A trial of oral Δ^1 -(trans)-tetrahydrocannabinol in reversible airways obstruction

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Davies, B. H., Radcliffe, Sheila, Seaton, A., and Graham, J. D. P. (1975). *Thorax*, 30, 80–85. A trial of oral Δ^1 -(trans)-tetrahydrocannabinol in reversible airways obstruction. Sixteen patients with proven reversible airways obstruction were admitted to a double-blind study to compare the bronchodilator effects of oral Δ^1 -(trans)-tetrahydrocannabinol (Δ^1 -THC) and salbutamol. Measurements of forced vital capacity, forced expired volume in one second, peak expiratory flow rate, and maximum expiratory flow rate at 50% vital capacity after 10 mg oral Δ^1 -THC did not differ significantly from the effect of placebo, whereas increases after salbutamol were significant. Analyses of mood, pulse rate, blood pressure, and electrocardiogram showed no important changes after oral Δ^1 -THC. In vitro studies with isolated tracheal muscle indicate that the activity of Δ^1 -THC is 1,000 times less than the equivalent dose of isoprenaline, and the effect of Δ^1 -THC is not abolished by β -adrenoreceptor blocking agents. It is concluded that oral Δ^1 -THC, at a dose of 10 mg, does not produce clinically significant bronchodilatation in patients with reversible airways obstruction.

The systemic pharmacological effects of cannabis and, more recently, of the tetrahydrocannabinols of the resin base of *Cannabis sativa* are being studied with growing interest in both animals and man (Paton, Pertwee, and Temple, 1972). A systemic effect noted in regular users of cannabis has been a prolonged and significant reduction in airways resistance (Vachon *et al.*, 1973; Tashkin, Shapiro, and Frank, 1973). This effect has been noted after both inhalation of herbal cannabis smoke and oral administration of the major psychoactive cannabinoid of the resin, Δ^1 -(trans)-tetrahydrocannabinol (Δ^1 -THC, the monoterpenoid notation; Δ^9 -THC, the dibenzopyran notation). The mechanism of action is unclear, both peripheral β -sympathetic stimulation (Beaconsfield, 1974) and central effects related to the euphoriant property of the drug having been postulated. The clinical implications in the use of a bronchodilator cigarette in the management of airways obstruction are self-evident. This study was planned to compare the bronchodilator properties of oral Δ^1 -THC with those of salbutamol, an oral bronchodilator of proven efficacy (Legge, Gaddie, and Palmer, 1971) on a double-blind basis in patients with reversible airways obstruction. Since the Δ^1 -THC was given to patients with no

previous experience of the drug, a dose regimen was administered which would produce minimal psychological effects.

PATIENTS AND METHODS

Sixteen subjects, 11 males and five females, mean age 46 (range 21–73) years, were admitted to hospital for the duration of the study. All stated that they had never previously used cannabis and all had previously documented reversible airways obstruction, as noted by a 15% improvement in either the peak expiratory flow rate (PEFR) or the forced expired volume in one second (FEV_{1.0}) after inhaled salbutamol. Clearance had been granted by the Ethical Committee of the University Hospital group. The study was conducted under the supervision of an appointed Home Office licensee (JDPG, Licence No. K 186) under the Misuse of Drugs Act 1971. Informed consent was obtained from all patients, who were told that they would receive a derivative of cannabis on two occasions during the study.

Each patient acted as his own control. All 16 patients were allocated, in a four by four latin square design, one of four apparently identical drugs on alternate days given on a double-blind basis. The drugs were as follows:

- salbutamol base 4 mg in ethanol 0.5 ml in syrup to 5 ml;
- ethanol 0.5 ml in syrup to 5 ml;

- (c) Δ^1 -THC 2.5 mg in ethanol 0.5 ml in syrup to 5 ml;
 (d) Δ^1 -THC 10 mg in ethanol 0.5 ml in syrup to 5 ml.

The Δ^1 -THC was supplied by the National Institute of Mental Health (USA) and was in the form of crude cannabis extract (CMF 69131) assayed at 25% Δ^1 -THC. In view of the instability of the preparation, assay by standard THC procedure was repeated at the termination of the study and found to be 20% Δ^1 -THC.

All bronchodilator drugs were discontinued 24 hours prior to the first study day and for the duration of the study. Ventilatory capacity was measured prior to, and at 30, 60, 90, 120, 180, 240, 300, and 360 minutes after administration of the drug. Each measurement of ventilatory capacity consisted of three satisfactory forced expirations from total lung capacity. The measurement with the greatest peak expiratory flow was chosen for analysis. The procedure was carried out with a 10-litre, low-resistance, waterless spirometer (Ohio 840) recording volume and, simultaneously, flow rates by an electronic differentiating circuit. Flow and volume were recorded on an X-Y oscilloscope. A timed expiratory spirogram was recorded simultaneously on an ultraviolet recorder. Measurements from these tracings were made of vital capacity (FVC), $FEV_{1.0}$, PEFR, and the expiratory flow rate at 50% of vital capacity ($MEFR_{50}$).

