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A PILOT STUDY OF ORALLY ADMINISTERED Δ^1-*TRANS*-TETRAHYDROCANNABINOL IN THE MANAGEMENT OF PATIENTS UNDERGOING RADIOTHERAPY FOR CARCINOMA OF THE BRONCHUS

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1 Δ^1-*trans*-tetrahydrocannabinol (Δ^1-THC; 10 mg) or a placebo was given orally on 7 days to two groups of six patients on a cross-over pattern with 7 days rest between.

2 The patients were hospitalized, suffering from inoperable bronchogenic carcinoma, subjected to radiation therapy, and anxious.

3 Self-rating mood scales were filled in before, and 2 and 6 h after ingestion on the first and seventh day of medication.

4 Records of sleep, pain, general well-being, temperature, cardiovascular and gastrointestinal parameters were kept.

5 Δ^1-THC caused drowsiness and improved night sleep, reduced pain, increased fatigue and confusion and reduced elation and vigour; it caused slight tachycardia and hypotension as also did placebo.

6 The effects of Δ^1-THC were stronger after 2 h than 6 h and no tolerance had developed at 7 days.

7 The management of stressful patients was considered to have been improved by the drug.

Introduction

An important constituent of the resin of *Cannabis sativa* is Δ^1-*trans*-tetrahydrocannabinol (Δ^1-THC). This substance is psychoactive when given orally to man (Isbell, Gorodetzsky, Jasinski, Claussen, Spulak & Korte, 1967), and the effect is dose related (Kiplinger & Manno, 1971; Hollister, 1971). There are a considerable number of reports of oral administration of Δ^1-THC to man (Hollister, Richards & Gillespie, 1968). The effects which are consistently observed are both psychic and somatic. The former include sedation (Cousens & Di Mascio, 1973), euphoria, increased friendliness, diminution of anxiety aggression and fear; impairment of short term memory (Abel, 1971) and of some psychomotor skills. In the case of smoking the incidence and intensity of these subjective changes is related not only to dose but to previous experience of the drug or naivety in this respect, to expectations aroused in advance and to the ambience in which the experiment is conducted (Jones, 1971). Physical changes usually include congestion of the conjunctivae, tachycardia (Weiss, Watanabe, Lemberger, Tamarkin & Cardon, 1972) and less regularly or after higher doses hypotension, hypothermia, but no obvious effect on respiration. Hollister (1971) recorded very little somatic disturbance in naive healthy volunteers given Δ^1-THC (0.6 mg/kg); this dose which may be approximated as 30 mg by mouth in an adult is greater than the threshold for the production of subjective effects of approximately 5 mg orally as reported by Isbell *et al.* (1967).

Radiotherapy for patients with carcinoma of the bronchus is often associated with changes in mood manifest as depression or anxiety. Anorexia and general constitutional disturbances are also encountered frequently. We thought that these accounts of Δ^1-THC, supplemented by the

numerous reports of the effects of smoking Cannabis leaf or resin, justified a pilot study in patients who were suffering from an incurable disease (bronchogenic carcinoma), undergoing a physically and mentally stressful regimen (radiation therapy) and who showed signs of tension and anxiety. We selected synthetic Δ^1-THC (10 mg) to be given orally as being a dose expected to produce beneficial psychological effects with the minimum of somatic reactions, and we were anxious to establish which aspects of therapy with Δ^1-THC would predominate in naive patients in a hospital environment, in a blind trial.

Methods

A detailed scheme having been submitted and approved by the Division of Medicine of the University Hospital of Wales acting in its capacity of Ethical Committee for Clinical Trials, twelve male patients between the ages of 50 and 70 years were admitted to the trial. The diagnosis of inoperable bronchogenic carcinoma had been made by clinical examination, radiography and in some cases histologically. Each patient gave a history of stressful reaction to his situation. Before admission to trial data were obtained as to location, extent, and duration of the carcinoma, previous and intended therapy, current consumption of analgesics, and past and recent psychiatric history. A full physical examination including ECG was made. Details are summarized in Table 1. Valid consent to participation was obtained by asking each patient to read, consider for an afternoon and discuss the consent form before signing. The form was phrased as follows: 'I understand that I will be given a dose (10 mg) of a new drug by mouth each morning for an unspecified period during the next 4 weeks. This drug, called tetrahydrocannabinol, is a product of Indian Hemp. It is offered with a view to helping me in my present illness but is not in itself a cure. I understand that my co-operation is sought on a purely voluntary basis and that I may cease to do so at any time. I agree to become a participating patient on these conditions.' This was the only information which patients were given about the proposed medication and it is unlikely that they associated the words cannabis and tetrahydrocannabinol with 'pot' or 'hash'; they made no further inquiry. Patients were allotted alternately to either of two groups until each numbered six. Each patient spent one week settling into hospital, beginning radiotherapy and receiving placebo medication, filling in questionnaires and self-rating mood scales by way of familiarization with the

