Cannabinoid–Opioid Interaction in Chronic Pain

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Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions. Twenty-one individuals with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone were enrolled in the study and admitted for a 5-day inpatient stay. Participants were asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2–4, and in the morning of day 5. Blood sampling was performed at 12-h intervals on days 1 and 5. The extent of chronic pain was also assessed daily. Pharmacokinetic investigations revealed no significant change in the area under the plasma concentration–time curves for either morphine or oxycodone after exposure to cannabis. Pain was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis. We therefore concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.

Selecting an appropriate treatment for chronic pain remains problematic. Although opioids are effective analgesics, dose-limiting side effects such as sedation, nausea and vomiting, and fear of dependence often limit their use at higher—and possibly more effective—doses. Of particular interest is the potential for enhanced analgesic effect with the use of cannabinoids and opioids in combination. Such a combination would allow for opioid analgesic effects to be achieved at lower dosages than are necessary when the opioids are used alone.[1–4] As increasing numbers of patients turn to medicinal cannabis to augment the effects of opioid analgesics, the data on the potential pharmacokinetic interactions and clinical safety of the combination need to be evaluated.

Cannabinoids and opioids share several pharmacologic properties, including antinociception; a tendency to induce hypothermia, sedation, and hypotension; and inhibition of intestinal motility and locomotor activity.[1,5,6] Initially, investigators postulated that cannabinoids and opioids act on the same pathways to produce their pharmacological actions.[7,8] Subsequent preclinical research conducted over the past decade has clarified the nature of the interaction; these data suggest the existence of independent but related mechanisms of antinociception for cannabinoids and opioids.[5]

Synergy in analgesic effects between opioids and cannabinoids has been demonstrated in animal models. The antinociceptive effects of morphine are mediated predominantly by mu opioid receptors but may be enhanced by delta-9-tetrahydrocannabinol (THC) activation of kappa and delta opiate receptors.[8] It has further been suggested that the cannabinoid–opioid interaction may occur at the level of their signal transduction mechanisms.[9,10] Receptors for both classes of drugs are coupled to similar intracellular signaling mechanisms that lead to a decrease in cyclic adenosine monophosphate production via G protein activation.[10–12] There is also some evidence that cannabinoids increase the synthesis and/or release of endogenous opioids.[2,3,12,13]

In addition to these potential pharmacodynamic interactions, there is the potential for pharmacokinetic interaction between cannabinoids and other drugs. Cannabinoids have been shown to affect the kinetics of other drugs in several ways. They inhibit the CYP450-mediated metabolism of some drugs, slow the absorption of others, and may also enhance penetration of some drugs into the brain.[14–16] Our prior study of oral delta-9-THC and smoked cannabis in patients with HIV on protease inhibitor therapies showed that oral THC had no effect on the pharmacokinetics of the antiviral agents.[17] However, smoked cannabis decreased the 8-h area under the plasma concentration–time curve (AUC) of both nelfinavir (−17.4%, $P = 0.46$) and indinavir (−14.5%, $P = 0.07$). In a study involving 24 patients with cancer, cannabis administered as a medicinal tea did not alter the pharmacokinetics of the chemotherapy agents irinotecan and docetaxel.[18]

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Inhalation of vaporized cannabis delivers levels of THC and other cannabinoids similar to those from smoked marijuana but without exposure to combustion products.[19] Here we describe the disposition kinetics of sustained-release morphine and oxycodone, as well as pain ratings and other subjective responses, before and after 4 days of treatment with vaporized cannabis.

