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A Multicenter Dose-escalation Study of the Analgesic and Adverse Effects of an Oral Cannabis Extract (Cannador) for Postoperative Pain Management

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Background: **Cannabinoids have dose-related antinociceptive effects in animals. This clinical study aimed to investigate whether a single oral dose of cannabis plant extract (Cannador; Institute for Clinical Research, IKF, Berlin, Germany) could provide pain relief with minimal side effects for postoperative pain.**

Methods: **Patients (aged 18–75 yr) were recruited and consented before surgery if patient-controlled analgesia was planned for provision of postoperative pain relief. Each patient received a single dose of 5, 10, or 15 mg Cannador if he or she had at least moderate pain after stopping patient-controlled analgesia. Starting with 5 mg, dose escalation was based on the number of patients requesting rescue analgesia and adverse effects. Pain relief, pain intensity, and side effects were recorded over 6 h and analyzed using tests for trend with dose.**

Results: **Rescue analgesia was requested by all 11 patients (100%) receiving 5 mg, 15 of 30 patient (50%) receiving 10 mg, and 6 of 24 patients (25%) receiving 15 mg Cannador (log rank test for trend in time to rescue analgesia with dose $P < 0.001$). There were also significant trends across the escalating dose groups for decreasing pain intensity at rest ($P = 0.01$), increasing sedation ($P = 0.03$), and more adverse events ($P = 0.002$). The number needed to treat to prevent one rescue analgesia request for the 10-mg and 15-mg doses, relative to 5 mg, were 2.0 (95% confidence interval, 1.5–3.1) and 1.3 (95% confidence interval, 1.1–1.7), respectively. The study was terminated because of a serious vasovagal adverse event in a patient receiving 15 mg.**

Conclusion: **These significant dose-related improvements in rescue analgesia requirements in the 10 mg and 15 mg groups provide a number needed to treat that is equivalent to many routinely used analgesics without frequent adverse effects.**

ACUTE pain after surgery remains a therapeutic problem because many of the commonly used drugs prove inadequate through lack of efficacy or side effects. Newer analgesic products are being developed through an in-depth understanding of the neurochemical systems involved in pain processing[1,2] including the endocannabinoid system.[3] Selective cannabinoid agonists have been demonstrated to suppress nociceptive transmission in spinal cord, periaqueductal gray, and thalamus in a dose-related manner.[1] Exogenous cannabinoids have been tested in clinical trials in chronic pain disorders such as visceral pain,[4] neuropathic pain,[5–10] and multiple sclerosis.[11–13] Results vary with the clinical setting, possibly because of the diversity of psychological and pathologic processes in chronic pain states. In postoperative pain, there are fewer effects of chronic disease, but more heterogeneity in patient conditions. However, a recent meta-analysis concluded that if specific standards were met, such as at least moderate pain to enter a study, a 6-h study duration, and avoidance of bias, then a study combining different surgical interventions could provide a high-level evidence base for analgesic response.[14]

Clinical trials of analgesic drugs have studied single cannabinoids such as synthetic δ-9-tetrahydrocannabinol (THC, dronabinol), ajulemic acid (CT-3), or cannabis extracts containing phytocannabinoid mixtures such as THC and cannabidiol. The advantages of ajulemic acid and cannabidiol are a lack of affective side effects and the potential for antiinflammatory activity.[10,15] For postoperative pain, a THC–cannabidiol mixture offers the potentially distinctive role of analgesia and antiinflammatory effects as well as relief of muscle spasm, reduction of nausea and vomiting, and appetite stimulation. It may thus support postsurgical recovery without adverse effects such as respiratory depression, renal failure, or gastrointestinal ulceration.

Results from the few clinical trials addressing the use of cannabinoids for acute postoperative pain have been

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mixed. No analgesic effects were reported from a randomized, double-blind, crossover study of 10 males who each received intravenous placebo, diazepam, or two doses of THC for dental extraction pain.[16] In a randomized, placebo-controlled trial of 56 postsurgical or trauma patients, the cannabinoid levonantradol provided non–dose-dependent pain relief, but adverse side effects limited further study.[17] More recently, THC, either as a capsule (in a randomized, placebo-controlled, double-blind trial) or sublingual spray (dose-escalation study), has been reported to have no analgesic effects at 5 mg after abdominal hysterectomy.[18] However, higher doses of THC were effective in the treatment of cancer pain.[19]

This study was designed to test whether a standardized cannabis plant extract was analgesic in the context of acute pain after surgery. We chose to deliver a single dose because clinical effects from the oral route can last as long as conventional oral analgesics, *i.e.*, up to 6 h.