Table 1 Data concerning the twelve male patients at the time of admission to the trial. Note the incidence of abnormality of the cardiovascular system. The analgesics administered were tab. codeine co.

Patient	*Age (years)*	*Site*	*X-ray*	*Histological type*	*BP*	*ECG*	*Consumption of analgesics**
1	63	Left upper lobe	Left upper lobe mass	Negative	125/70	Atrial Fibrillation	Min
2	50	Right hilum	Right hilar mass	Squamous	130/80	Atrial Fibrillation	Min
3	69	Left lower lobe	Left lower lobe collapse	Squamous	110/70	Ischaemic	Mod
4	69	Right upper lobe	Right upper lobe collapse	Negative	110/80	Old Anterior Infarct.	Nil
5	54	Right middle lobe	Right middle lobe collapse	Squamous	120/70	Normal	Nil
6	61	Left upper lobe	Left upper lobe mass	Negative	150/70	Nodal Rhythm	Min
7	62	Left hilum	Left hilar mass	Oat cell	150/80	Ischaemic	Nil
8	70	Left hilum	Left hilar mass	Negative	150/70	Normal	Nil
9	68	Right upper lobe	Right upper lobe mass	Negative	160/100	Normal	Mod
10	69	Right lower lobe	Right lower lobe collapse	Squamous	150/80	Normal	Nil
11	61	Right upper lobe	Right upper lobe collapse	Negative	170/100	Ischaemic	Nil
12	54	Right hilum	Right hilar mass	Oat cell	160/90	Old Inferior Infarct.	Mod

* Min, minimal 1 tablet/day. Mod, moderate 3-4 tablets/day.

routine. The trial was conducted in so far as possible on a double blind pattern, but, as with most active psychopharmacological agents, the medical staff soon recognized the different effects of the dummy and the active preparations, and the patients appreciated in retrospect that the medicine varied in its effect. Active drug consisted of synthetic Δ^1-THC (10 mg) dissolved in ethanol (0.5 ml), dispensed by one person by syringe from a stock bottle kept in the dark at 4° C into orange juice (20 ml), mixed and swallowed at once. The placebo was identical except for the absence of THC and similarly administered. The bottles were labelled A or B. Group 1 (6 patients) were medicated with active drug daily at 08.15 h for 7 days, group 2 with placebo at the same hour. All patients then had 7 days rest without medication followed by 7 days on the alternative medication (a crossover test). This routine was supplemented by sessions in a Radiation Therapy Unit. The total dose of Δ^1-THC per person was thus 70 mg. On the first and last day of each 7-day period, recumbent pulse rate, blood pressure, respiratory rate and oral temperature was recorded by the same nurse on each occasion and once daily between times. A record of appetite (doctor-rated), bowel movements, tab. codeine co. consumed, hypnotics requested, and any noticeable alteration in mood or behaviour was also kept daily. There were seven self-rating scales from McNair & Lorr (1964) which are designed to assess subjective feelings of (1) 'tension–anxiety', (2) 'depression', (3) 'anger–hostility', (4) 'fatigue', (5) 'confusion', (6) 'vigour', (7) 'friendliness', and two from Green (1965) used to assess (8) 'surgency', measured by self ratings on the following items–'carefree', 'playful', 'witty', 'lively' and 'talkative', and (9) 'elation'. The patient was given an instruction sheet to read and then the randomized list of 71 key words. Examples of some of the words are 'tense', 'angry', 'energetic', 'muddled', 'alert' and 'forgetful'. The total list of words is subdivided under the nine headings which have been outlined above. Proceeding without pause he had to assess his degree of feeling at that moment in response to each listed word and place a tick in the appropriate column which was headed (1) 'not at all', (2) 'a little', (3) 'quite a bit', or (4) 'extremely'. The records were decoded, quantified, and multifactorial analyses performed relating to mood, drug or placebo effect, time after ingestion and order of presentation of placebo and drug. Patients also recorded their retrospective feeling on a numerical scale from 1 to 5 on the subjects of pain, feeling generally better or worse, sleep and appetite, at the end of each week. The Δ^1-THC used in this trial was imported by Messrs Digby & Co., London (under licence) from the Jerusalem laboratories of Professor R. Mechoulam. As received it was dissolved in carbon tetrachloride; this was evaporated under vacuum at room temperature, the Δ^1-THC taken up in ethanol and the concentration checked by standard GLC procedure, and adjusted to 20 mg/ml. This investigation was completed shortly before the recent introduction of regulations for the control of cannabinoids under the Misuse of Drugs Act (1971).