Before administration of the drug, and at 210 minutes after, the supine and sitting blood pressure and pulse rate were measured and an electrocardiogram was recorded. At the same time psychological assessment was carried out using self-rating mood scales (McNair and Lorr, 1964; Green, 1965). Details of these techniques have been reported previously (Davies *et al.*, 1974).

IN VITRO STUDIES OF BRONCHODILATOR ACTIVITY OF Δ^1 -THC
 The relative bronchodilator activity of isoprenaline and Δ^1 -THC was determined on isolated spiral strips of guinea-pig tracheal smooth muscle, 20 in number mounted in 5 ml of Krebs' solution at 37°C, gassed with 5% CO_2 in O_2 at 200 mg tension. Muscle tone was recorded isotonicly with a forced displacement recorder. The bronchodilator activity was then repeated with the addition of 2 μ g/ml of propranolol, a β -adrenoreceptor blocking agent.

STATISTICAL ANALYSES Two factors were taken account of in planning the analyses. First, a considerable variation was noted in the initial measurements of ventilatory capacity of the subjects. Secondly, in a number of subjects changes in ventilatory capacity followed lunch, taken three hours after the administration of the drug. A sophisticated approach, involving the fitting of a dose response curve, was not therefore considered to be justified, and all results after the third hour were excluded from the analyses. The initial measurements of ventilatory capacity and those following drug administration were standardized to the average individual and the average pre-drug measurements. For each index of ventilatory capacity in each patient the mean of the five timed measurements up to three hours after drug administration has been used as a measure of response, and the variation

between the four drugs has been determined using an analysis of variance. To improve the sensitivity of this approach, the pre-drug measurement has been used as a co-variate. Analysis was completed before the study code was broken. The cardiovascular and mood effects were analysed by a paired Student *t* test on the mean values obtained for the 16 subjects.

RESULTS

VENTILATORY CAPACITY The mean values of $FEV_{1.0}$, FVC, PEFR, and $MEFR_{50}$ in the 16 patients before and after each of the four drugs are recorded in Table I. It is apparent that changes in ventilatory capacity likely to be of clinical significance followed salbutamol only, though small increases in $FEV_{1.0}$ and $MEFR_{50}$ also occurred after 10 mg Δ^1 -THC. The standardized results showing the initial measurements and the mean of the five measurements to the third hour after drug administration are recorded in Table II. Salbutamol was significantly better than placebo, 2.5 mg Δ^1 -THC, and 10 mg Δ^1 -THC in all four measurements— $FEV_{1.0}$ (F ratio = 6.1), FVC (F ratio = 4.8), PEFR (F ratio = 5.3), and $MEFR_{50}$ (F ratio = 3.4) on 44 degrees of freedom. There was no significant change in any of the indices of ventilatory capacity following placebo, 2.5 mg Δ^1 -THC or 10 mg Δ^1 -THC. However, the pre-drug measurements for 10 mg Δ^1 -THC are somewhat lower than those for placebo and 2.5 mg Δ^1 -THC, and it may be that slight bronchodilator activity of 10mg Δ^1 -THC was not apparent in the standardized analyses. Nevertheless the initial measurements before 10 mg Δ^1 -THC were similar to those before salbutamol, which showed significant bronchodilator activity, and it is therefore unlikely that significant bronchodilator activity of Δ^1 -THC was missed in the analyses.

CARDIOVASCULAR AND PSYCHOLOGICAL EFFECTS
 Analysis of blood pressure, supine and sitting, showed no significant difference following the four different drugs. Pulse rate analysis showed a significant tachycardia after salbutamol, a mean increase of 18 beats per minute over the initial reading ($p < 0.001$) when compared with the placebo. Mean increases in pulse rate after 2.5 mg Δ^1 -THC (5 beats per minute) and 10 mg Δ^1 -THC (10 beats per minute) were not significantly different from the placebo (12 beats per minute). Analysis of the self-rating mood scales revealed only minimal change. A slight reduction in tension after placebo was noted, an increased sense of fatigue after salbutamol, an increased sense of bewilderment after 2.5 mg Δ^1 -THC, and a slight reduction in depression after 10 mg Δ^1 -THC. No electrocardiographic change was noted in any of the 16 subjects receiving Δ^1 -THC.

