Thorax (1976), **31**, 720.

Bronchodilator effect of Δ^1-tetrahydrocannabinol administered by aerosol to asthmatic patients

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Williams, S. J., Hartley, J. P. R., and Graham, J. D. P. (1976). *Thorax*, **31**, 720–723. **Bronchodilator effect of Δ^1-tetrahydrocannabinol administered by aerosol to asthmatic patients.** Ten volunteer inpatient asthmatics in a steady state were given a single inhalation of an aerosol (63 μl) delivered in random order, on each of three consecutive days, in the laboratory of a respiratory unit. Before, and for one hour after treatment the pulse, blood pressure (lying and standing), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), peak flow rate (PFR), and self-rating mood scales (SRMS) were recorded. Treatments were placebo-ethanol only; Δ^1-tetrahydrocannabinol (THC) 200 μg in ethanol; or salbutamol 100 μg (Ventolin inhaler), administered double blind. Salbutamol and THC significantly improved ventilatory function. Maximal bronchodilatation was achieved more rapidly with salbutamol, but at 1 hour both drugs were equally effective. No cardiovascular or mood disturbance was detected, and plasma total cannabinoids at 15 minutes were undetectable by radioimmunoassay. The mode of action of THC differs from that of sympathomimetic drugs, and it or a derivative may make a suitable adjuvant in the treatment of selected asthmatics.

Δ^1-Trans-tetrahydrocannabinol (Δ^1-THC) is the principal psychoactive constituent of *Cannabis sativa* (hemp). Considerable interest has been shown of recent years in the therapeutic possibilities of other properties of cannabis preparations (Lancet, 1975) and in particular in its bronchodilator activity. It has been shown that significant reduction in airways resistance occurred in drug-experienced healthy young men who smoked herbal cannabis (marihuana) (Tashkin, Shapiro, and Frank, 1973; Vachon *et al.*, 1973) and that this treatment reversed experimentally induced bronchospasm in known asthmatics (Tashkin, Shapiro, and Frank, 1974). Taken in this way, the drug was less effective than isoprenaline but the action persisted for longer (Tashkin *et* al., 1975). Until very recently (Olsen *et al.*, 1976) attempts to deliver THC in effective amounts by aerosol were defeated by the difficulty of selecting a suitable non-foaming non-irritant solvent, and orally administered THC in doses which do not cause undue psychic disturbance are not very effective (Davies *et al.*, 1975). The present report concerns the results of a double-blind controlled comparison of aerosols of THC in ethanol, salbutamol, and placebo in drug-naïve patients.

PATIENTS AND METHODS

Ten asthmatic subjects (six male; mean age 53 years) signed a valid consent form and entered the trial. None admitted to previous contact with any preparation of cannabis. All were hospital inpatients who had recently recovered from an attack of severe asthma and were considered to be in a steady state, as indicated by stable pulse rates, peak flow rates (PFR), and forced expiratory volumes in 1 sec (FEV_1), and by relief of symptoms. All had reversible airways obstruction, as shown by an increase in PFR of at least 20% after inhalation of 100 μg salbutamol (Ventolin inhaler). All had typical asthmatic stigmata in

their sputum (Sanerkin and Evans, 1965) and four had positive skin tests to common allergens. They were maintained on a fixed oral dose of prednisone (10–20 mg daily); all other medication was withdrawn 12 hours before the trial began.

The treatments, which consisted of ethanol as placebo, 200 μg Δ¹-THC in ethanol, or 100 μg salbutamol, were supplied in identical standard metered aerosol cans labelled with an identifying letter. One puff delivered 63 μl. Administration of a single metered dose was made in latin square order, once on each of three consecutive days at 10.00 hours and was preceded by recording (1) self-rating mood scales (SRMS), which grade the answers to 72 questions covering nine aspects of mood (McNair and Lorr, 1964), (2) cardiovascular (CVS) measurements, PFR with a Wright peak flow meter (Airmed), FEV_1 with vital capacity (FVC) with a dry spirometer (Vitalograph). Respiratory and CVS measurements were repeated at 5, 15, 30, 45 and 60 minutes, venous blood was drawn at 15 minutes, and SRMS were repeated at one hour. All patients acted as their own controls, and scores before and after treatments were compared by Student's *t* test for dependent data. Comparisons of drug effects at selected times were made by *t* test for independent means. Total reacting cannabinoids (THC and its metabolites) in plasma were estimated by radioimmunoassay (RIA) by Dr. J. D. Teale, of the Department of Biochemistry, University of Surrey, Guildford (Teale *et al.*, 1975). The project was supervised by the holder of Home Office Licence No. M414 under the Misuse of Drugs Act (1971). Δ¹-THC in ethanol was supplied by the National Institute on Drug Abuse, Rockville, Ma, USA via the Medical Research Council as distributor.

