

BRONCHODILATOR EFFECT OF Δ^1 -TETRAHYDROCANNABINOL

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- 1 Δ^1 -trans-tetrahydrocannabinol, (Δ^1 -THC) produces bronchodilatation in asthmatic patients.
- 2 Administered in 63 μ l metered volumes containing 50–200 μ g by inhalation from an aerosol device to patients judged to be in a steady state, it increased peak expiratory flow rate (PEFR) and forced expiratory volume in 1 second (FEV₁).
- 3 The rate of onset, magnitude, and duration of the bronchodilator effect was dose related.

Introduction

The principal psycho-active constituent of cannabis, Δ^1 -trans-tetrahydrocannabinol (Δ^1 -THC) has bronchodilator activity in man, both in normal subjects (Vachon, Fitzgerald, Solliday, Gould & Gaensler, 1973; Tashkin, Shapiro & Frank, 1973) and in asthmatic patients (Tashkin, Shapiro & Frank, 1974). It may be given orally, but in order to achieve significant effects, doses in excess of 10 mg must be used and patients then experience psychic disturbance. A dose of 200 μ g, is an effective bronchodilator when delivered by inhalation from a pressurized aerosol, and no measurable systemic absorption takes place (Williams, Hartley & Graham, 1976). Higher doses frequently cause transient coughing and chest discomfort in asthmatic patients. The present study was undertaken to examine the effect of smaller doses of Δ^1 -THC on ventilatory function, in terms of maximal response, duration and dose-response relation.

Methods

Five asthmatic patients (female, age range 25–65 years) gave written informed consent to the study. None had taken cannabis previously in any form. They were in-patients who had recovered from attacks of asthma, and were in a relatively stable state awaiting discharge. Two patients were atopic. To demonstrate reversibility of the airways obstruction an increase in peak expiratory flow rate (PEFR) of at least 20% was established in each patient following the inhalation of 200 μ g of salbutamol before inclusion in the study. All patients were on prednisone (10–15 mg/day), which was continued throughout the period

of investigation. Bronchodilator drugs were withheld for 12 h before each test began.

Each patient was studied for four consecutive days, a different aerosol being administered double blind each morning according to an extended latin square design. Ventilatory function was measured by peak expiratory flow rate (PEFR) using a Wright Peak Flow Meter (Airmed) and forced expiratory volume in one second (FEV₁) using a dry wedge spirometer (Vitalograph). On each occasion the best of three technically satisfactory readings was noted. Three sets of readings at 5 min intervals were recorded before administration of aerosol, the single best values for PEFR and FEV₁ being used as baseline values. After one puff only of aerosol, measurements were made at 5, 15, 30, 45, 60, 90, 120, 240 and 360 min.

The results were analysed by three-way analysis of variance which compared the total drug response over 6 h for the three doses of Δ^1 -THC.

Drugs

The Δ^1 -THC was supplied in ethanol by the National Institute of Drug Abuse, U.S.A. and put up in identical canisters which were made as previously described (Williams *et al.*, 1976). These delivered 63 μ l per puff containing 50, 100 or 200 μ g Δ^1 -THC in ethanol and propellant as placebo. They were labelled A–D respectively.

Results

All given doses of Δ^1 -THC caused bronchodilatation, as reflected by increases in both PEFR and FEV₁. The

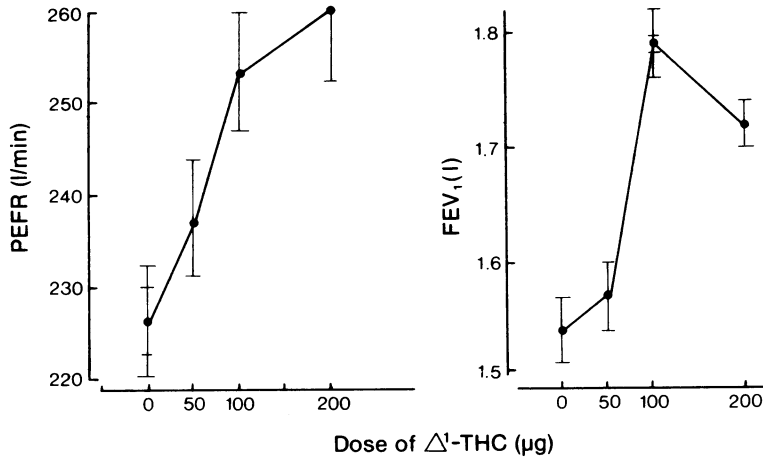


Figure 1 The mean \pm s.e. mean for PEFR and FEV₁ for eleven observations on each of five subjects for placebo and 50, 100 and 200 μg of Δ^1 -THC by aerosol.

