Vaporization as a Smokeless Cannabis Delivery System: A Pilot Study

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Although cannabis may have potential therapeutic value, inhalation of a combustion product is an undesirable delivery system. The aim of the study was to investigate vaporization using the Volcano® device as an alternative means of delivery of inhaled *Cannabis sativa*. Eighteen healthy inpatient subjects enrolled to compare the delivery of cannabinoids by vaporization to marijuana smoked in a standard cigarette. One strength (1.7, 3.4, or 6.8% tetrahydrocannabinol (THC)) and delivery system was randomly assigned for each of the 6 study days. Plasma concentrations of Δ-9-THC, expired carbon monoxide (CO), physiologic and neuropsychologic effects were the main outcome measures. Peak plasma concentrations and 6-h area under the plasma concentration–time curve of THC were similar. CO levels were reduced with vaporization. No adverse events occurred. Vaporization of cannabis is a safe and effective mode of delivery of THC. Further trials of clinical effectiveness of cannabis could utilize vaporization as a smokeless delivery system.

The Institute of Medicine (10 m) report on Marijuana as Medicine published in 1999 concluded that "scientific data indicate the potential therapeutic value of cannabinoid drugs, primarily THC, for pain relief, control of nausea and vomiting, appetite stimulation; smoked marijuana, however is a crude THC delivery system that also delivers harmful substances".[1] The report recommended that clinical trials of cannabinoid drugs for symptom management should be conducted with the goal of developing rapid onset, reliable, and safe delivery systems. While acknowledging therapeutic potential, the IOM report stressed that cannabis is not a completely benign substance, but a powerful drug with a variety of effects, but "except for the harms associated with smoking, the adverse effects are within the range of those tolerated for other medications." The report comments that "because of the health risks associated with smoking, smoked cannabis should generally not be recommended for long-term medical use. Nonetheless, for certain patients, such as the terminally ill or those with debilitating symptoms, the long-term risks are not of great concern." The Institute of Medicine sends a clear message suggesting that smoking is not a desirable delivery system for the potential therapeutic effects of cannabis.

Cannabis vaporization is a technology for delivering inhaled tetrahydrocannabinol (THC) and other cannabinoids while reducing toxic byproducts of smoked cannabis primarily caused by combustion.[2,3] By heating cannabis to a temperature between 180 and 200°C, it is possible to vaporize the cannabinoids that reside on the trichomes on the surface of cannabis flowers and leaves, while avoiding combustion (which occurs at 230°C and above) and attendant smoke toxins. Vaporization is a relatively new technology. Various vaporizer designs are currently under development. The feasibility of vaporization of THC has been demonstrated in a series of laboratory studies involving different vaporizer designs.[2] An electric vaporizer was shown to release substantial amounts of the THC while producing no measurable amounts of the benzene, toluene, and naphthalene, which are generated when marijuana is smoked. Reductions in carbon monoxide (CO) and tar generation were also observed under vaporization compared to smoking. Although no measurements were made of other smoke toxins, it is quite possible that the vaporizer eliminated or substantially reduced the polycyclic aromatic hydrocarbons and other combustion-generated toxins commonly found in cannabis smoke, as they form at the higher temperatures of pyrolysis.

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A recent evaluation of the Volcano® vaporizer device used herbal cannabis or pure cannabinoid ethanolic solution preparations to test the efficacy and reproducibility of THC delivery into the balloon receptacle.[4] Cannabinoids were measured in the THC-containing materials before and after vaporization, and in the vapor that was generated by the device and collected within the balloon. The results validated the Volcano® vaporizer as an efficient and reproducible mode of delivery of Δ-9-THC. On average, 54% of the applied dose of THC was recovered in the balloon receptacle.

This study investigated vaporization using the Volcano® device compared to smoked cannabis. This is the first pharmacokinetic and pharmacodynamic evaluation conducted in humans to determine whether the Volcano® may be an appropriate system for use in clinical effectiveness studies.