RESULTS

Study participants

A total of 315 potential participants were assessed for eligibility between January 2007 and February 2009; most of them were deemed ineligible because they either did not have pain, were not taking the appropriate opioids, or were receiving opioids three times a day. A total of 24 participants were enrolled, 13 of whom were on morphine treatment and 11 on oxycodone. Of those on morphine, 3 participants did not complete the study, leaving 21 evaluable participants (10 on morphine, and 11 on oxycodone) (see **Table 1**). Most of the participants (11 men and 10 women) were white. The average age was 42.9 (range = 33–55) years in the morphine cohort and 47.1 (range = 28–61) years in the oxycodone cohort. The mean morphine dose was 62 mg twice a day (range = 10–200 mg) and the mean oxycodone dose was 53 mg twice a day (range = 10–120 mg). The origin of the participants' pain was musculoskeletal (not otherwise specified) (seven); posttraumatic (four); arthritic (two); peripheral neuropathy (two); cancer, fibromyalgia, migraine, multiple sclerosis, sickle cell disease, and thoracic outlet syndrome (one each).

Pain

Pain ratings on day 1 (before exposure to vaporized cannabis) and on day 5 (after exposure to vaporized cannabis) are shown in **Table 2**. Participants on oxycodone had higher mean pain scores at baseline (mean = 43.8; 95% confidence interval (CI) = 38.6, 49.1) compared with those on morphine (mean = 34.8; 95% CI = 29.4, 40.1). Participants in both groups reported statistically significant reductions in pain ratings on day 5 as compared with day 1. The mean percentage change in pain was statistically significant overall as well as for the patients on morphine, but not for those on oxycodone.

Table 1 Participant characteristics

	Morphine group	Oxycodone group
n	10	11
Women	4	6
Caucasian	8	9
Mean age (range)	42.9 (33–55)	47.1 (28–61)
Mean opioid dose (mg) (range)	62 Twice daily (10–200)	53 Twice daily (10–120)
Mean pain score day 1 (95% CI)	34.8 (29.4, 40.1)	43.8 (38.6, 49.1)

CI, confidence interval.

Opioid disposition kinetics

Mean plasma concentration–time curves for morphine and oxycodone with and without cannabis treatment are shown in **Figure 1**. There was no statistically significant change in the AUC_{12} for either of these opiates (see **Table 3**). There was a statistically significant decrease in maximum concentration (C_{max}) of morphine sulfate during cannabis exposure. The time to C_{max} of morphine tended to be delayed during cannabis treatment, although this effect was not statistically significant. Cannabis had no significant effect on oxycodone kinetics. During cannabis treatment, there were no significant changes in the AUCs of the metabolites of either morphine or oxycodone or in the ratios of individual metabolites to the parent drug.

Plasma THC levels

Mean plasma THC levels were 1.8 ng/ml (SD = 1.5) at baseline, 126.1 ng/ml (SD = 86.2) at 3 min, 33.7 ng/ml (SD = 28.9) at 10 min, 10.9 ng/ml (SD = 9.3) at 30 min, and 6.4 ng/ml (SD = 5.6) at 60 min. The peak THC concentration occurred at 3 min in all the participants. THC plasma levels did not vary significantly by opioid group.

Monitoring of effects

Cannabis inhalation produced a subjective "high" that was not present with the use of opioids alone (see **Figure 2**). In addition, the participants in the morphine cohort felt significantly more stimulated and less hungry on day 5 than on day 1 (see **Table 4**), whereas those in the oxycodone group were less anxious on day 5 as compared with day 1. Other than these, there were no significant changes in the subjective effects measured. No clinically significant adverse events were reported. Pulse oximetry monitoring did not reveal any episodes of lowered oxygen saturation after cannabinoids were added to the participants' stable opioid regimens.

DISCUSSION

Our study findings support preclinical observations that cannabis augments the analgesic effects of opioids. We studied individuals with chronic pain who were taking stable doses of sustained-

Table 2 Pain by study day

		Day 1	Day 5	Difference	Percentage change
	n	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Overall	21	39.6 (35.8, 43.3)	29.1 (25.4, 32.8)	−10.7 (−14.4, −7.3)	−27.2 (−45.5, −8.9)
Morphine	11	34.8 (29.4, 40.1)	24.1 (18.8, 29.4)	−11.2 (−16.5, −6.0)	−33.7 (−63.8, −3.5)
Oxycodone	10	43.8 (38.6, 49.1)	33.6 (28.5, 38.6)	−10.3 (−14.8, −5.8)	−21.3 (−47.0, 5.3)

CI, confidence interval.