Results

The physician in charge formed the opinion that management of restless, unhappy patients was made easier by the drug therapy; patients expressed the opinion that they 'felt better' and self rated themselves nearer to the end of the scale which expressed this. The consumption of tab. codeine co. was not high with any patient, but those who felt a need for it (it was available freely on demand) expressed themselves as entirely free from pain when receiving Δ^1-THC. Appetite did not alter significantly, all patients having good and bad days; there were no gastro-intestinal upsets nor significant alterations in oral temperature. Patients were invariably made drowsy by the drug and spent most of the day reclining on their day bed or in an armchair; one only suffered psychic disturbance on first taking Δ^1-THC which he considered unpleasant. This consisted of a sensation of floating, of being disembodied and of his person being suspended somewhere outside the ward window and was accompanied by palpitations. Since this man was a teetotal presbyterian he concluded that he was intoxicated and he did not like the idea. It was not experienced to an equal degree on repetition of the drug, nor on placebo. There were no reports of insomnia or nightmares, or residual symptoms such as headache next morning. Patients did not receive hypnotics routinely but nitrazepam was available on request; 7 out of 12 expressed an improvement in ease of falling asleep and in duration and refreshing quality of sleep on their self-rating scale while receiving Δ^1-THC as compared with placebo. No attempt was made to record respiratory parameters because they were altered as a result of radiotherapy. No radiation sickness was reported during 3 weeks treatment, which is contrary to our usual experience. No-one complained of dry mouth or blurring of vision. The final clinical impression was that the drug had done no harm and that patients (Group 1) who were put on Δ^1-THC firstly settled down quickly and maintained their passivity throughout their stay in hospital whereas some of the other patients

(Group 2) did not so readily accept their condition until they were put on Δ^1-THC therapy.

In Table 2 the overall effect of Δ^1-THC therapy on systolic and diastolic blood pressure and on heart rate is compared with that of placebo therapy, and each with the drug-free interlude. It can be seen that THC caused its widely accepted effect of tachycardia with a mean gain of 5 beats/minute. This was just significant ($P < 0.05$); but the interesting finding is that placebo therapy did likewise and to a greater extent with a mean gain of 8 beats/minute. This is also significant ($P < 0.01$) and there was no difference between drug and placebo. A slight fall in systolic blood pressure (15 mmHg, $P = < 0.01$) and in diastolic pressure (4 mmHg, NS) was likewise matched by the effect of placebo (systolic 11 mmHg, $P = < 0.05$, diastolic 1 mmHg, NS). There was, therefore, no difference between drug and placebo in effect on the cardiovascular system. It made no difference whether Δ^1-THC was given firstly (Group 1) or secondly (Group 2). On each occasion it caused some reddening of the conjunctivae but no attempt was made to quantify this and neither nursing staff nor patients commented upon it.

The effects of ingestion of Δ^1-THC (10 mg) on self ratings of mood are summarized in Table 3. When the self-rated changes associated with the drug were compared with the changes following placebo administration, there were significant differences on four scales. Subjective feelings of fatigue (e.g. 'weary', 'sluggish', 'fatigued') and confusion ('muddled', 'bewildered', 'unable to concentrate') were greater after the drug. The changes associated with the drug were greater 2 h after ingestion as compared with 6 h and the change in feelings of confusion was not significant 6 h after ingestion. The drug also produced significant reductions in patients' feelings of vigour ('lively', 'energetic', 'cheerful'), and these effects were apparent up to 6 h after the drug had been taken. In view of these changes, it is not surprising that the drug produced a significant reduction in patients' reports of elation ('elated', 'pleased'). This effect had, however, disappeared 6 h after ingestion.