RESULTS

Baseline characteristics of study subjects

A total of 68 patients were screened for eligibility between August 2004 and May 2005. Of these, 47 were not enrolled (33 patients were unavailable to commit to a 6-day hospitalization, 10 patients were excluded as a result of their medical history or concurrent illness, and four patients were excluded because of active substance abuse). Twenty-one patients were randomly assigned; however, three patients did not complete the intervention of the study phase (one patient for non-adherence to the General Clinical Research Center (GCRC) rules of comportment, one patient for acute influenza, and one patient withdrew consent), leaving 18 total patients for analysis.

Participants were predominately men (83%), Caucasian (72%), with some college education (94%). All of the participants were active marijuana users (median 5–6, range 3–10 marijuana cigarettes in the past 30 days). None had used the Volcano® device, although one participant had previously experienced vaporized marijuana using a similar device.

Primary outcome measure

The mean and 95% confidence intervals (CIs) for the plasma concentrations of THC at each time point for each strength of THC using both vaporization and smoking are presented in **Figure 1**. The vaporizer resulted in higher plasma concentrations of THC compared to smoked marijuana at 30 and 60 min at each strength (**Table 1**). The two modalities were not significantly different from one another at any of the three strengths in the 6-h area under the plasma THC concentration–time curve (AUC), or for the peak THC plasma concentrations measured at 2 min.

There was evidence of decreasing bioavailability and/or titration of THC intake with increasing strength of THC. The plasma THC AUC derived from the vaporizer normalized for the THC strength was highest at 1.7% THC (27.1 ng h/ml/%) and was progressively lower at higher THC strengths (3.4% THC: 20.5 ng h/ml/% and 6.8% THC: 14.3 ng h/ml/%; **Table 1**), suggesting higher bioavailability and/or more intensive puffing at lower THC potency. This decline was

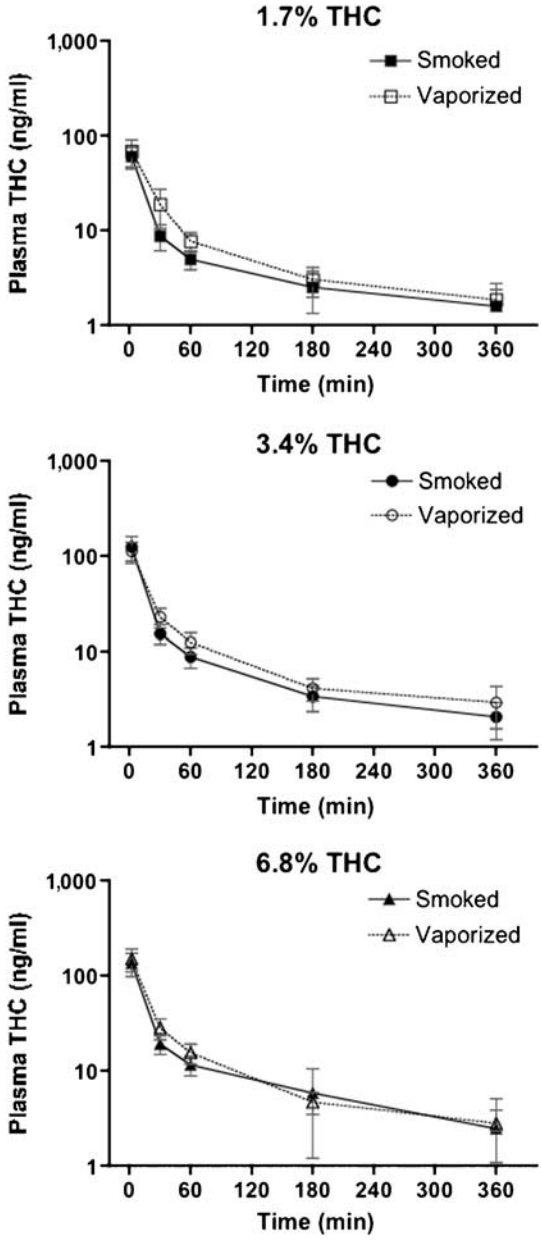

Figure 1 Plasma THC using vaporizer and smoked cannabis by THC strength (mean and 90% CI).

statistically significant (ratio: 0.87; 95% CI: 0.84, 0.90; $P<0.001$ per 1% increase in THC strength) and did not appear to differ between vaporization and smoking (ratio for interaction: 0.92; 95% CI: 0.79, 1.05; $P=0.25$) in a mixed model which included fixed effects for randomization, a linear term for THC strength, and a term for the interaction between these effects.