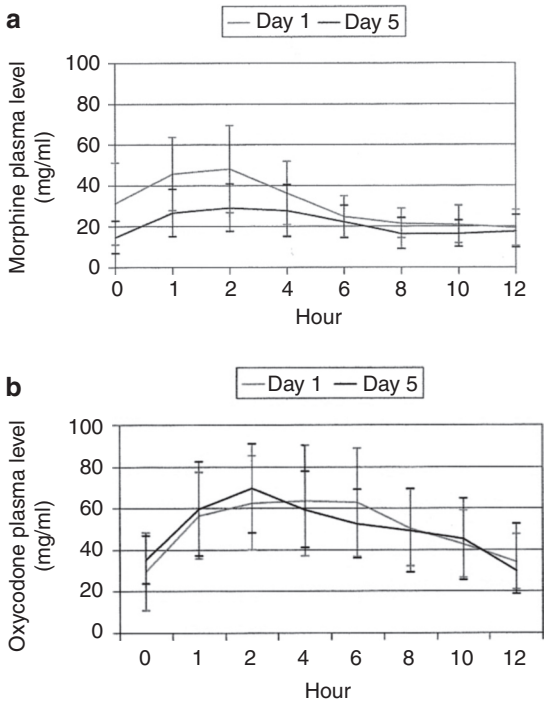

Figure 1 Plasma concentration–time curves for sustained-release (**a**) morphine and (**b**) oxycodone before and after exposure to inhaled cannabis.

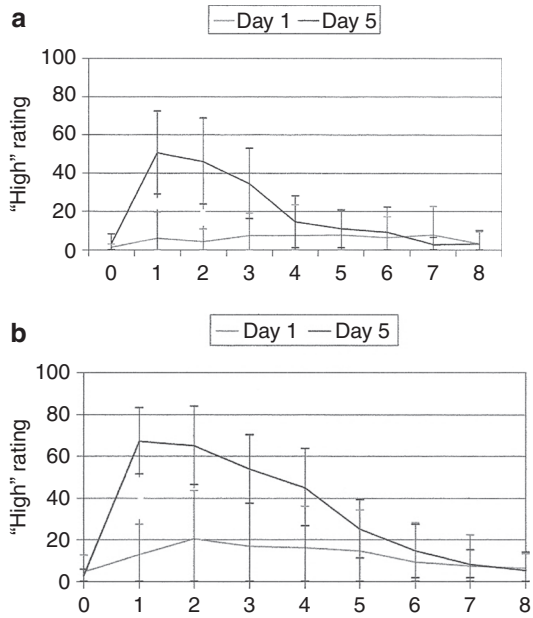

Figure 2 Subjective highs experienced when cannabis was combined with (**a**) morphine and (**b**) oxycodone on day 5.

release morphine or oxycodone. The participants experienced less pain after 5 days of inhaling vaporized cannabis; when the morphine and oxycodone groups were combined, this reduction in pain was significant. This is the first human study to demonstrate that inhaled cannabis safely augments the analgesic effects of opioids. Several other studies have examined the analgesic interaction between oral THC and opioids. Two of those studies involved healthy volunteers exposed to experimental pain conditions.[14,20] THC had little effect in either of the studies, whereas the combination of THC and morphine had synergistic effects on affective responses to pain in one study and on response to electrical stimulation in the other. A placebo-controlled trial in patients taking opioids for chronic pain found that oral dronabinol (delta-9-THC) decreased pain significantly.[15]