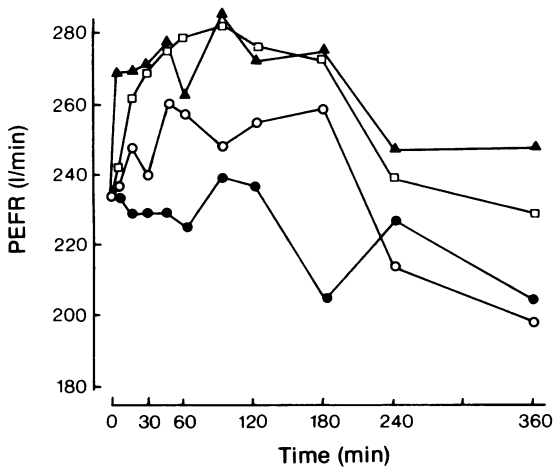


Figure 2 The changes in PEFR (means of five subjects) over time (0–360 min) for placebo (●) and 50, (○) 100 (□) and 200 (▲) μg Δ^1 -THC as an aerosol. The effect lasts for 4–6 h.

effect was dose related (Figure 1). The maximum improvement was seen at approximately 60 min and was sustained for at least 3 h. Thereafter the response to 50 μg declined sharply but that to the higher doses was maintained for at least one further hour (Figure 2). There was no difference in maximal response between 100 μg and 200 μg Δ^1 -THC for PEFR from 1–4 h, but the maximal response to 50 μg Δ^1 -THC was considerably less. A similar pattern was obtained for FEV₁. The effect of 100 and 200 μg Δ^1 -THC was similar at 3 h. A marked improvement of FEV₁ persisted for more than 6 h after the higher doses. Analysis of variance for total drug response, eleven observations, showed that all doses of Δ^1 -THC were significantly better than placebo with respect to PEFR (Table 1). Both 200 μg and 100 μg were better than 50 μg and 200 μg was more effective than 100 μg . Changes with respect to FEV₁ also showed all doses of Δ^1 -THC were significantly better than placebo with respect to PEFR (Table 1). Both 200 μg and 100 μg were better than 50 μg and 200 μg was more effective than 100 μg . Changes with respect to FEV₁ also showed all doses of Δ^1 -THC to be better

Table 1 Analysis of variance of PEFR and FEV₁ in five subjects, eleven observations each over 6 h after placebo or Δ^1 -THC 50, 100 or 200 μg by aerosol

| Comparison | PEFR | P | FEV ₁ | P |
|-----------------|---------------|---------|------------------|---------|
| Plac/THC 50 | THC > placebo | < 0.001 | THC > placebo | < 0.05 |
| Plac/THC 100 | THC > placebo | < 0.001 | THC > placebo | < 0.001 |
| Plac/THC 200 | THC > placebo | < 0.001 | THC > placebo | < 0.001 |
| THC 50/THC 100 | 100 > 50 | < 0.001 | 100 > 50 | < 0.001 |
| THC 50/THC 200 | 200 > 50 | < 0.001 | 200 > 50 | < 0.001 |
| THC 100/THC 200 | 200 > 100 | < 0.05 | 100 > 200 | < 0.05 |

than placebo. Both 200 µg and 100 µg were better than 50 µg. 100 µg was just significantly better than 200 µg. All the patients responded to Δ^1 -THC in a similar fashion, although the degree of response varied between patients. Occasionally, cough was experienced after inhalation. There was no subjective response or tachycardia.

Discussion

Doses of Δ^1 -THC which are large enough to cause bronchodilatation when taken orally are invariably associated with psychological effects, and direct bronchial administration of a smaller dose is, therefore, more appropriate. Smoking marijuana can cause bronchodilatation in asthmatic patients (Tashkin *et al.*, 1974) and prevent experimentally-induced bronchospasm (Tashkin, Shapiro, Lee & Harper, 1975) but the dose is difficult to control, the smoke irritates the airways and long-term use can impair lung function (Henderson, Tennant & Guerry, 1972). More recently, therefore, aerosolized Δ^1 -THC has been investigated. The smallest dose which has previously been shown to cause bronchodilatation when given by aerosol to asthmatic patients is 200 µg (Williams *et al.*, 1976). Other workers have found larger doses given in this way to be effective, but not without psychological or local irritant effects (Tashkin, Reiss, Shapiro, Calvaresi, Olsen & Lodge, 1977; Vachon, Robins & Gaensler, 1976).