AEROSOL FORMULATION Note by Dr. N. A. Armstrong, Department of Pharmaceutics, School of Pharmacy, University of Wales Institute of Science and Technology, Cardiff.

Packaging: Containers—Aluminium monobloc, 20 ml normal capacity, Neotechnic Engineering, Clitheroe. Valve: Metered valve 63 μl capacity, Bespak Ltd, Enfield. Propellants: Dichlorodifluoromethane (Arcton 12, ICI Ltd). The aerosols were prepared using an Aerofill Pilotpak filling machine. Each pack contains 0·81 g ethanolic THC, or ethanol, 7·15 g propellant. 63 μl of ethanolic THC diluted with 5·3 ml of propellant contains 200 μg THC. Each container delivers about 100 doses.

RESULTS

VENTILATORY MEASUREMENTS The data are displayed in Tables I and II. Salbutamol 100 μg, and Δ¹-THC, 200 μg, increased ventilatory function

TABLE I

INITIAL FEV_1 AND CHANGE IN FEV_1 (LITRES BTPS) IN 10 SUBJECTS

		Salbutamol	P (S and P)	Placebo	P (THC and P)	THC
Initial FEV_1		1·76 (0·59)	> 0·1	1·84 (0·66)	> 0·1	1·73 (0·52)
Change in FEV_1 (time after drug administration)	5 min	+ 0·3 (0·12)	< 0·01	− 0·075 (0·14)	< 0·05	+ 0·09 (0·19)
	15 min	+ 0·41 (0·17)	< 0·01	− 0·075 (0·17)	< 0·01	+ 0·18 (0·2)
	30 min	+ 0 4 (0·21)	< 0·01	− 0·135 (0·12)	< 0·01	+ 0·28 (0·2)
	45 min	+ 0·45 (0·19)	< 0·01	− 0·14 (0·19)	< 0·01	+ 0·35 0·26)
	60 min	+ 0·46 (0·26)	< 0·01	− 0·22 (0·3)	< 0·01	+ 0·41 (0·2)

Means ± SD of mean. P = placebo; S = salbutamol 100 μg; THC = Δ¹-THC 200 μg.

TABLE II

CHANGES IN PFR AND FVC AT 60 MIN (MEAN ± SD OF MEAN) IN 10 SUBJECTS

	Salbutamol	P (S and P)	Placebo	P (THC and P)	THC
PFR (l/min)					
Initial PFR	234 (73)	> 0·1	236 (88)	> 0·1	233 (74)
Change in PFR	+ 69 (41)	< 0·01	− 2·5 (23)	< 0·01	+ 85 (39)
FVC (l BTPS)					
Initial FVC	2·98 (0·8)	> 0·1	3·06 (0·97)	> 0·1	3·00 (0·85)
Change in FVC	+ 0·4 (0·31)	< 0·01	− 0·15 (0·17)	< 0·01	+ 0·36 (0·26)

significantly compared with placebo in all tests at all times. Salbutamol produced a significantly greater effect than THC when measured at 5 minutes ($P<0.01$ for FEV_1) and at 15 minutes ($P<0.02$) but thereafter there was no difference ($P<0.1$). The slower increase in bronchodilatation as measured by FEV_1, and the linear time relationship leading to equal effectiveness with salbutamol after one hour, are illustrated in the Figure. The data for PFR and FVC are shown in Table II. While THC appears superior to salbutamol at one hour for PFR, this does not achieve statistical significance.