The mechanism by which cannabis augments the analgesic effects of opioids could be pharmacokinetic and/or pharmacodynamic. Cannabinoids have been shown to inhibit the metabolism of certain other drugs, both *in vitro* and *in vivo*.[16,21,22] THC has been shown to slow gastrointestinal motility, resulting in the slowing of absorption of orally administered drugs such as pentobarbital and ethanol. THC has also been shown to slow the intranasal absorption of cocaine.[23–25] In animals, cannabinoids have been shown to enhance the uptake of drugs, including cocaine and phencyclidine, into the brain; however, the mechanisms involved are not fully understood.[26]

In the present study, we examined the effects of vaporized cannabis administered three times a day on the steady-state pharmacokinetics of sustained-release morphine and oxycodone administered at 12-h intervals. In the case of morphine, we found that cannabis treatment was associated with a significant decrease in the maximal concentration. On average, the time to maximal morphine concentration was longer during cannabis administration, although this effect was not significant. There were no significant effects of cannabis treatment on the AUCs of morphine's metabolites or on the ratios of metabolites to parent morphine, indicating that cannabis had no effects on metabolic pathways. Vaporized cannabis had no significant effect on oxycodone kinetics or metabolite levels. The finding of a lower maximal concentration of morphine without any accompanying changes in metabolite levels during cannabis treatment is probably due to delayed absorption of morphine, presumably because of slowed gastrointestinal motility. Why such an effect was not seen for oxycodone is not clear. From the pharmacokinetic findings, it is clear that the observed augmentation of analgesia by cannabis cannot be explained on the basis of inhibition of morphine or oxycodone metabolism leading to higher plasma levels of these drugs.

Our findings suggest that cannabis augments opioid analgesia through a pharmacodynamic mechanism. However, prior research in rodents has shown that THC and cannabidiol enhance the penetration of certain other drugs, including cocaine and phencyclidine, into the brain.[26] If cannabinoids also enhance opioid penetration into the brain in humans, this might constitute a pharmacokinetic mechanism for enhancing the analgesic effects of opioids.

The participants reported a subjective high after inhaling cannabis, with little or no high after taking the oral opioids alone. Although we do not have data on the high in these participants in the absence of opioids (that is, with cannabis alone), the magnitude and time course of the high in the participants in the morphine group were similar to our observations in a previous study of inhaled cannabis in healthy subjects.[19] The high in the oxycodone group after cannabis treatment appeared to be more sustained than that in the morphine group, and also as compared with that of our previously studied healthy subjects.

Table 3 Morphine, oxycodone, and their metabolites: mean AUC and CV by study day

	Day 1			Day 5			Day 5/day 1			
	n	Geometric mean	CV	*n*	Geometric mean	CV	Ratio	95% CI	*P* value	
									Par	N-par
Morphine and its metabolites										
Morphine										
T_{max}[a]	10	3.1		10	4.74		1.64	−1.01, 4.30	0.19	0.2
C_{max}	10	43.68	15.95	10	29.66	15.74	0.9	0.85, 0.95	**0.003**	**0.002**
AUC	10	42.01	18.7	10	32.23	15.23	0.95	0.84, 1.05	0.17	0.23
M3g										
C_{max}	10	1,123.94	6.89	10	887.14	4.56	0.97	0.93, 1.00	0.06	0.08
AUC	10	821.39	9.54	10	756.73	7.41	1	0.92, 1.07	0.74	1
M6g										
C_{max}	10	188.67	16.28	10	153.22	6.53	0.97	0.92, 1.01	0.11	0.16
AUC	10	128.25	10.41	10	130.45	10.94	1.02	0.90, 1.15	0.95	0.85
M3g/morphine	10	6.32	17.66	10	6.92	6.92	1.06	0.98, 1.15	0.23	0.19
M6g/morphine	10	3.79	22.69	10	4.13	4.13	1.09	0.98, 1.21	0.25	0.08
Oxycodone and its metabolites										
Oxycodone										
T_{max}[a]	11	3.63		11	2.52		−1.11	−3.66, 1.43	0.35	0.9
C_{max}	11	64.91	12.87	11	62.74	16.67	0.99	0.89, 1.10	0.84	1
AUC	11	76.86	13.38	11	58.67	19.18	0.94	0.84, 1.04	0.18	0.32
Noroxycodone										
C_{max}	11	52.72	14.69	11	65.17	11.78	1.07	0.96, 1.17	0.22	0.46
AUC	11	38.67	15.1	11	36.97	17.11	1.01	0.85, 1.16	0.86	0.7
Oxymorphone										
C_{max}	11	1.42	203.31	11	1.39	175.91	0.15	−1.67, 1.96	0.9	0.82
AUC	10	1.32	334.96	10	1.25	302.37	0.63	0.00, 1.26	0.78	0.77
Noroxycodone/oxycodone	11	2.34	18.33	11	2.49	21.91	1.09	0.93, 1.25	0.31	0.37
Oxymorphone/oxycodone	10	1.07	328.32	10	1.05	354.88	0.7	−0.01, 1.41	0.63	0.63

