Pain 106 (2003) 169–172

PAIN

www.elsevier.com/locate/pain

Lack of analgesic efficacy of oral δ-9-tetrahydrocannabinol in postoperative pain

Donal J. Buggy[b], Lynn Toogood[a], Shelagh Maric[a], Paul Sharpe[a], David G. Lambert[a], David J. Rowbotham[a,*]

[a]*Department of Anaesthesia, Critical Care and Pain Management, University of Leicester & University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester LE1 5WW, UK*
[b]*Mater Misericordiae Hospital, Dublin, Ireland*

Received 12 May 2003; received in revised form 23 July 2003; accepted 31 July 2003

Abstract

We have evaluated the efficacy of δ-9-tetrahydrocannabinol (δ-9-THC), the main psychoactive constituent of cannabis, in postoperative pain. In a randomized double-blind, placebo-controlled, single-dose trial, we investigated 40 women undergoing elective abdominal hysterectomy. Randomization took place when postoperative patient-controlled analgesia was discontinued on the second postoperative day. When patients requested further analgesia, they received a single, identical capsule of either oral δ-9-THC 5 mg ($n = 20$) or placebo ($n = 20$) in a double-blind fashion. The primary outcome measure was summed pain intensity difference (SPID) at 6 h after administration of study medication derived from visual analogue pain scores on movement and at rest. Secondary outcome measures were time to rescue medication and adverse effects of study medication. Mean (SD) VAS pain scores before medication in the placebo and δ-9-THC groups were 6.3(2.6) and 6.4(1.3) cm on movement, and 3.2(1.9) and 3.3(0.9) on rest, respectively. There were no significant differences in mean (95% confidence interval of the difference) SPID at 6 h between the groups [placebo 7.9, δ-9-THC 4.3(−1.8 to 9.0) cm h on movement; placebo 8.8, δ-9-THC 4.9(−0.2 to 8.1) cm h at rest] and time to rescue analgesia [placebo 217, δ-9-THC 163(−22 to 130) min]. Increased awareness of surroundings was reported more frequently in patients receiving δ-9-THC (40 vs 5%, $P = 0.04$). There were no other significant differences with respect to adverse events. This study demonstrates no evidence of an analgesic effect of orally administered δ-9-THC 5 mg in postoperative pain in humans.

Keywords: Cannabinoids; δ-9-Tetrahydrocannabinol; Pain; Postoperative; Randomized control trial

1. Introduction

There is significant evidence that cannabinoids have antinociceptive properties in animals (Martin and Lichtman, 1998) and the role of cannabinoid receptors in the modulation of pain has been described (Meng et al., 1998). Anecdotal accounts of the benefits of cannabinoids in the treatment of pain in humans are reported frequently (Hirst et al., 1998; Holdcroft et al., 1997; Ravenscroft et al., 2000; Voth and Schwartz, 1997; Ware et al., 2003). For example, in a population of 209 chronic non-cancer pain patients attending a pain management unit in Canada, 15% confirmed that they had used cannabis for pain relief (Ware et al., 2003).

However, the evidence-base for the use of cannabinoids for pain relief is yet to be established. A recent qualitative systematic review described the paucity of good quality data from controlled clinical trials in this area (Campbell et al., 2001).

δ-9-Tetrahydrocannabinol (δ-9-THC) is the main psychoactive constituent of cannabis (Ashton, 1999; Hirst et al., 1998; Kirk and De Wit, 1999) and is licensed in some countries as an anti-emetic for chemotherapy and an appetite stimulant in HIV (Voth and Schwartz, 1997). We report the first randomized, double-blind, placebo-controlled study investigating the analgesic efficacy of orally administered δ-9-THC in postoperative pain.

* Corresponding author. Tel.: +44-116-258-5291; fax: +44-116-285-4487.
E-mail address: djr8@le.ac.uk (D.J. Rowbotham).

0304-3959/$20.00
doi:10.1016/S0304-3959(03)00331-2

2. Methods

2.1. Participants

With local Ethics Committee approval and written informed patient consent, patients (American Society of Anesthesiologists classification I or II) scheduled for elective total abdominal hysterectomy were recruited on admission to the Leicester Royal Infirmary and Leicester General Hospital, UK. Patients with a history of drug or alcohol abuse, previous cannabis use and past or present psychiatric illness were excluded.