TABLE I

EFFECT OF SALBUTAMOL, 10 mg Δ^1 -THC, 2.5 mg Δ^1 -THC, AND PLACEBO ON MEAN (STANDARD ERROR) DYNAMIC LUNG VOLUMES (LITRES BTFS) AND FLOW RATES IN 16 SUBJECTS

	Basal	30 min	60 min	90 min	120 min	180 min
Salbutamol						
FEV _{1.0} (l. BTFS)	1.38 (0.69)	1.64 (0.70)	1.71 (0.78)	1.75 (0.68)	1.71 (0.76)	1.70 (0.77)
FVC (l. BTFS)	2.96 (0.84)	3.11 (0.99)	3.23 (1.02)	3.27 (1.01)	3.27 (0.99)	3.20 (0.96)
PEFR (l/min)	232 (80)	271 (107)	284 (108)	292 (114)	292 (104)	280 (97)
MEFR ₅₀ (l/min)	55 (49)	59 (50)	72 (72)	87 (82)	77 (82)	71 (63)
10 mg Δ^1 -THC						
FEV _{1.0} (l. BTFS)	1.40 (0.55)	1.55 (0.62)	1.50 (0.56)	1.46 (0.53)	1.50 (0.59)	1.50 (0.57)
FVC (l. BTFS)	3.04 (0.90)	3.06 (0.93)	2.99 (0.86)	2.90 (0.86)	2.96 (0.84)	2.94 (0.97)
PEFR (l/min)	244 (88)	248 (80)	260 (87)	249 (75)	262 (85)	249 (85)
MEFR ₅₀ (l/min)	44 (23)	53 (29)	50 (29)	50 (29)	51 (33)	52 (32)
2.5 mg Δ^1 -THC						
FEV _{1.0} (l. BTFS)	1.55 (0.78)	1.60 (0.70)	1.55 (0.73)	1.50 (0.68)	1.53 (0.70)	1.50 (0.69)
FVC (l. BTFS)	3.08 (0.96)	2.99 (0.93)	2.93 (0.86)	2.91 (0.86)	2.91 (0.88)	2.94 (0.92)
PEFR (l/min)	270 (97)	268 (95)	258 (94)	261 (98)	267 (103)	257 (108)
MEFR ₅₀ (l/min)	62 (59)	62 (58)	61 (56)	59 (55)	61 (52)	59 (52)
Placebo						
FEV _{1.0} (l. BTFS)	1.53 (0.72)	1.55 (0.73)	1.49 (0.69)	1.49 (0.64)	1.50 (0.58)	1.46 (0.62)
FVC (l. BTFS)	3.01 (0.92)	2.97 (0.92)	2.94 (0.92)	2.95 (0.84)	2.96 (0.89)	2.92 (0.92)
PEFR (l/min)	260 (92)	245 (109)	260 (95)	248 (76)	258 (95)	257 (86)
MEFR ₅₀ (l/min)	61 (49)	59 (49)	58 (46)	56 (43)	58 (41)	55 (31)

TABLE II

MEAN VALUES OF DYNAMIC LUNG VOLUMES AND FLOW RATES FOR SALBUTAMOL, 10 mg Δ^1 -THC, 2.5 mg Δ^1 -THC, AND PLACEBO, STANDARDIZED FOR SUBJECT AND DAY VARIATIONS

	FEV (l. BTFS)	FVC (l. BTFS)	PEFR (l/min)	MEFR ₅₀ (l/min)
Basal	1.46	3.02	251	56
Salbutamol	1.75	3.21	293	71
10 mg Δ^1 -THC	1.53	2.96	257	59
2.5 mg Δ^1 -THC	1.49	2.90	253	55
Placebo	1.46	2.96	252	53
Standard error of mean	0.035	0.048	6.2	3.5

IN VITRO STUDIES As may be seen in the Figure, the dose response curves for isoprenaline and Δ^1 -THC (in Tween 80, 25 μ g/ml) are parallel, but the ED₅₀ dose ratio is 1,000 to 1 in favour of isoprenaline. The smooth muscle relaxation noted after Δ^1 -THC

was not antagonized by propranolol but the effect of isoprenaline was abolished. The bronchial smooth muscle relaxation noted after Δ^1 -THC is therefore not mediated by stimulation of β -adrenoreceptors.

DISCUSSION

The results of this study show that Δ^1 -THC, in a 10 mg dose, is not an effective oral bronchodilator in subjects with reversible airways obstruction. Previous work has suggested that the effect might be more pronounced. Vachon *et al.* (1973) noted changes in specific airways conductance and expiratory flow rates at 25% of vital capacity following inhalation of smoke from herbal cannabis by experienced drug users. Tashkin *et al.* (1973) also reported increases in specific airways conductance after oral Δ^1 -THC in experienced drug users, which compared well with those obtained after inhalation of isoprenaline.