Statistically significant values are in bold face. AUC, area under the plasma concentration–time curve; CI, confidence interval; C_{max}, maximum concentration; CV, coefficient of variation; M3g, morphine-3-glucuronide; M6g, morphine-6-glucuronide; N-par, nonparametric; Par, parametric; T_{max}, time to maximum concentration.

[a]T_{max} values are expressed as arithmetic means on each study day with standard deviation as the measure of variance. Comparisons of T_{max} values on day 1 and day 5 are expressed as the paired difference in these values (day 5 – day 1).

Our study has some limitations. The number of participants was relatively small, although we were powered to detect a 25% change in the 12-hour AUC (AUC_{12}). With respect to pain assessment, our study was not placebo-controlled, and therefore we cannot rule out the possibility that cannabis-enhanced analgesia was a placebo effect or a time effect of changes in activity levels associated with confinement in the inpatient research ward setting throughout the duration of the study. The intervention we used was vaporized cannabis, which delivers levels of THC and other cannabinoids similar to those of smoked cannabis without exposing the user to the combustion products of cannabis cigarettes, which could affect the metabolism and pulmonary uptake of other drugs. Oral cannabis is commonly used to deliver medicinal THC and results in high first-pass levels of cannabinoids in the liver, which could have effects on opioid metabolism different from those caused by vaporized cannabis. Therefore, further research is needed to determine how different cannabis delivery systems affect the metabolism of opioids and other drugs.

In conclusion, we found that vaporized cannabis augments analgesia in individuals with chronic pain on a treatment regimen of stable doses of sustained-release morphine or oxycodone, and that the mechanism of augmentation is not explained by elevation of plasma opioid concentrations or inhibition of opioid metabolism. Cannabis appears to slow morphine absorption such that maximal concentrations for a dosing interval are lower. The effect of inhaled cannabis in enhancing opiate analgesia is most likely achieved through a pharmacodynamic mechanism. These results suggest that further controlled studies of the synergistic interaction between cannabinoids and opioids are warranted.

Table 4 Subjective effects: morphine vs. morphine/cannabis and oxycodone vs. oxycodone/cannabis