Materials and Methods

Study Design

This was a dose-escalation study of the postoperative pain-relieving qualities of oral cannabis (Cannador). The study recruited all types of surgical patients requiring overnight patient-controlled analgesia with morphine. Cannador was given after patients chose to stop patient-controlled analgesia use and when oral analgesic administration was clinically indicated. Rescue analgesia was available at all times based on the standard postoperative guidelines at each participating hospital.

Patient Selection

For inclusion, patients had to be aged 18–75 yr, be experiencing at least moderate pain, weigh more than 50 kg to avoid overdosing with a fixed dose, be able to take oral medications, have treatment for hypertension or chronic pain stabilized, and have an American Society of Anesthesiologists physical status of I or II. The exclusion criteria were nausea, abnormal liver or renal function, pregnancy or lactation, coronary heart disease, central nervous system–related drugs such as sedatives and anxiolytics, history of psychosis or depression, epilepsy, diabetes, reported cannabis use in the 6 weeks before surgery, and nut allergy.

Study Drug, Doses, and Sample Size

Cannador provided a product of pharmaceutical quality containing a mixture of cannabinoid plant extracts and was donated by the Institute for Clinical Research (IKF, Berlin, Germany). THC and cannabidiol extracts predominated and were in the ratio of 1:0.3 for the 5-mg dose group and 1:0.5 for the other groups. Each capsule contained 2.5 mg THC in a gelatin base, and the dose related to the THC content. For this single-dose study, the choice of dose (5, 10, or 15 mg) was based on the work of Noyes *et al.*[19] using THC alone in patients with cancer pain.

Dose escalation was based on the proportion of patients requesting rescue analgesia to minimize the number of patients receiving inadequate pain relief. Beginning with 5 mg, each dose was given to either 14 or 30 consecutive patients. If 11 or more of the first 14 patients requested rescue analgesia during the subsequent 6 h, the dose would be increased. If 10 or fewer of the first 14 patients made this request, a total of 30 patients would receive the dose. This used the optimal two-stage design of Simon[20] to minimize the expected sample size under the null hypothesis. The sample size calculation for each stage assumed that 80% of patients on a poor dose and 50% on an adequate dose would request rescue analgesia, and set the probability of rejecting an adequate dose or accepting a poor dose at 0.05.

Study Measures

The frequency and timing of rescue analgesia provided an indicator of analgesic efficacy. Pain relief at rest was assessed using a verbal rating scale (VRS) of 0–4 (none, slight, moderate, good, complete). Pain intensity at rest and on movement was assessed using a VRS of 0–3 (none, mild, moderate, severe). Sedation was scored from 0 to 3 (alert, mildly drowsy, moderately drowsy, asleep), and mood was scored by a 100-mm visual analog scale anchored at each end (0 = best I could feel, 100 = worst I could feel). Nausea, vomiting, and vital signs (pulse, blood pressure, and respiratory rate) were recorded. Assessments were made before drug administration and then hourly for 6 h. In addition, pain relief, pain intensity at rest, and sedation were recorded at 30 and 90 min to estimate the timing of peak effects more precisely. At the end of the study, both patient and researcher made independent global assessments of treatment effectiveness on a VRS from 0 to 4 (poor, fair, good, very good, excellent).

Adverse events were recorded by the researchers at the time of the event with follow-up where necessary until the event was resolved. Severity was recorded as mild, moderate, or severe, and causality was recorded as none, remote, possibly, probably treatment related, or not assessable. Serious adverse events were recorded separately in accordance with International Conference on Harmonisation Good Clinical Practice guidelines.#

Study Administration

Twelve centers contributed patients between October 2001 and July 2003. Multicenter and local research ethics committees and the Medicines and Healthcare products

International Conference on Harmonisation of Technical Requirements of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice 1996. Available at: www.ich.org/pdfifpma/e6.pdf. Accessed October 12, 2005.