There was also evidence of titration of intake of THC with increasing THC strength based on puffing behavior. The number of puffs taken using smoked marijuana remained stable with increasing strength THC (mean puffs, 95% CI: 6.1 (4.8, 7.3), 5.9 (4.9, 6.8), and 6.4 (5.3, 7.6) for 1.7, 3.4, and 6.8% THC, respectively; mixed model analysis ratio: 1.01; 95% CI: 0.96, 1.05; $P=0.81$). The number of puffs taken

Table 1 THC pharmacokinetics for vaporized cannabis and ratio of vaporized vs smoked cannabis[a,b]

	Vaporizer				Vaporizer/smoked ratio		
THC, % outcome measure	Mean	95% CI	Minimum	Maximum	Odds ratio	95% CI*	*P*-value
1.7%							
AUC_{0-6}	46.00	34.89, 57.11	15.59	98.08	1.26	0.94, 1.68	0.12
C_{max} (=C_2)	68.95	46.99, 90.91	6.00	186.20	1.01	0.65, 1.58	0.97
C_{30}	18.94	10.57, 27.32	4.90	79.90	1.95	1.37, 2.80	0.001
C_{60}	7.56	6.02, 9.50	3.70	16.50	1.56	1.26, 1.93	0.001
C_{180}	3.05	1.99. 4.00	0.10	9.40	1.31	0.83, 2.06	0.25
C_{360}	1.87	0.97, 2.77	0.20	8.20	1.17	0.82, 1.66	0.38
Puffs	10.06	8.81, 11.30	7.00	17.00	1.71	1.47, 2.00	0.001
AUC/THC %	27.06	20.52, 33.60	9.17	57.69	1.26	0.94, 1.68	0.12
3.4%							
AUC_{0-6}	69.76	52.91, 86.62	22.30	140.44	0.99	0.81, 1.21	0.95
C_{max} (=C_2)	112.45	84.55, 140.65	36.70	201.10	1.07	0.64, 1.80	0.80
C_{30}	23.04	17.74, 28.35	28.35	43.20	1.50	1.29, 1.73	0.001
C_{60}	12.58	9.46, 15.70	3.30	24.20	1.41	1.11, 1.79	0.006
C_{180}	4.14	3.05, 5.24	1.40	10.10	1.24	1.06, 1.46	0.008
C_{360}	2.94	1.55, 4.34	0.60	12.90	1.34	1.03, 1.75	0.03
Puffs	9.17	8.23, 10.10	4.00	13.00	1.58	1.36, 1.84	0.001
AUC/THC %	20.52	15.56, 25.48	6.56	41.31	0.99	0.81, 1.21	0.95
6.8%							
AUC_{0-6}	96.79	67.51, 126.06	18.98	278.20	1.22	0.98, 1.54	0.08
C_{max} (=C_2)	187.12	100.65, 273.59	22.50	813.20	1.19	0.86, 1.65	0.30
C_{30}	28.80	22.19, 35.41	9.20	50.00	1.45	1.16, 1.82	0.001
C_{60}	15.99	12.41, 19.58	4.60	29.40	1.38	1.13, 1.69	0.002
C_{180}	4.81	3.65, 5.96	1.10	9.20	1.15	0.88, 1.52	0.31
C_{360}	2.99	0.79, 5.20	0	19.50	0.88	0.53, 1.45	0.62
Puffs	8.55	7.72, 9.40	5.00	11.00	1.43	1.11, 1.85	0.006
AUC/THC %	14.23	9.93, 18.54	2.79	40.91	1.22	0.98, 1.54	0.08

AUC, area under the curve; CI, confidence interval; THC, tetrahydrocannabinol. [a]AUCs in ng h/ml; C_{max} values in ng/ml. [b]Analysis conducted using mixed models to adjust for day of observation.

using vaporized marijuana tended to decrease with increasing strength of THC, but the trend was not significant (mean puffs, 95% CI: 10.1 (8.8, 11.3), 9.2 (8.2, 10.1), and 8.6 (7.7, 9.4) for 1.7, 3.4, and 6.8% THC, respectively; mixed model ratio: 0.97; 0.92, 1.01; $P = 0.17$).