FIGURE. The dose response curve for isoprenaline (10–80 ng/ml) on isolated guinea-pig tracheal strip is parallel to that for Δ^1 -THC (10–80 μ g/ml). The isoprenaline response was abolished by propranolol, 2 μ g/ml, but the response to Δ^1 -THC was not. This experiment was performed by Dr. D. M. F. Li, of the Department of Pharmacology, Welsh National School of Medicine, Cardiff.

The same authors (Tashkin, Shapiro, and Frank, 1974) subsequently reported a study of both oral Δ^1 -THC and inhaled herbal cannabis in asthmatic subjects, the majority of whom had previously used the drug and found similar but less marked increases in specific airways conductance.

Several explanations may be offered for this apparent conflict in findings. First, measurements of airways conductance are more sensitive to smaller changes in airways diameter than the measurements of ventilatory capacity used in this study. However, this present study was constructed to indicate changes which may be of clinical significance in patients with reversible airways obstruction rather than to detect minor physiological effects. A second possible explanation is that different dose regimens and preparations of cannabis have been used. Previous studies have employed higher doses of Δ^1 -THC, but these were administered to experienced drug users. We did not feel justified in using these higher doses in our naïve subjects as we had no previous experience of the psychological effects

which might have occurred at these higher doses. The preparation of cannabis used in this study, although containing a high concentration of Δ^1 -THC, may contain different cannabinoids, and these may possibly influence the response to Δ^1 -THC (Kubena and Barry, 1972). However, we suggest that the most likely reason for the disparity in findings is that in previous reports experienced users of Δ^1 -THC were studied, whereas in the present report subjects who had never experienced the drug were studied. It is known that for psychological effects the incidence and intensity of the subjective mood change are related not only to the dose but to previous experience of the drug, to expectations aroused in advance, and to the ambience in which the study is performed (Jones, 1971). Analysis of self-rating mood scales used in our study showed only minimal change whereas, in the studies previously quoted, it was noted that experienced users of Δ^1 -THC recognized the psychological effects of the drug. Even in the study of asthmatics (Tashkin *et al.*, 1974) the majority of subjects were experienced

drug users, and there was a significant correlation between the bronchodilator effect of the drug and the subjective psychological effects noted by the subjects. This variation in response between the experienced users of Δ^1 -THC and naïve subjects may be related to differences in metabolism of the cannabinoids. Mechoulam *et al.* (1972) have suggested the presence of an intermediate metabolite of Δ^1 -THC possessing greater potency than Δ^1 -THC. The enzyme controlling this reaction is thought to be inducible by the parent compound.

The mode of action of Δ^1 -THC in producing bronchodilatation, if not related to its psychotropic action, is unclear. Beaconsfield (1974) has suggested that stimulation of the β -adrenoreceptors of the sympathetic nervous system may occur, but the *in vitro* studies reported above on the response of guinea-pig tracheal smooth muscle do not support this hypothesis.

Studies previously reported from our laboratories also indicate that there is no inhibitory effect on the adrenergic receptors, the pressor effect of nor-adrenaline being potentiated by injected Δ^1 -THC (Graham and Li, 1973). A more recent pharmacological effect of Δ^1 -THC, noted in isolated seminal vesicles, is an inhibition of the synthesis of prostaglandins E_1 and E_2 (Burstein, Levin, and Varanelli, 1973). The effect of prostaglandins on bronchial muscle is now well established (Horton, 1969), prostaglandins E_1 and E_2 being bronchodilators and $F_{2\alpha}$ being a potent bronchoconstrictor. No studies have been reported on the effect of Δ^1 -THC on prostaglandin $F_{2\alpha}$ synthesis, but it is possible that Δ^1 -THC may exert its weak bronchodilator effect through modulation of the response of the bronchial smooth muscle to prostaglandins.

The long-term effects of cannabis smoking are as yet unknown. A recent report (Henderson, Tennant, and Guerry, 1972) suggests that symptoms of pharyngitis, bronchitis or rhinitis may occur as a direct result of cannabis smoking. Bronchoscopic biopsy in some of these subjects showed abnormal respiratory mucosae with atypical cells. The subjective benefit of cannabis in asthma has been noted previously. Salter (1860), in a treatise on asthma, noted its cultivation as an anti-asthmatic in India. The effects were described as 'the same effects as coffee, only in a more marked degree:—it exhilarates, imparts great activity and intensity to the intellectual faculties and exalts the functions of animal life'. It may well be that its potency relates to that of coffee rather than that of the more recently developed β -sympathetic stimulating drugs.

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