Regulatory Agency (London, United Kingdom) gave approval. Home Office licenses were granted to participating consultants and pharmacists. Independent oversight was provided by a Trial Steering Committee and Data Monitoring and Ethics Committee; the latter reviewed rescue analgesia and adverse events before dose increases.

Study Process

Detailed screening logs were kept for a 3-month period from April to June 2003 so that the study recruitment process could be monitored. A total of 135 patients were found to be eligible at preoperative screening, and 44 gave written consent (33%). Of these, 34 (77%) received patient-controlled analgesia postoperatively, and 20 (59%) of these fulfilled the postoperative inclusion criteria and received Cannador capsules. During this 3-month period, 20 (15%) of the 135 patients eligible preoperatively were studied postoperatively.

Protocol Violations

There were nine protocol violations out of the entire study population who fulfilled the postoperative inclusion criteria. Three patients had mild nausea at baseline (one at 5 mg, two at 10 mg), three patients had only mild resting pain intensity at baseline (one at 5 mg, two at 10 mg), one patient (10 mg) had not had elective surgery, one patient (10 mg) was studied 12 days after surgery, and one patient (15 mg) vomited the capsules shortly after administration and no further assessments were made. All patients who received Cannador were included in the analysis.

Statistical Analysis

Pain relief during the 6-h assessment period was summarized using the sum of the total pain relief VRS scores at the eight assessments (0.5, 1, 1.5, 2, 3, 4, 5, and 6 h). Pain intensity was summarized by the sum of the pain intensity VRS differences from baseline ($P_0 - P_t$), where P_0 is the baseline score. Sedation VRS and mood visual analog scale were analyzed in a similar way to pain intensity. If rescue analgesia was required, all subsequent scores were set to baseline (or zero for pain relief). Higher values for summary measures therefore correspond to improvements in pain relief, pain intensity, sedation, or mood.

Statistical analysis consisted of tests for trend with dose: logistic regression for binary data (*e.g.*, presence/absence, yes/no), a nonparametric test for trend for continuous nonnormal data (*e.g.*, sum of the total pain relief VRS scores),[21] and a log rank test for trend for time to rescue analgesia. In a *post hoc* analysis, given the lack of analgesic effect in the 5-mg dose group, the number needed to treat (NNT) to prevent one rescue analgesia request for the 10-mg and 15-mg dose groups compared with 5 mg was calculated. The NNT is the reciprocal of the absolute risk difference.[22]

Results

Numbers Studied for Each Dose

The first 11 patients at the 5-mg dose all requested rescue analgesia, so the dose was considered to provide inadequate analgesia and was stopped. For the 10-mg dose, only 6 of the first 14 patients required rescue analgesia, so recruitment continued for 30 patients. At 15 mg, 3 of the first 14 patients required rescue analgesia, and recruitment was subsequently stopped according to the predetermined protocol when the 24th patient had a serious adverse event.

Baseline Characteristics

The number of centers contributing patients increased from two for the 5-mg dose to eight for the 15-mg dose. There were no significant trends with dose for age, physical and medical characteristics, baseline values for pain intensity at rest and on movement, sedation, nausea, and mood assessments except diastolic blood pressure ($P = 0.03$; table 1). No patients had detectable urinary cannabinoids on screening. Apart from the different distribution of surgical types, the three dose groups were similar at baseline.

Outcome Measures for Each Dose

Rescue Analgesia. Rescue analgesia was requested by all 11 patients receiving the 5-mg dose (100%), 15 of 30 (50%) of patients receiving the 10-mg dose, and 6 of 24 (25%) of patients receiving the 15-mg dose (table 2). There was a highly significant linear trend ($P < 0.001$) in time to rescue analgesia with dose (fig. 1). There is a clear separation of the curve for the 5-mg dose from 2 h after capsule administration, whereas the curves for the 10-mg and 15-mg doses do not diverge until 4 h. The NNT to prevent one request for rescue analgesia for the 10-mg and 15-mg doses, relative to 5 mg, were 2.0 (95% confidence interval, 1.5–3.1) and 1.3 (95% confidence interval, 1.1–1.7), respectively.