Secondary outcome measures

The levels of exhaled CO increased very little after vaporization; mean = −1.9 p.p.m.; 95% CI: −4.4, 0.6 for 1.7% THC; mean = −1.8 p.p.m.; 95% CI: −3.7, 0.7 for 3.4% THC; and mean = −0.5 p.p.m.; 95% CI: −1.9, 0.9 for 6.8% THC), whereas there was a substantial increase after smoking marijuana (mean = 15.5 p.p.m.; 95% CI: 11.0, 20.1 for 1.7% THC; mean = 11.9 p.p.m.; 95% CI: 6.8, 17.1 for 3.4% THC; mean = 7.0 p.p.m.; 95% CI: 4.0, 10.0 for 6.8% THC) (**Figure 2**). This difference was statistically significant ($P < 0.001$) at each THC strength. The increase in CO (AUC for CO) decreased during smoking ($P = 0.003$ for trend), but not vaporization ($P = 0.25$) with increasing THC strength. The expired CO AUC per puff is an indicator of how much smoke is inhaled per puff for the smoked marijuana. The CO AUC per puff decreased progressively (1.7% THC: [mean, 95% CI]: 2.8 (2.2, 3.3); 3.4% THC: 2.1 (1.1, 3.0); 6.8% THC: 1.2 (0.6, 1.9); $P < 0.001$ for trend), consistent with taking smaller puffs with increasing THC content in the marijuana.

Subjective and safety observations

Self-reported high did not differ during vaporization compared to smoking overall (6-h AUC) or at any observation after consumption of cannabis (**Figure 3**). Self-reported high did increase significantly during both vaporization and smoking with increasing strength of THC ($P < 0.001$).

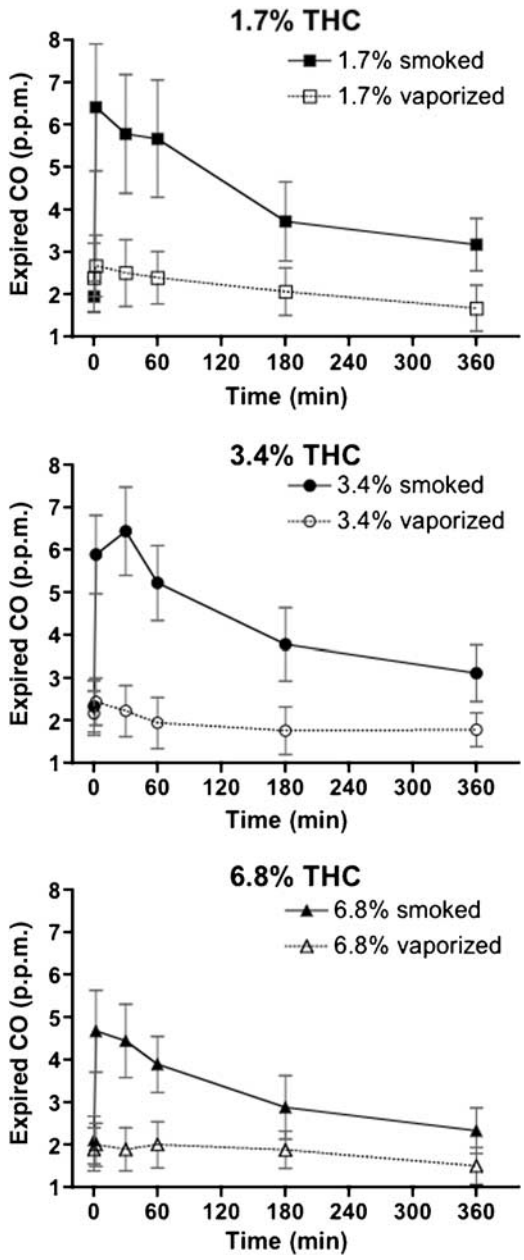

Figure 2 Expired CO at each time point for each mode of administration and THC strength (mean and 95% CI).