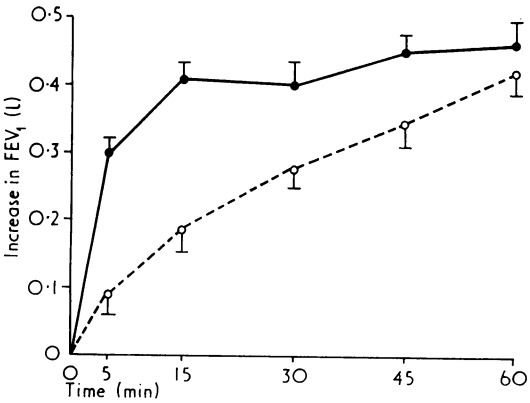

FIGURE *Increase in FEV_1 after inhalation of* 100 μg *salbutamol (solid line) or* 200 μg Δ^1-*THC (interrupted line). Each point is the mean of the differences between FEV_1 before and after treatment* ±*SD for* 10 *patients.*

CIRCULATION No significant alteration in resting pulse rates or standing or lying blood pressures was recorded. There was no significant difference in these measurements after placebo, THC or salbutamol. All values for P were greater than 0·1.

MOOD AND BEHAVIOUR No statistically significant change in any of the nine estimates of subjective feeling was detected after treatment. No abnormal behaviour occurred. Patients, when asked at the end of the tests, declared that they had not noticed anything unusual.

PLASMA CANNABINOIDS The levels of reacting cannabinoids were not detectable by RIA, which is sensitive to low ng/ml levels.

DISCUSSION

The results of this study show that Δ^1-THC dissolved in ethanol may safely be administered to asthmatic patients in a metered aerosol dose of 200 μg in 63 μl. This concentration is tolerable, but higher concentrations are irritant and may induce coughing. Ethanol by itself is not irritant, nor is the vehicle used for salbutamol (Ventolin A & H). Tashkin *et al.* (1974) and Vachon *et al.* (1973) have reported bronchodilatation after the inhalation of smoke from herbal cannabis and after oral THC. In other work from our laboratories (unpublished) we have been unable to produce a significant effect using THC in suspension in aqueous alcohol delivered from a nebulizer driven by oxygen, nor have we found oral doses of 10–30 mg of THC in sesame oil convincing in this respect. It is gratifying, therefore, that the drug has been shown to work well by simple tests of ventilatory function, when administered in the form of a metered dosage aerosol with which these patients are familiar, and in an amount which has no side effects. In this experiment placebo was associated with an increase in airways resistance, but it should be noted that these patients had been deprived of bronchodilator medication for 12 hours, and it is known that forced expiratory manoeuvres may produce bronchoconstriction in asthmatic subjects (Orehek *et al.*, 1975). Salbutamol in a dose of 100 μg was rapidly effective, but the two drugs were equally effective after one hour, and there is reason to hope (Tashkin *et al.*, 1975) that THC has a longer duration of action than compounds which stimulate beta-adrenoceptors. The relative potency of the two drugs in this trial (approximately 2 : 1 in favour of salbutamol) is different from that found by *in vitro* testing on guinea-pig bronchial muscle (approximately 1000 : 1 in favour of isoprenaline) (Davies *et al.*, 1975), but isoprenaline is many times more potent than salbutamol in such tests, and the insolubility of THC in water makes interpretation of an assay difficult. By inhalation in humans Δ^1-THC and salbutamol are comparable in efficacy. The differing patterns of the response curves with time for the two drugs, coupled with the fact that the effect of THC is not inhibited by beta-receptor blocking drugs (Davies *et al.*, 1975) and that the oil : water partition coefficients of the two are vastly different, implies a difference in the modes of action. We speculate that the highly lipophilic THC alters the state of the membrane of the bronchial smooth muscle, whereby tone is

altered, by a change in permeability to electrolytes (Gibermann *et al.*, 1974). The practical question whether or not THC in aerosol is effective in preventing the onset of bronchospasm in exercise-induced asthma, and the problems of the mechanisms of action, are currently under investigation.

We are grateful to Dr. A. Seaton, Director of the Asthma Research Unit, Sully Hospital, for access to patients, advice, and help; to Dr. N. Armstrong for the formulation and manufacture of the aerosols; to Dr. J. D. Teale of the Department of Biochemistry, University of Surrey, Guildford, GUS 5XH for the immuno assay; to NIDA and MRC for supplies of THC; and, above all, to the volunteer patients who cheerfully took part in the experiment.

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