Pain. Summary measures for pain relief and pain intensity are presented in table 2. There was no significant linear trend with dose for sum of the total pain relief VRS scores ($P = 0.17$). Mean pain relief for each assessment is shown in figure 2 and was similar for all three doses up to 1.5 h but then fell off more rapidly for 5 mg. There were significant linear trends for improvement in pain intensity with dose for sum of the pain intensity VRS differences at rest ($P = 0.01$). Sum of the pain intensity VRS differences on movement, and the global evaluation scores did not show significant trends with dose.

Other Effects. There were significant trends for sedation ($P = 0.03$) and nausea ($P = 0.06$) with increasing dose (table 3). There were no significant trends for vomiting ($P = 0.2$) or mood ($P = 0.6$).

There were no statistically significant trends in the proportion of patients showing a clinically important

Table 1. Baseline Characteristics for Each Dose Group

Variable	5 mg (n = 11)	10 mg (n = 30)	15 mg (n = 24)	*P* Value
No. of centers contributing patients	2	5	8	
Age, yr	45 ± 7	50 ± 13	53 ± 12	0.09
Weight, kg	81 ± 14	79 ± 19*	77 ± 13	0.5
Height, m	1.6 ± 0.08	1.7 ± 0.12	1.7 ± 0.11	0.2
BMI, kg/m^2	31 ± 5	28 ± 5	28 ± 5	0.13
Male sex	1(9)	12(40)	5(21)	0.9
Race				
Black	1 (9)	5 (17)	1 (4)	
White	10 (91)	22 (76)	23 (96)	
Mixed	0 (0)	2 (7)	0 (0)	
Type of surgery				
Breast	1 (9)	4 (13)	0 (0)	
General	0 (0)	2 (7)	2 (8)	
Gynecologic	6 (55)	5 (17)	16 (67)	
Orthopedic	1 (9)	17 (57)	5 (21)	
Plastic	3 (27)	2 (7)	1 (4)	
ASA physical status I, *i.e.*, no medical problems	9 (82)	19/28 (68)	19 (79)	0.9
Heart rate, beats/min	74 ± 9	84 ± 10	77 ± 12	0.9
Systolic blood pressure, mmHg	116 ± 15	126 ± 17	123 ± 15	0.4
Diastolic blood pressure, mmHg	75 ± 13	76 ± 11	69 ± 8	0.03
Pain intensity VRS at rest				1.0
Mild	1 (9)	2 (7)	0 (0)	
Moderate	9 (82)	26 (87)	24 (100)	
Severe	1 (9)	2 (7)	0 (0)	
Pain intensity VRS on movement				0.9
Moderate	4 (36)	19 (63)	11 (46)	
Severe	7 (64)	11 (37)	13 (54)	
Sedation				0.2
Alert	5 (50)	22 (73)	18 (75)	
Mildly drowsy	5 (50)	8 (27)	6 (25)	
Nausea				
Mild	1 (10)	2 (7)	0 (0)	0.5
Postoperative vomiting	3 (27)	4 (13)	6 (25)	0.9
Treatment for postoperative nausea and vomiting	5 (45)	14 (47)	12 (50)	0.8
Mood VAS†	53 [43–65]	48 [34–68]	36 [27–70]	0.4

Summary measures are mean ± SD, number (%), or median [interquartile range]. *P* value from test for trend with dose.

* n = 29. † Higher visual analog scale (VAS) scores indicate worse mood.

ASA = American Society of Anesthesiologists; BMI = body mass index; VRS = verbal rating scale.

change in cardiovascular measures (*i.e.*, 20% increase or decrease from baseline), and no patient required pharmacologic treatment. However, heart rate increased by more than 20% in 19 patients, and one patient in each of the 10-mg and 15-mg groups reached 50–60 beats/min above normal. Systolic and diastolic blood pressure decreases of more than 20% were measured in 9 and 10 patients, respectively, at the higher doses.