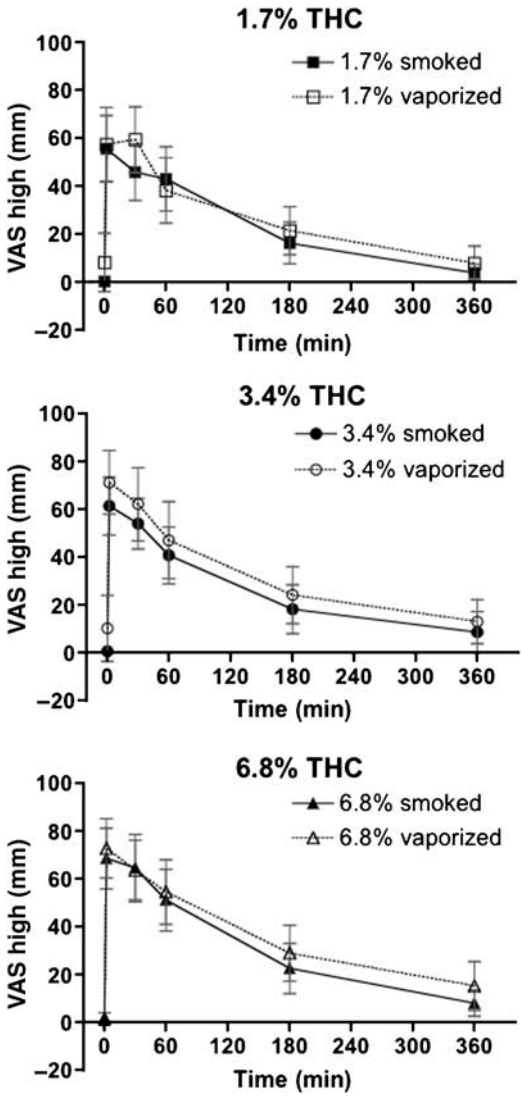

Figure 3 Self-reported "high" at each time point for each mode of administration and THC concentration (mean and 95% CI).

Although blinded with regard to dose, eight participants selected the day they received 3.4% THC (seven vaporized, one smoked) as their most preferred treatment day; four participants selected the day they received 6.8% THC via vaporization, and six participants had no treatment day preference. Overall, vaporization was the preferred method of administration by 14 participants, smoking was preferred by two, and two reported no preference. During the course of the study, no adverse events were reported.

DISCUSSION

Our study provides novel data on the absorption of THC from marijuana inhaled via the Volcano® vaporizer system compared to smoking marijuana cigarettes. We found that THC levels were generally similar over 6 h for the two types of delivery. The vaporizer was associated with higher plasma THC concentrations at 30 min and 1 h compared to smoking at each THC strength, suggesting that absorption was faster with the vaporizer.

Bioequivalence criteria developed for drugs require that the CIs for the ratios of AUC for the test and reference products be between 80 and 125% to be judged bioequivalent.[5] Using these criteria, we were not able to establish the bioequivalence of vaporization and smoking of marijuana. A much larger study would be needed to establish bioequivalence in this setting.

Of interest was that the systemic dose of THC, as estimated by the plasma AUC, normalized for the THC content of the cannabis, varied with THC strength. The dose of THC normalized for concentration of THC in the cannabis was greater at lower compared to higher THC strengths, both

for vaporized and smoked cannabis. This observation suggests either dose-dependant bioavailability or self-titration of THC intake. Self-titration of drug intake means that smokers adapt their smoking behavior to obtain desired levels of THC from the particular delivery system, taking more puffs and/or inhaling more efficiently at lower compared to higher THC strengths. Supporting the idea of titration was the trend to take more puffs at lower THC concentrations of vaporized marijuana and the higher CO per puff at lower THC concentrations of smoked marijuana. The phenomenon of self-titration of psychoactive drug intake from an inhaled delivery system is well documented for nicotine from cigarette smoking,[6] but to our knowledge has not been previously reported for marijuana.