2.2. Design

General anesthesia was standardized. Induction was with propofol 1–2 mg/kg and atracurium 0.5 mg/kg to facilitate endotracheal intubation and positive pressure ventilation. Anesthesia was maintained with isoflurane (1–2 MAC) in a 50% nitrous oxide–oxygen mixture and morphine 0.1–0.2 mg/kg. Patient-controlled analgesia (PCA) using morphine (bolus dose 1 mg, lockout-time 5 min) was provided for the first 24 postoperative hours in all patients.

Randomization took place when PCA was discontinued on the second postoperative day and the patient requested further analgesia. Patients were randomized to receive a single, identical capsule of either oral δ-9-THC 5 mg or placebo in a double-blind fashion. Identical capsules were prepared by the hospital pharmacy in coded tablet bottles using a randomization table. Patients were consented before anesthesia but were not randomized and investigated if they were unable to tolerate oral fluids or were complaining of nausea or vomiting.

2.3. Measures

Pain was recorded hourly for 6 h and then at 8 and 24 h using a 10-cm visual analogue scale (VAS) on movement (sitting forward and coughing) and at rest. The primary outcome measure of this study was the sum of the pain intensity differences (SPID) on movement and at rest over a 6-h period. A secondary outcome measure was time to request for rescue analgesia (oral codeine 30 mg). Patients were able to ask for this at any time during the study.

At each time point and at 24 h after study medication, patients were asked to volunteer the nature and severity of any adverse events. They were then asked if they experienced any of the following specific symptoms: increased awareness of surroundings, drowsiness, dry mouth, dizziness, confusion, blurred or double vision, palpitations, sense of well-being, change of mood, slurred speech, difficulty with memory, hallucinations, headache, tremor and muscle twitching.

2.4. Statistical analysis

Data were tested for normality with the Kolmogorov–Smirnov test and compared using Student's *t*-test, MANOVA for repeated measures and Fisher's-exact test, as appropriate. For calculation of the SPID, if a patient requested escape analgesia before the end of the 6-h study period, subsequent pain intensity difference (PID) scores were set to zero. This is a recognized technique for handling such data (Curtis et al., 1999). We used two sets of data to power the study. In a previous study performed in our hospital investigating a similar group of patients receiving morphine PCA after abdominal hysterectomy, the standard deviation of VAS pain scores was 2.2 cm (Ali et al., 1998). Taking a 2 cm reduction in VAS as clinically significant, 20 patients were required in each group for $\alpha = 0.05$ and $\beta = 0.2$. Also, using data from a study (Curtis et al., 1999) which utilized the same postoperative pain model (pain after hysterectomy) to measure the efficacy of oral analgesics, our sample size would be able to detect a difference in mean PID of 15 mm ($\alpha = 0.05$, $\beta = 0.2$).

3. Results

3.1. Demographic variables

Fifty patients were consented for the study, 10 were not randomized because they did not fulfill the inclusion criteria at time of request for analgesia after PCA (four vaginal hysterectomy, two laparoscopic assisted procedure, two withdrawal of consent, one inability to tolerate oral fluids, one inadvertent administration of supplementary analgesia). No patient withdrew from the study after randomization. The groups were well matched for age, weight and pain scores before administration of study medication (Table 1).

3.2. Pain measures

After study medication, there were no differences in mean VAS pain scores (Table 2) or PID scores on movement and at rest (Fig. 1). Data for 8 and 24 h are not shown because the majority of patients received escape analgesia by 8 h (85% placebo, 100% δ-9-THC). There were no differences in mean SPID at 6 h or time to rescue analgesia (Table 3).

Table 1
Mean (SD) patient characteristics and baseline VAS pain scores. No significant differences

	Placebo ($n = 20$)	δ-9-THC ($n = 20$)
Age (yr)	47.8(10.2)	44.8(8.5)
Weight (kg)	61.1(9.8)	60.3(8.5)
Baseline VAS movement (cm)	6.3(2.6)	6.4(1.3)
Baseline VAS rest (cm)	3.2(1.9)	3.3(0.9)

Table 2
Mean (SD) VAS pain scores (cm) and number of evaluable patients at 0, 2, 4 and 6 h. No significant differences