In summary, self ratings made by the patients indicate that the drug was associated with some worsening in their subjective state. On the scales used, these changes were limited to fatigue, confusion, vigour and elation. There were no significant changes in patients' ratings of tension–anxiety, depression, and feelings of friendliness and surgency. It is not possible to evaluate the scores on any scale as being high or low since reliable norms from the general population are not available. Ratings made by the clinicians responsible for these patients do suggest, however, that the changes in mood did not reach serious proportions. They certainly did not reach a point where they became a clinical problem. The drug was more effective in producing fatigue and confusion when it was given in the order placebo-rest period–drug than in the order drug–rest period–placebo; this finding may reflect the exhaustion due to continuing hospitalization and the effects of radiation rather than a difference due to the order of presentation of Δ^1-THC. There was no difference as between the

Table 2 Effect of Δ^1-THC (10 mg orally) or placebo on the cardiovascular system (combined data from 1st and 7th days of treatment), at 2 h after ingestion for both groups of patients

Δ^1-THC v. Rest period	*Placebo v. Rest period*	*Δ^1-THC v. Placebo*
	Mean systolic blood pressure (mmHg)	
123 ± 16 v. 138 ± 16.8 $t = 3.17$ $P = <0.01$	127 ± 17.3 v. 138 ± 16.8 $t = 2.23$ $P = <0.05$	123 ± 16.1 v. 127 ± 17.3 $t = 0.82$ $P =$ NS
	Mean diastolic blood pressure (mmHg)	
77 ± 9.8 v. 81 ± 8.8 $t = 1.49$ $P =$ NS	80 ± 13.1 v. 81 ± 8.8 $t = 0.47$ $P =$ NS	77 ± 9.8 v. 80 ± 13.1 $t = 0.9$ $P =$ NS
	Pulse rate (beats/min)	
85 ± 9.9 v. 80 ± 4.3 $t = 2.27$ $P = <0.05$	88 ± 7.3 v. 80 ± 4.3 $t = 4.65$ $P = <0.01$	85 ± 9.9 v. 88 ± 7.3 $t = 1.2$ $P =$ NS

NS, not significant.
The results are shown as mean ± s.d. ($n = 24$), and were analysed using Student's t test.

Table 3 The effect of Δ^1-THC (10 mg, orally) at 2 h and 6 h on self-rated mood. Δ^1-THC increased feelings of fatigue and confusion and reduced vigour and elation, but had no effect on the tendency to feel anger. These effects were stronger at 2 h after ingestion than at 6 hours. The scale numbers are described in the methods section. The results were analysed using the Student's *t* test.

Scale number	Δ^1-THC_2 *v.* Δ^1-THC_6	P_2 *v.* P_6	Δ^1-THC_2 *v.* P_2	Δ^1-THC_6 *v.* P_6	*Effect of* Δ^1-*THC on mood*
1 Tension-anxiety	NS	NS	NS	NS	nil
2 Depression	NS	NS	NS	NS	nil
3 Anger-hostility	NS	NS	NS	NS	nil
4 Fatigue	2 > 6 ($P < 0.05$)	NS	Δ^1-THC > P ($P < 0.001$)	THC > P ($P < 0.05$)	increased
5 Confusion	NS	NS	Δ^1-THC > P ($P < 0.001$)	NS	increased
6 Vigour	2 > 6 ($P < 0.02$)	NS	Δ^1-THC < P ($P < 0.001$)	THC < P ($P < 0.05$)	reduced
7 Friendliness	NS	NS	NS	NS	nil
8 Surgency	NS	NS	NS	NS	nil
9 Elation	NS	NS	Δ^1-THC < P ($P < 0.01$)	NS	reduced

P, placebo; NS, not significant.
Subscript 2 and 6 refer to hours after ingestion.

effects of Δ^1-THC when administered for the first time or the seventh with the somewhat doubtful exception of effect on fatigue which was marginally greater on the first than the last day ($P < 0.05$), but the placebo also produced more fatigue on the first than the seventh day. There was therefore no evidence of the development of tolerance to Δ^1-THC (10 mg) in 7 days.