	Day 1			Day 5			Day 5 – day 1		
	n	Mean	SD	*n*	Mean	SD	Difference	95% CI	*P* value
Morphine vs. morphine/cannabis									
Like effect									
C_{max}	9	54.56	24.38	10	63.5	29	6.89	−8.49, 22.26	0.33
AUC	10	2.99	2.99	10	2.01	1.2	−0.98	−3.00, 1.04	0.3
High									
C_{max}	10	13.6	24.57	10	54.7	30.76	41.1	20.85, 61.35	**0.001**
AUC	10	0.74	1.44	10	1.96	1.25	1.22	0.24, 2.20	**0.02**
Stimulated									
C_{max}	10	11.7	23.24	10	37.6	31.91	25.9	9.03, 42.77	**0.007**
AUC	10	0.55	1.08	10	1.5	1.6	0.96	−0.10, 2.01	0.07
Anxious									
C_{max}	10	31.8	27.84	10	27.4	29.33	−4.4	−25.12, 16.32	0.64
AUC	10	1.73	1.84	10	1.29	2.01	−0.44	−2.02, 1.14	0.54
Sedated									
C_{max}	10	36.9	32.42	10	36.5	24.67	−0.4	−21.64, 20.84	0.97
AUC	10	2.75	2.89	10	1.74	1.47	−1.01	−3.03, 1.00	0.29
Hungry									
C_{max}	10	64.8	34.57	10	42	29.44	−22.8	−44.71, −0.89	**0.04**
AUC	10	2.89	2.3	10	1.34	1.28	−1.55	−3.09, −0.02	**0.05**
Dry mouth									
C_{max}	10	32	22.97		25.8	30.75	−6.2	−31.82, 19.42	0.6
AUC	10	2.29	2.34	10	1.28	2.13	−1.01	−3.16, 1.15	0.32
Oxycodone vs. oxycodone/cannabis									
Like effect									
C_{max}	11	62.91	30.03	11	78.27	17.84	15.36	−3.14, 33.86	0.09
AUC	11	2.92	1.74	11	3.21	1.49	0.29	−0.69, 1.28	0.52
High									
C_{max}	11	23.73	29.35	11	72.73	23.22	49	27.82, 70.18	**0.001**
AUC	11	0.96	0.91	11	3.47	1.58	2.5	1.65, 3.36	**0.001**
Stimulated									
C_{max}	11	32.64	32.09	11	30	28.42	−2.63	−23.05, 17.77	0.78
AUC	11	1.21	1.12	11	1.76	2.27	0.55	−0.76, 1.87	0.37
Anxious									
C_{max}	11	49.73	34.04	11	33.39	33.39	−16.45	32.02, 0.89	**0.04**
AUC	11	2.22	1.87	11	1.88	1.88	−0.55	−1.55, 0.46	0.26
Sedated									
C_{max}	11	37.18	32.46	11	30.74	30.74	14.73	−10.06, 39.51	0.22
AUC	11	1.67	1.51	11	1.38	1.38	0.57	−0.96, 2.10	0.42
Hungry									
C_{max}	11	61.18	24.12	11	28.56	28.56	4.1		0.92
AUC	11	3.27	2.33	11	2.15	2.15	−0.5	−2.46, 1.45	0.58
Dry mouth									
C_{max}	11	22.18	19.6	11	33.65	33.65	23.45	−7.38, 54.29	0.12
AUC	11	1	1.07	11	1.32	1.32	0.6	−0.77, 7.97	0.35

Statistically significant values are in bold face. AUC, area under the plasma concentration–time curve; CI, confidence interval; C_{max}, maximum concentration.

METHODS

Study participants. The participants were adults >18 years of age who were experiencing chronic pain and receiving ongoing analgesic therapy with sustained-release morphine sulfate (MS Contin) or oxycodone hydrochloride (OxyContin) every 12 h. The participants were required to have been on a stable medication regimen for at least 2 weeks prior to the commencement of the study. Hepatic transaminase levels were required to be within 5 times the upper limit of normal and serum creatinine to be <2.0 mg/dl (177 μmol/l). A negative pregnancy test was required for female participants. Exclusion criteria included severe coronary artery disease, uncontrolled hypertension, cardiac ventricular conduction abnormalities, orthostatic mean blood pressure drop of >24 mm Hg, severe chronic obstructive pulmonary disease, history of renal or hepatic failure, active substance abuse, neurologic dysfunction or psychiatric disorder severe enough to interfere with assessment of pain, current use of smoked tobacco products or a confirmed cotinine level, and, in women, pregnancy, breastfeeding, or not using adequate birth control.