	0 h	2 h	4 h	6 h
Placebo				
Movement	6.3(2.6)	5.5(2.4)	5.7(2.0)	4.7(2.1)
Rest	3.2(1.9)	2.6(1.5)	2.8(1.4)	2.3(1.4)
	$n = 20$	$n = 13$	$n = 8$	$n = 5$
δ-9-THC				
Movement	6.4(1.3)	6.5(2.6)	6.1(2.1)	5.5(2.2)
Rest	3.3(0.9)	3.3(1.7)	3.0(1.4)	2.8(1.5)
	$n = 20$	$n = 15$	$n = 7$	$n = 4$

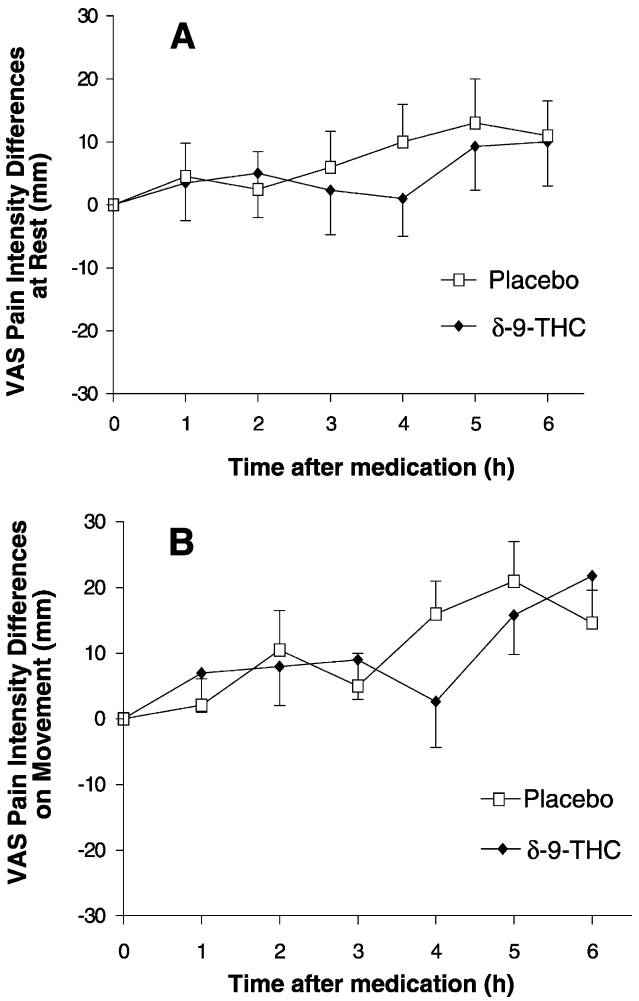

Fig. 1. Mean (SEM) VAS pain intensity differences (A) at rest and (B) on movement. No significant differences (MANOVA for repeated measures).

3.3. Side-effects

There was a significant increase in the incidence of increased awareness of surroundings in the δ-9-THC group (40 vs 5%, $P < 0.05$) but no differences in other adverse events (Table 4).

Table 3
Mean (SEM) and 95% confidence interval of the differences of summed pain intensity differences over 6 h ($SPID_{6h}$) (cm h) on movement and at rest, and mean (SEM) time to rescue analgesia (min). No significant differences

	Placebo ($n = 20$)	δ-9-THC ($n = 20$)	95% CI of differences
$SPID_{6h}$ moving (cm h)	7.9(2.5)	4.3(1.0)	−1.8 to 9.0
$SPID_{6h}$ at rest (cm h)	8.8(1.7)	4.9(1.2)	−0.2 to 8.1
Time to rescue analgesia (min)	217(34)	163(17)	−22 to 130

Table 4
Incidence of adverse events

Adverse event	Placebo, *n* (%)	δ-9-THC, *n* (%)
Increased awareness of surroundings	1(5)	8(40)*
Drowsiness	19(95)	18(90)
Dry mouth	15(75)	16(80)
Palpitations	5(25)	8(40)
Change of mood	6(30)	8(40)
Difficulty with memory	3(15)	2(10)
Slurring of speech	2(10)	3(15)
Blurred vision	3(15)	2(10)
Dizziness	6(30)	5(25)
Hallucinations	1(5)	0(0)
Headache	10(50)	8(40)
Involuntary muscle twitching	3(15)	3(15)
Tremor	2(10)	1(5)

Values shown are number of patients (%) reporting spontaneously, or on direct questioning, an adverse event at any time up to 24 h after study medication. *$P = 0.04$.

