rate, respiratory rate, spirometry (FVC, FEV1, and FEF25-75%), and plethysmography (Raw, Vtg, and SGaw). In addition, a catheter was inserted into a peripheral vein to obtain serial 1-ml samples of blood for subsequent determination of plasma concentrations of Δ9-THC and metabolites. Two sets of control measurements 15 min apart were obtained before administration of the scheduled drug preparation, and measurements and blood sampling were repeated at 5, 15, 30, 60, 90, and 120 min and hourly thereafter until 6 hours after drug administration. In addition, at each measurement period, subjects were asked to rate their level of intoxication, or "high," on a scale of 0 to 7, the latter representing the maximal "high" they had ever experienced in the past. They were also asked to indicate whether or not they experienced any other unusual reactions after drug administration, such as dryness of the mouth or throat, bronchial irritation, cough, discomfort in the chest, or nausea.

After completion of studies in the healthy subjects, the effects of aerosolized Δ9-THC were also evaluated in 5 patients with clinically stable bron-
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chial asthma. The asthmatic subjects consisted of 3 men and 2 women 31 to 64 years of age. Four of the asthmatic subjects had used cannabis in the past; however, 2 of these 4 subjects had sampled marijuana only in conjunction with previous studies of the bronchial effects of Δ9-THC (3, 4). The asthmatic subjects were studied using a protocol identical to that followed for the healthy subjects, except that smoked marijuana, oral Δ9-THC, and the aerosol preparation delivering 20 mg of Δ9-THC were omitted, and venous blood samples were not obtained. In addition, the asthmatic subjects were requested not to take oral or inhaled bronchodilator medication for 8 hours and 4 hours, respectively, before study. None of the asthmatic subjects was on corticosteroids or disodium cromoglycate therapy at the time of the study.

Calculations. The 2 sets of baseline control measurements on any study day were averaged for each subject. At each time interval after drug administration, post-drug measurements were calculated as percentage changes from the mean control values.

Results

Normal subjects. Mean anthropometric and baseline pulmonary function data are indicated in Table 1. All subjects smoked marijuana at least occasionally, and 5 subjects did not smoke tobacco. All subjects had normal baseline lung function.

Aerosolized, oral, and smoked Δ9-THC resulted in no detectable changes in systolic, diastolic, or mean blood pressure, respiratory rate, or FVC. Spirometric flows (FEV₁ and FEF₂₅₋₇₅%) increased significantly 15 min to 2 hours after smoked marijuana and 15 min to 3 hours after all doses of aerosolized Δ9-THC, but not after either placebo aerosol or oral Δ9-THC. Peak increases in FEV₁ after 5 to 20 mg of aerosolized Δ9-THC ranged from 6.4 to 7.8 per cent greater than baseline values. Peak increases in FEF₂₅₋₇₅% after 5 to 20 mg of aerosolized Δ9-THC ranged from 17.4 to 19.1 per cent more than baseline values. These increases in flows were significantly greater than the changes after placebo aerosol. No significant differences were observed among increases in spirometric flows after various doses of aerosolized Δ9-THC or between aerosolized Δ9-THC and smoked marijuana.

The changes in SGaw at various times after the different doses of aerosolized THC and after 1.25 mg of isoproterenol are shown in figure 1. Small, but significant, mean increases in SGaw (9 to 21 per cent) were noted 1 to 6 hours after placebo aerosol compared with baseline, pre-drug values. After 5 to 20 mg of aerosolized Δ9-THC, SGaw increased immediately, was maximal at 1 to 2 hours, and remained signific-

TABLE 1

<table>
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<tr>
<th>Subjects</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (inches)</th>
<th>FVC (% pred.)</th>
<th>FEV₁ (% pred.)</th>
<th>FEF₂₅₋₇₅% (% pred.)</th>
<th>SGaw† (liter/sec/cm H₂O/liter)</th>
<th>DLCO (% pred.)</th>
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Definition of abbreviations: FVC = forced vital capacity; FEV₁ = forced expiratory volume in 1 sec; FEF₂₅₋₇₅% = forced expiratory flow during the middle half of the FVC; SGaw = specific airway conductance; DLCO = diffusing capacity of the lung for CO; % pred. = per cent of the predicted value.