Whereas smoking marijuana increased CO levels as expected for inhalation of a combustion product, there was little if any increase in CO after inhalation of THC from the vaporizer. This indicates little or no exposure to gaseous combustion toxins. Combustion products are harmful to health and reflect a major concern about the use of marijuana cigarettes for medical therapy as expressed by the Institute of Medicine. Although we did not measure other combustion products such as polycyclic aromatic hydrocarbons and oxidant gases, the observation of little or no CO exposure suggests little or no exposure to these other compounds. The vaporizer was well tolerated, with no reported adverse effects. Most subjects preferred the vaporizer compared to marijuana smoking, supporting its potential for medical therapy. Thus, the Volcano® is an acceptable system and may provide a safer way to deliver THC than smoking marijuana cigarettes.

In summary, we provide data indicating that the availability of THC delivered by the Volcano® vaporizer is comparable to that of marijuana cigarettes. Vaporization of marijuana does not result in exposure to combustion gases, and therefore is expected to be much safer than smoking marijuana cigarettes. The vaporizer was well tolerated and preferred by most subjects compared to marijuana cigarettes. The Volcano® device is an effective and apparently safe vehicle for THC delivery, and warrants further investigation in clinical trials of cannabis for medicinal purposes.

METHODS

Study patients. Participants were healthy adults between the ages of 21 and 45 years who were current cannabis users and had smoked cannabis within the past 30 days but in an amount totaling less than 10 cannabis cigarettes or the equivalent. Subjects with active substance abuse (*e.g.*, recurrent or continuous drug and/or alcohol use) or diagnosed with marijuana dependence as defined in DSM-IV code no. 304.30. were excluded. Subjects were required to abstain from smoking cannabis for 48 h before their admission into the GCRC at San Francisco General Hospital (SFGH). 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 Food and Drug Administration, and the National Institute on Drug Abuse. Written informed consent was obtained from all patients. The trial was monitored by an independent Data Safety Monitoring Board (DSMB) established by the University of California Center for Medicinal Cannabis Research.

Study medication. The National Institute on Drug Abuse provided pre-rolled cannabis cigarettes, weighing on average 0.9 g and containing 1.7, 3.4, and 6.8% Δ-9-THC, respectively. The cigarettes were kept in a locked and alarmed freezer until they were dispensed to a locked freezer in the San Francisco General Hospital General Clinical Research Center where the in-patient study was conducted. The cigarettes were bisected; one half to be smoked and the contents of the other half to be vaporized. The half cigarettes were rehydrated in a humidifier overnight before their use. Patients were housed in a room with a fan ventilating to the outside. Research staff monitored patients during smoking sessions, weighed the cannabis cigarettes immediately before and after they were administered to patients, and returned all leftover material to the pharmacy. To maximize standardization of inhaled doses, patients followed the Foltin uniform puff procedure where inhalation for 5 s is followed by a 10 s breath hold, then exhalation; the entire process is repeated after 45 s.[7] Study participants smoked or vaporized cannabis once a day. Subjects were instructed to continue puffing until they exhausted smoke or vapor from the delivery device or until they had inhaled as much as they could tolerate.

The vaporizer device. The Volcano® vaporizer was obtained from Storz & Bickel GmbH & Company (Tuttlingen, Germany) and was employed according to the manual provided. The device works as a vaporizer that evaporates the active substances or aromas from plant material by using a hot airflow (**Figure 4**). Cannabis placed in the filling chamber is heated by the device to 190°C. The vaporized compounds are collected in the inflatable, detachable bag fitted with a mouthpiece and a one-way valve that allows the vapor to remain in the balloon until inhalation. It required two to three balloon inflations to vaporize each half cigarette. Subjects also followed the Foltin puff procedure when inhaling the vaporization product.

Study design and procedures. The study was a 6-day "proof of concept" pilot study to investigate the delivery of cannabinoids by way of vaporization of cannabis compared to cannabis smoked in a standard cigarette. The in-patient setting permitted us to measure plasma THC concentration over time and to rigorously assess the primary and secondary outcome variables in a controlled clinical environment.