Adverse Effects

There were 26 adverse events recorded among 19 patients (table 4). There was a significant linear trend with dose in the proportion of patients with any adverse events ($P = 0.002$). There was one serious vasovagal adverse event (transient hypotension, pallor, bradycardia, and oxygen desaturation that recovered rapidly without pharmaceutical intervention) at the 15-mg dose, and recruitment to the trial was therefore stopped. The majority of adverse events affected the central nervous (14 of 26) or cardiovascular (6 of 26) systems; none persisted after the study.

Discussion

In this dose-escalation study of a single dose of 5, 10, or 15 mg cannabis extract, the two higher doses reduced demands and extended time lag for rescue analgesia (50% and 75% of patients having no additional analgesia) and decreased pain intensity at rest. The study had adequate power to detect differences between groups. It required a large number of patients to be assessed for recruitment because of the high dropout rate before the study. This rate was not unexpected given postoperative exclusion factors such as nausea and sedation that are common complications of patient-controlled analgesia with morphine. The 5-mg low dose had no demonstrable clinical effects, and these results from a cannabinoid mixture of 1:0.3 THC/cannabidiol are similar to those reported by Buggy *et al.*[18] for pain intensity difference after a capsule of 5 mg THC alone (*i.e.*, without the addition of other cannabinoids) in a double-blind, placebo-controlled study in women after hysterectomy. The only difference between the studies was in the fre-

Table 2. Outcome Measures: Rescue Analgesia, Pain Relief, Pain Intensity, and Global Assessment of Effectiveness

Outcome Measure	5 mg (n = 11)	10 mg (n = 30)	15 mg (n = 24)	*P* Value
Rescue analgesia	11 (100)	15 (50)	6 (25)	< 0.001*
Pain relief				
TOTPAR VRS†	4 [1–15]	11 [7–16]	14 [3–18]	0.17
Pain intensity				
SPID VRS at rest†	3 [−1 to 5]	3 [0–6]	5 [1–9]	0.01
SPID VRS on movement†	0 [0–3]	1 [0–3]	1 [0–5]	0.7
Global evaluation: assessor				0.9
Poor	4 (36)	4 (14)	5 (22)	
Fair	1 (9)	10 (34)	7 (30)	
Good	3 (27)	11 (38)	5 (22)	
Very good	3 (27)	4 (14)	5 (22)	
Excellent	0 (0)	0 (0)	1 (4)	
Global evaluation: patient				0.8
Poor	2 (18)	4 (14)	6 (26)	
Fair	3 (27)	3 (10)	3 (13)	
Good	3 (27)	18 (62)	9 (39)	
Very good	3 (27)	3 (10)	4 (17)	
Excellent	0 (0)	1 (3)	1 (4)	

Data are number (%) or median [interquartile range]. *P* value from test for trend with dose.

* Log rank test for trend in time to rescue analgesia. † Higher values of summary measures indicate improvement.

SPID = sum of pain intensity differences; TOTPAR = total pain relief; VRS = verbal rating scale.

quency of side effects. For THC alone, 40% of women reported altered awareness, which differed significantly from placebo and from the current study, where adverse events were minimal in the 5-mg group, and may be due to differences in formulation of the cannabinoids, the type of surgery, or lack of blinding.

The analgesic effect of Cannador can be demonstrated using the NNT. We used the 5-mg cohort as a surrogate for a placebo group because lack of clinical activity has been demonstrated in this and in other studies.[18] The estimated NNT to prevent one request for rescue analgesia for the 10-mg and 15-mg Cannador dose groups relative to the 5-mg group is 2.0 for 10 mg and 1.3 for 15 mg. These values are similar to the NNTs of commonly used orally administered drugs for moderate pain intensity such as morphine, paracetamol, and ibuprofen[23] and indicate a potential role for cannabinoids in postoperative pain management.