*Predicted values for spirometric indices and for DLCO are based on the regression equations of Morris and associates (14) and of Cotes (15), respectively.

†Normal values ≥ 0.15 liter/sec/cm H₂O/liter based on data from our laboratory.
cantly greater than baseline values for 5 to 6 hours and greater than placebo values for 3 to 5 hours (figure 1). Although the mean changes after the largest dose of Δ9-THC were generally greater than those after the smaller doses, these differences were not significant. The mean increases in SGaw after isoproterenol were greater than or comparable to those after aerosolized Δ9-THC at 5 to 30 min, but were significantly less than those after Δ9-THC at subsequent time intervals.

Comparison of the changes in SGaw after 20 mg of smoked, aerosolized, and oral Δ9-THC is shown in figure 2. After both smoked and aerosolized Δ9-THC, SGaw increased immediately and remained significantly greater than values after oral Δ9-THC for 1 hour. The SGaw increased significantly 1 hour after ingestion of Δ9-THC and remained increased for 6 hours. After 1 hour, the changes in SGaw that followed smoked marijuana decreased progressively and were significantly less than the changes that followed aerosolized and oral Δ9-THC at 3 to 6 hours.

The effects of various doses of aerosolized Δ9-THC, 1.25 mg of isoproterenol, 20 mg of smoked Δ9-THC, and 20 mg of oral Δ9-THC on heart rate are shown in figure 3. After placebo aerosol, heart rate decreased slightly. Aerosolized Δ9-THC resulted in significant increases in heart rate, with maximal increases (9 to 13 per cent) occurring 5 min after inhalation. Heart rate returned to values not significantly different from placebo 30 min after 5 mg, and 90 and 120 min after 10 and 20 mg of Δ9-THC, respectively. A late increase in heart rate occurred 5 to 6 hours after 20 mg of Δ9-THC. A dose-response effect was noted, in that pulse increments after 20 mg of Δ9-THC were significantly greater than those after 5 and 10 mg of Δ9-THC at 5 to 90 min. After isoproterenol, heart rate increased significantly only at 5 min. After oral Δ9-THC, heart rate did not change. The changes in heart rate during the first 30 min after both smoked and aerosolized Δ9-THC were significantly greater than those after 5 and 10 mg of Δ9-THC at 5 to 90 min. After isoproterenol, heart rate increased significantly only at 5 min. After oral Δ9-THC, heart rate did not change. The changes in heart rate during the first 30 min after both smoked and aerosolized Δ9-THC were significantly greater than those after oral Δ9-THC, and the increases in heart rate after smoked marijuana significantly exceeded those after aerosolized Δ9-THC.

Effects of aerosolized, smoked, and oral Δ9-THC on subjective "high" are shown in figure 4. No significant "high" was experienced after placebo aerosol. The slight "high" reported after 5 and 10 mg of Δ9-THC persisted for as long as 3 hours. After 20 mg of Δ9-THC, the "high" was significantly greater than that observed after 5 or 10 mg of Δ9-THC, most often 15 to 240 min after inhalation of the aerosol. During the

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Fig. 1. Mean percentage changes (% Δ) in specific airway conductance with time, after 1.25 mg of isoproterenol, and after 0, 5, 10, and 20 mg of aerosolized Δ9-tetrahydrocannabinol (Δ9-THC) in 11 normal subjects. Vertical bars represent 1 SEM.
first hour after smoked Δ9-THC, the "high" experienced was significantly greater than that after aerosolized or oral Δ9-THC, and the "high" experienced after aerosolized Δ9-THC was significantly greater than that after oral Δ9-THC. Subsequently, the intoxicating effects of Δ9-THC administered by all 3 routes were comparable.

Aside from a pleasant feeling of intoxication and slight dryness of the throat in one subject after smoking, no other side effects were reported after smoked marijuana or oral Δ9-THC. Only 2 subjects reported side effects after placebo aerosol (dry mouth and moderate throat irritation). No adverse side effects of aerosolized Δ9-THC were volunteered by 7 of the 11 subjects on direct questioning. Reported side effects after 5 to 20 mg of aerosolized Δ9-THC included slight to moderate throat irritation in 4 subjects, dry mouth in one subject, bronchial irritation in 3 subjects, slight chest discomfort in 2 subjects, slight cough in 3 subjects, and moderate nausea in one subject. Most reported side effects occurred within 5 min of inhalation of the aerosol, subsided within 15 min, and were of a similar magnitude after all doses of aerosolized Δ9-THC.