The present study has demonstrated that small doses of Δ^1 -THC given by aerosol can cause bronchodilatation as measured by improvement in PEFR and FEV₁. These tests were used because they give acceptable measure of clinically useful bronchodilatation. It is possible to construct an approximate dose-response curve for both PEFR and FEV₁. The optimal dose would appear to be 100 µg. The

differences between 100 and 200 µg were small. We have found that doses higher than this commonly cause coughing and retrosternal discomfort, even in normal subjects, and this is more pronounced in asthmatics, in whom a transient increase in airways obstruction may be found. It is possible that the local irritant effect of Δ^1 -THC even at 200 µg caused bronchoconstriction in all but the largest airways, which opposed the direct bronchodilator activity of the drug, and this may have been responsible for the inversion of the dose response effect with respect to FEV₁.

Our highest dose, 200 µg of Δ^1 -THC was determined by practical considerations of patient tolerance. Reduction of the inhaled dose to 50 µg resulted in a significant loss of bronchodilator activity but no unpleasant respiratory symptoms. A dose of 100 µg delivered as two puffs of 50 µg each from a pressurized aerosol, would appear to be the most suitable one for further studies. At this dose, no measurable absorption from the lungs occurs, and neither psychological, nor cardiovascular effects are found (Williams *et al.*, 1976).

The mechanism of action of the drug, though not as yet known, does not appear to be related to β -adrenoceptor stimulation or to cholinergic blockade (Shapiro, Tashkin & Frank, 1973; Davies, Radcliffe, Seaton & Graham, 1975). Naturally-occurring and synthetic cannabinoid compounds which are without psychological activity are now available, and may hold therapeutic potential if they can be shown to retain bronchodilator activity.

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References

- DAVIES, B.H., RADCLIFFE, S., SEATON, A. & GRAHAM, J.D.P. (1975). A trial of oral Δ^1 -(trans)tetrahydrocannabinol in reversible airways obstruction. *Thorax*, **30**, 80–85.
- HENDERSON, R.L., TENNANT, F.S. & GUERRY, R. (1972). Respiratory manifestations of hashish smoking. *Arch. Otolaryng.*, **95**, 248–251.
- SHAPIRO, B.J., TASHKIN, D.P. & FRANK, I.M. (1973). Mechanism of increased specific airways conductance with marijuana smoking in healthy young men. *Ann. intern. Med.*, **78**, 832–833.
- TASHKIN, D.P., SHAPIRO, B.J. & FRANK, I.M. (1973). Acute pulmonary physiologic effects of smoked marijuana and oral Δ^9 tetrahydrocannabinol in healthy young men. *New Engl. J. Med.*, **289**, 336–341.
- TASHKIN, D.P., SHAPIRO, B.J. & FRANK, I.M. (1974). Acute effects of smoked marijuana and oral Δ^9 -tetrahydrocannabinol on specific airways conductance in asthmatic subjects. *Am. Rev. Resp. Dis.*, **109**, 420–428.
- TASHKIN, D.P., SHAPIRO, B.J., LEE, J.E. & HARPER, C.E. (1975). Effects of smoked marijuana in experimentally-induced asthma. *Am. Rev. Resp. Dis.*, **112**, 377–386.
- TASHKIN, D.P., REISS, S., SHAPIRO, B.J., CALVARESE, B., OLSON, J.L. & LODGE, J.W. (1977). Bronchial effects of aerosolized Δ^9 -tetrahydrocannabinol in healthy and asthmatic subjects. *Am. Rev. Resp. Dis.*, **115**, 57–65.
- VACHON, L., FITZGERALD, M.X., SOLLIDAY, N.H., GOULD, I.A. & GAENSLER, E.A. (1973). Single-dose effect of marijuana smoke. *New Engl. J. Med.*, **288**, 985–989.
- VACHON, L., ROBINS, A.G. & GAENSLER, E.A. (1976). Airways response to micro-aerosolized Δ^9 -tetrahydrocannabinol. *Chest*, **70**, 444.
- WILLIAMS, S.J., HARTLEY, J.P.R. & GRAHAM, J.D.P. (1976). Bronchodilator effect of Δ^1 -tetrahydrocannabinol administered by aerosol to asthmatic patients. *Thorax*, **31**, 720–723.

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