For all drugs, their benefits must be weighed against adverse effects. One method is to use a global assessment so that the overall value of a drug for a patient is measured. The test for trend demonstrated no change for these subjective measures, and this result may reflect our unblinded study design. More objective physiologic assessments were also in place. For example, the reported cardiovascular effects of cannabis in humans are tachycardia on acute ingestion[24] and hypotension and bradycardia after prolonged ingestion.[25] A vasovagal episode was documented by Notcutt *et al.*[9] 1 h after the first administered dose of sublingual THC and was attributed to the sitting position and a high dose. Dizziness was also reported and is common in most other studies,

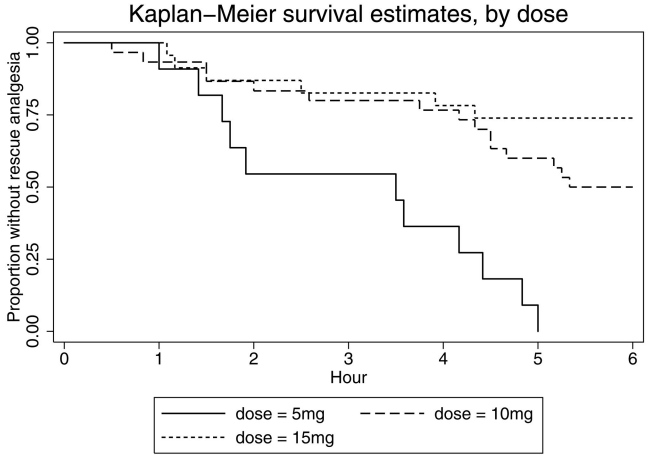

Fig. 1. Kaplan-Meier plot of the time to rescue analgesia for 5-, 10-, and 15-mg doses (log rank test for trend with dose $P < 0.001$).

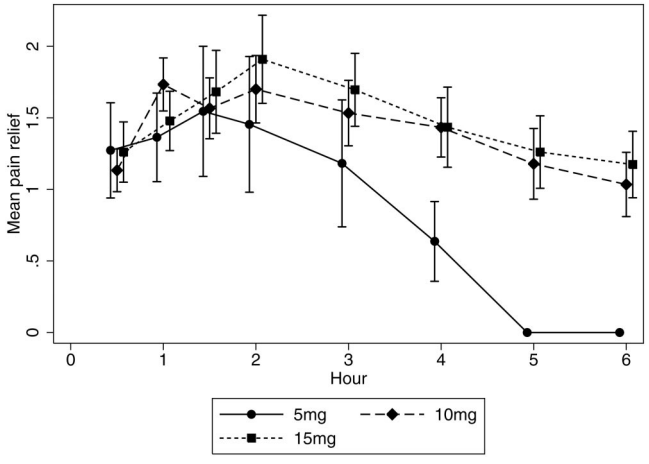

Fig. 2. Mean pain relief (as verbal rating scale, 0 = no to 4 = complete) at each assessment for each dose. Pain relief set to zero after rescue analgesia. *Bars* correspond to ±1 SE.

Table 3. Other Effects: Sedation, Nausea, Vomiting, Mood, Heart Rate, and Blood Pressure

Variable	5 mg (n = 11)	10 mg (n = 30)	15 mg (n = 24)	*P* Value
Nausea	1 (9)	0 (0)	6 (25)	0.06
Vomiting	1 (9)	0 (0)	4 (17)	0.2
Change in sedation VRS*	0 [−1 to 0]	−2 [−4 to 0]	−3 [−8 to 0]	0.03
Change in mood VAS*	−11 [−82 to 16]	41 [0 to 89]	−8 [−38 to 96]	0.6
Maximum increase from baseline heart rate > 20%	2 (18)	8 (27)	9 (38)	0.2
Maximum decrease from baseline heart rate > 20%	0 (0)	1 (3)	2 (8)	0.3
Maximum increase from baseline systolic blood pressure > 20%	1 (9)	1 (3)	2 (8)	0.9
Maximum decrease from baseline systolic blood pressure > 20%	0 (0)	4 (13)	5 (21)	0.12
Maximum increase from baseline diastolic blood pressure > 20%	0 (0)	3 (10)	3 (13)	0.3
Maximum decrease from baseline diastolic blood pressure > 20%	1 (9)	4 (13)	6 (25)	0.2

Data are number (%) or median [interquartile range]. *P* value from test for trend with dose.

* Higher values of summary measures indicate improvement.