Screening visit. Once a subject for the protocol had been identified, details of the study were carefully discussed and the subject was asked to read and sign a consent form. Subjects were asked questions about their medical history including psychiatric illness and substance abuse. Subjects were asked to abstain from smoking or ingesting cannabis 48 h before their hospitalization based on our prior studies which indicated that after 24 h of abstinence, plasma THC concentrations are sufficiently low so that the concentration-time curve could be determined after the experimental exposure.[8]

GCRC in-patient hospitalization (days 1-6). Subjects inhaled three strengths of cannabis (1.7, 3.4, and 6.8% THC) as smoked cigarettes and three as vaporized cannabis using the Volcano® device. Half of one cigarette was inhaled via one of the two delivery systems on each of the 6 in-patient GCRC days. The uniform puff procedure described above was utilized to attempt to standardize inhalation. Blood was drawn at 2, 30, 60, 180, and 360 min after smoking on each of the 6 inhalation days to measure the concentrations of THC. Expired CO was measured using the Ecolyzer® before inhalation, and 2, 30, 60, 180, and 360 min after inhalation.

Subjects rated the subjective "high" they experienced using a 100 mm visual analog scale anchored by "none" and "highest ever". On day 5 before discharge, subjects were asked to choose which in-patient day they preferred. Subjects were asked to rate their preferences from 1 to 5 with 1 indicating very satisfied and 5 indicating very dissatisfied.

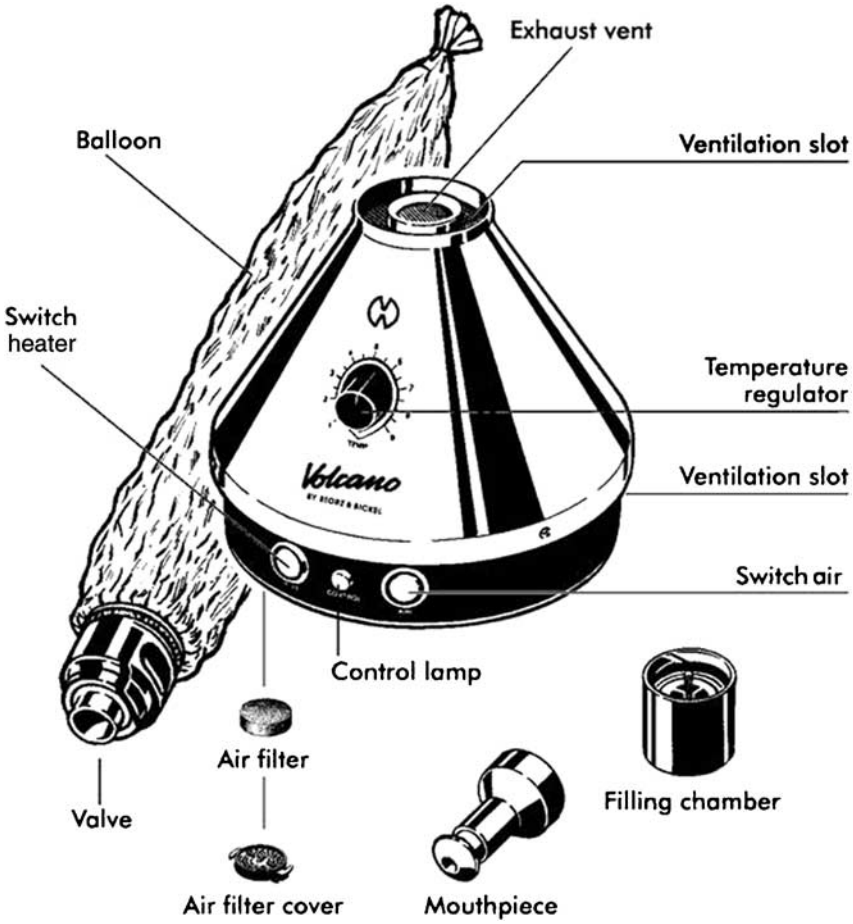

Figure 4 Volcano® apparatus.