4. Discussion

We have shown no significant effect of oral δ-9-THC 5 mg on accumulative VAS pain scores over 6 h in patients with postoperative pain. The confidence intervals of the differences show that we are unlikely to have missed an important clinically significant analgesic effect of δ-9-THC. The limit of the 95% confidence interval of the SPID on movement over 6 h in favor of δ-9-THC was 1.8 cm, an average of 0.3 cm/h. Indeed, there was a non-significant tendency for less pain in the placebo group. Mean (SD) VAS pain scores on movement before administration of study medication (placebo 6.3(2.6) cm; δ-9-THC 6.4(1.3) cm) were sufficient to ensure adequate sensitivity of the study.

In 1975, it was suggested that 10 mg of δ-9-THC may have analgesic effects in patients with advanced cancer but the study was poorly controlled and relatively insensitive (Noyes et al., 1975). At this dose, 70% of patients reported sedation, 32% mental clouding, 29% ataxia and 29% 'disconnected thought'. This high incidence of adverse events and the fact that the recommended starting dose of δ-9-THC for appetite stimulation is 2.5 mg bd (Beal et al., 1995), led us to choose a dose of 5 mg for our study. In a case report of a patient with abdominal pain associated with familial Mediterranean fever, a higher dose was used but the patient was already obtaining pain relief by smoking

cannabis and was receiving regular morphine (Holdcroft et al., 1997).

We did not measure blood concentrations of δ-9-THC. However, there is little reason to suspect that it was not absorbed, as only patients who could tolerate oral fluids and those who were not suffering from nausea and/or vomiting were recruited. Furthermore, studies of this design have been able to show significant analgesic effects of other drugs administered orally under identical circumstances (Curtis et al., 1999). After oral administration of δ-9-THC, the onset of action is usually within 0.5–1 h with a duration of effect of 4–6 h. Therefore, our study period of 6 h should have been able to detect any analgesic effect. A recognized adverse effect of cannabinoids use is an increased awareness of surroundings (Adams and Martin, 1996) and this was reported by 40% of our patients who received δ-9-THC (placebo 5%).

In conclusion, we have shown that oral δ-9-THC 5 mg was ineffective for postoperative pain in the conditions of our study. Further investigation of a larger dose or repeated administration may be warranted, but this has been associated with a high incidence of side-effects (Noyes et al., 1975). Data on the effect of other cannabinoids for postoperative pain are lacking.

References

Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. Addiction 1996;91:1585–614.

Ali PB, Cotton BR, Williamson KM, Smith G. Intraperitoneal bupivacaine or lidocaine does not provide analgesia after total abdominal hysterectomy. Br J Anaesth 1998;80:245–7.

Ashton CH. Adverse effects of cannabis and cannabinoids. Br J Anaesth 1999;83:637–49.

Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage 1995;10:89–97.

Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative, systematic review. Br Med J 2001;323:13–16.

Curtis GB, Johnson GH, Clark P, Taylor R, Brown J, O'Callaghan R, Shi M, Lacouture PG. Relative potency of controlled-release oxycodone and controlled-release morphine in a postoperative pain model. Eur J Clin Pharmacol 1999;55:425–9.

Hirst RA, Lambert DG, Notcutt WG. Pharmacology and potential therapeutic uses of cannabis. Br J Anaesth 1998;81:77–84.

Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, Evans F. Pain relief with oral cannabinoids in familial Mediterranean fever. Anaesthesia 1997;52:483–6.

Kirk JM, De Wit H. Responses to oral delta-9-tetrahydrocannabinol in frequent and infrequent marijuana users. Pharmacol Biochem Behav 1999;63:137–42.

Martin BR, Lichtman AH. Cannabinoid transmission and pain perception. Neurobiol Dis 1998;5:447–61.

Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. Nature 1998;395:381–3.

Noyes R, Brunk SF, Avery DH, Canter A. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther 1975;18:84–9.

Ravenscroft A, Ahmed YS, Burnside IG. Chronic pain after SCI. A patient survey. Spinal Cord 2000;38:611–4.

Voth EA, Schwartz RH. Medicinal applications of delta-9-tetrahydrocannabinol and marijuana. Ann Intern Med 1997;126:791–8.

Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. Pain 2003;102:211–6.