All the participants were required to have prior experience of smoking cannabis (six or more times in their lifetime) so that they would know how to inhale and what neuropsychologic effects to expect. Current users were asked to discontinue cannabis use for 30 days prior to commencement of the study, and such abstention was confirmed by a negative urine THC assay prior to study enrollment.

The study was approved by the institutional review board at the University of California, San Francisco; the Research Advisory Panel of California; the Drug Enforcement Administration; the US Food and Drug Administration, and the National Institute on Drug Abuse. Written informed consent was obtained from all the participants. The ClinicalTrials.gov registration number was NCT00308555.

Study medication. The National Institute on Drug Abuse provided cannabis in the form of cigarettes weighing 0.9 g on average and containing 3.56% delta-9-THC. The cigarettes were kept in a locked freezer with an alarm device attached until they were dispensed to a locked freezer in the San Francisco General Hospital Clinical Research Center where the inpatient study was conducted. The frozen cigarettes were thawed and rehydrated overnight in a humidifier. The cannabis was removed from the prerolled cigarettes and administered in a Volcano vaporizer (Model #0100 CS; Tuttlingen, Germany), heated to 190 °C.[27] The study participants were housed in a room with a fan ventilating to the outside. To maximize standardization of the vaporized doses, the subjects followed a uniform puffing procedure: the cannabis was inhaled for 5 s and then held for 10 s, with a 45-s pause before a repeat inhalation.[28] The participants were encouraged to inhale the entire vaporized dose of 0.9 g of 3.56% delta-9-THC or as much as they could tolerate.

In a previous study we had demonstrated that this vaporization procedure results in plasma THC levels similar to those induced by smoked marijuana but without significant exposure to carbon monoxide and other combustion products.[19]

Opioid disposition kinetics. Opioid pharmacokinetics were determined on days 1 and 5 from blood samples drawn at baseline and again at 1, 2, 4, 6, 8, 10, and 12 h after oral opioid administration. Given that the opioids were administered every 12 h, these measurements represent plasma concentration levels at steady state. On day 5, in addition to the opioid pharmacokinetics samples, THC plasma levels were measured at baseline and at 3, 10, 30, and 60 min to determine THC exposure for purposes of comparison with findings of prior and future studies. Our previous studies had demonstrated that this time course encompasses most of the THC AUC.[19]

The main outcome measure was the AUC_{12} for morphine and its glucuronide metabolites, or for oxycodone and its major metabolites, oxymorphone and noroxycodone.

Samples were shipped in a frozen state to the Center for Human Toxicology at the University of Utah, where they were analyzed for cannabinoids, morphine, and oxycodone using published procedures. Briefly, morphine, morphine-3-glucuronide, and morphine-6-glucuronide were measured using liquid chromatography with electrospray ionization–tandem mass spectrometry, with lower limits of quantification of 0.50 and 0.25 ng/ml for morphine and the glucuronides, respectively.[29] Oxycodone, oxymorphone, and noroxycodone were measured using liquid chromatography with electrospray ionization–tandem mass spectrometry, with lower limits of quantification of 0.2 ng/ml for all analytes.[30]

Cannabinoid measurements were obtained using a combination of modifications of previously published methods. The samples underwent liquid–liquid extraction,[31] and both extracts were combined and then derivatized and analyzed as previously described,[32] except that the method was modified to suit a different instrument (i.e., a Hewlett Packard 5890 GC (Palo Alto, CA) equipped with a DB-5 MS, 30 m × 0.25 mm, 0.25-mm column and interfaced with a Finnigan MAT SSQ 7000 MS (San Jose, CA) in negative chemical ionization mode).