Blood concentrations of Δ9-THC and metabolites after aerosolization of various doses of Δ9-THC and after the smoking and ingestion of 20 mg of Δ9-THC are not yet available.

**Asthmatic subjects.** Anthropometric and baseline physiologic data for the asthmatic subjects are indicated in Table 1. The asthmatic subjects had mild to moderately severe airway obstruction (FEV1 values 74 to 46 per cent of predicted) without evidence of diffusion impairment. The plethysmographic responses of each asthmatic subject to 1.25 mg of nebulized isoproterenol and 0 (placebo), 5, and 10 mg of aerosolized Δ9-THC are shown in figure 5. The presence of reversible bronchospasm was documented by increases in SGaw of 24 to 185 per cent (mean increase, 119 per cent) within 30 min of inhalation of isoproterenol. After placebo aerosol, SGaw showed little change in 3 subjects, increased moderately in one subject, and decreased in another subject. After 5 and 10 mg of aerosolized Δ9-THC, 2 subjects developed moderate to severe bronchospasm, requiring dis-
Fig. 3. Mean percentage changes (% Δ) in heart rate with time, after 1.25 mg of isoproterenol, and after 0, 5, 10, and 20 mg of aerosolized Δ⁹-THC (Δ⁹-THC), 20 mg of smoked Δ⁹-THC, and 20 mg of oral Δ⁹-THC in 11 normal subjects. Vertical bars indicate 1 SEM.

Fig. 4. Average subjective level of intoxication, or "high," at various times after 0, 5, 10, and 20 mg of aerosolized Δ⁹-THC (Δ⁹-THC), 20 mg of smoked Δ⁹-THC, and 20 mg of oral Δ⁹-THC in 11 normal subjects.
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Fig. 5. Specific airway conductance, in liter/sec per cm H2O/liter, as a function of time after 0, 5, and 10 mg of aerosolized Δ9-tetrahydrocannabinol (Δ9-THC), and after 1.25 mg of isoproterenol in 5 asthmatic subjects.

continuation of the study after 0.5 to 2 hours in one of these patients. On the other hand, in the other 3 subjects, both doses of aerosolized Δ9-THC resulted in marked bronchodilatation (maximal increases in SGaw of 100 to 252 per cent above control values).

The effects of isoproterenol and 0 to 10 mg of aerosolized Δ9-THC on FEV1 in the asthmatic subjects are shown in figure 6. All subjects demonstrated a 10 per cent or greater initial increase in FEV1 after isoproterenol. Placebo aerosol was followed by little change in FEV1 in 3 subjects, an early decrease in FEV1 in one subject, and a sustained increase in FEV1 in the remaining subject. Both doses of aerosolized Δ9-THC caused modest to moderate, sustained increases in FEV1 in 3 subjects, a slight decrease in FEV1 in one subject, and a moderate decrease in FEV1 in the remaining subject. Adverse side effects of nebulized Δ9-THC in the asthmatic subjects included, in addition to bronchospasm, mild to severe throat constriction, dry mouth, and chest discomfort in 2 subjects, and cough in 4 subjects. The 2 patients in whom bronchospasm developed exhibited the worst cough and were the only ones who complained of chest discomfort. These side effects were noted within 5 min of inhalation of the aerosol and persisted for 15 min after the 5-mg dose and for as long as 120 min after the 10-mg dose, although symptoms persisting beyond 15 min were of only mild severity.

Discussion
The development of significant physiologic changes after inhalation of aerosolized Δ9-THC indicates that Δ9-THC can be effectively administered by this route. The finding of cardiac and psychologic, as well as bronchial, effects indicates that the administered Δ9-THC was systemically absorbed after inhalation of the aerosol. Systemic absorption of Δ9-THC probably occurred at least partially from the respiratory tract and/or oropharyngeal cavity, because systemic effects were noted almost immediately after aerosolization of the drug, compared with
the delay in onset of psychophysiologic effects after ingestion of orally administered Δ9-THC. On the other hand, some aerosolized Δ9-THC may have been absorbed across the gut after swallowing of pharyngeally deposited aerosol, because cardiac effects tended to be greater 2 to 6 hours after aerosolized Δ9-THC compared with effects noted during the same time period after smoking the same quantity of Δ9-THC. This possibility is also suggested by previous findings indicating gastrointestinal absorption of a major fraction of nebulized, radiolabeled isoproterenol (16). The relatively short duration of systemic effects after nebulized isoproterenol, in contrast to aerosolized Δ9-THC, is probably due to the rapid conversion of isoproterenol to inactive metabolites after absorption (16), in contrast to the metabolism of Δ9-THC to active compounds (17).