Mood = sum of mood visual analog scale changes from baseline; Nausea = any worsening from baseline nausea VRS during 6-h assessment period; Sedation = sum of sedation verbal rating scale changes from baseline; VAS = visual analog scale; Vomiting = any vomiting during 6-h assessment period; VRS = verbal rating scale.

although without blood pressure measurement to confirm a cardiovascular origin.[8,13] In rodents, acute administration of THC elicits hypotension and bradycardia through central and peripheral activities.[26] Therefore, our report of a serious adverse event presenting as supine hypotension, pallor, bradycardia, and oxygen desaturation at the 15-mg dose is not unexpected. The paleness of the skin without any change in blood volume would suggest mesenteric vasodilation, similar in mechanism to that described for endogenous cannabinoids.[27] Nevertheless, the overall results of our study do not demonstrate dose-related cardiovascular effects.

Table 4. Adverse Events

Variable	5 mg (n = 11)	10 mg (n = 30)	15 mg (n = 24)	*P* Value
Any adverse event	1 (9)	6 (30)	12 (50)	0.002
All adverse events*	1	6	19	
Adverse event timing*				
Before rescue analgesia	0	4	15	
After rescue analgesia	1	2	4	
Adverse event severity*				
Mild	1	5	13	
Moderate	0	0	3	
Severe	0	1	2	
Serious	0	0	1	
Adverse event causality*				
Remote	0	1	4	
Possible	1	2	5	
Probable	0	3	10	
Central nervous system*	1	4	9	
Acutely paranoid			2	
Cognitive function			1	
Dizzy or light-headed	1	1	2	
Unpleasant mood effect		2	2	
Sensory disturbance			1	
Sleep disturbance			1	
Headache		1		
Cardiovascular system*	0	2	4	
Hypotension		1		
Hypoxia			1	
Cholinergic			1	
Pulmonary embolism		1		
Tachycardia			2	
Gastrointestinal system*	0	0	3	
Dry mouth			2	
Vomit			1	
Whole body*	0	0	3	
Pallor			2	
Pyrexia			1	

Data are total number (% of patients). *P* value from test for trend with dose.

* All adverse events; there may be more than one adverse event per patient.

Sedation is commonly reported after cannabinoid administration and was included as one of our outcome measures. There was a small but significant increase in sedation with dose. These results contrast both with scores of 24 out of 34 for sedation at 10 mg and 32 out of 34 at 20 mg THC in the Noyes *et al.*[19] study of cancer pain and with longer-term multiple sclerosis studies where the placebo group had a similar amount of somnolence as the THC or cannabis extract group.[11,13]

Cannabinoids such as nabilone are licensed as antiemetic drugs, and THC is licensed as an appetite stimulant. Nausea and vomiting were therefore outcome measures. There were no significant trends, although the high-dose group reported more nausea and vomiting. Unfortunately, these equivocal results are limited by the lack of a placebo group. Postsurgical analgesic drugs that lack emetic effects are preferred. Interestingly, antiemetic effects have not been a major outcome measure in any of the recent clinical trials of cannabinoids in pain patients.[18] We advocate further trials to investigate the efficacy of cannabinoids in alleviating postoperative nausea and vomiting.

Effects of central-acting cannabinoids on mood have been repeatedly investigated. The cannabis extract chosen for this study was not selective to the nociceptive system, and central nervous system effects were unavoidable. Therefore, for safety, the study design was to increase the dose with full unblinded monitoring. Our study used a visual analog scale to assess mood effects. In addition, there were four reports of unpleasant mood effects at the higher doses. All patients had experienced morphine through the patient-controlled analgesia regimen before entering the study. In future studies, consideration will have to be given to recruitment of cannabis users, recruitment of young adults, and tests for a prepsychotic condition.[28]

The study design chosen allowed analgesic and side effect differences between the doses to be detected in the context of different types of surgery as advocated for such studies.[14] Secondary effects that add quality to postoperative pain relief such as reduced pain on movement and prevention of postoperative nausea and vomiting were not demonstrated. Other results included instability in cardiovascular effects and mood effects, but these were not dose related and may be an inherent limitation in an open study in which there is no comparison with placebo. The optimal dose was determined to be 10 mg Cannador because it was effective in providing pain relief at rest without serious or severe side effects in a fit adult group of postsurgical patients.

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