Effects monitoring. Objective and subjective effects were measured to assess whether vaporized cannabis increases or attenuates the side effects associated with opioid analgesics. Subjective effects were assessed via participants' self-reports using the Drug Effects Questionnaire administered before the morning opioid dose and again at 30 min and 1, 2, 4, 6, 8, 10, and 12 h after drug administration on days 1 and 5. This questionnaire records subjective findings using standard visual analog scales where 0 is "no effect" and 100 is "maximal effect."[33] Assessment of drug effects included pain, stimulation, anxiety, sedation, feeling "down," hunger, mellowness, confusion, irritation, depression, feeling withdrawn, dizziness, nausea, and dryness of the mouth. In addition, the subjects were evaluated by the nursing staff for side effects every 4 h, recording scores for anxiety, sedation, disorientation, paranoia, confusion, dizziness, nausea, urinary retention, constipation, emesis, headache, swollen extremities, twitching, excitement, and level of consciousness on a scale from 0 to 4. The participants were monitored daily for nausea and vomiting using the Rhodes Index of Nausea, Vomiting, and Retching Questionnaire.[34] Because there was a concern that enhanced opioid effects could lead to respiratory depression, continuous pulse oximetry was performed every night, with the results documented every 2 h on the nursing flowsheet.

Statistical analysis.

Sample size: In a published study of individuals who took morphine on an empty stomach, the standard deviation of the within-person change in log (AUC_{10}) for a morphine solution was 20% over the course of 12 months.[35] Using this information, we estimated that, with a sample of 10 subjects, the study would have 80% power to detect a 25% percent change in the AUC_{12} between days 1 and 5. This estimate was based on a standardized effect size (E/S) of 1.25, using an alpha of 0.05, where E is the within-subject effect size (25%) and S is the standard deviation of the mean of the paired differences (20%) using a paired *t*-test.[36,37] In prior pharmacokinetics studies, a 30% change in AUC was thought to be clinically significant.[38] Therefore, we set the target size at 25% to ensure that we would be able to capture a clinically significant change in AUC_{12}. We enrolled at least 10 participants in each of the two (morphine and oxycodone) groups.

Data analysis: We described the characteristics of the participants at study entry overall and within each opioid group. We presented the mean (with 95% CI) plasma levels for each opioid over the 12-h observation period on days 1 and 5.

The primary outcome was the change in the AUC_{12} for morphine or oxycodone before and after cannabis exposure. We standardized plasma levels for each opioid to doses of 60 mg b.i.d. (observed opioid plasma level × (60 mg/administered opioid dose)). The standardized AUC_{12} was derived using the trapezoidal method over the dosing interval. We estimated the geometric mean and coefficient of variation in

the standardized AUC on days 1 and 5. We then computed the ratio of the geometric means (with 95% CI) for day 5/day 1. We tested the hypothesis of a statistically significant change in standardized AUC_{12} of at least 25%, using paired *t*-tests and nonparametric Wilcoxon signed-rank tests. We also assessed the percentage change in the geometric mean for C_{max} and the arithmetic mean for time to maximum concentration from the plasma concentration-vs.-time data for each subject. We used similar methods to describe results and assess changes for plasma concentrations of the metabolites of morphine (morphine-3-glucuronide and morphine-6-glucuronide) and oxycodone (oxymorphone and noroxycodone). We assessed the mean THC plasma levels (with 95% CIs) for a duration of 1 h, for the participants overall as well as by opioid group.

We described the mean pain ratings on days 1 and 5, both overall and within each opioid group, using mean values and 95% CIs. We assessed the mean values (with 95% CI) of individual differences and percentage changes in pain between days 1 and 5, both overall and within each opioid group, using paired *t*-tests.

Next, we assessed the subjective effects of vaporized marijuana among these participants. We represented the mean perceived high over the dosing period on days 1 and 5 for each opioid group. In addition, we estimated the mean value (with 95% CI) of each subjective effect on days 1 and 5 and determined statistically significant changes in the mean values (with 95% CI) of individual differences, using paired *t*-tests for each opioid group.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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