In the small number of subjects studied, changes in SGaw did not appear to be related to the dose of inhaled drug, whereas the changes in heart rate and “high” were dose dependent. It is of interest that the smallest dose of aerosolized Δ9-THC (5 mg) resulted in a peak bronchodilator effect approximating 80 per cent of that after 20 mg of Δ9-THC and 72 per cent of that after 1.25 mg of isoproterenol. In addition, the bronchodilator effect of 5 mg of Δ9-THC was longer-lasting than that of isoproterenol (5 hours versus 30 min). Moreover, the bronchodilatation after 5 mg of aerosolized Δ9-THC was accompanied by only a modest (8 per cent), short-lived (15-min) increase in heart rate and no significant “high,” in contrast to significant cardiac changes of 1 to 2 hours’ duration after 10 to 20 mg of aerosolized Δ9-THC and a “high” lasting 6 hours after the 20-mg dose. The 8 to 16 per cent increase in SGaw 1 to 6 hours after placebo aerosol may represent diurnal variation (18) and underscores the need for placebo control measurements even in normal subjects.

Comparison of the same dose of Δ9-THC administered by smoking, by aerosol, and by ingestion revealed a comparable speed of onset and peak bronchodilator effect of the aerosolized and smoked drug, in contrast to a slower onset and smaller peak bronchodilatation after oral Δ9-THC. The duration of bronchodilatation after aerosolized Δ9-THC was comparable to that after oral Δ9-THC, but longer than that after smoked marijuana. The pulse increments and “high” were greater after smoked marijuana than after aerosolized Δ9-THC and greater after aerosolized Δ9-THC than after oral Δ9-THC during at least the first 30 min after drug administration.

These findings in healthy subjects suggest possible therapeutic advantages of aerosolized Δ9-THC, particularly in low doses (5 mg), over both smoked and orally administered Δ9-THC, with respect to the greater magnitude, speed of onset, and duration of bronchodilatation and the lesser cardiac and central nervous system effects; however, the throat and chest discomfort associated with inhalation of aerosolized Δ9-THC suggests that the relatively large particles of Δ9-THC generated by our Freon-propelled nebulizer were deposited in the upper and central airways, causing mucosal irritation. This irritating effect on the airways of normal subjects produced only minimal discomfort and did not prevent the development of significant bronchodilatation in these persons with normally reactive airways. On the other hand, in the 5 asthmatic subjects studied, aerosolized Δ9-THC resulted in more frequent and severe cough and chest discomfort than was observed in the healthy subjects and caused moderate to severe bronchoconstriction in 2 of the asthmatic subjects, although marked bronchodilatation was noted in the other 3.

The observations described suggest that aerosolized Δ9-THC may be unsuitable for therapeutic use in patients with bronchospastic dis-
ease; however, in preliminary studies involving a few asthmatic subjects, Vachon and associates (19) have minimized bronchial irritation by nebulizing a solution containing a small concentration of Δ9-THC (1.25 per cent) using a cascade-type of aerosol delivery device, which produced particles with a mean aerodynamic diameter of 2 μm, and none more than 5 μm, presumably minimizing delivery of relatively large amounts of Δ9-THC to any one site in the airway. Unfortunately, the particle size of the aerosols of Δ9-THC used in the present study was not measured. Additional studies would be of interest to determine the local airway and systemic effects of low doses of aerosolized Δ9-THC in the small- to medium-sized particle range in patients with reversible airway obstruction. Another approach toward developing a potentially useful cannabinoid compound for therapeutic bronchodilatation involves the synthesis of chemical derivatives of the Δ9-THC molecule, which might retain the bronchodilator activity of the parent compound when orally administered, but not the unwanted psychophysiologic effects.

References