All adverse events were spontaneously reported by the subject or observed by the study personnel and/or GCRC nursing staff, documented along with any medical intervention, and evaluated according to standardized criteria in terms of severity, frequency, duration, and relationship to study drug. Adverse events were graded using the NIH Division of AIDS table for scoring severity of adult adverse experiences.[9]

Randomization. The order of administration of the six combinations of THC strength and delivery method for the 18 participants was randomized in three 6×6 Latin squares. This ensured balance in the sense that each of the six combinations occurred exactly three times on day 1, exactly three times on day 2, and so on. In addition, the orders were restricted so that the two delivery methods for the same strength always occurred on consecutive days. This was to prevent patients from developing an early preference for one delivery method if it was used with a higher strength cigarette than the other. Randomization was computer-generated, and study drug distribution was managed by a research pharmacist. Subjects and study personnel were blinded to the THC strength.

Statistical analysis. The 18-patient target sample size was based on a standardized effect size to calculate sample size and power for the study. With a sample of 18 subjects, we had an 80% power to detect a true standardized effect size (E/S) of 0.70, using an α of 0.05, where E is the effect size and S is the standard deviation of the paired differences.[10,11] This calculation assumes use of a paired t-test using data at a single concentration of THC.

The primary outcome was the within-person ratio for the 6-h area under the curve (AUC_{0-6}) for plasma concentration of THC, comparing the vaporizer with smoking cannabis cigarettes. AUC_{0-6} was computed using the linear trapezoidal method, assuming zero THC concentration at baseline. This assumption was based on our previous research that observed undetectable plasma concentration of THC 8 h after smoking in all subjects.[8] For each mode of administration and THC strength, we plotted the mean and 95% CIs of the observed values at each time point. To assess the within-person ratio comparing vaporization to smoking, each outcome (AUC_{0-6}, C_2, C_{30}, C_{60}, C_{180}, C_{360}, number of puffs, AUC_{0-6} per THC percent, and AUC_{0-6} per puff) was log transformed for analysis using mixed effects models. The overall effect of vaporization compared to smoking for each parameter was assessed by fitting a fixed effect term for randomization (vaporization vs smoking), controlling for strength of THC (indicators for 3.4% THC and 6.8% THC cannabis, relative to 1.7% THC cannabis). Each patient was treated as a random effect. Another model was fit to assess THC strength-specific effects of vaporization compared to smoking. This model included fitting additional fixed effects for the use of the vaporizer at each strength of THC (vaporization at 1.7% THC, vaporization at 3.4% THC, and vaporization at 6.8% THC).

We also assessed the potential presence of order effects due to the study day of observation, as well as potential practice effects due to additional experience using the vaporizer. To assess the presence of order effects, additional variables were added to both the overall and strength-specific models to assess whether day of observation impacted the outcomes, as well as whether there was a difference

in measurements taken on the first day of the study compared to other study days. In these models, day of observation was treated as a linear variable with and without an additional indicator variable for the first study day. Similarly, to assess the presence of practice effects, additional variables were added to both the overall and strength-specific models to assess whether previous use of the vaporizer impacted the outcomes. These models included either a linear variable for how many days the participant had used the vaporizer or separate indicator variables for each day of vaporizer use.

To explore possible evidence of titration of THC intake and dose-dependent changes in bioavailability, we created additional mixed models for number of puffs and AUC_{0-6} per THC percent, which included fixed effects, as above, for randomization (vaporization vs smoking), as well as linear terms for strength of THC, and the interaction between randomization and strength of THC. As above, these models included a random effect for each patient. These models assess not only whether the ratio of the number of puffs or the AUC per THC percent differs during vaporization and smoking but also whether the ratio increases or decreases with increasing strength of cannabis, and whether this increase or decrease differs during vaporization compared to smoking.

We compared the observed values for expired CO and self-reported high using similar methods. We plotted the mean and 95% CIs of response measures at each time point for each mode of administration and THC strength. We also fit mixed models for the 6-h AUC for expired CO and self-reported high, as described above, to compare within-person effects using vaporization and smoking. For 6-h AUC for CO, we fit models for the within-person arithmetic difference in effects, because we were unable to fit models for the ratio of effects for 6-h AUC for CO due to the presence of many negative values (and therefore non-valid log transformation of these values) during vaporization. For 6-h AUC for self-reported high, we fit models for the within-person ratios in effects, as above.

All analyses were conducted using SAS 8.2.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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