Discussion

Jones (1971) has commented on the marked differences between both subjective change and objective findings as between inexperienced and experienced persons smoking Cannabis. This influence of expectation and ambience is generally accepted but all his subjects could expect some sort of Cannabis-experience since they were openly taking part in a smoking experiment. It is doubtful whether our patients related their medication to the much publicized Cannabis-experience despite the wording of the consent form. They were naive about all drugs. The medicament was given orally and the drug and placebo were indistinguishable; the subjects were older than those who use Cannabis as a leisure drug and they did not expect anything. It was not surprising, therefore, that the psychoactivity was sedative, that only one experience was judged to be unpleasant and that no side effects were observed other than a single bout of palpitations. The observations that certain aspects of mood changed but others did not is consistent with a body of evidence which suggests that behavioural change in human beings can be remarkably specific (Mischel, 1968). The incidence of slight tachycardia and hypotension with placebo which matches that for Δ^1-THC was observed in both groups of patients on both recording days and with both orders of presentation. Weil, Zinberg & Nelson (1968) gave Δ^1-THC by smoking impregnated leaf; they reported a considerable tachycardia from the placebo (extracted leaf) and no dose response relation to Δ^1-THC, whereas Fink, Volavka, Dornbush & Crown (1972) were convinced that euphoria, tachycardia and EEG changes were dose related. Such inconsistencies are characteristic of the literature on Cannabis. The principal object of the trial was deemed to have been achieved, namely to determine whether or not Δ^1-THC could be given readily and safely to patients in a hospital setting and to establish an active but non-toxic dose. Further pilot studies of this drug in situations where illness is stressful, and for longer periods, may probably be embarked upon with safety. The state of passivity and relaxation shown in the above patients suggests

that the anodyne may find a place in the management of patients undergoing psychologically disturbing therapy or investigations, e.g. other aspects of radiotherapy, some diagnostic procedures such as bronchography or air encephalographic studies. This pilot study was not designed to compare Δ^1-THC with other sedatives or hypnotics as a tranquillizer. All of them give rise to varying degrees of drowsiness in a hospital situation such as that employed here, where quiet, rest and privacy are encouraged. It remains to be determined whether Δ^1-THC has advantages over the others for certain situations such as the terminal state.

References

ABEL, E.L. (1971). Marihuana and memory. *Nature, Lond.*, **227**, 1151-1152.

COUSENS, K. & DI MASCIO, A. (1973). (−) Δ^9-THC as an hypnotic. *Psychopharmacol. (Berl.)*, **33**, 355-364.

FINK, M., VOLAVKA, J., DORNBUSH, R. & CROWN, P. (1972). Effects of Δ^9-THC, marijuana, and hashish on E.E.G., mood and heart of volunteers. *Psychopharmacol. (Berl.)*, **26**, Suppl. 126.

GREEN, R.F. (1965). *On the measurement of mood.* Tech. Report No. 10. Res. Proj. N.R. 171-342. Dept. Psychology Univ. Rochester, Mass. U.S.A.

HOLLISTER, L.E., RICHARDS, R.K. & GILLESPIE, H.K. (1968). Comparison of tetrahydrocannabinol and synhexyl in man. *Clin. Pharmac. Ther.*, **9**, 783-791.

HOLLISTER, L.E. (1971). Actions of various marihuana derivatives in man. *Pharmac. Rev.*, **23**, 349-358.

ISBELL, H., GORODETZSKY, C.W., JASINSKI, D., CLAUSSEN, U., VON SPULAK, F. & KORTE, F. (1967). Effects of (−) Δ^9-trans-tetrahydrocannabinol in man. *Psychopharmacol. (Berl.)*, **11**, 184-188.

JONES, R.T. (1971). Marihuana induced "high"; influence of expectation, setting and previous drug experience. *Pharmac. Rev.*, **23**, 359-367.

KIPLINGER, G.F. & MANNO, J.E. (1971). Dose-response relationships to cannabis in human subjects. *Pharmac. Rev.*, **23**, 339-347.

McNAIR, D.M. & LORR, M. (1964). An analysis of mood in neurotics. *J. abnorm. soc. Psychol.*, **69**, 620-627.

MISCHEL, W. (1968). *Personality and Assessment.* New York: J. Wiley & Sons.

WEIL, A.T., ZINBERG, N.E. & NELSON, J.M. (1968). Clinical and psychological effects of marihuana in man. *Science*, **162**, 1234-1242.

WEISS, J.L., WATANABE, A.M., LEMBERGER, L., TAMARKIN, N.R., CARDON, P.V. (1972). Cardiovascular effects of delta-9-tetrahydrocannabinol in man. *Clin. Pharmac. Ther.*, **13**, 671-684.

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